Synthesis of $N$-Heterocycles and Their Reactive Precursors via Novel Pd/Cu-Catalyzed One-Pot Sequences

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__________________________
(Eugen Merkul)
To my beautiful wife Kateryna with love and gratitude
Il semble que la perfection soit atteinte non quand il n'y a plus rien à ajouter, mais quand il n'y a plus rien à retrancher.

(Vollkommenheit entsteht offensichtlich nicht dann, wenn man nichts mehr hinzuzufügen hat, sondern wenn man nichts mehr wegnehmen kann.)

{A designer knows he has achieved perfection not when there is nothing left to add, but when there is nothing left to take away.}

Antoine de Saint-Exupéry,

*Terre des Hommes (Wind, Sand und Sterne)* {Wind, Sand and Stars}
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This cumulative dissertation is based on the following published papers (in the reverse chronological order):

**Publications**


Additionally, following publications, which are not part of this thesis, appeared while it was in progress:


Additionally, following patents have been filed while this work was in progress and contain some methods or substances which resulted from this thesis (however, these results are not part of this thesis in the first line):

**Patent Applications**


Three additional patents have been registered: DE 102010049877.7 (01.11.2010), DE 102011008352.9 (12.01.2011), and DE 102011009961.1 (01.02.2011).
Additionally, parts of this thesis have been presented in form of oral and poster contributions:

**Oral Presentations**


Poster Presentations


Zusammenfassung


Im Rahmen dieser Arbeit konnten daher folgende Ziele erreicht werden:

1) Die Entwicklung einer Dreikomponentensynthese von schwer zugänglichen 2,4-disubstituierten Pyrrolen auf der Basis der Sonogashira-Kupplung.\[399]\n
2) Die Konzeption und methodische Etablierung einer Pseudo-Vierkomponenten-Synthese von 1,4-di(hetero)arylsubstituierten 1,3-Diinen durch eine Sequenz aus der Sonogashira-Alkinylierung und nachfolgender Glaser-Homokupplung.\[161]\n
5) N-Heteroaromatische Carbonsäuren und α-Oxocarbonsäuren können mittels einer in situ-Aktivierung mit Oxalylchlorid den Alkinylierungen nach Sonogashira oder Stephens-Castro zugeführt werden und gestatten erstmals die effiziente Transformation schwieriger N-heterocyclischer Substrate.\[91]\n
8

7) Die Konzeption und methodische Etablierung einer Dreikomponenten-Sequenz aus Sonogashira-Kupplung und nachfolgender Azid-Alkin-Cycloaddition (“Click”-Reaktion) zur Herstellung von (aza)indolylsubstituierten Triazolen. Mit dieser Methode gelang die Findung einer neuen Leitstruktur für selektive PDK1-Inhibitoren.\(^{[227]}\)
Schema 1 fasst das grundlegende Prinzip dieser Dissertation zusammen:


Abstract

Heterocycles are found in a plethora of natural products and active ingredients and their preparation touches the very core of Organic Synthesis. Therefore, efficient syntheses of heterocycles are of paramount importance.

The goal of this thesis was the development of novel one-pot reactions based on palladium- and/or copper-catalysis for the efficient synthesis of heterocycles or their precursors. Starting from simple building blocks and using simple catalyst systems, diverse functional molecules should be prepared by these methodologies.

In the context of this work following goals were accomplished:

1) Development of a three-component synthesis of difficult-to-access 2,4-disubstituted pyroles based on Sonogashira coupling.[399]

2) Conception and methodological establishment of a pseudo-four-component synthesis of 1,4-di(hetero)aryl substituted 1,3-diynes via sequential Sonogashira alkynylation–Glaser homocoupling.[161]

3) Establishment of a decarbonylative alkynylation of heteroaromatic glyoxylyl chlorides as a new variation of Sonogashira coupling. On this basis a conceptually novel three-component synthesis of ynones, which are important building blocks in many heterocycle syntheses, was devised.[355]

4) Conception and methodological establishment of a novel three-component synthesis of heterocyclic ynediones via catenation of glyoxylation and subsequent catalytic Stephens-Castro alkynylation in a one-pot fashion. Because the chemistry of ynediones is scarcely explored, the selective synthesis of 5-acyl pyrazoles was chosen to exemplify the synthetic potential of these reactive intermediates.[303]

5) N-Heteroaromatic carboxylic acids and α-oxo carboxylic acids can be in situ activated with oxalyl chloride for Sonogashira or Stephens-Castro alkynlations and allow for the first time an efficient transformation of notoriously difficult N-heterocyclic substrates.[91]
6) The sequentially Pd-catalyzed Masuda borylation–Suzuki coupling synthesis, which was established as a one-pot process, offers a direct and efficient strategy for the synthesis of 3-(hetero)aryl substituted (aza)indoles and 2,4-di(hetero)aryl substituted pyrroles. Besides the synthesis of 7-azaindole derivatives as analogs of variolin B this methodology was transposed to the preparation of symmetrical heterocycle-bridged bisindoles and to concise total syntheses of the marine alkaloids meridianin G, meridianin A,[464] and hyrtianadine A.[481] The obtained compounds were biologically evaluated in collaboration with Merck Serono, Darmstadt, on human cancer cell lines and on a broad panel of kinases, emphasizing that this methodology opens a rapid and efficient access to biologically active lead structures.

7) Conception and methodological establishment of a three-component Sonogashira coupling–azide-alkyne cycloaddition (“Click” reaction) sequence for the preparation of (aza)indolyl substituted triazoles. By this methodology a new lead structure for selective PDK1 inhibitors was found.[227]
Scheme 1 summarizes the basic principle of this thesis:

![Scheme 1](image)

**Scheme 1. Basic concept of this thesis: simple building blocks + simple catalysts = complex functionalized chemical targets.**

All presented one-pot syntheses can be conducted under mild reaction conditions and are broad with respect to the substrate range. They are preparatively very simple, start from simple reactants and utilize simple catalyst systems. Moreover, the synthetic versatility of oxalyl chloride as a reagent in catalytic couplings for the introduction of the $C_1$-carbonyl synthon ("surrogate for carbon monoxide") is successfully demonstrated for the first time.
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Abbreviations

[ ] catalytic amount
A2780 ovarian tumor cell line; ECACC 93112519
Abl Abelson (tyrosin kinase)
Ac acetyl
acac acetylacetonate
Ad 1-adamantyl
AGC cAMP-dependent protein kinase/protein kinase G/protein kinase C
‘Am tert-amyl ( tert-pentyl)
API active pharmaceutical ingredient
aq. aqueous
Asc ascorbate
atm atmosphere(s)
ATP adenosine-5’-triphosphate
[bmim]PF6 1-butyl-3-methylimidazolium hexafluorophosphate
Bn benzyl
Boc tert-butyloxy carbonyl
bp boiling point
Bpin pinacol boronate, pinacolborane
B₂pin₂ bis(pinacolato)diboron
BrettPhos 2-(dicyclohexylphosphino)-3,6-dimethoxy-2’,4’,6’-triisopropyl-1,1’-biphenyl
Bu butyl
°C degrees Celsius
calcld calculated
cAMP 3’-5’-cyclic adenosine monophosphate (cyclic AMP)
CDK cyclin-dependent kinase
CK1 casein kinase 1
CML chronic myeloid leukemia
CoA coenzyme A
COD 1,5-cyclooctadiene
Cp cyclopentadienyl
Cp*  pentamethyl cyclopentadienyl
CuAAC  Cu-catalyzed Azide – Alkyne Cycloaddition
Cy  cyclohexyl
CyDMEDA  trans-N,N'-dimethyl-1,2-cyclohexanediamine
d  day(s) or molecular orbital (“diffuse”)
D  Dalton
Δ  thermal conditions
dabco  1,4-diazabicyclo[2.2.2]octane
dba  dibenzylideneacetone
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DPPA  diphenylphosphoryl azide
dppb  1,4-bis(diphenylphosphino)butane
dppe  1,2-bis(diphenylphosphino)ethane
dppf  1,1'-bis(diphenylphosphino)ferrocene
dppp  1,3-bis(diphenylphosphino)propane
DCM  dichloromethane
DCS  di(N-succinimidyl)carbonate
DEPT  Distortionless Enhancement by Polarization Transfer
DIPA  diisopropylamine
DIPEA  diisopropylethylamine (Hünig’s base)
DMAP  4-dimethylaminopyridine
DME  dimethoxyethane
DMEDA  N,N'-dimethylethylenediamine
DMF  N,N-dimethylformamide
DMF-DMA  N,N-dimethylformamide dimethyl acetal
DMPU  N,N'-dimethylpropyleneurea
dppp  1,3-bis(diphenylphosphino)propane
dtbpy  2,6-di-tert-butylpyridine
(E)  “entgegen”, configuration of double bond according to E/Z notation
ECACC  European Collection of Cell Culture
ED  effective dose
EDG  electron donating group
EI  Electron Impact Ionization
equiv(s)  equivalent(s)  
Et  ethyl  
EWG  electron withdrawing group  
F₆-acac  1,1,1,5,5,5-hexafluoroacetylacetone  
FG  leaving group  
g  gram(s)  
GSK-3  glycogen synthase kinase 3  
Gu  guanidine  
h  hour(s)  
Hal  halide  
HE  hexanes  
HCT116  colon tumor cell line; ATCC CCL-247  
HIV  human immunodeficiency virus  
HMG-CoA  3-hydroxy-3-methyl-glutaryl-CoA reductase  
i  iso  
IC₅₀  half maximal inhibitory concentration  
IR  infrared (spectroscopy)  
J  coupling constant  
Kᵢ  inhibition constant of a drug  
L  ligand or liter(s)  
M  metal  
m  meta  
MAP  mitogen-activated protein  
MCM-41  Mobil Composition of Matter No. 41  
MCR  multicomponent reaction  
Me  methyl  
MEM  methoxyethoxymethyl  
min  minute(s)  
MOM  methoxymethyl  
Mp  melting point  
MS  mass spectrometry or molecular sieves  
µW  microwave  
n  normal (linear, not branched)
NHC  \(N\)-heterocyclic carbene
NMP  \(N\)-methylpyrrolidone
NMR  Nuclear Magnetic Resonance (spectroscopy)
NPs  nanoparticles
Nu  nucleophile
\(o\)  ortho
\(p\)  para
\(\pi\)  aromatic system
PA-Ph 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphadadamantane
Pd/C palladium on charcoal
PDK1 3-phosphoinositide-dependent protein kinase-1
PE petroleum ether (boiling range 40-60 °C)
\(pH\) pondus Hydrogenii
Piv pivaloyl
Ph phenyl
phen 1,10-phenanthroline
PMB \(p\)-methoxybenzyl
po peroral
ppm parts per million
Pr propyl
PTK protein tyrosine kinase
PTSA \(p\)-toluenesulfonic acid
psi pound per square inch; 1 psi = 0.068948 bar
Py pyridine
rt room temperature
RT reverse transcriptase
RuAAC Ru-catalyzed Azide-Alkyne Cycloaddition
RuPhos 2-(dicyclohexylphosphino)-2',6'-diisopropoxy-1,1'-biphenyl
\((S)\)  absolute configuration according to RS-system
SAR structure-activity relationship
sc supercritical
SMR structure-metabolism relationship
stoich. stoichiometric amount

t 
 tert
TBAF tetra-n-butylammonium fluoride
TBTA tris(benzyltriazolyl)methyl amine
Tf trifluoromethanesulfonyl (triflyl)
TFA trifluoroacetate
Th thienyl
THF tetrahydrofuran
THP tetrahydropyran-2-yl
TIPS triisopropylsilyl
TLC Thin Layer Chromatography
TMEDA \(N,N,N',N'\)-tetramethyl-1,2-ethylenediamine
TMHD 2,2,6,6-tetramethyl-3,5-heptanedionate
TMS trimethylsilyl
TMSA trimethylsilylacetylene
Tol methylphenyl
Ts 4-toluenesulfonyl (tosyl)
vs versus
W watt
Xantphos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl
X-ray X-radiation
(Z) “zusammen”, configuration of double bond according to \(E/Z\) notation
Introduction

Catalysis

Catalysis is one of the main principles of modern synthetic methodologies and is a key technology to achieve objectives of sustainable (green) chemistry.\cite{1} The most important domain of metal-catalysis is the direct carbon-carbon bond coupling,\cite{2} which has been considered to be the main goal for organic chemists for many decades. With the formulation of the concept of “click chemistry”, the alternative philosophy of making carbon-heteroatom bonds\cite{3} in an easy way is now strongly in development, with catalysis again playing the central role.

Heterocycles

Heterocyclic chemistry is one of the most important topics in synthetic organic chemistry that covers a wide variety of potent molecules. The prevalent number of drugs contains heterocyclic moieties. Efficient syntheses of heterocycles are therefore of paramount importance for pharmaceutical industry. In particular, nitrogen containing heterocycles are structural constituents of many bioactive natural products, medicinally important compounds, and organic materials. Moreover, natural products containing heterocycles often possess unprecedented structures, which represent considerable synthetical challenges for organic chemists and encourage their creativity.
Concept of the ideal synthesis

Contemporary requirements for new synthetic methods go far beyond the traditional quests for chemo-, regio-, and stereoselectivity and include additional factors such as:

- Use of simple and readily available starting materials
- Experimental simplicity
- Favorable economic factors, including the cost of raw materials, human resources, and energy
- Low environmental impact: minimization of waste and Trost’s atom economy\(^4\)
- Concepts of step economy (Wender and Baran),\(^5\) redox economy (Baran and Hoffmann),\(^6\) and recently introduced pot economy (Clarke)\(^7\)
- Synthetic elegance

These and other requirements are expressed in the concept of the “ideal” synthesis (Figure 1),\(^8\) which is an ideal goal that certainly can only be approached asymptotically but which can still serve as a useful guideline for development of new synthetic methods.

![Diagram of Ideal Synthesis](image)

Figure 1. The ideal synthesis – showing the way (adapted from [55]).

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One-pot and multicomponent reactions

Nature with its chemistry going through cascade catalysis and multistep conversions in “one-pot” (living cells) provides concepts of high value for designing sustainable organic syntheses, which already have found applications on pilot or industrial scale.\[^9\] From a practical aspect, one-pot reactions can accelerate the search for pharmaceuticals.\[^10\]

“For this reason, development of processes that allow creation of several bonds in a single operation has become one of the most attractive scientific challenges. Multicomponent reactions (MCRs) can be defined as convergent chemical processes where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials.”\[^385a\] MCRs can be successfully implemented in the synthesis of diverse heterocycles. “For a long time multicomponent syntheses of heterocycles have been a domain of classical carbonyl condensation chemistry, with isocyanide-based Ugi chemistry being still prevalent in this area of research.”\[^11\] However, the advent and rapid evolution of transition metal catalysis not only has revolutionized strategies in heterocyclic synthesis by uni- and bimolecular transformations but the past decade has also witnessed the rapid development of transition metal catalysis in new MCRs. Transition metal catalysis, and especially sequential catalysis, with palladium occupying a dominant but not monopolistic position\[^12\],[^13],[^14]\ offers numerous possibilities to develop new MCRs due to the mild reaction conditions and generality of scope, favorable features that are shared by many cross-couplings.\[^15],[^16]\
Pd- and Cu-catalysis

Palladium and copper are the most widely used late transition metals with numerous applications in organic synthesis.

Pd- and Cu-assisted methods often work in a complementary fashion, giving for example different chemoselectivities. On the other hand, the combination of these two metals in a cooperative way plays a key role in some important transformations. The most prominent example is the Sonogashira-Hagihara cross-coupling where two catalytic cycles coexist, cooperate, and interlock with each other (Scheme 2).

Scheme 2. Pd and Cu cycles in the proposed mechanistic rationale for the Sonogashira coupling.
Natural products

“Natural products are the richest source of small molecules that bind to proteins with high specificity thanks to millions of years of evolution”.\textsuperscript{[107]} Hence, “medicine and natural products have been closely linked for thousands of years by the use of traditional medicine and natural poisons. It has been estimated that over half the drugs currently used for the treatment of cancer are either natural products or drugs derived from them. Even today, in the century of combinatorial chemistry, secondary metabolites of plants, fungi, marine organisms, and microorganisms are an important source for the development of new drugs.\textsuperscript{[17]} Approximately 50 \% of drugs introduced to the market are derived directly or indirectly from small molecules of natural origin”.\textsuperscript{[401]}

Kinase inhibitors

Protein kinases catalyze the phosphorylation of serine, threonine, tyrosine, and histidine residues in proteins.\textsuperscript{[18]} Reversible phosphorylation is one of the major modes of cellular signal transduction and plays a regulatory role in most metabolic pathways. Hence, virtually every aspect of cellular physiology, such as cell growth, metabolism, differentiation, and apoptosis, is inherently linked to the proper functioning of these enzymes. Abberant regulation of kinase activity has been implicated in many diseases including cancer. Hence, kinases are among the most promising drug targets.\textsuperscript{[19]} Frequently, kinase inhibitors are small molecules suitable for development and preparation in chemical laboratories on a big scale. For this reason, small heterocyclic molecules play an immensely important role in oncology,\textsuperscript{[20]} and investigations of new strategies for kinase inhibitor design remains an active area of research with direct relevance to drug development. Currently, it is estimated that approximately one-third of the drug discovery programs target protein kinases.\textsuperscript{[21]} For medicinal chemists, protein kinases represent a goldmine of design opportunities.
1 Goal of This Work

The goal of this work was to develop novel one-pot Pd and/or Cu-catalyzed reaction sequences for the efficient construction of heterocycles or their immediate precursors. The reactions should be mild, preparatively convenient, and allow to synthesize biologically active heterocyclic molecules for biological studies as well as natural products in a concise sequential or consecutive fashion starting from easily accessible materials and using simple catalysts (Scheme 3).

2 General Part – Literature Overview

2.1 Multicomponent Reactions and Sequential Catalysis

“One of the major research endeavors in synthetic chemistry over the past decades is the exploration of synthetic methods that maximize atom utilization”.[70] “By generating structural complexity in a single step from three or more reactants, MCRs make it possible to synthesize target compounds with greater efficiency and atom economy. The history of such reactions can be traced back to the mid-19th century when Strecker first produced α-aminonitriles from the condensation of aldehydes with ammonia and hydrogen cyanide”.[26a] An exceptionally beautiful first example for the utility of a MCR in the total synthesis of natural products is the tropinone synthesis by Robinson, published in 1917 (Scheme 4).[22]

Scheme 4. First total synthesis of natural product tropinone via MCR.

“Recently, academic chemists have revitalized their interest in MCRs.[23] In part, pharmaceutical industry has fueled this resurgence because of the growing need to assemble libraries of structurally complex substances for evaluation as lead compounds in drug discovery and development programs.[24],[32] The application of MCRs, however, remains limited by the relatively small number of traditionally proved reactions”[26a] such as Strecker (1850), Hantzsch (1882), Biginelli (1891), Mannich (1912), Passerini (1921), and Ugi (1959).[25] Not surprising, therefore, is the recent development of novel logic-based strategies for the engineering of new MCRs.[26]
In terms of classification, “domino reactions are regarded as sequences of uni- and bimolecular elementary reactions that proceed without isolation or workup of intermediates as a consequence of the reactive functionality that has been formed in the previous step. Besides uni- and bimolecular domino reactions that are generally referred to as “domino reactions”, the third class is called multimolecular domino reactions or multicomponent reactions (MCRs). Whereas uni- and bimolecular domino reactions inevitably cause a significant increase in the degree of molecular complexity, MCRs inherently lead to an increase in molecular diversity. Therefore, MCRs bear some significant advantages over uni- and bimolecular domino reactions. Besides the facile accessibility and high diversity of starting materials, multicomponent syntheses promise high convergence and enormous exploratory potential. In addition to a purist standpoint, where all ingredients of MCRs have to be present from the very beginning of the process (MCRs in a domino fashion), nowadays sequential (subsequent addition of reagents in a well defined order without changing the conditions) and consecutive (subsequent addition of reagents with changing the conditions) one-pot reactions are counted as well in the class of MCRs (Figure 2).

![Multicomponent and domino reactions diagram](image)

Figure 2. Multicomponent and domino reactions (adapted from [55]).
Sequential catalysis is defined as a combination of identical, related, or significantly different\textsuperscript{[29]} (metal)-catalyzed processes that occur in a sequential or consecutive fashion in the same reaction vessel without addition of further amounts of catalyst to the reaction media.\textsuperscript{[13]} Fogg and dos Santos provided a classification review on one-pot catalytic processes involving sequential elaboration of an organic substrate via multiple catalytic transformations with the focus on tandem catalysis.\textsuperscript{[30]} Cooperative multicatalyst systems for one-pot organic transformation are also of high interest, with Pd and Cu-catalyzed \textit{Sonogashira} coupling being one of the most prominent examples.\textsuperscript{[31]}

“Multicomponent and sequential one-pot processes address very fundamental principles of synthetic efficiency\textsuperscript{[32]} and reaction design and they are steadily gaining a considerable and increasing academic, economic, and ecological interest”.\textsuperscript{[293]} According to the basic principles of MCRs the products of consecutive transformations should preferentially contain substantial fragments of all starting materials, thus providing a high degree of atom-efficiency (or atom economy,\textsuperscript{[4]} defined as the number of atoms of the reactants which can be found in the product).

MCRs belong to highly sophisticated tools in the repertoire of an organic chemist. They are masterpieces and require intelligent reaction design and a judicious choice of appropriate reaction conditions to combine different transformations into a one-pot process. Hence, it is not surprising that the separate steps of a reaction sequence have to be efficient by themselves to give an efficient and clean one-pot transformation. Otherwise, undesired byproducts will accumulate leading to a loss of efficiency and product purity. However, one-pot reactions are frequently more than just a clever combination of already known methods. They can include the generation of unstable intermediates, thus leading to higher product yields than the corresponding separated reactions. An even more sophisticated situation occurs if a byproduct generated during the first reaction promotes the second reaction in the same sequence. In the framework of this thesis both cases were experienced during the design of new one-pot reactions.
2.2 Cross-Coupling Reactions

Transition metal-catalyzed cross-coupling is recognized as one of the most powerful C–C bond-forming reactions.\textsuperscript{[2]} “Cross-coupling is a generic term used to denote a $\sigma$-bond metathesis reaction between a nucleophilic and an electrophilic reagent, and thus can be regarded as a generalization of nucleophilic substitution. Coupling reactions take place only in the presence of a catalyst.”\textsuperscript{[42d]}

The Pd-catalyzed coupling of aryl halides or their synthetic equivalents with aryl metals is very often employed in the synthesis of biaryl molecules,\textsuperscript{[33]} whose scaffolds can be found in a wide range of important compounds including pharmaceuticals,\textsuperscript{[34]} natural products, and functional organic materials (Scheme 5).

\[
\text{Aryl}^1\text{Hal} + \text{M–Aryl}^2 \xrightarrow{[\text{Pd(0)}]} \text{Aryl}^1\text{Aryl}^2
\]

Scheme 5. Pd-catalyzed cross-coupling reactions for the synthesis of biaryls.

“The role of the catalyst is generally believed to take part in successive oxidative addition, transmetalation, and reductive elimination reactions”\textsuperscript{[42d]} (Scheme 6).

Scheme 6. A simplified representation of the proposed general mechanism for Pd-catalyzed cross-coupling reactions using monodentate ligands.
Cross-coupling reactions have found numerous applications in the synthesis of biologically active molecules, heterocycles,\textsuperscript{35} and total synthesis of natural products,\textsuperscript{36} and have become a standard tool for the synthetic chemist.

Halides are the most frequently used electrophilic partners in coupling reactions. Following the dissociation energies of the sp\textsuperscript{2}-C–Hal bonds (272, 339, and 402 kJ mol\textsuperscript{-1} at 298 K for PhI, PhBr, and PhCl, respectively), aryl iodides are by far more reactive than bromides and chlorides. In recent years, “the acquisition of the ability to utilize inexpensive aryl chlorides has been of particular interest in the cross-coupling research arena.”\textsuperscript{37} However, by far the largest application of cross-coupling chemistry occurs in the medicinal and discovery groups of pharmaceutical companies and in academic laboratories. For the vast majority of these cases the scope, experimental ease, and reliability of a method is much more important than whether aryl chlorides can be used rather than aryl bromides or aryl iodides.”\textsuperscript{195d}

Although the vast majority of synthetic methods is typically exemplified with simple aryl substrates, heterocyclic,\textsuperscript{35} especially N-heterocyclic, substrates have remained demanding and challenging for the method development and, therefore, have been far less investigated. Heteroaromatics tend to be good ligands for transition metals, hence substrate and/or product inhibition are quite common. Moreover, free amino and alcohols groups often poison the metal catalyst via ligation or act as nucleophiles and need protection (Ts, Boc, Bn, Ac). Cross-coupling with heteroarenes is therefore highly topical and rapidly developing area of research. Just recently, methods of coupling two heteroarenes were reviewed, emphasizing the importance of this issue.\textsuperscript{38}
2.3 Pd/Cu-Catalyzed Reactions

Pd reagents have decisively changed the synthetic strategies, especially of natural products, and altered even the way of thinking of organic chemists. They contributed to a change in synthetic schemes from previously linear to currently convergent strategies. “Today, cross-coupling is so closely associated with palladium catalysis that both terms are often regarded as inseparable parts of an idiom”.[42d] The element palladium possesses several unique features that render it highly suitable for cross-couplings:

- “The middle atom size (second transition metal row) between that of Ni and Pt leads to a moderate stability of Pd-complexes. They are more stable than the Ni-, but more reactive than Pt-complexes, thus being synthetically highly useful. There are sufficient coordination sites for catalytic reactions.

- Pd prefers two oxidation states: 0 and +II. The change between these two states is very facile, so that Pd is perfectly suited for performing oxidative addition and reductive elimination steps. The active species can be easily regenerated, closing the catalyst cycle. There is little tendency toward one electron radical processes.

- Pd is a late transition metal and realizes d\(^{10}\) and d\(^{8}\) complexes. In connection with its medium size, the high number of electrons makes it “soft”. It possesses high affinity to unpolar \(\pi\)-systems such as alkynes, alkenes, arenes, as well as “soft” phosphane ligands.

- High electronegativity (2.2 according to Pauling electronegativity scale; C: 2.5). The unpolar C–Pd bonds display low reactivity toward polar functionalities, unlike polar organolithium or organomagnesium compounds. Therefore, Pd-catalyzed reactions are highly tolerant to functional groups. A very important exception are acyl halides, which are very reactive toward palladium and are extensively used as substrates\(^{[39]}\) (vide infra).
synthetic transformations have been developed that use palladium compounds, such as carbon-carbon and carbon-heteroatom coupling reactions: Buchwald-Hartwig, Heck-Mizoroki, Kumada-Corriu, Negishi, Nozaki-Hiyama, Sonogashira-Hagihara, Stille-Migita, Suzuki-Miyaura, and Tsuji-Trost. An extremely important domain of Pd-catalysis are carbonylative reactions, which allow the introduction of the most important functionality, the carbonyl group.\textsuperscript{[40]} All these reactions are gaining increasing popularity as they are generally tolerant to a wide range of functional groups and can therefore be applied to complicated advanced molecules.

Cu-catalyzed transformations belong to the basic processes in the organic chemistry. Indeed, copper was the ancestor of palladium in the cross-coupling domain. “Classical \textit{Ullmann} chemistry has been known for a full century and served well for C–N, C–S, C–O, and some other bond formation reactions. Moreover, C–C bond formation has been the priority domain of organocuprate chemistry. However, after the discovery and with the dramatic development of the Pd-catalyzed cross-coupling methodologies, Cu-mediated transformations became far less important and have fallen into oblivion. A critical point was the discovery and fast development of the Pd-catalyzed amination, known as \textit{Buchwald-Hartwig} chemistry, which conquered the last stronghold of Cu – the synthesis of arylamines in which the classical \textit{Ullmann} and \textit{Goldberg} reactions had kept an exclusive and unshakable position”\textsuperscript{[41]} However, Cu possesses several very attractive features making it extremely versatile:

- “The most important feature of Cu is an easy accessability of four oxidation states from 0 to +III. Most likely, the cross-coupling catalytic cycle with Cu is operated by +I/+III oxidation states.

- Accessibility of odd-electron states in Cu, implying that Cu can take part in redox single-electron transfer processes.

- Cu is much cheaper than Pd. Despite of that, industrial processes need to be catalytic in Cu.

- \textit{N-} or \textit{O-}ligands required for the Cu-catalysis are usually cheap and easily accessible. Many of them are common analytical or general purpose reagents.

- Cu shows wide tolerance to functional groups and double bonds.”\textsuperscript{[41]}
For these reasons, in the past years there has been a true renaissance of the Cu-chemistry, and a plenty of very exciting novel reactions were discovered and continue to appear in the literature.\textsuperscript{[42],[43]}

Pd- and Cu-catalysis can be applied complementarily, for instance in arylations to give regioisomeric products. \textit{Buchwald} reported an orthogonal catalyst system for the chemoselective $O$- and $N$-arylation of aminophenols, using Cul/picolinic acid or CyDMEDA and Pd/BrettPhos, respectively.\textsuperscript{[44]} In the same group an orthogonal catalytic system for the chemoselective $C$- and $N$-arylation of oxindoles has been developed using Pd/XPhos or RuPhos and Cul/CyDMEDA, respectively.\textsuperscript{[45]}

An interesting orthogonal system has been developed for arylation of aromatic carboxylic acids with boronic acids.\textsuperscript{[46]} Under Pd-catalysis, biarylS were obtained, whereas the Cu-catalyst gives rise to the formation of carboxylic esters (Scheme 7).

![Scheme 7. Orthogonal catalyst systems for arylation of aromatic acids.](image-url)
Palladium and copper can also work cooperatively in a variety of important transformations.

Cu is widely used to accelerate the reoxidation of Pd(0) to Pd(II) with O₂ as in the industrially important Wacker process for the aerobic oxidation of alkenes to aldehydes (Scheme 8).[^47a]

\[
\begin{align*}
\text{[PdCl₄]^{2-}} + C₂H₄ + H₂O & \xrightarrow{-2 \text{ HCl}} \text{Pd}^{0} + \text{CH₃CHO} \\
Pd^{0} + 2 \text{CuCl}_2 + 2 \text{Cl}^- & \xrightarrow{\text{}} [\text{PdCl₄}]^{2-} + 2 \text{CuCl} \\
2 \text{CuCl} + \frac{1}{2} \text{O}_2 + 2 \text{HCl} & \xrightarrow{\text{}} 2 \text{CuCl}_2 + \text{H}_2\text{O}
\end{align*}
\]

Net: \(C₂H₄ + \frac{1}{2} \text{O}_2 \rightarrow \text{CH₃CHO}\)

Scheme 8. Individual reactions of the Wacker process (scheme taken from [47a]).

Both Pd and Cu were required in the decarboxylative cross-coupling of \(\alpha\)-oxo-carboxylates and aryl bromides reported by Gooßen (Scheme 9).[^48] The method is applicable to the synthesis of simple biaryl ketones.

\[\text{R}^1\text{CO}_2\text{K}^+ + \text{Br-R}^2 \xrightarrow{1 \text{ mol} \% \text{Pd(F₃-acac)}_2, 2 \text{ mol} \% \text{P(o-Tol)}_3, 15 \text{ mol} \% \text{CuBr, 15 mol} \% \text{1,10-phenanthroline}} \xrightarrow{\text{NMP/quinine, 170 °C, 16-36 h}} \text{R}^1\text{R}^2\]

\(\text{R}^1 = \text{Aryl, 2-Th, 2-Furyl, 'Bu, 'Bu, Bn}\)
\(\text{R}^2 = \text{Aryl, 3-Py, 3-Th}\)

25 examples

26-99 %

Scheme 9. Decarboxylative cross-coupling according to Gooßen.

The postulated mechanism consists of Pd- and Cu-catalytic cycles, Cu being responsible for the decarboxylation of the Cu glyoxylate and transmetalation of the aroyl
residue to Pd. However, for practical applications high reaction temperatures and prolonged reaction times are less favorable. Moreover, many additives and rigorously dried solvents are indispensable.

Similarly, both metals were used for the synthesis of biaryls via catalytic decarboxylative coupling of acids with aryl bromides according to Gooßen.\textsuperscript{[49]} Later, the same group reported a decarboxylative coupling of carboxylate salts with triflates,\textsuperscript{[50]} tosylates\textsuperscript{[51]} and aryl chlorides,\textsuperscript{[52]} a microwave-assisted coupling of carboxylates with aryl bromides,\textsuperscript{[53]} as well as a one-pot three-component synthesis of azomethines from \(\alpha\)-oxo-carboxylates, amines, and aryl bromides.\textsuperscript{[54]}

The most prominent example of Pd and Cu working in a cooperative fashion is the bimetallic \textit{Sonogashira-Hagihara} cross-coupling, which will be discussed below in chapter \textit{2.3.2 Sonogashira-Hagihara coupling}. In Müller’s group Pd/Cu-catalyzed alkyne activation has been extensively used as an entry to diverse heterocycles (vide infra).\textsuperscript{[55]}

Both metals have been shown to be essential also in the related alkyne homocoupling, where Cu is believed to possess a dual role, first being utilized to mediate the alkynyl transfer to Pd(II), and second in the reoxidation of Pd(0) to Pd(II).\textsuperscript{[144b]} This reaction will be discussed in chapter \textit{2.3.4 Glaser-type acetylene couplings}. 
2.3.1 *Stephens-Castro* coupling

In 1963, *Stephens* and *Castro* disclosed that diarylacetylenes can be produced in good yields upon treatment of aryl iodides with copper(I) acetylides in refluxing pyridine (Scheme 10).\[^{[56]}\]

\[
\text{Aryl} = \text{EWG-Aryl, EGC-Aryl}
\]

8 examples

75-99 %


Although the initial reaction conditions were quite harsh requiring refluxing pyridine and stoichiometric amounts of potentially explosive acetylides, this finding paved the way for the further development of alkynylation reactions based on cross-coupling methodologies. Later, catalytic variants ("copper-only Sonogashira coupling") and milder conditions have been developed rendering the reaction more general.\[^{[57]}\]

The reaction is also suitable for the preparation of ynones (for the detailed discussion on ynones, see chapter 2.6.1, *Syntheses and reactivity of ynones*). In 1999, *Kundu* described a catalytic *Stephens-Castro* coupling of aromatic acid halides with terminal alkynes (Scheme 11). Triethylamine was used as a base and solvent.\[^{[58]}\]

No diyne byproducts, which are usually formed in Pd-catalyzed reactions of terminal alkynes (vide infra), have been observed.

A microwave-assisted coupling of acid chlorides appeared in 2001 (Scheme 12).\(^{[59]}\)

![Scheme 12. Microwave-assisted synthesis of yrones.](image)

The first carbonylative *Stephens-Castro* coupling of aryl iodides with alkynes using Cu(TMHD)\(_2\) as a catalyst and triethylamine as a base was described in 2008 and proceeded at 90 °C and under 20 atm of CO pressure.\(^{[60]}\) Simple aromatic yrones were obtained in moderate to good yields.

In 2003, a mild catalytic *Stephens-Castro* coupling of monooxalyl chlorides was reported (Scheme 13).\(^{[61]}\) Here, triethylamine was used in slight excess.

![Scheme 13. Catalytic *Stephens-Castro* coupling of monooxalyl chlorides.](image)

The reaction was highly suitable for the synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides. However, prior to this work this direct approach has been neither extended into a one-pot protocol nor applied to the functionalization of heterocycles. The potential of ynediones as versatile building blocks has not been explored to a proper extend.
2.3.2 Sonogashira-Hagihara coupling

Soon after the pioneering report by Stephens and Castro, in 1975 Sonogashira demonstrated that terminal alkynes react smoothly with bromoalkenes, iodoarenes, and bromopyridines in the presence of catalytic amounts of bis(triphenylphosphane)palladium dichloride and cuprous iodide in diethylamine at room temperature (Scheme 14).[62]

\[
\begin{align*}
R^1\text{-Hal} + \equiv \equiv R^2 & \xrightarrow{[\text{PdCl}_2(\text{PPh}_3)_2/\text{CuI}]} \quad R^1\equiv \equiv R^2 \\
R^1 = \text{Alkenyl, Aryl, 2-Py} & \\
R^2 = \text{H, Ph, CH}_2\text{OH} & \\
\text{Hal} = \text{I, Br} & \\
\text{(base and solvent)} & \\
\text{rt, 3-6 h} & \\
16 \text{ examples} & \\
27-99 \% & 
\end{align*}
\]


The authors proved that CuI was essential for the reaction to proceed under very mild conditions and proposed a mechanism which involved the generation of an active Pd(0)-species and of the crucial Pd(II)-alkynyl complex via a Cu-acetylide formed by the assistance of Cu(I) and the amine base (Scheme 15). Although the main features of the Pd catalytic cycle have been established, the Cu catalytic cycle is still poorly understood.
Scheme 15. General mechanistic rational for Sonogashira coupling with triethylamine as a base.

It should be mentioned that in the same year Cassar\textsuperscript{63} and Heck\textsuperscript{64} reported their catalytic systems based on Pd(0) and Pd(II) triphenylphosphane complexes. However, the Cu-cocatalyzed mild method of Sonogashira turned out to be more practical.\textsuperscript{65}
In order to synthesize an unsymmetrical tolane, the Sonogashira coupling of aryl halides with trimethylsilylacetylene can be performed to provide TMS-protected alkynes, which have to be protodesilylated to obtain terminal alkynes that in turn can be coupled with another aryl halide to obtain the desired tolane. This stepwise procedure is tedious, thus the one-pot sila-Sonogashira coupling has been introduced by Mori and later generalized by Brisbois and Grieco in 2002 (Scheme 16). Symmetrical and unsymmetrical tolanes are obtained in good yields.

Scheme 16. Sila-Sonogashira coupling for the preparation of symmetrical and unsymmetrical tolanes.

Eventually, a recent one-pot procedure described the synthesis of unsymmetrical diarylalkynes via coupling of two different aryl halides and TMSA. The TMS-alkyne formed after the first coupling step is deprotected with aq. KOH and coupled again without additional Pd/Cu-catalysts.

In the arena of alkyne chemistry, the Sonogashira coupling is one of the most significant developments over the past 35 years. The Sonogashira reaction possesses several features that render it one of the most efficient and reliable C–C cross-coupling reactions:
• The reaction is very general and includes (hetero)aryl or vinyl halides as electrophiles and terminal alkyl, alkenyl, (hetero)aryl, and silyl substituted alkynes or acetylene as nucleophiles.

• The catalysts are readily available. Cu(I)-sources are typically CuI or CuBr; typical Pd(II)-precatalysts are PdCl₂(PPh₃)₂ or Pd(PPh₃)₄.

• A base is required. Typically, amine bases are used, often as solvents.

• Solvents do not need to be rigorously dried (but deoxygenation is required!).

• A wide functional group tolerance. Therefore, useful in the synthesis of natural products and active pharmaceutical ingredients (APIs). However, 1-alkynes containing an EWG directly attached to the ethynyl carbon atom hardly react with aryl halides.

• Mild reaction conditions with reactions typically proceeding at room temperature or slightly above. At higher temperatures, alkynes are prone to undergo side reactions.

• Cu-acetylidides are catalytically generated in situ.

• Good scaleability of the process.

In 1977, Sonogashira and Hagihara reported a coupling of acid chlorides with terminal alkynes to form ynone, a useful class of synthetic intermediates (Scheme 17).⁶⁶⁹

Both coupling partners were used in exactly stoichiometrical amounts.

\[
\begin{align*}
\text{R}^1\text{Cl} + \equiv\text{R}^2 & \xrightarrow{\text{[PdCl}_2(\text{PPh}_3)_2/\text{Cul]} \text{NET}_3} \text{R}^1\equiv\text{R}^2 \\
\text{R}^1 & = \text{Alkyl, (Hetero)Aryl, Styryl, NMe}_2 \\
\text{R}^2 & = \text{Ph, } ^t\text{Bu}
\end{align*}
\]

Scheme 17. Sonogashira coupling of acid chlorides.
The reactivity of acid chlorides toward alkyne addition is more pronounced as compared to other carbonyl compounds, thus making them attractive substrates for alkynylation (Scheme 18).[70]

![Diagram of carbonyl compounds reactivity](attachment:image)

Scheme 18. Reactivity of carbonyl compounds toward alkynylation.

Under classical conditions, the amine base is used as a solvent in large excess. In 2003, a useful modification of Sonogashira coupling of acid chlorides with terminal alkynes was introduced by Müller using exactly one equivalent of triethylamine as a base (Scheme 19).[71],[72] This amount is stoichiometrically required and is consumed by scavenging the hydrogen chloride formed during the reaction.

![Diagram of modified Sonogashira coupling](attachment:image)

Scheme 19. Modified Sonogashira coupling using exactly one equivalent of triethylamine.

This subtle modification has the significant advantage of milder reaction conditions. The ynones formed under essentially neutral conditions can be now converted to a huge variety of O-, S-, and N-heterocycles in diverse one-pot reactions (see discussion in chapter 2.6.1 Synthesis and reactivity of ynones).

A number of other conditions has been reported utilizing the reactivity of acid chlorides toward alkynes in Sonogashira reactions: (1) very efficient copper-free coupling
using phosphane-free oxime-derived palladacycle and triethylamine as a base, according to Nájera,[73] (2) coupling in water as solvent using a catalytic amount of sodium lauryl sulfate as a surfactant and K₂CO₃ as a base;[74] (3) recyclable nanosized MCM-41 anchored palladium bipyridyl complex-catalyzed coupling with very low catalyst loadings;[75] and (4) recyclable polystyrene-supported Pd(0)-complex under copper- and solvent-free conditions,[76] only to mention a few.

Certainly, the major limitation of using acid chlorides as substrates for metal-catalyzed cross-coupling reactions is the inherent need for protection of reactive functionalities such as OH and NH₂ groups. Moreover, acid chlorides are not always commercially available and have to be prepared from the corresponding acids. For that reason, an interesting alternative is the utilization of carboxylic acids,[77] which are readily available, stable, and easy-to-handle compounds, representing very attractive substrates for cross-couplings. These methodologies proceed mostly with a decarboxylative outcome. The first herald was a Cu-catalyzed biaryl synthesis reported in 1966 by Nilsson.[78] However, this approach was “reinvented” by Myers[79] and became very popular only in recent years.[80],[81] α-Oxo-acids are also known to undergo decarboxylative cross-couplings under Pd[82] and Pd/Cu-catalysis.[48],[54] Although the initially drastic conditions[83] have mellowed, the major inherent disadvantage of these methods is the loss of the precious carbonyl group—a circumstance that frequently gives rise to the formation of products which are of little interest from the synthetical point of view and can be made by numerous other methods. However, there are notable exceptions working also with 5-ring electron rich heterocyclic substrates such as thiazole, oxazole, and pyrrole carboxylic acids.[84] In one report, a nicotinic acid derivative was coupled under decarboxylative conditions.[85] Further, indole carboxylic acids could be arylated via Pd-catalyzed decarboxylations.[86] Ultimately, a protodecarbonylation reaction, catalyzed by Ag₂CO₃/AcOH, is broadly applicable with diverse heterocyclic acids including pyridine carboxylic acids.[87]

In situ activation of acids in metal-catalyzed cross-couplings in analogy to methods applied in the peptide synthesis has been described by Gooßen. As activators, DCS (Scheme 20),[88] Piv₂O,[89],[250] (MeOOC)₂O,[90] and Boc₂O[251] have been utilized. However, generally no N-heterocyclic carboxylic acids have been used as substrates. The activators were applied in excess (1.2-3.0 equivs), and the method required special ligands and additives.
1) 3 mol % Pd(F₆-acac)₂, 9 mol % PCy₃

\[
\text{Na}_2\text{CO}_3 (2.0 \text{ equiv})
\]

THF, rt, min

2) \( R^2-\text{B(OH)}_2 \) (1.2 equiv)

rt to 80 °C, 20 h

23 examples
37-95 %

\( R^1 = \text{Alkyl, Ph, EDG-Aryl, EWG-Aryl, 3-Th, 3-Furyl, 4-Py} \)

\( R^2 = \text{Ph, EDG-Aryl, EWG-Aryl, 3-Th, 2-Furyl} \)

Scheme 20. In situ activation of carboxylic acids with DCS as an activator.

In conclusion, prior to this work carboxylic acids have never been used in alkynylation. Since many heterocyclic acids but not the corresponding chlorides are commercially available, a method to produce ynone from acids would beneficially complement already existing methods for the generation of ynone. Additionally, oxalyl chloride has never been used as an activator of carboxylic acids in metal-catalyzed cross-couplings (for a discussion, see chapter 2.7 Oxalyl chloride in organic synthesis).
In the framework of this thesis, the synthetic utility of oxalyl chloride was exploited in novel activation – alkynylation sequences in collaboration with M. Sc. Christina Boersch, who performed the experimental work. Heterocyclic carboxylic acids and α-oxo-carboxylic acids could be efficiently converted to the corresponding acid chlorides via clean reaction with oxalyl chloride. The resulting acid chlorides were reacted in a one-pot fashion with alkynes under Sonogashira or catalytic Stephens-Castro coupling conditions giving rise to the formation of ynone and ynediones (Scheme 21 and Scheme 22). Astonishingly, a wide variety of N-heterocyclic acids could be successfully brought to reaction, although N-heterocycles are notoriously difficult substrates in cross-couplings.

Scheme 21. One-pot synthesis of ynone from carboxylic acids.\textsuperscript{[91]}

Scheme 22. One-pot synthesis of ynediones from α-oxo-carboxylic acids.\textsuperscript{[91]}
This strategy represents a novel approach to ynone and ynedione using standard catalytic systems without need for exotic ligands or additives. Upon addition of guanidinium salts, a one-pot three-component synthesis of pyrimidines is feasible as illustrated by a concise one-pot preparation of the pharmacophore of the blockbuster drugs imatinib and nilotinib,[486],[494] both acting as tyrosine kinase inhibitors to combat cancer (Scheme 23).[91]

![Scheme 23. One-pot synthesis of the pharmacophore of Gleevec® and Tasigna®](image)

This approach represents the most concise synthesis of this highly important structural motif (for a discussion, see chapter 2.11 Kinases and kinase inhibitors).

These results are part of this cumulative dissertation (publication 3.1).
2.3.3 Carboxylative Sonogashira coupling

Given the case that acid chlorides are not readily available, another useful modification, such as carboxylative Sonogashira coupling, can be envisioned for the construction of ynones. Carboxylative alkynylation is recognized as the coupling of halides with terminal acetylens in the presence of carbon monoxide. This transformation is a very useful approach and attracts much attention. However, high reaction temperatures and pressure of carbon monoxide are necessary in order to achieve selective carboxylative coupling.\textsuperscript{[92]} For example, in a recent synthesis of the quinolone key substructure of the protease inhibitor BI LN 2061 via carboxylative Sonogashira coupling, the reaction was run at 120 °C under 250 psi CO.\textsuperscript{[93]} Nicolaou utilized the carboxylative Sonogashira coupling in the total synthesis of the natural product biouyanagin A, working at 100 °C under 200 psi CO.\textsuperscript{[94]} Several syntheses of heterocycles via carboxylative Sonogashira coupling have been reported. Flavons and chromones\textsuperscript{[95]} as well as 4-quinolones\textsuperscript{[96]} were prepared by Kalinin from o-iodophenols and o-iodoanilines, respectively (120 °C/20 atm CO). Simultaneously, Torii reported similar approaches to 4-pyridone-3-carboxylic esters (90 °C/40 atm CO),\textsuperscript{[97]} 4-dialkylaminoquinolines (70 °C/10 kg cm\textsuperscript{-2} CO),\textsuperscript{[98]} as well as 4-quinolone-3-carboxylic esters\textsuperscript{[99]} and 4-quinolones\textsuperscript{[100]} (120 °C/20 kg cm\textsuperscript{-2} CO).\textsuperscript{[101]} A further example is the synthesis of (E)-3-aryliden-5-aryl-2-(3H)-furanones, performed at 110-120 °C and under 300-1200 psi CO pressure.\textsuperscript{[102]}

Not surprisingly, attempts have been made to find milder conditions. For instance, a reaction under normal pressure of carbon monoxide but with a twofold excess of relatively precious aryl iodides can be applied.\textsuperscript{[103]} A mild (30 °C/1 atm CO) Pd/Cu-catalyzed carboxylative coupling of iodonium salt was achieved, with a drawback of using rather precious starting materials.\textsuperscript{[104]} For the coupling of vinyl triflates, a mild carboxylative alkynylation (60 °C/1 atm CO) using Pd(OAc)\textsubscript{2}/dppp/NEt\textsubscript{3} system has been described as early as in 1991.\textsuperscript{[105]} At the same time, the same authors performed studies on Pd-catalyzed carboxylative coupling of 2-hydroxyaryl iodides with ethynylarenes at 60 °C under 1 atm of CO pressure.\textsuperscript{[106]} In this work, however, mixtures of flavones and (Z)-aurones were generally obtained.
In recent years, several mild procedures for carbonylative alkynylation of aryl iodides have been developed which allow couplings at ambient temperatures and pressure of carbon monoxide.

First report by Yang in this direction appeared in 2000 and described synthesis of flavones[107] at 40-45 °C under a balloon pressure of CO using PdCl₂(PPh₃)₂-thiourea-dppp complex.

The carbonylative Sonogashira coupling under mild conditions was generalized by Mori in 2003 (Scheme 24).[108]

![Scheme 24. Carbonylative Sonogashira coupling according to Mori.](attachment:scheme.png)

The authors claimed that aqueous ammonia as a base was superior to triethylamine and decisive for the carbonylative outcome of the reaction. The choice of the catalytic system depends on the electronic nature of substituents on the iodide and on the alkyne. The formation of the noncarbonylated product could be suppressed; only in some cases the byproduct was formed in 1-7% yield. However, the method was demonstrated to proceed only with simple substrates.

Later, this approach was extended by the same group for a one-pot construction of pyrazoles and isoxazoles.[109]

In 2005, a Pd-catalyzed copper-free carbonylative alkynylation of aryl iodides for the synthesis of ynones and flavones in water as a solvent under ambient temperature and CO pressure was reported by Yang.[110]
Also in 2005, we used a mild carbonylative Sonogashira coupling as a key step in the total synthesis of natural products meridianins and a variolin B analog.\textsuperscript{[448]} The synthesis of the key ynone structures has been performed at room temperature and using 1 atm of carbon monoxide and was particularly well suited for N-Boc protected 3-iodo (aza)indoles as substrates (see discussion in chapter 2.10.1.1 Meridianins).

Ultimately, in 2009 Capretta presented an access to flavones via microwave-assisted one-pot three- and four-component carbonylative sequences working at 1 atm of CO.\textsuperscript{[111]} PA-Ph was shown to be an effective ligand in these transformations.

However, these examples rather represent exceptions since newer reports continue to work under high temperatures and pressures of carbon monoxide: (1) coupling in an ionic liquid [bmim]PF\textsubscript{6} using PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}/NEt\textsubscript{3} (120 °C/20 atm CO);\textsuperscript{[112]} (2) magnetically separable and recoverable heterogeneous catalyst Pd/Fe\textsubscript{3}O\textsubscript{4} (130 °C/2.0 MPa CO);\textsuperscript{[113]} (3) synthesis of alkyl alkylnyl ketones using PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}/NEt\textsubscript{3} under photoirradiation conditions (500 W xenon lamp, Pyrex/45 atm CO);\textsuperscript{[114]} (4) coupling of aryl bromides using [(cinnamyl)PdCl\textsubscript{2}]/BuPAd\textsubscript{2}/K\textsubscript{2}CO\textsubscript{3} (100 °C/10 bar CO);\textsuperscript{[115]} and (5) coupling of aryl triflates using [(cinnamyl)PdCl\textsubscript{2}]/Xantphos/NEt\textsubscript{3} (110 °C/10 bar CO).\textsuperscript{[116]} Obviously, the success of the selective carbonylative alkylnylation without formation of the direct coupling product is strongly substrate dependent and remains matter of careful optimization. Additionally, it should be noted that all methods reported deal with rather simple substrates such as aryl iodides and aryl alkynes; no complex or N-heterocyclic halides and alkynes have been utilized.

In general, a palladium-catalyzed reaction in the presence of carbon monoxide\textsuperscript{[40]} proceeds slower than under an inert atmosphere since CO serves as a strong ligand with electron withdrawing characteristics. Certainly, long reaction times are a significant drawback of carbonylative methods. Furthermore, the success of the carbonylative reactions using carbon monoxide is strongly dependent on the solubility or diffusion of the gas into the bulk, which can be controlled by the pressure of CO (however, increasing CO pressure causes additional coordination to the catalytic intermediates slowing down the reaction) and/or the surface area-to-volume ratio,\textsuperscript{[117]} causing reproducibility and scaleability problems. Moreover, since carbon monoxide is a highly toxic gas,\textsuperscript{[118]} which has no smell, color, or taste, special equipment is required for safety reasons. Moreover, synthetic organic chemists are reluctant to use high-pressure equipment. Thus, attempts have been made to replace it with other CO
sources (see discussion in chapter 2.5 Oxalyl chloride in organic synthesis). A prominent CO surrogate is molybdenum hexacarbonyl Mo(CO)$_6$, which is utilized quite frequently.

An example of its use is the procedure described by Kondo in 2007 (Scheme 25).$^{[119]}$ Aryl iodides could be reacted, and P$^t$Bu$_3$ was essential for smooth conversion and facilitated the formation of yrones rather then the direct Sonogashira coupling products.

![Scheme 25. Carbonylative alkynylation using Mo(CO)$_6$ as a CO source.](image)

A similar approach was used by Stonehouse in one-pot syntheses of pyrazoles and pyrimidines.$^{[120]}$

Despite its nontoxicity and nonproblematic handling, Mo(CO)$_6$ as a CO source has one significant disadvantage of being typically used in large excess, rendering such processes not economical considering the high costs of this reagent.

In conclusion, the Sonogashira reaction with its numerous modifications has established itself as one of the most powerful and popular synthetic methods for the synthesis of substituted alkynes.$^{[121]}$ It is technically simple, efficient, high yielding, and tolerant toward a wide variety of functional groups. However, couplings of aryl bromides$^{[122]}$ and especially chlorides,$^{[37],[123]}$ as well as tosylates and mesylates$^{[124]}$ are not efficient with the standard catalytic system, and higher temperatures lead to alkyne side reactions. For this reason, improvements are still necessary, and the Sonogashira coupling remains an active research domain.$^{[125]}$ New catalyst systems
and ligands are being developing, and numerous metal complexes have been reported to catalyze the C(sp)–C(sp²) coupling.¹²⁶ Due to the generality and mild reaction conditions, Sonogashira coupling is highly suitable for designing various one-pot sequences containing this transformation.¹²⁷

“It appears from the recent literature on applications of the Sonogashira coupling in organic synthesis that the synthetic community is hesitant to apply the new highly efficient Pd catalysts that have been developed. Still, a very significant proportion of Sonogashira coupling reactions are carried out with the classical catalysts such as PdCl₂(PPh₃)₂ and Pd(PPh₃)₄ and aryl iodides as substrates. Although a catalyst loading in the 1-5 mol % range may be required, with typical yields of around 75 %, the transformation relies on an established protocol. Copper-only procedures (catalytic Stephens-Castro coupling) with aryl iodide substrates are already competitive with Pd-catalyzed reactions. From a practical point of view, the simplicity of the copper-only catalytic systems is a strong argument in favor of their application in organic synthesis, whereas Pd-based Sonogashira catalysts are characterized by their outstanding efficiency.”¹²⁶a

Finally, the reaction is fraught with a limitation, in that it often results in considerable yields of the homocoupling product (Glaser-type or Hay product). This aspect will be discussed in chapter 2.3.4 Glaser-type acetylene couplings.
2.3.4 Glaser-type acetylene couplings

The synthetic studies of 1,3-disubstituted diyne derivatives via the homocoupling reaction of terminal alkynes has an extremely long history. As early as in 1869, Glaser made the observation that the alcoholic solution of copper phenylacetylide undergoes smooth homocoupling in the presence of aqueous ammonia when exposed to air (Scheme 26).\textsuperscript{[128]}

![Scheme 26. Glaser coupling.](image)

Baeyer provided an early demonstration of the synthetic utility of the method in his 1882 synthesis of indigo (Scheme 27).\textsuperscript{[129]} In this synthesis, potassium ferricyanide was used as an oxidizing agent.

![Scheme 27. Baeyer synthesis of indigo.](image)

Nevertheless, the original Glaser reaction had a significant drawback of need for isolating potentially explosive copper acetylide, which was often tedious in view of the poor crystallization properties of most copper salts.
Therefore, many groups have modified and improved the reaction to obtain useful approaches to symmetrical and unsymmetrical butadiynes. Acetylene couplings as well as their synthetic applications were comprehensively reviewed by Diederich in 2000.\textsuperscript{130}

Particularly important was the observation of Zalkind and Aizikovich in 1937 that tertiary alkynols coupled directly in the presence of CuCl and NH\textsubscript{4}Cl to afford the corresponding diacetylene dicarbinols. The possibility of forming the copper(I) acetylide in situ paved the way for intensive investigations of the factors influencing the oxidative coupling of various substituted acetylenes, such as the proportion of copper(I) salt, oxidizing agent, pH, time, temperature, solvent, and character of the alkyne, which ultimately led to improved convenience and scope of the reaction and to industrial applications.

In 1956, Eglinton and Galbraith introduced the copper(II) mediated coupling in methanolic pyridine using an excess of Cu(OAc)\textsubscript{2}, which turned out to be very useful in the preparation of unsaturated macrocycles.\textsuperscript{131}

Another milestone in the evolution of oxidative acetylene coupling was reported in 1962 by Hay. In this important modification a Cu(I)-salt was used in the presence of an amine such as pyridine\textsuperscript{132} or the bidentate ligand TMEDA\textsuperscript{133} that promoted facile homocoupling of terminal acetylenes at room temperature in the presence of oxygen (Scheme 28). The modification provided better solubility of the reactive Cu(I)-species and allowed mild conditions, high efficiency, and catalytic amounts of Cu(I) and amine to be realized.

\begin{center}
\begin{tikzpicture}
  \node[shape=circle,draw=black,fill=white] (a) at (0,0) {R};
  \node[shape=circle,draw=black,fill=white] (b) at (1,0) {=};
  \node[shape=circle,draw=black,fill=white] (c) at (2,0) {=};
  \node[shape=circle,draw=black,fill=white] (d) at (3,0) {\text{5 mol \% CuCl}};
  \node[shape=circle,draw=black,fill=white] (e) at (4,0) {\text{5 mol \% TMEDA}};
  \node[shape=circle,draw=black,fill=white] (f) at (5,0) {\text{acetone, } O_{2}};
  \node[shape=circle,draw=black,fill=white] (g) at (6,0) {R};
  \node[shape=circle,draw=black,fill=white] (h) at (7,0) {=};
  \node[shape=circle,draw=black,fill=white] (i) at (8,0) {=};
  \node[shape=circle,draw=black,fill=white] (j) at (9,0) {R};
  \node[shape=circle,draw=black,fill=white] (k) at (10,0) {5 examples};
  \node[shape=circle,draw=black,fill=white] (l) at (11,0) {82-97 \%};

  \draw[->] (b) -- (d);
  \draw[->] (d) -- (e);
  \draw[->] (e) -- (f);
  \draw[->] (f) -- (g);
  \draw[->] (g) -- (h);
  \draw[->] (h) -- (i);
  \draw[->] (i) -- (j);
\end{tikzpicture}
\end{center}

\textbf{Scheme 28. Hay coupling.}

The Cu-mediated homocouplings described above and the heterocoupling conditions according to Cadiot–Chodkiewitz, utilizing coupling of terminal acetylenes with 1-bromoalkynes,\textsuperscript{134} still remain popular, and new Cu-promoted methods continue to
appear.\textsuperscript{[135]} Just recently, a comprehensive investigation of the influence of bases and ligands on the outcome of the Cu(I)-catalyzed oxidative homocoupling of terminal alkynes to 1,4-disubstituted 1,3-diynes using oxygen as an oxidant (i.e. Glaser-Hay coupling) was performed by Beifuss.\textsuperscript{[136]}

Instead of terminal alkynes alkynylsilanes can be coupled in a \textit{sila} modification introduced by Mori (Scheme 29).\textsuperscript{[137]} The method allows preparation of symmetrical and unsymmetrical 1,3-butadiynes. Nevertheless, the method was not extended into a one-pot alknylation – oxidative dimerization sequence and still requires alkynylsilanes as starting materials.\textsuperscript{[138]} A further drawback is the need for a stoichiometric amount of CuCl.

\[
\begin{align*}
R-\equiv-\equiv-TMS & \quad \xrightarrow{\text{CuCl (1.0 equiv)}} \quad R-\equiv-\equiv=R \\
& \quad \text{DMF, 60 °C, 3 h} \\
& \quad \text{air} \\
& \quad 5 \text{ examples} \\
& \quad 70-99 \% (\text{GC yields})
\end{align*}
\]

\[
R = \text{Ph, } p\text{-MeOC}_6\text{H}_4, \quad p\text{-MeCOC}_6\text{H}_4 \\
\text{2-Th, } \eta^7\text{He}
\]

\textbf{Scheme 29. Coupling of TMS-alkynes to symmetrical diynes.}

Palladium is also a competent metal for acetylene couplings. An early observation was the formation of symmetrical diynes in the course of Sonogashira coupling.\textsuperscript{[62]} In 1985, Rossi optimized this process as a homocoupling for terminal acetylenes (Scheme 30).\textsuperscript{[139]} (Hetero)aryl substituted alkynes are excellent substrates for this reaction.\textsuperscript{[139],[140]}

\[
\begin{align*}
R-\equiv & \quad \xrightarrow{2 \text{ mol } \% \text{ Ph(PPPh}_3)_4, \ 8 \text{ mol } \% \text{ Cul}} \quad R-\equiv-\equiv=R \\
& \quad \text{NET}_3 (2.0 \text{ equiv}), \text{ CICH}_2\text{COCH}_3 (1.0 \text{ equiv}) \\
& \quad \text{benzene, N}_2, \text{ rt} \\
& \quad 2 \text{ examples} \\
& \quad 87-94 \%
\end{align*}
\]

\textbf{Scheme 30. Pd/Cu-catalyzed synthesis of diynes.}

Pd(0) alone can be used in the presence of allyl bromide and phase transfer catalysts.\textsuperscript{[141]} Another modification using PdCl\(_2\)(PPPh\(_3\))\(_2\)/Cul as a catalytic system, 'Pr\(_2\)NH
as a base, and iodine as an oxidizing agent was reported by Burton.\textsuperscript{[142]} Several new reports stem from the last decade: (1) room temperature coupling using PdCl\(_2\)(PPh\(_3\))\(_2\)/Cul/Pr\(_2\)NH and ethyl bromoacetate as an initiator;\textsuperscript{[143]} (2) efficient room temperature diyne synthesis “using standard Sonogashira conditions”, i.e. PdCl\(_2\)(PPh\(_3\))\(_2\)/PPh\(_3\)/Cul/NEt\(_3\);\textsuperscript{[144]} (3) amine- and phosphine-free Pd(II)/Cu(I)-catalyzed homocoupling with NaOAc as a base and Me\(_3\)NO as an oxidant;\textsuperscript{[145]} (4) NHC-Pd(II)/Cu(I)-catalyzed homocoupling;\textsuperscript{[146]} and (5) ligand- and base-free low-loading Pd/C-Cul-catalyzed homocoupling.\textsuperscript{[147]}

Some reports dealing with studies on both Glaser and Sonogashira reactions under similar conditions deserve a special mention. Nájera described in 2003 an efficient low-catalyst homocoupling catalyzed by oxime-derived palladacycle and Cul with pyrrolidine as a base and air as an oxidant.\textsuperscript{[148]} Under very similar conditions, Sonogashira coupling (palladacycle/Bu\(_4\)NOAc) and sila-Sonogashira coupling (palladacycle/Cul/pyrrolidine) were also effective. In 2005 Li published a study dealing with a catalytic system which was very effective in both Glaser-type (Pd(OAc)\(_2\)/Cul/DABCO/O\(_2\)) homocoupling and Sonogashira coupling (Pd(OAc)\(_2\)/DABCO/O\(_2\)) reactions.\textsuperscript{[149]} A report by Wu in 2007 dealt with cyclopalladated ferrocenylimine/Cul/KOAc/O\(_2\) as a catalytic system for the homocoupling. A similar palladacycle in the presence of Bu\(_4\)NBr and KOAc was also applied for Sonogashira couplings.\textsuperscript{[150]} Despite all these reports described almost identical conditions for both alkyne couplings, no combination of these reactions in a one-pot transformation has been attempted.

The two processes are very closely related indeed. A similar Pd/Cu-catalyzed Glaser-type homocoupling is believed to be responsible for the generation of the catalytically active Pd(0) species at the beginning of the Sonogashira reaction.\textsuperscript{[62],[139]} But the same process also leads to the unwanted alkyne dimerization, which is a known “plague” of the Sonogashira cross-coupling (Scheme 31).
Scheme 31. Mechanistic rationale for the formation of a symmetrical diyne along with the generation of the catalytically active palladium(0) species.

To avoid the diyne formation, even special strategies such as coupling under a hydrogen and nitrogen atmosphere have been developed (Scheme 32).\textsuperscript{[151]} The method allowed to suppress the homocoupling and less than 2 % of diynes were formed.

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{II} \quad \text{Cl} \\
\text{Ph}_3\text{P} & \quad \text{Pd} \quad \text{Cl} \\
\text{transmetalation} & \\
\text{Cu} & \quad \equiv \quad \text{R} \\
\text{CuHal} & \\
\oplus & \quad \oplus \\
\text{HNEt}_3\text{Hal} & \\
\text{NEt}_3 & + \quad \equiv \quad \equiv \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad \text{II} \quad \equiv \quad \text{R} \\
\text{Ph}_3\text{P} & \quad \text{Pd} \quad \equiv \quad \text{R} \\
\text{reductive elimination} & \\
\text{R} & \quad \equiv \quad \equiv \quad \text{R} \\
\end{align*}
\]

\[\text{[Pd}^0]\]

\[
\begin{align*}
\text{R} & = \text{Me, OMe, NMe}_2, \text{NEt}_2 \\
\text{TMS} & = \text{trimethylsilyl} \\
\end{align*}
\]

Scheme 32. Sonogashira reaction with diminished homocoupling.

Just very recently, a click-reagent version of the Sonogashira coupling, i.e. coupling using Cu(II)/NaAsc system, has been introduced with no or dramatically reduced homocoupling.\textsuperscript{[152]}

However, prior to this work no attempts have been undertaken to make use of this obstacle and to combine Sonogashira and Glaser couplings into a one-pot procedure to synthesize diyynes using the same catalytic system.
Diynes and higher polyynes are frequently found in natural products making up more than 1000 isolated compounds with two or more conjugated triple bonds.\[153\] Symmetrical 1,3-butadiynes can be used for the construction of chalcogene heterocycles such as thiophenes and selenophenes,\[154\] nitrogen heterocycles such as pyridines and pyrroles,\[155\] 3,3'-disubstituted 2,2'-biindoles,\[156\] as well as the indolo[2,3-a]carbazole ring system,\[157\] which is present in several biologically active molecules such as arcryaflavin A and the potent antitumor agent rebeccamycin. A representative example of the utility of 1,4-di(hetero)aryl-1,3-butadiynes in the organic synthesis is the preparation of 2,2'-bisindole, which requires a linear stepwise approach (Scheme 33).\[158\]

![Scheme 33. Synthesis of 2,2'-bisindole via 1,3-diynе.](image)

Typically, although the same catalytic system and the same base are required, the synthesis of the key diyne was performed in separate steps rather than in a one-pot procedure.

In conclusion, prior to this work no one-pot sequentially catalyzed method of synthesis of symmetrical 1,3-diynes starting directly from (hetero)aryl halides was known. However, just recently, two one-pot syntheses appeared in the literature starting from aryl iodides. In the first method, Kim described a Pd/Cu-catalyzed approach relying
on coupling of iodoarenes and propionic acid via Sonogashira reaction followed by a Pd-catalyzed decarboxylative homocoupling (Scheme 34).\textsuperscript{[159]}

\[ R-I + \overset{2.0 \text{ equiv}}{\text{CO}_2\text{H}} \rightarrow R-R \]

1) \(5\ \text{mol} \%\ \text{PhCl}_2(\text{PPh}_3)_2, 10\ \text{mol} \%\ \text{Cul},\ \text{NEt}_3 (3.5\ \text{equiv}), \) DMF, rt. 6 h

2) \(\text{Ag}_2\text{CO}_3 (2.0\ \text{equiv}), 130 \, ^\circ\text{C}, 20\ \text{h}\)

11 examples
54-90 %

\( R = \text{Ph, EDG-Aryl, EWG-Aryl, 2-Th, 3-Py}\)

Scheme 34. \textit{Kim’s} one-pot synthesis of 1,3-diynes via Sonogashira coupling – decarboxylative homocoupling.

The major disadvantages of this procedure are the use of silver carbonate as a stoichiometric oxidant and the formation of 1-10 \% of the corresponding tolane as a byproduct giving inseparable mixtures with the desired product.

The second method also works under Pd/Cu-catalysis and uses \(\text{K}_2\text{CO}_3\) instead of \(\text{Ag}_2\text{CO}_3\) (Scheme 35).\textsuperscript{[160]}

\[ R-I + \overset{1.2 \text{ equiv}}{\text{CO}_2\text{H}} \rightarrow R-R \]

\[ 5\ \text{mol} \%\ \text{PhCl}_2(\text{PPh}_3)_2, 10\ \text{mol} \%\ \text{dppb}, 10\ \text{mol} \%\ \text{Cul},\ \text{DBU} (2.4\ \text{equiv}), \text{K}_2\text{CO}_3 (1.2\ \text{equiv}), \] 

DMSO, air, 30 \, ^\circ\text{C}, 6\ \text{h} \rightarrow 80 \, ^\circ\text{C}, 3\ \text{h}

13 examples
44-92 %

\( R = \text{Ph, EDG-Aryl, EWG-Aryl, 2-Th, 3-Py}\)

Scheme 35. \textit{Lee’s} one-pot synthesis of 1,3-diynes via Sonogashira coupling – decarboxylative homocoupling.

This procedure resembles the preceding precisely in scope and shares the same disadvantage of producing 4-33 \% of the corresponding tolane.
In the framework of this thesis, two catalytic alkyne coupling reactions have been combined in the sense of a consecutive sequentially Pd/Cu-catalyzed process to furnish a novel one-pot pseudo-four-component synthesis of a broad variety of symmetrically substituted 1,4-di(hetero)aryl-1,3-butadiynes in good to excellent yields starting from easily available (hetero)aryl iodides and using air oxygen as an oxidant (Scheme 36).\textsuperscript{[161]} Pd and Cu species as well as triethylamine as a base are essential for both couplings, which proceed with higher efficiency if performed in a one-pot sequence. The synthetic procedure is extremely simple to carry out, works for a variety of electronically different heterocyclic iodides and tolerates many functional groups including free hydroxy and amino groups.

\textit{Sonogashira Coupling- TMS-Deprotection-Glaser Coupling Sequence}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {SiMe$_3$};
\node (B) at (1,0) {Me$_3$Si};
\node (C) at (4,0) {[Pd/Cu] \text{NET$_3$ (2.0 equiv)}};
\node (D) at (5,0) {...(Hetero) Aryl...};
\node (E) at (6,0) {F\textsuperscript{−}, air};
\node (F) at (8,0) {...(Hetero) Aryl...};
\node (G) at (9,0) {...(Hetero) Aryl...};
\node (H) at (10,0) {26 examples};
\node (I) at (11,0) {51-93 \%};
\node (J) at (12,0) {in one-pot};
\node (K) at (1,1) {(Hetero) Aryl...I...I...(Hetero) Aryl...};
\draw [-,thick] (A) -- (B);
\draw [-,thick] (B) -- (C);
\draw [-,thick] (C) -- (D);
\draw [-,thick] (D) -- (E);
\draw [-,thick] (E) -- (F);
\draw [-,thick] (F) -- (G);
\draw [-,thick] (G) -- (H);
\draw [-,thick] (H) -- (I);
\draw [-,thick] (I) -- (J);
\draw [-,thick] (J) -- (K);
\end{tikzpicture}
\end{center}

Scheme 36. One-pot synthesis of symmetrical diynes.\textsuperscript{[161]}

These results are part of this cumulative dissertation (\textit{publication 3.2}).
2.3.5 *Suzuki-Miyaura* coupling

In 1981, *Suzuki* and *Miyaura* described a palladium-catalyzed coupling of aryl halides or pseudo halides with aryloboronic acids (Scheme 37).\(^{[162]}\) The decisive breakthrough was achieved by the addition of a base, which is essential for this reaction.\(^{[163]}\)

![Chemical reaction diagram](image)


The *Suzuki* coupling reaction has established itself as a powerful and general method for the formation of C–C bonds,\(^{[164]}\) especially those involving sp\(^2\)-hybridized centers. The reaction is extremely popular in the synthetic community for the synthesis of biaryl compounds where it usually involves the Pd(0)-mediated linking of an aryl halide with an aryloboronic acid or aryloboronic ester.\(^{[165]}\)

There are several significant advantages of this methodology:

- Mild reaction conditions and extreme versatility allowing the coupling of a wide range of carbons in aryl, alkenyl, alkyl, and alkynyl groups under a wide variety of conditions.
- High efficiency and reliability.
- Wide applicability and functional group tolerance, hence the reaction is highly suitable for designing one-pot methodologies.
- The coupling is stereo- and regioselective and is little affected by steric hindrance.
- No stoichiometric amounts of heavy metals are required.
• Boronate reagents as well as byproducts are nontoxic, usually stable, and environmentally safe (in contrast, organostannanes used in the Stille coupling are toxic).

• The inorganic byproducts are easily removed from the reaction mixture, making the reaction suitable for industrial processes.

Although this method is well established, improvements are still necessary, promoting development of new and efficient rationally developed catalyst and ligand systems.\textsuperscript{[166]} Heteroaromatic substrates deserve a special attention due to their importance in many areas of research and difficulties associated with their couplings.\textsuperscript{[167]} The cross-coupling reactions of such substrates are generally considered to be problematic because these substrates can bind to the metal center and deactivate the catalyst. In the past, heteroaryl halides with heteroatom substituents bearing labile atoms such as OH and NH\textsubscript{2} were generally found to be unsuitable coupling partners. Further investigations are currently directed toward strategies for orthogonal functionalization of complex molecules, especially devising new sophisticated boron reagents.\textsuperscript{[168]} On the other hand, normally used boronate reagents are frequently expensive and difficult to access. Furthermore, coupling of electron deficient arylboronic acids or arylboronates, especially those bearing an $\alpha$-nitrogen atom, is a real challenge. The difficulty can be attributed to several factors: electron deficient heteroaryl boron derivatives undergo transmetalation at a relatively slow rate, and these reagents rapidly decompose by a protodeborylation pathway.

For this reason, several strategies directed to solve this problem have recently been described (Scheme 38,\textsuperscript{[169]} Scheme 39,\textsuperscript{[170]} and Scheme 40\textsuperscript{[171]}).
(Hetero)Aryl—Hal + Li(PrO)₂B_2

\[
\begin{align*}
\text{(1.5 equiv)} & \quad \text{1-1.5 mol \% Pd} \quad \text{H}_2 \quad \text{X} \\
\text{dioxane, 110 °C, 20 h} & \quad \text{K}_2 \quad (3.0 \text{ equiv}) \\
\end{align*}
\]

Hal = Br (X = Ph), Cl (X = tBu)
R = H, OMe, F, X

20 examples
40-92 %

Scheme 38. Strategy described by Buchwald.

\[
\begin{align*}
\text{(Hetero)Aryl—Hal} + \text{Cul (1.0 equiv)} & \quad \text{Cs}_2\text{CO}_3 \quad (2.0 \text{ equiv}) \\
\text{DMF, 100 °C, 16 h} & \quad \text{5 mol \% Pd(OAc)}_2 \\
\text{10 mol \% dppf} & \quad (2.0-2.5 \text{ equiv}) \\
\end{align*}
\]

Hal = I, Br, Cl, OTf
R = H, Me, OMe, F, Cl, CF₃, CN
X = CH, N

16 examples
42-97 %

Scheme 39. Strategy described by Deng and Paone.

\[
\begin{align*}
\text{(Hetero)Aryl—Hal} + \text{CsF (2.0-3.0 equiv)} & \quad \text{3 mol \% PdCl}_2\text{(PClBu)}_2 \\
\text{tPrOH, 90 °C, 18 h} & \quad (1.2-2.0 \text{ equiv}) \\
\end{align*}
\]

Hal = I, Br, Cl
R = H, Me, OMe, CF₃, Cl, Br, CF₃, CN, NEt₂

20 examples
15-80 %

Scheme 40. Strategy described by Li and Shen.
However, all these strategies have a common disadvantage: the need for an excess of the precious boronate or boronic ester component.

“The mechanism of the Suzuki coupling is known to be complex in its details, and the oxidative addition, transmetalation, and reductive elimination steps have all been reported to be rate-determining in certain cases”[172] (Scheme 41).

Scheme 41. Proposed mechanistic rationales for the Suzuki reaction.

“The reaction is still not fully understood and much remains to be clarified. The base is crucial for the transmetalation that can proceed inter- or intramolecularly. The choice of arylboron reagent may profoundly affect the outcome of a given coupling reaction, particularly since it usually determines the selection of other key reaction parameters such as solvent, base, and palladium(0) source. In contemporary practice, Suzuki couplings often employ widely differing reaction chemistries depending on whether arylboronic acids or arylboronate esters are used as reagents.

All other factors being equal, best results are usually obtained when the aryl halide coupling partner is electron deficient and the arylboron partner electron rich, a situation that favors oxidative addition and transmetalation, respectively. However, with complex, polyfunctionalized substrates it may not always be easy to judge which ring should be which component. Alternatively, tactical considerations may require a particular coupling reaction be carried out with the coupling partner roles inverted with
respect to those that are a priori desirable. The outcome of a given coupling may be significantly affected by the assignment of partner roles.\textsuperscript{[172]}

A study on *Suzuki* coupling involving indoles revealed some interesting points.\textsuperscript{[172]} 5-, 6-, or 7-Bromo indoles were coupled with aryloboronic acids or pinacol esters, then the partner roles were swapped (Scheme 42).

\[
\begin{align*}
\text{Scheme 42. Study on the *Suzuki* coupling involving indoles.}
\end{align*}
\]

The yields of the *Suzuki* coupling depended on:

- Whether aryloboronic acids or arylpinacolboronate esters were used.
- Whether the heterocycle was the aryl halide or the aryloboron coupling partner.
- Whether the heterocycle was protected or not, which provides a means of modulating the electronic character of the heterocycle.

A careful selection of the aryloboron reagent, of the coupling partner roles, and of the protective groups was essential to ensuring optimum results in these *Suzuki* couplings. This study is very instructive also for coupling of other heterocycles since it gives an impression how the influences of different factors can affect the outcome of the *Suzuki* coupling reaction.

In 2010, *Suzuki*, *Heck*, and *Negishi* were awarded with the Nobel Prize in recognition of the enormous utility of Pd-catalyzed cross-coupling methodologies developed by these researchers, among others.\textsuperscript{[173]}
2.3.6 Miyaura and Masuda borylations

The main limitation of the Suzuki-Miyaura reaction is the accessibility of the boronic acids or esters used as the nucleophilic partner. They are expensive and only a limited number of them are commercially available. The other issue is their sensitivity toward air and moisture as well as chromatographic instability. Classically, boronates are prepared by the transmetalation of Li- or Mg-organyls with borane compounds that contain good leaving groups such as halogen or alkoxy groups. These approaches suffer from functional group intolerance.

Among boronic species, pinacolboronic esters are the most convenient nucleophilic coupling partners in Suzuki cross-couplings because they are generally stable to air, moisture, and temperature and are much more amenable to chromatographic purification and spectroscopic characterization.

In 1995, Miyaura described a Pd-catalyzed coupling reaction between bispinacolato-diboron with halo arenes to give a direct procedure for preparation of arylboronic esters (Scheme 43).

![Scheme 43. Miyaura borylation.](image)

As in the case of the Suzuki coupling, a suitable base is also essential for this borylation. Potassium acetate was found to be the best base, which did not promote the undesired Suzuki coupling reaction of starting halide with the formed boronic ester. The reaction is accelerated in polar solvents. Among Pd-precatalysts, PdCl₂dppf gave the best results. The reaction was found to proceed more efficiently with electron withdrawing substituents on aryl halide; iodides performed better than bromides. Various functional groups are tolerated including polar functionalities incompatible with Grignard or lithium reagents (ester, ketones, cyano groups).
The key step in the mechanism is believed to be the transmetalation between bispinacolatodiboron and acetoxopalladium(II) intermediate formed by the ligand exchange with acetoxy anion (Figure 3).

![Chemical diagram showing the mechanism of the Miyaura borylation](attachment:image.png)

Figure 3. Proposed mechanism of the Miyaura borylation.

The main advantage of bispinacolatodiboron as a source of boron nucleophile is its thermal stability and insensitivity toward air, making it easy to handle.
In 1997, *Masuda* reported a further improvement of this procedure using the cheaper pinacolborane.[175] The reaction now became highly elegant and atom economical (Scheme 44).[176]

\[
\begin{align*}
R-\text{Hal} + H-\text{B} & \rightarrow 3 \text{ mol \% PdCl}_2\text{dpf} \\
\text{NEt}_3 (3.0 \text{ equiv}) & \quad \text{dioxane, 80-100 °C, 1-18 h}
\end{align*}
\]

\[R = \text{EDG-Aryl, EWG-Aryl, 2-Th}
\]
\[\text{Hal} = I, Br, OTf\]

Scheme 44. *Masuda* borylation.

Aryl iodides gave the best yields. Only two heteroaromatic substrates have been investigated. Since pinacolborane tolerates various functional groups (ketone, ester, cyano, carbamate, and others), this borylation is broadly applicable. The typical by-product of this reaction is the dehalogenative hydrogenation as a result of the behavior of pinacolborane as a hydride donor. Triethylamine is the base of choice, allowing to minimize the reduction. The authors pointed out that the reaction was efficiently catalyzed by the palladium(II)-complexes having two equivalents of phosphane ligands such as PdCl$_2$dpf and PdCl$_2$(PPh$_3$)$_2$, and additional phosphane ligand retarded the reaction. Very low yield was observed for Pd(PPh$_3$)$_4$ as a catalyst. The solvent does not play an important role; however, polar solvents such as DMF cause low yields.

The reaction works best with electron rich halides, thus indicating that the mechanism should be different from the usual mechanism of cross-coupling reactions, which would start with the oxidative addition of the aryl halide on the Pd(0) species, followed by a transmetalation of boryl anion generated by deprotonation of pinacolborane with triethylamine, and concluded by a reductive elimination (however, at present this mechanism can not be ruled out). The mechanism could be rationalized to proceed via the first oxidative addition of pinacolborane to the Pd(0)-catalyst, followed by $\sigma$-bond metathesis between a B–Pd and a C–Hal bond (Scheme 45).
Scheme 45. Mechanistic rationale of Masuda borylation.

In 2006, a Cu(II)-catalyzed borylation of aryl iodides was reported using pinacolborane and NaH as a base (Scheme 46).[177]

\[
R - I + \text{H-BOR} \xrightarrow{10 \text{ mol}\%\text{ CuI}} \text{NaH (1.5 equiv)} \xrightarrow{\text{THF, rt, 5-12 h}} \text{R-BOH} \\
(1.5 \text{ equiv}) \quad \text{14 examples} \quad 81-83\% \]

R = EDG-Aryl, EWG-Aryl, 2-Th

Scheme 46. Cu(II)-catalyzed borylation of aryl iodides.

An interesting borylation procedure was described by Maleczka Jr. and Smith III in 2009 for Boc-protected heterocycles.[178] This Ir-catalyzed borylation allows to introduce the pinacolboronate group directly involving C–H bond activation (Scheme 47).

\[
\text{Boc} \xrightarrow{1.5 \text{ mol}\%\text{ [Ir(OMe)COD]}_2} 3 \text{ mol}\%\text{ dtbpy} \xrightarrow{\text{HBpin (1.0-3.5 equiv)}} \text{solvent, rt to 60 °C, 1.5-96 h}} \text{Boc} \\
 \quad \text{X = C (CH) or N} \quad \text{9 examples} \quad 14-90\% 
\]

Scheme 47. Ir-catalyzed borylation of N-Boc heterocycles.

Thus, pyrroles, indoles, azaindoles, and pyrazole can be selectively functionalized at C–H positions β to the nitrogen atom. The Boc protective group was shown to be eas-
ily removed by thermal deprotection (except for 7-azaindole products); however, a temperature of 180 °C was required. In one case the possibility of performing the subsequent Suzuki coupling reaction in one-pot procedure has been demonstrated. However, the Pd-precatalyst and XPhos as a ligand had to be added; moreover, solvents used in the borylation step had to be removed and replaced by a solvent appropriate for the Suzuki coupling step (Scheme 48).

Scheme 48. An example of the Ir-catalyzed borylation – Pd-catalyzed Suzuki coupling reaction.

Despite the obvious utility of this methodology, the borylation has to be performed in a glovebox, which is not very practical.

An example for the construction of heterocycle-linked bisindole compounds using Masuda borylation and Suzuki coupling includes separate reaction steps and two different Pd-precatalysts (Scheme 49)."
Scheme 49. Synthesis of bisindole compounds using Masuda borylation and Suzuki coupling as separate steps.

The same strategy was applied in the synthesis of a 3,4-disubstituted pyrrole as the pivotal subtarget toward the cytotoxic marine natural alkaloid halitulin (Scheme 50).[^180]
Scheme 50. Synthesis of a substituted pyrrole using Masuda borylation and Suzuki coupling as separate steps.

Since both the Miyaura and Masuda borylations are Pd-catalyzed reactions, it lies at hand to combine both reactions in a one-pot process to avoid the isolation of the intermediate pinacol boronic esters. This approach considerably improves the utility of the Suzuki coupling, since it allows to connect directly two organic halides that are broadly available. Moreover, time and materials needed for the isolation of arylboronate intermediates, are saved. In order to carry out the two steps in one-pot effectively, the boronate ester formation needs to be clean and proceed with complete conversion. The same holds true for the subsequent Suzuki coupling. Thus, a judicious selection of reaction conditions, such as catalyst, solvent, base, reaction temperature, and protective groups (where appropriate) is very essential for the success of this endeavor.

An example of a one-pot Miyaura borylation – Suzuki coupling sequence is the recent synthesis of some bisindoles, bibenzofurans and biflavones (Scheme 51).\textsuperscript{[181]} It should be noted that two different Pd-catalysts, PdCl\textsubscript{2}dpf and Pd(PPh\textsubscript{3})\textsubscript{4}, are required and only symmetrical biheteroaryls could be prepared.
Scheme 51. Synthesis of bridged bisindoles via Miyaura borylation – Suzuki coupling sequence.

Huang reported on synthesis of 7-azaindolyl pyrimidines related to compounds prepared in the presented work. In this case, Miyaura borylation and Suzuki coupling have been performed in two separate steps, and two different Pd-precatalysts have been utilized (Scheme 52).\textsuperscript{1182} Interestingly, the authors underlined that the protection of 7-azaindole with phenylsulfonyl group was critical for the success of the reaction, and unprotected or Boc protected 7-azaindole failed to give the desired product. Phenylsulfonyl group remained uncleaved after the Suzuki coupling step, thus two equivalents of the amine had to be used (cleavage of the PhSO\textsubscript{2} group consumed one equivalent of the amine reagent).
Scheme 52. Synthesis of 7-azaindolyl pyrimidines according to Huang.

The biological activity of the obtained compounds will be discussed in chapter 2.10.1.3 Meriolins.

The idea of reacting two (hetero)aromatic halides to form a biaryl compound directly in a one-pot sense is very attractive because of the easy availability of halides. The direct coupling of two aryl iodides has precedence; however, the method suffers from intrinsic selectivity problems if unsymmetric biaryl synthesis is attempted (Scheme 53).[183] Hence, the reactivity difference between two iodo arenes and their employed ratios are crucial for the selectivity. One component is used in excess, which represents a serious limitation of this approach.
Scheme 53. Pd(II)-catalyzed coupling of aryl iodides to unsymmetrical biaryls.

Another strategy is to prefix the umpolung of one electrophilic component (aryl iodide) in situ and perform the coupling upon addition of a second electrophilic component without isolation of the intermediate. There are several reports on successful implementation of the Masuda borylation using pinacolborane in combination with the Suzuki coupling in a one-pot manner.

This approach was pioneered by Baudoin in 2000 in the course of investigations toward the total synthesis of the antimitotic (-)-rhazinilam (Scheme 54).[184] The focus of this work was placed on the investigation of the Masuda borylation of ortho-substituted bromides, whereas the subsequent Suzuki coupling was only described for very few examples of special biphenyls. No heterocyclic halides were used. The sequence also required the Buchwald biphenyl ligand. With Pd(PPh$_3$)$_4$ as a catalyst, 0 % yield was obtained (5 mol % Pd(PPh$_3$)$_4$, 100 °C, 14 h).

Scheme 54. Masuda borylation – Suzuki coupling sequence according to Baudoin.
The authors figured out that the choice of the borylation and cross-coupling component depends on the nature of the substituents present on the aromatic ring (Scheme 55).

Scheme 55. Electronic requirements for the *Masuda* borylation – *Suzuki* coupling step according to *Baudoin*.

Thus, the borylation should be performed on the component that bears an electron rich group (EDG) and the coupling of the resulting boronate with the component bearing an electron poor group (EWG). The reason may be that electron rich boronates are more reactive in the transmetalation step, and the electron deficient halides in the oxidative addition step of the *Suzuki* coupling.

Using this strategy, special 2-phenylindoles as possible intermediates in the synthesis of paullone, have been prepared (Scheme 56).[^185] Here, 2-bromindoones were used as heterocyclic components. However, a two-fold excess of the halide, which was supposed to be borylated, was used in order to achieve good yields, thus making the reaction less efficient.

In 2003, Levacher presented a one-pot Masuda borylation – Suzuki coupling sequence for the synthesis of a special 2-naphthylpyridine required for the investigations on a bicyclic lactam construction (Scheme 57).\textsuperscript{[186]}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {\textbf{Scheme 57. Preparation of a 2-naphthylpyridine via Masuda borylation – Suzuki coupling sequence according to Levacher.}};
  \node at (0,0) {\includegraphics[scale=0.5]{scheme57}};
\end{tikzpicture}
\end{center}

Although this sequence worked well for the synthesis of a heterocyclic product, these conditions have not been extended to other substrates and no generalization has been undertaken.

Colobert described in 2004 another sequence for the preparation of biaryls (Scheme 58).\textsuperscript{[187]} Again, only few examples of rather simple biaryls have been presented, and no heterocyclic halides have been investigated. The sequence worked with DPEphos as a ligand, and a second charge of the precatalyst Pd(OAc)\textsubscript{2} had to be added in the Suzuki coupling step.
Scheme 58. Masuda borylation – Suzuki coupling sequence according to Colobert.

Eventually, in 2006 Huleatt and Chai reported the synthesis of a broad range of homo- and heterobisindoles using XPhos as a ligand.\textsuperscript{[188]} The dimerization of bromoindoles was performed using the Miyaura borylation – Suzuki coupling procedure, whereas unsymmetrical bisindoles have been prepared by the Masuda borylation – Suzuki coupling sequence (Scheme 59). In the latter sequence, the authors observed precipitation of palladium during the borylation step, thus the addition of a second batch of Pd(0) was necessary in the second step. The bromo indoles used as starting materials were either unprotected or protected with the electron donating Bn group.
Scheme 59. Synthesis of bisindoles according to Huleatt and Chai.

In summary, prior to this work no general method for coupling of two heterocyclic halides via umpolung of one component with pinacolborane resulting in a Masuda borylation – Suzuki coupling sequence and using simple catalytic system was known.
2.4 Cu(I)-Catalyzed Reactions and Azide–Alkyne Cycloaddition (CuAAC)

2.4.1 Cu(I) catalysis

The copper-mediated Ullmann biaryl synthesis,\textsuperscript{189} arylation of amines, phenols (Ullmann condensations),\textsuperscript{190} amides, carbamates (Ullmann-Goldberg condensations),\textsuperscript{191} and activated methylene compounds (Ullmann-Hurtley condensations)\textsuperscript{192} are well-documented methods that were discovered several decades prior to palladium and nickel-catalyzed procedures. Such copper-mediated coupling reactions have found numerous industrial applications. However, until 2000 the synthetic scope of the Ullmann-type coupling reactions was restricted because of the often harsh reaction conditions, a limited range of suitable substrates, and the only moderate yields obtained. The condensations were usually conducted in high-boiling polar solvents such as NMP, nitrobenzene, or DMF, at temperatures as high as 210 °C, often with stoichiometric amounts of copper reagents and usually with activated aryl halides.

In 2001, two research groups achieved important breakthroughs with the discovery of versatile and very efficient new Cu/ligand systems for the formation of C–C, C–N, and C–O bonds that enabled the use of only catalytic amounts of metal under much milder conditions (90-110 °C).\textsuperscript{193} In the past few years, a plenty of novel exciting Cu-catalyzed reactions appeared in the literature, leading to a spectacular renaissance of this metal in organic synthesis.\textsuperscript{42,43} Recent examples of Cu-catalyzed processes cover an extremely wide range of very distinct transformations, making copper the metal of choice for numerous useful processes such as Ullmann-type couplings,\textsuperscript{43,194} N-arylations of NH-heterocycles,\textsuperscript{195} halogen exchange,\textsuperscript{196} cyanations,\textsuperscript{197} diverse syntheses of heterocycles,\textsuperscript{198,199} trifluoromethylations,\textsuperscript{200} and C–H activations,\textsuperscript{201,202} only to mention a few.

CuI is a widely utilized source of catalytically active Cu(I) species, although numerous other salts and complexes are currently in use.
As an example for the utility of Cu(I)-catalysis in modern organic chemistry, a Pd-free Sonogashira-type reaction under mild conditions using a nonexpensive 1,3-dicarbonyl ligand by Monnier and Taillefer should be mentioned (Scheme 60).\textsuperscript{[203]} Although a Cu(II) salt is used as a precatalyst, the catalytic active species is assumed to be Cu(I).

\begin{equation}
\text{R}^1\text{=EDG, EWG} \quad \text{R}^2\text{=Aryl, Alkyl}
\end{equation}

Scheme 60. Pd-free Sonogashira-type coupling.

Further examples of these copper-only procedures were already discussed in chapter \textit{2.3.1 Stephens-Castro coupling}.
2.4.2 CuAAC

Probably the most exciting Cu-catalyzed reaction developed in the last decade is the azide-alkyne cycloaddition reaction (CuAAC).\cite{204} This transformation belongs to and is meanwhile the premier example of “click” reactions, the term coined by Sharpless in 2001 and defined as “a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C)”.\cite{205,206} 1,4-Disubstituted 1,2,3-triazoles, which are the exclusive products of this transformation, are electron poor 5-membered heterocycles, which possess several properties rendering them interesting structural elements in medicinal chemistry,\cite{207} drug discovery,\cite{208} bioconjugate chemistry,\cite{209} as well as in polymer and material science:

- Triazoles are among the most metabolically stable heterocycles as revealed by SMR studies.\cite{210} They are stable to acid and base hydrolysis and reductive and oxidative conditions, even at high temperature, indicative of a high aromatic stabilization.

- Triazoles are rigid linking units and peptidomimetics with the distance of 5.1 Å between N-1 and N-3 compared with 3.9 Å found in peptides.\cite{211} Unlike peptides, they are not susceptible to hydrolytic cleavage.

- Triazoles possess a large dipole moment (4.8–5.6 Debye) and are able to participate actively in hydrogen bond formation as well as in dipole-dipole and π-stacking interactions. Thus, they can interact productively with biological molecules, as well as with organic and inorganic surfaces and materials.

The crucial observation was made independently by the groups of Sharpless and Meldal in 2002,\cite{212} who described the acceleration of the Huisgen 1,3-dipolar cycloaddition\cite{213} by a factor up to 10^7 if the reaction was catalyzed by Cu(I). Moreover, 1,4-disubstituted 1,2,3-triazoles were exclusively formed rather than a statistical mixture of two possible isomers, which is obtained thermally. More recently, Ru complexes have been shown to give 4,5-disubstituted 1,2,3-triazoles,\cite{214} but the reaction
has to be further developed to obtain such a broad scope and convenience compar-able to CuAAC (Scheme 61).

\[
\begin{align*}
N\equiv N & \quad \Delta \\
N\equiv N & \quad [\text{Cu(I)}] \\
N\equiv N & \quad [\text{Ru}]
\end{align*}
\]

Scheme 61. Regioselectivities of the thermal 1,3-dipolar cycloaddition, CuAAC, and RuAAC.

This remarkable transformation is accompanied by several extremely attractive features:

- CuAAC is a very straightforward way for making covalent connections between building blocks containing various functional groups and is conceptually (but not mechanistically) simple.

- The reaction is extremely user friendly and can often be carried out under aerobic atmosphere, without need for dry solvents, and at ambient temperature or slightly above (25–70 °C). The products are frequently obtained as crystalline solids, which can be isolated by simple filtration without chromatographical purification.\textsuperscript{[215]}

- CuAAC proceeds in high yields (often > 95 %) and with 100 % atom economy. Little or no byproducts (e.g. diynes via the Glaser homocoupling) are formed.
The reaction proceeds under very mild conditions in most organic solvents. It is not sensitive to water and tolerates a wide range of pH values.

The source of Cu(I) can be very different: (1) Cu(I)-salts such as Cul; (2) Cu(II) salts such as CuSO₄, accompanied by a reducing reagent such as sodium ascorbate; or (3) Cu(II) and Cu(0), often simply copper wire, furnishing Cu(I) via synproportionation. Typically, about 0.25–2 mol % of Cu(I) catalyst are used.

No sophisticated additives or ligands are typically required, although TBTA\textsuperscript{[216]} as a ligand and triethylammonium chloride as an additive\textsuperscript{[217]} have been shown to promote the reaction. However, 1–5 equivalents of a base are usually used to generate the Cu(I)-acetylide in organic solvents.

1,4-Disubstituted triazoles are formed regiospecifically.

The reaction tolerates most functional groups including unprotected alcohols, carboxylic acids, and amino groups, which makes protective groups futile in many cases. Therefore, CuAAC is highly reliable and became very popular in the synthetic community within a very short time. Not tolerated are electron deficient or strained double bonds, free thiols, and electron deficient nitriles.

The reaction is usually insensitive to steric shielding effects.

Both alkynes and azides are high in chemical potential energy, and their fusion to triazoles is an irreversible process with a strong thermodynamic driving force of > 45 kcal mol\textsuperscript{-1} (by contrast, equilibrium aldol reactions are energetically favored by less than 3 kcal mol\textsuperscript{-1}). However, alkynes and azides are kinetically stable, and this stability is responsible for a slow uncatalyzed cycloaddition.

Alkynes and azides can be easily introduced into organic molecules and are inert toward many reaction conditions such as nucleophiles, electrophiles, and solvents. The azide is a rare example of a 1,3-dipole to have these qualities. Both alkynes and azides are small, incapable of significant hydrogen bonding, and relatively nonpolar functionalities. Thus, they are essentially unreactive toward biological molecules.
“The key C–N bond-forming event takes place between the nucleophilic, vinylidene-like β-carbon atom of copper(I) acetylide and the electrophilic terminal nitrogen atom of the coordinated organic azide (Scheme 62). [Cu] is either a single-metal center CuLₙ or a di-/oligonuclear cluster CuₘLₙ.”[204b]

Scheme 62. Simplified representation of the C–N bond-forming step of the CuAAC.

Interestingly, other metals known to catalyze various transformations of alkynes have not so far yielded effective catalysts for the conversion of azides and terminal alkynes to 1,4-triazoles. The unique catalytic function of Cu(I) may be explained by the fortuitous combination of its ability to engage terminal alkynes in both σ- and π-interactions and the rapid exchange of ligands in its coordination sphere. When an organic azide is a ligand, the synergistic nucleophilic activation of the alkyne and electrophilic activation of the azide drives the formation of the first C–N bond.

Besides aiming to improve the biocompatibility of the method, recent efforts in the field of CuAAC have focused on one-pot multicomponent reactions based on the in situ generation of the azide component,[218] in situ utilization of TMS-acetylenes,[219] or the direct Cu(I)-catalyzed C–H-bond arylation of the obtained triazoles.[220] The attraction of these approaches is the minimization of time-consuming workup and purification protocols. Additionally, handling of potentially explosive organic azides is avoided. However, despite the obvious similarity of the Sonogashira coupling and CuAAC in terms of reaction conditions, Cu-acetylides being the putative essential intermediates[221] and Cu(I) the catalytically active species in both reactions, no attempts have been made to combine the two reactions into a one-pot procedure until recently.

Eventually, when this thesis was in progress, two reports appeared in the literature describing essentially the same one-pot approach based on the Sonogashira coupling of halides with trimethylsilylacetylene, followed by in situ deprotection of the
TMS group and CuAAC upon addition of an azide. In 2009, Novák reported a sequential Sonogashira coupling – CuAAC reaction starting from simple aryl and heteroaryl iodides (Scheme 63).\textsuperscript{[222]}

\[ \text{R}^1\text{I} \xrightarrow{1\text{ mol} \% \text{PdCl}_2(\text{PPh}_3)_2, \text{5 mol} \% \text{CuI}} \xrightarrow{\text{TMSA (1.1 equiv), DIPA (2.0 equiv), EtOH, 25 °C, 2-26 h}} \xrightarrow{\text{R}^2\text{N}_3 (1.05 \text{ equiv})} \xrightarrow{5 \text{ min}} \xrightarrow{\text{TBAF x 3 H}_2\text{O (1.05 equiv)}, \text{rt, 12 h}} \text{20 examples, 24-77 %} \]

R\(^1\) = Aryl, 2-Th, 3-Py, 4-Py  
R\(^2\) = Bn, CH\(_2\)SPh, Alkyl, Ad

Scheme 63. One-pot Sonogashira coupling – CuAAC sequence according to Novák.

In 2010, another very similar microwave assisted approach was reported by Boons (Scheme 64).\textsuperscript{[223]} The new aspect of this synthesis was the possibility to react acid chlorides to yield 4-acyl triazoles. It should be noted, however, that in this approach a second charge of CuI had to be added in the second step and the total loading of 20 mol % catalyst was considerably high. Alternatively, CuF\(_2\) was used, however in excess (2.0 equivs). Moreover, the CuAAC was performed at 120 °C. This can cause problems if less stable azides are used as starting materials.
Scheme 64. One-pot Sonogashira coupling – CuAAC sequence according to Boons.

Ultimately, just recently Kolarović presented a one-pot three-component synthesis of 1,4-disubstituted 1,2,3-triazoles using aryl iodides and alkynoic acids that proceeded via decarboxylation.\textsuperscript{[224]} In addition to the accessibility issue of alkynoic acids, no heterocyclic iodides or propynoic acids have been applied.

CuAAC has already been used in several approaches to synthesize kinase inhibitors,\textsuperscript{[225]} for instance in a recent synthesis of 3-triazolyl substituted pyrazolo[3,4-d]pyrimidines (Scheme 65).\textsuperscript{[226]} Typically, the Sonogashira coupling for the preparation of the terminal alkyne and the CuAAC for the construction of triazole are performed in separate steps using two different Cu(I)-catalysts.
Scheme 65. Preparation of 3-triazolyl substituted pyrazolo[3,4-d]pyrimidines for the evaluation of their kinase inhibitory activity.

Two compounds showed activity toward the PfPK7 kinase of *Plasmodium falciparum* (IC\textsubscript{50} values in 10-20 \(\mu\)M range), the organism responsible for the most virulent form of malaria.

In conclusion, prior to this work no synthesis of 3-triazolyl substituted indole and its aza analogs and investigations of their kinase inhibitory activity have been reported.
In the framework of this thesis, a very general one-pot three-component synthesis of NH-heterocyclic triazoles has been developed (Scheme 66).[^227] N-Boc iodo NH-heterocycles were reacted with trimethylsilylacetylene, the corresponding TMS-alkynes were deprotected and converted to N-Boc protected triazoly1 heterocycles via Cu-catalyzed azide-alkyne cycloaddition (CuAAC), all in a one-pot fashion. After mild deprotection, the final products were obtained in fair yields. The strategy was found to be applicable for indole and virtually all indole isosters such as azaindoles, as well as indazole, deazapurines, and diazaindole. Some other heterocycles such as pyrrole and pyrazole could be reacted as well.

![Scheme 66. One-pot synthesis of indolyl triazoles by a Sonogashira coupling – TMS-deprotection – CuAAC sequence with subsequent deprotection.][^227]

[^227]: The specific reference number is not provided in the text.
7-Azaindolyl triazole was found to be a submicromolar inhibitor of the kinase PDK1\textsuperscript{[228]} a target of high relevance for oncology (Figure 4). This compound became a new lead structure and was used for the synthesis of further analogs.\textsuperscript{[229]} An X-ray structure analysis of this compound in PDK1 revealed the detailed binding mode of the molecule in the kinase. Interestingly, an isomeric compound differing only in the permutation of substituents on N-1 and C-4 atoms and following in the dipole moment of the triazole unit showed no activity on the kinase PDK1 (Figure 4).\textsuperscript{[227]}

![Figure 4. Comparison of PDK1 inhibitory activities of two isomeric 3-triazolyl 7-azaindoles.\textsuperscript{[227]}](image)

The strategy could be easily extended to four-component sequences with in situ N-Boc-protection of the NH-heterocyclic halide or in situ generation of azide via halide-azide exchange demonstrating high flexibility of this methodology.

These results are part of this cumulative dissertation (publication 3.3).
2.5 Decarbonylations

Carbonylations\(^{[40]}\) and decarbonylations\(^{[230]}\) belong to the most important elementary reactions occurring in the coordination sphere of a metal and constitute the very “heart” of the organometallic chemistry. The process of carbon monoxide insertion, i.e. the migratory insertion, is reversible depending on the pressure of carbon monoxide and temperature. The opposite process is a decarbonylation, i.e. the migratory deinsertion or extrusion.

In 1965, Tsuji and Ohno described a decarbonylation of aldehydes with stoichiometric amounts of Wilkinson’s catalyst RhCl(PPh\(_3\))\(_3\).\(^{[231]}\) This Rh-mediated transformation is now well known as Tsuji-Wilkinson decarbonylation of aldehydes (Scheme 67).\(^{[232]}\)

\[
\text{RCHO} + \text{RhCl(PPh}_3\text{)}\text{)_3} \rightarrow \text{RH} + \text{RhCl(CO)(PPh}_3\text{)}\text{)_2} + \text{PPh}_3
\]

Scheme 67. Tsuji-Wilkinson decarbonylation of aldehydes.

The formation of the very stable carbonyl complex trans-[RhCl(CO)(PPh\(_3\))\(_2\)] prevents catalysis by Rh around room temperature. Only at temperatures above 200 °C the complex RhCl(CO)(PPh\(_3\))\(_2\) becomes a catalyst.\(^{[233]}\) Tsuji and Ohno immediately realized the immense synthetic potential of decarbonylative methods as they postulated that “decarbonylation reactions would be very useful in organic chemistry if they can be carried out smoothly under mild conditions.”\(^{[233a]}\)

Although later the reaction has been made catalytic in rhodium\(^{[234]}\) and can proceed even at room temperature,\(^{[234b]}\) still many current applications in total synthesis use Wilkinson’s catalyst in stoichiometric amounts or even in a slight excess.\(^{[235]}\) In order to realize the efficient decarbonylation of aldehydes, elevated reaction temperatures (typically > 160 °C) are indispensable. The other possibility is to use an associated chemical scavenger of the evolved CO, i.e. by an accompanying carbonylation reaction\(^{[339]}\) or by addition of DPPA.\(^{[234b]}\) CO is a strong ligand and can therefore be a catalyst poison.

Over the past years, a plenty of decarbonylation methods have been developed which utilize various substrates such as acyl halides, cyanides, phosphonates, silanes, stannanes, anhydrides, esters, thioesters, imides, aldehydes, ketones, 1,2-
diketones, and others, catalyzed by transition metals such as Rh, Ni, Cu, Ru, Pd, Ir, Pt.\textsuperscript{[236]}

A decarbonylation event is often coupled with a concomitant carbonylative reaction proceeding as a tandem process\textsuperscript{[348]-[353]} (for a discussion, see chapter 2.7 Oxaly chloride in organic synthesis) or with a cross-coupling reaction. Biaryls have been prepared from carboxylic anhydrides, which serve as synthetic equivalents of halides, and from triaryl boroxines via Rh-catalyzed decarbonylative Suzuki coupling.\textsuperscript{[237]} Despite harsh reaction conditions (160 °C, 8 h), the nondecarbonylated byproduct is also formed in substantial amounts.

Acid chlorides are also suitable substrates for metal-catalyzed decarbonylative transformations. In fact, Ohno and Tsuji first described decarbonylations of acyl halides using stoichiometric amounts of Wilkinson’s catalyst at rt-180 °C or catalytic amounts of RhCl(CO)(PPh$_3$)$_2$ at 190-250 °C to form olefins or the corresponding halides depending on the acyl halide used.\textsuperscript{[233a,c]} Notably, the Rh acyl complexes formed via an irreversible oxidative addition of acyl halides were stable and could be isolated and characterized. Almost simultaneously, Blum reported decarbonylation of aroyl chlorides to aryl chlorides under similar conditions.\textsuperscript{[238]} To date, decarbonylations of acid chlorides are known to proceed with Rh,\textsuperscript{[239]} Ir,\textsuperscript{[240]} and Pd.\textsuperscript{[241]}

For the first time a Pd-catalyzed decarbonylation of aldehydes was disclosed as a side reaction of the Rosenmund reduction.\textsuperscript{[242]} Later, in 1960 Hawthorn and Wilt described a preparative procedure operating with 5 % Pd/C at 179-250 °C.\textsuperscript{[243]} Interestingly, although a Pd-catalyzed decarbonylation of acid chlorides and aldehydes, which proceeded at 180-220 °C with Pd/C or PdCl$_2$ as a catalyst, was described by Ohno and Tsuji in the same year as the Tsuji-Wilkinson decarbonylation reaction,\textsuperscript{[244]} it has not received a synthetic utility comparable to the latter process. In contrary, Pd-catalyzed decarbonylations received much less attention. Besides decarbonylation of aroyl chlorides under extremely high temperature (360 °C)\textsuperscript{[245]} and decarbonylative carbostannylation of alkynes with acylstannanes catalyzed by Pd/C,\textsuperscript{[246]} salt-free decarbonylative Heck reactions using anhydrides as substrates were known.\textsuperscript{[247]} However, reaction conditions are harsh (NMP, 140-190 °C, 90-180 min).

In the last decade, Gooßen revitalized this strategy and reported salt-free Heck olefinations of p-nitrophenyl esters\textsuperscript{[248]} and enol esters,\textsuperscript{[249]} which however still proceed under harsh reaction conditions (160 °C, 16 h) in NMP as a solvent (Scheme 68).
Scheme 68. Decarbonylative Heck olefinations.

Other examples involve the in situ generation of acid anhydrides starting from aliphatic carboxylic acids. The activation can proceed with Piv₂O\(^{[250]}\) or Boc₂O.\(^{[251]}\) The mixed anhydrides are then decarbonylated under Pd-catalysis to give olefins. The reactions proceed at 110-120 °C for 16 h and use 2-3 equivs of anhydrides as activators.

In conclusion, prior to this work no decarbonylative alkynylation methods were known. A minor amount (4 %) of a decarbonylated product was detected by an attempt to perform the Sonogashira coupling with methylxalyl chloride, along with 4 % of the nondecarbonylated product.\(^{[252]}\)
2.6 Ynones and Ynediones as Valuable Synthetic Building Blocks

2.6.1 Synthesis and reactivity of ynones

$\alpha,\beta$-Acetylenic carbonyl compounds (propargyl ketones, ynones)$^{253}$ are of great interest because they represent very useful synthetic intermediates$^{254}$ especially for the preparation of natural products$^{255,285,286,448}$ and of a huge number of heterocyclic molecules.$^{257}$ The main feature of ynones is the presence of two electrophilic centers: the carbon atom of the carbonyl group and the $\beta$-carbon atom of the triple bond, which is activated toward Michael addition. As a consequence, ynones react with nucleophiles via Michael addition and with binucleophiles via Michael addition − cyclocondensation reactions. This reactivity has been extensively used in numerous syntheses of a wide range of important heterocycles (Scheme 69).$^{253}$

![Scheme 69. Reactivity of ynones.](image)

Ynones as versatile three-carbon building blocks can be easily converted to 5, 6-, and 7-ring $N$-, $O$-, and $S$-heterocycles such as pyroles,$^{258}$ pyrrolin-4-ones,$^{259}$ indoles,$^{260}$ furans,$^{261}$ bifurans,$^{262}$ furanones,$^{263}$ oxazoles,$^{264}$ thiophenes,$^{265}$ pyrazoles,$^{266}$ pyrazolo[1,5-a]pyridines,$^{267}$ triazoles,$^{268}$ isoxazoles,$^{269}$ indolizines, pyrones,$^{270}$ chromones,$^{271}$ pyrimidines,$^{272}$ pyridazines, pyridopyrimidines, pyridines (Bohlmann-Rahtz synthesis),$^{273}$ pyridinones, quinolines,$^{274}$ naphthyridines,$^{275}$ ben-
zonaphthyridinones,[276] 4-oxo-indeno[1,2-b]pyrroles,[277] benzoheterozepines, and some others. In a very recent approach, a phosphane-mediated construction of 1,4-oxazepines and 1,3-oxazines from ynones and 2-azido alcohols was described.[278]

Besides their useful synthetic potential, ynones can possess interesting biological properties in their own right. Kundu reported uracil and its corresponding nucleosides substituted at C-5 by an acetylenic ketone functionality displaying promising cytotoxic activity against CCRF-CEM human lymphoblastoid cells and L1210 mouse leukemia cells in culture. These compounds were also shown to be inhibitors of thymidylate synthase, an essential enzyme needed for cellular multiplication processes.[279] As a further example, diphenylpropynone derivatives have been recently synthesized for in vivo use to image β-amyloid (Aβ) plaques in the brain of patients with Alzheimer’s disease. Binding experiments in vitro revealed high affinity for Aβ (1-42) aggregates at a Kᵢ value ranging from 6 to 326 nM.[280]

Not surprisingly, a considerable effort has been devoted to the development of efficient and general syntheses of ynones (Scheme 70).[281]

\[ \text{Scheme 70. Synthetic approaches toward ynones.} \]

Classical approaches toward ynones (Scheme 70, path A) are mainly based on the reaction of organometallic acetylides with carboxylic acid derivatives such as acid chlorides,[282] Weinreb amides or morpholides,[283] or with aldehydes followed by oxidation of the formed propargyl alcohols.[284] An illustration of this strategy, which is still often used, is the synthesis of a chemopreventive agent (±)-deguelin with a quite complex ynone as a key intermediate (Scheme 71).[285]
Scheme 71. Synthesis of (±)-deguelin via an ynone as a key intermediate.

In recent years, numerous catalytic approaches by direct reactions of acid chlorides with terminal alkynes appeared, which are more elegant, efficient, and atom economical (Scheme 70, path B; for a discussion, see chapter 2.3.2 Sonogashira-Hagihara coupling). From a synthetic point of view, Pd and/or Cu are the most practical transition metals for these transformations.

However, the most interesting and efficient syntheses of heterocycles involve the in situ generation of ynones with the subsequent conversion to diverse heterocycles in a one-pot sense.\cite{286,287} In Müller’s group, syntheses of diverse heterocycles such as furans,\cite{297} oxazoles,\cite{298} pyrazoles,\cite{288} isoxazoles,\cite{289} pyrimidines,\cite{290} indolizines,\cite{291} quinolines,\cite{292} tetrahydro-β-carbolines,\cite{293} 4H-thiochromen-4-ones,\cite{294} 1,5-benzodiazepines,\cite{295} and 1,5-benzothiazepines\cite{296} have been developed on the basis of the Sonogashira coupling.

In 2005, we reported a new one-pot synthesis of 2,5-disubstituted 3-halo furans via a three-component one-pot reaction. In the first reaction step acid chlorides were coupled with THP-protected propargyl alcohol in the sense of the modified Sonogashira coupling. The intermediate ynone was then converted to the furan in the course of Michael addition – deprotection – cyclocondensation sequence.\cite{297} The iodo furans could be isolated or transformed into 3-aryl substituted furans by an additional Suzuki coupling step, still in a one-pot fashion (Scheme 72).

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Scheme 72. One-pot synthesis of 3-halo and 3-aryl furans.

In 2006, we described the formation of 2,5-disubstituted oxazoles in the course of acylation of the propargyl amine with an acid chloride, the modified Sonogashira coupling of the resulting amide with another equivalent of an acid chloride, and an acid-mediated cycloisomerization sequence (Scheme 73).\textsuperscript{298} Again, an ynone was the key intermediate in this synthesis.
The carbonylative alkylation (Scheme 70, path C; for a discussion, see chapter 2.3.3 Carbonylative Sonogashira coupling) is a highly convergent approach and an increasingly popular tool for the construction of yrones. In 2005, we published the first application of this method in the synthesis of natural products meridianins, a class of marine indole alkaloids (for a discussion, see chapter 2.10.1.1 Meridianins). The major drawback of carbonylative alkylations is the preparative nuisance associated with toxic carbon monoxide.

Recently, a new approach (Scheme 70, path D) was demonstrated utilizing propynoic acids as substrates (Scheme 74).\textsuperscript{[299]} However, the practical limitation is the accessibility of the starting materials.

Scheme 73. One-pot synthesis of oxazoles.

Scheme 74. Carbonylative alkylation of (hetero)aryl iodides via decarboxylative coupling with alkynyl carboxylic acids.
Despite numerous syntheses of yrones bearing simple aryl substituents have been reported, only a very limited number of N-heterocyclic examples exists. Prior to this thesis, no general and broadly applicable method for obtaining these potentially highly requested building blocks was known.
2.6.2 Synthesis and reactivity of ynediones

The chemistry of ynones is well explored, and many approaches exist toward this structural motif (for a discussion, see chapter 2.6.1 Synthesis and reactivity of ynones). On the other hand, ynediones are very difficult to access, and therefore only little attention has been paid to them as building blocks in organic synthesis. However, ynediones possess an additional carbonyl group and therefore a 1,2-diketone motif, which makes them very promising structural elements in diversity oriented synthesis of various classes of heterocycles (Scheme 75).

![Scheme 75. Some modes of potential reactivity of ynediones.](image)

The 1,2-diketone functionality of diynediones has been used in the synthesis of ortho-dialkynyl (hetero)cycles via cyclocondensations with diaminomaleic acid dinitrile or (hetero)aromatic ortho-diamines (Scheme 76).[301]
Scheme 76. Preparation of ortho-dialkynyl (hetero)arenes from diynediones.

A rare example of a synthetic application of ynediones is a Au(III)-catalyzed reaction with nucleophiles (used in excess) followed by cyclization to form furanones (Scheme 77).[302]

Scheme 77. Au(III)-catalyzed synthesis of furanones from ynediones.

This reactivity was not addressed in the investigations described in this thesis. In conclusion, prior to this thesis neither general accesses to ynediones have been described nor the reactivity of ynediones has been thoroughly investigated.
In the framework of this thesis, by omitting Pd responsible for the decarbonylative outcome of the Sonogashira coupling of glyoxylyl chlorides,\textsuperscript{[355]} ynediones as novel useful synthetic intermediates can be obtained in a mild, concise, and straightforward fashion (Scheme 78).\textsuperscript{[303]}

\begin{align*}
\text{Scheme 78. One-pot synthesis of ynediones as valuable synthetic building blocks.}\textsuperscript{[303]}
\end{align*}

The sequence is not restricted to indoles and 7-azaindole but could also be successfully extended to other electron rich heterocycles such as pyrroles, pyrazoles, thiophenes, and furans. No exotic ligand or additives are required, and the sequence gives a direct access to ynediones, whose synthetic potential has yet to be disclosed.
As an illustration of the versatility of the obtained ynediones in the synthesis of heterocyclic compounds, 5- and 6-membered \( N \)-heterocycles could be constructed via novel four-component syntheses (Scheme 79).\textsuperscript{[303]} An unprecedented strategy toward selective and convenient synthesis of 5-acylpyrazoles was disclosed.

![Scheme 79. One-pot syntheses of diverse heterocycles using ynediones as intermediates.\textsuperscript{[303]}](image)

Diverse heterocycles are obtained in an atom economical fashion since all reactants are used in strictly equimolar amounts.

These results are part of this cumulative dissertation (publication 3.4).
2.7 Oxalyl Chloride in Organic Synthesis

Development of novel processes involving small molecules is a tremendously important area of research in synthetic organic chemistry. Oxalyl chloride\cite{304} is an extremely versatile and extensively used C\textsubscript{2} reagent in the organic synthesis. Despite being a very reactive biselectrophile, it can be handled conveniently in the laboratory without the need for special equipment and can be simply transferred to the reaction flask via syringes in the air atmosphere.

As a donor of two carbonyl groups, oxalyl chloride has found applications in reactions with binucleophiles such as silyl enol ethers and 1,3-bis-silyl enol ethers to form various oxygen heterocycles,\cite{305} in a synthesis of 5-oxo-2,5-dihydro-1\textit{H}-pyrroles,\cite{306} or in an approach to \textit{N}-methylisatinis\cite{307}.

Moreover, oxalyl chloride is a reagent of choice in several important transformations such as Swern oxidation and Vilsmeier-Haack formylation. In these reactions oxalyl chloride readily decomposes to generate an active species, which is required for the key step (Scheme 80).

\begin{equation}
\begin{align*}
\text{S}^+\text{O}^- & \quad \text{Cl}^- \quad \text{O} \quad \text{Cl}^- \\
& \quad \text{Cl}^- \quad \text{CO}_2 \quad \text{CO} \\
\end{align*}
\end{equation}

 chlorosulphonium salt
(\textit{Swern oxidation})

\begin{equation}
\begin{align*}
\text{N} & \quad \text{O} \quad \text{Cl}^- \quad \text{CO}_2 \quad \text{CO} \\
& \quad \text{Cl}^- \quad \text{N}=\text{Cl}^- \\
\end{align*}
\end{equation}

 chloromethyliminium salt
(\textit{Vilsmeier reagent})

\begin{equation}
\begin{align*}
\text{S}^+\text{O}^- & \quad \text{Cl}^- \quad \text{O} \quad \text{Cl}^- \\
& \quad \text{Cl}^- \quad \text{CO}_2 \quad \text{CO} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{N} & \quad \text{O} \quad \text{Cl}^- \quad \text{CO}_2 \quad \text{CO} \\
& \quad \text{Cl}^- \quad \text{N}=\text{Cl}^- \\
\end{align*}
\end{equation}

chloromethyliminium salt
(\textit{Vilsmeier-Haack formylation})

Scheme 80. Generation of active species in the \textit{Swern} oxidation and \textit{Vilsmeier-Haack} formylation reactions.
Since only volatile byproducts are formed (CO and CO₂), the reactions are generally very clean. This offers opportunities for designing efficient one-pot reactions.

In a large-scale preparation of a useful building block 4-chloropyridine-2,6-dicarbonyl dichloride, oxalyl chloride was crucial to achieve an excellent yield of the desired product (Scheme 81).[308]

![Deoxygenative chlorination of a pyridine N-oxide with oxalyl chloride](image)

Scheme 81. Deoxygenative chlorination of a pyridine N-oxide with oxalyl chloride.

Amides can be reacted with oxalyl chlorides to give imidoyl chlorides. Recently, this reaction could be used in a deprotection of secondary acetamides (Scheme 82).[309] The reaction conditions are mild enough to allow for a deprotection without epimerization of the amino center.

![Deprotection of secondary acetamides using oxalyl chloride](image)

Scheme 82. Deprotection of secondary acetamides using oxalyl chloride.

In another recent application, in situ formed imidoyl chlorides are utilized in a one-pot synthesis of 2-imidazolines via reaction with aziridines.[310]

Oxalyl chloride can be used as a reagent for the preparation of carboxylic acid chlorides from carboxylic acids or their salts (Scheme 83).[311] Usually, an excess of oxalyl chloride is used, especially in the case of the phenylglyoxylic acid.[312]
Scheme 83. Preparation of carboxylic acid chlorides from carboxylic acids using oxalyl chloride.

Again, only gaseous byproducts are formed during this clean reaction (Scheme 84). DMF is often applied as a catalyst to activate oxalyl chloride via formation of the Vilsmeier reagent (Scheme 83).\textsuperscript{313}

Scheme 84. Mechanism of the chlorodehydration of carboxylic acids.

Just recently, this in situ activation of aliphatic carboxylic acids was used in a Barton reductive decarboxylation using chloroform as a solvent and as a hydrogen atom donor.\textsuperscript{314} Similarly, phosphine oxide reacts with oxalyl chloride to form the chlorophosphonium salt, again releasing only gaseous CO and CO\textsubscript{2} as byproducts, and can be
used as a catalyst in dichlorination of epoxides under 
*Appel* conditions.\(^{[315]}\) Another interesting recent application is the synthesis of 2,3,4,5-tetramethoxybenzoyl chloride, which was reported to be a constituent of the fruiting body of the fungus *Antrodia camphorata*, in order to prove the correctness of the structure assignment of the natural product.\(^{[316]}\)

In 1954, *Speeter and Anthony* reported an ingenious reaction of oxalyl chloride with indoles to give glyoxylyl chlorides in a very smooth way (Scheme 85).\(^{[317]}\) The reaction belongs to the *Friedel-Crafts*-type acylations, thus electron rich unprotected or EDG-protected indoles are suitable substrates. The reaction conditions are very mild, proceeding typically in ethereal solvents at 0 °C or room temperature without need for *Lewis* acid assistance. The reaction has been developed to gain an efficient access to tryptamine derivatives.

\[
\begin{align*}
\text{R}^1 & = \text{H, OBn} \\
\text{R}^1 & = \text{H, } \text{BOH} \\
\text{R}^1 & = \text{OH, } \text{Me} \\
\text{R}^1 & = \text{OH, } \text{Ph} \\
\text{R}^1 & = \text{OEt, } \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{glyoxylyl chlorides} & \quad \text{R}^1 = \text{H, } \text{R}^2 = \text{H: Tryptamine} \\
& \quad \text{R}^1 = \text{OH, } \text{R}^2 = \text{H: Serotonin} \\
& \quad \text{R}^1 = \text{OH, } \text{R}^2 = \text{Me: Bufotenine} \\
\end{align*}
\]

Scheme 85. The *Speeter-Anthony* reaction of indoles with oxalyl chloride.

Glyoxylyl chlorides are obtained as beautiful bright yellow or orange crystalline solids in very high yields. They can be isolated, but are typically immediately used due to the limited stability to storage. In most cases, oxalyl chloride is used in excess (1.2-3.0 equivs) and is removed after the reaction is complete.

The reaction has been found to be very general for indoles and tolerates many functional groups including OMe, OBn, OAc, Alkyl, Aryl, Cl, F, OCF₃, and other functionalities at C-2, C-4, C-5, C-6, and C-7. This reaction has found numerous applications in the synthesis of natural products and biologically active molecules.\(^{[318]}\) In the most cases, it is used in the beginning of a synthesis.
A typical example is the synthesis of psilocin and psilocybin, two principal hallucinogenic constituents of “magic mushrooms” (Scheme 86).[319]

Scheme 86. Synthesis of psilocin and psilocybin using the Speeter-Anthony reaction.

The marine natural product hyrtiosin B, a bisindole alkaloid isolated from the Okinawan marine sponge *Hyrtios erecta*, has been synthesized using the glyoxylation of 5-methoxy- or 5-benzyloxyindole (Scheme 87).[320]

Scheme 87. Glyoxylation in the synthesis of hyrtiosin B.
A similar strategy has been applied for the synthesis of coscinamides A and B, indolyl enamides isolated from the marine sponge *Coscinoderma* sp.[321]

Another cytotoxic marine bisindole alkaloid (±)-dragmacidin from the deep water sponge *Dragmacidin* sp. has been synthesized using the glyoxylation reaction (Scheme 88).[322]

![Scheme 88. Glyoxylation in the synthesis of (±)-dragmacidin.](image)

Examples of glyoxylation reactions of substrates other than indole are rare. The 3-position of azaindoles is known to be inert in comparison to that of indole as a consequence of the electron deficient nature of the pyridine moiety, which reduces the overall nucleophilicity of the heterocyclic system. This is further complicated by the potential of oxalyl chloride, which is typically used in excess, to acylate the pyridine nitrogen atom. For that reason, the reaction of 7-azaindole with oxalyl chloride in Et₂O was unproductive, while indole, under the same conditions, provided the corresponding 3-glyoxylated product in an excellent yield.[323] Benzyl protected 7-azaindoles, however, have been shown to react with oxalyl chloride in a similar way as indoles, but the reflux temperature was needed due to the diminished π-nucleophilicity of 7-azaindole compared to indole.[324]

Pyrrolyl glyoxylyl chloride has been used as intermediate in the synthesis of the corresponding ester in a rather low yield (Scheme 89).[325]
Scheme 89. Glyoxylation of pyrrole.

An interesting method has been described for the preparation of pyrazole-4-carboxylic acids (Scheme 90). The reaction of pyrazoles with an excess of oxalyl chloride led to decarbonylation of the intermediate glyoxylyl chlorides.

Scheme 90. Glyoxylation of pyrazoles.

The hydrocarbon azulene was reacted with oxalyl chloride to form the corresponding glyoxylyl chloride. After trapping with an alcohol, a new colored azulen-1-yloxo-acetyl (Az) protective group was introduced, which is useful in the sugar chemistry (Scheme 91).

Scheme 91. Reaction of azulene with oxalyl chloride.
Very soon after the discovery of *Speeter* and *Anthony*, an attempt was undertaken to perform a decarbonylative reaction of the 3-indoleglyoxylyl chloride.\textsuperscript{[328]} However, thermal decomposition in tetrachloroethane at 115-120 °C yielded only 16-23 % of the corresponding 3-indole carbonyl chloride along with polymeric amide arising from selfamidation.

Moreover, a facile decarbonylation of Pd(II)-alkyloxalyl complexes at room temperature in solution has been described to give the corresponding alkylloxycarbonyl complexes. Interestingly, by addition of phosphane ligands, the decarbonylation was retarded or even inhibited.\textsuperscript{[329]} In contrary, the Pt(II)-alkyloxalyl complexes are stable at room temperature in solution. Despite these findings, no preparatively useful method utilizing metal-catalyzed decarbonylative reaction of glyoxylyl chlorides has been described so far.

Ultimately, oxalyl chloride can be used as a CO donor in combination with *Lewis* acids. *Gribble* demonstrated that (COCl)\textsubscript{2}/AlCl\textsubscript{3} can be used as synthetic equivalent of phosgene in reaction with N-PhSO\textsubscript{2} protected indole (Scheme 92).\textsuperscript{[330]} However, a large excess of both reagents had to be used.

![Scheme 92. (COCl)\textsubscript{2}/AlCl\textsubscript{3} as a synthetic equivalent of COCl\textsubscript{2}.](image)

Consequently, metal salts tend to promote the decarbonylation. For example, a decarbonylation was observed when a mixed alkynylalane was coupled with oxalyl chloride.\textsuperscript{[282a]} The corresponding diynone was obtained in a preparatively useful yield. This behavior of oxalyl chloride is typical of reactions under *Friedel-Crafts* conditions.

Furthermore, a copper-mediated decarbonylation of indolyl glyoxylyl chloride has also been described to deliver an acyl cyanide,\textsuperscript{[331]} which was used in the synthesis of bisindole alkaloids (nor)topsentins (Scheme 93).\textsuperscript{[332]} An excess of oxalyl chloride

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and copper cyanide had to be used and the decarboxylation proceeded at elevated temperatures.

\[
\begin{align*}
1) & \quad \text{(COCl)}_2 \\
& \quad \text{(1.5 equiv)} \\
& \quad \text{Et}_2\text{O}, 0^\circ\text{C}, 1 \text{~h} \\
2) & \quad \text{CuCN} \quad \text{(1.9 equiv)} \\
& \quad \text{C}_2\text{H}_3\text{CN}, \text{toluene} \\
& \quad \Delta \quad \text{(Et}_2\text{O}) \\
& \quad 110^\circ\text{C}, 8 \text{~h}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 93. Cu-mediated decarboxylative cyanation of the indolyl glyoxyxyl chloride.}
\end{align*}
\]

Despite the fact that glyoxylic chlorides are very reactive and potentially very useful electrophilic components in cross-coupling reactions, prior to this work no attempts have been made to investigate this reactivity.

Interestingly, although oxalyl chloride is a very “carbonyl group rich” compound, it has found little attention in catalytic carboxylative reactions. Stoichiometric reactions of two equivalents of organometallic compounds, such as Grignard reagents, organolithium, organotin, or organocopper compounds, with oxalyl chlorides to give 1,2-diorgano-1,2-diones are more common.\textsuperscript{[333]} A representative example is the preparation of symmetrical diynediones used in the synthesis of (hetero)arenes as already discussed in chapter 2.6.2 Synthesis and reactivity of ynediones (Scheme 94).\textsuperscript{[301]}
Scheme 94. Synthesis of symmetrical diynediones.

One report appeared in the literature, where oxalyl chloride was used as a one carbonyl donor (Scheme 95).\textsuperscript{[334]} However, copper was applied in a stoichiometric rather than catalytic amount. Moreover, oxalyl chloride had to be used in excess.

Scheme 95. Synthesis of cyclopentadienones using oxalyl chloride as a CO donor and stoichiometric amount of Cu(I).

Later, the same group developed a Cu(I)-catalyzed approach to cycopentenones by a reaction of zirconacyclopentenes with oxalyl chloride, which served as a C\textsubscript{1} synthon.\textsuperscript{[335]}

In 1979, Stille made the observation that acetone was produced in 10 % yield in the reaction of oxalyl chloride with tetramethyltin under Pd-catalysis.\textsuperscript{[336]} The assumption
was made that unreactive Pd carbonyl complexes were formed resulting in a low yield of the decarbonylated product. As a consequence, the utilization of oxalyl chloride in this direction was not further investigated.

Very recently, in 2010 oxalyl chloride has been reported to serve as a C\textsubscript{1} carbonyl synthon in carboxylations of triarylbi
muth and triarylindium nucleophiles under palladium catalysis.\textsuperscript{337} Symmetrical ketones with simple aryl substituents can be obtained in moderate to good yields (Scheme 96). However, this method can hardly become synthetically useful due to the need for bismuth or indium organyls as starting materials. Moreover, oxalyl chloride is used in excess.

\[
\text{Aryl}_3\text{M} \quad \xrightarrow{9 \text{ mol}\% \text{ Pd(PPh}_3)_4} \quad \text{Aryl} \quad \text{Aryl} \\
(1.0 \text{ equiv}) \quad (2.0 \text{ equiv}) \quad \xrightarrow{1,4\text{-dioxane, 80 ℃, 4 h}} \quad \xrightarrow{\text{or THF, 60 ℃, 4 h}} \\
\]

\( M = \text{Bi}: 15 \text{ examples} \quad (70-89\%) \)

\( M = \text{In}: 15 \text{ examples} \quad (67-83\%) \)

Scheme 96. Synthesis of symmetrical ketones from triarylbi
muth and –indium organometallics.

In conclusion, many reagents have been described as CO surrogates in carbonyla
tive reactions\textsuperscript{338,339} including metal carbonyls, especially the nontoxic Mo(CO)_6,\textsuperscript{119,120,340} carbamoylsilanes and –stannanes,\textsuperscript{341} DMF,\textsuperscript{342} DMF/POCl\textsubscript{3},\textsuperscript{343} formic acid,\textsuperscript{344} acetic formic anhydride,\textsuperscript{345} Ac\textsubscript{2}O/HOOLi,\textsuperscript{346} chloroform/KOH,\textsuperscript{347} methyl and 2-pyridymethyl formates,\textsuperscript{348} benzyl formate,\textsuperscript{349} ammonium formate,\textsuperscript{350} formaldehyde,\textsuperscript{351} benzaldehydes,\textsuperscript{352} and cinnamaldehyde.\textsuperscript{353} However, the “carbonyl group rich” oxalyl chloride has found undeserved little attention. In spite of that, it possesses an enormous synthetic potential and its utility as a C\textsubscript{1} synthon and as a surrogate for the malicious toxic gas phosgene\textsuperscript{354} (bp 8 ℃) and for the toxic gas carbon monoxide in cross-coupling reactions should be explored more intensively.
In the framework of this thesis, it was shown that decarbonylative carbonylation by a consecutive glyoxylation of electron rich heterocycles such as indoles, 7-azaindole, or pyrroles with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation with terminal alkynes furnishes alkynones in fair yields under mild conditions (Scheme 97).\textsuperscript{[355]} The sequence works under standard Sonogashira coupling conditions (PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}/Cul/NEt\textsubscript{3}) without need for exotic ligands or additives. No reagent excess is needed as well. The unprecedented decarbonylative alkynylation is a new modification of the Sonogashira-Hagihara coupling procedure.

Scheme 97. One-pot synthesis of ynones via glyoxylation – decarbonylative Sonogashira coupling sequence.\textsuperscript{[355]}
As an illustration for the utility of the obtained ynones in the heterocycle synthesis, 4-(indol-3-yl)- and 4-(7-azaindol-3-yl)-2-amino pyrimidines, derivatives of the natural products meridianins and their 7-azaindole analogs meriolins, can be readily obtained in one step (Scheme 98)\(^{[355]}\).

![Scheme 98. Implementation of ynones in the synthesis of 2-amino pyrimidines.\(^{[355]}\)](image)

These results are part of this cumulative dissertation (**publication 3.5**).
2.8  **N-Heterocycles**

Nitrogen-heterocyclic frameworks are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Especially, small “drug-like” heterocycles are predominant building blocks in medicinal chemistry.\cite{120} Privileged scaffolds, the term coined by Evans in 1988,\cite{356} are dominated by heterocyclic motifs, especially by \textit{N}-heterocycles.\cite{357}

Despite numerous available methods, there is an ongoing search for simple and straightforward routes to heterocycles. Among new synthetic approaches to this compounds, many transition metal-catalyzed syntheses continue to appear.\cite{358}

MCRs offer a plenty of possibilities to design novel heterocycle syntheses. Besides domino MCRs that are purely based on organometallic catalysis the sequential and consecutive combination with condensation, addition, and cycloaddition steps opens a vast playground for the invention of new sequences and strategies in heterocyclic synthesis\cite{15,359} or with heterocycles as substrates.\cite{360}
2.8.1 Indoles

The indole scaffold represents one of the most important privileged structures since it is capable of binding to multiple receptors with high affinity.[34] Favorable features rendering indole an outstanding privileged structure are discussed in a recent review by Fraga.[361] Indole is broadly widespread in nature[362],[460] and pharmaceutically relevant compounds.[402] Selected examples of natural products with hydroxylated indole units are displayed in Scheme 99. Further representatives, especially those bearing heteroaryl substituents at C-3 position of an indole, will be discussed in chapter 2.10 Indole alkaloids.

![Scheme 99. Hydroxylated indole – a frequent structural motif in alkaloids.](image)

Not surprisingly, the synthesis and functionalization of indoles has been the object of research for over 100 years and for many generations of researchers. Today, this scaffold continues to attract considerable interest of synthetic chemists, and numerous metal-catalyzed approaches continue to be developed, with Pd-catalyzed reactions such as Larock and Cacchi indole syntheses being the most popular methodologies.[363]

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2.8.2 Indole bioisosters

Besides indoles, their aza analogs, i.e. indazole and azaindoles, play an increasingly important role as scaffolds for biologically active molecules. The azaindole and indazole moieties differ only by the presence of an additional nitrogen atom, and thus exhibit an excellent potential as bioisosters\textsuperscript{364} of the indole ring system. Although considerably less frequent in nature, they constitute essential subunits in many pharmaceutically important compounds, and have been very valuable for synthetic and medicinal chemists. “Indazole is a relatively seldom used but effective pharmacophore in medicinal chemistry as illustrated by its applications in pharmaceutical agents in fields as diverse as CNS disorders (granisetron), antiinflammatory area (bendazac and benzydamine), oncology (lonidamine), and HIV protease inhibition (SE063)”.\textsuperscript{373b} Azaindoles represent an extremely rich source of potentially active molecules with numerous possibilities for the preparation of analogs with different and unexpected behavior and improved drug properties such as metabolic stability, solubility, and oral bioavailability.\textsuperscript{365} As early as in 1955, 7-azigramine, 7-azascatole, and 7-azatryptophan were prepared as aza analogs of the alkaloid gramine, the fragrance scatole, and the amino acid tryptophan.\textsuperscript{366} More recently, azaindole analogs of melatonin, the key neurotransmitter in the CNS, have been prepared (Scheme 100).\textsuperscript{367}

![Scheme 100. Melatonin and its 7-azaindole analogs.](image-url)
7-Azaindole is of particular interest because of its pronounced ability to bind to the hinge region of kinases via its H-donor/H-acceptor motif, thus mimicking purine (i.e. the pyrimidine portion of ATP). Consequently, the chemistry of 7-azaindole increased tremendously in the last decade leading to a wide variety of new synthetic methods for the preparation of derivatives for use in medicinal chemistry. Synthesis, reactivity, and biologically active derivatives of this interesting heterocycle were recently reviewed. Similarly, 7-deazapurine and pyrazolo[1,2-b]pyridine are important structural motifs found in a wide range of biological niches. In contrast, 4,7-diazaindenole core structure is a new promising scaffold that will certainly lead to many interesting derivatives in the near future.

Also in biologically active indole bioisosters, aromatic and heterocyclic substituents at C-3 position are very common (Figure 5).

![Figure 5. Indole bioisosters with (hetero)aryl substituents at C-3.](image)

For example, the 3-furylindazole YC-1 is a potent inhibitor of platelet aggregation. RWJ 68354 is a strong, selective, and orally active inhibitor of p38 kinase in vitro (IC$_{50}$ = 9 nM) and in vivo (ED$_{50}$ < 10 mg/kg po). Azaindol-3-yl-dipyridodiazepinones are analogs of nevirapine (i.e. viramune, non-nucleoside inhibitor of reverse transcriptase (RT)) that have been investigated as inhibitors of wild-type RT as well as its mutants but were not further pursued due to their high toxicity. These compounds showed different activities dependent on the presence and position of an additional nitrogen atom in the indole moiety. 3-(4-Fluorophenyl)-2-(pyridine-4-yl)-1H-pyrrolo[3,2-b]pyridine is the core structure of p38 MAP kinase in-
hibitors with \( R = (S)\)-2-hydroxypropyl being a potent, selective, and orally bioavailable inhibitor.\(^{[376]}\)

The development of further biologically active compounds with indole bioisosters as core structures is an extraordinarily active area of research in the medicinal chemistry.
2.9 Syntheses of Pyrroles

Pyrroles are among most prominent 5-membered heterocycles since they constitute important classes of natural products and synthetic pharmaceuticals.

The pyrrole nucleus is widespread in nature and is the key structural fragment of heme, vitamin B$_{12}$, chlorophyll, and cytochromes – tetrapyrrrole pigments essential for life. Moreover, numerous secondary metabolites produced mainly by marine organisms and bacteria contain pyrrole.$^{[377]}$

Many substituted pyrroles show important biological activities. A very prominent example of a pyrrole containing drug is the cholesterol lowering agent atorvastatin, world’s largest selling pharmaceutical (2008 sales of US$: 12.4 billion). The “blockbuster” was developed by Pfizer and functions by binding to the active site of HMG-CoA reductase, thus inhibiting the enzyme (Figure 6). Sunitinib is a multiple inhibitor of receptor tyrosine kinases and is used clinically against GIST and renal cell carcinoma (Figure 6).

![Atorvastatin](image1.png) ![Sunitinib](image2.png)

Figure 6. Structures of pyrrole-containing drugs atorvastatin (Lipitor®) and sunitinib.

Classical methods for the preparation of pyrroles include Knorr,$^{[378]}$ Paal-Knorr,$^{[379],[380]}$ Hantzsch,$^{[381]}$ and Piloty-Robinson$^{[382]}$ condensation reactions. How-
ever, these methods have some limitations with respect to harsh reaction conditions, as well as the regioselectivity and substitution patterns that can be assembled.

Therefore, the development of new pyrole syntheses and synthetic strategies has remained an ongoing challenge, and numerous syntheses continue to appear. In particular, one-pot and multicomponent approaches have inevitably become increasingly important due to their elegance and practicability. For example, a four-component synthesis of 2,3,5-trisubstituted and 1,2,3,5-tetrasubstituted pyroles was reported by Müller, which combined cross-coupling methodology (Sonogashira reaction) with classical condensation (Paal-Knorr pyrole synthesis) chemistry (Scheme 101).

![Scheme 101. The Sonogashira coupling – isomerization – Stetter – Paal-Knorr sequence for the preparation of tri- and tetrasubstituted pyroles.](image)

In contrast to a great number of approaches giving the classical Paal-Knorr products, the quest for mild synthetic methods for compounds with unusual substitution patterns such as 2,4-disubstituted pyroles has turned out to be not trivial. The difficulty to obtain this substitution pattern can be illustrated by a rather complicated approach via rearrangement of 2-furanyl carbamates developed by Padwa (Scheme 102). The synthesis requires multiple steps to accomplish the task.
Scheme 102. Synthesis of 2,4-disubstituted pyroles by Padwa.

Interestingly, as early as in 1981 a Pd(II)-catalyzed pyrrole synthesis from 1-amino-3-alkyn-2-ols, which are obtained from the corresponding alkynones via addition of highly toxic TMSCN on the carbonyl group and subsequent reduction with LiAlH₄, was described by Utimoto.[390] The rather tedious preparation of the starting materials is a strong limitation of this method.

A rare example of a strategy toward 2,4-substituted pyroles bearing N-heterocyclic substituents has been presented by Yamamoto in 2004 (Scheme 103).[391] However, the substituent at C-4 of the pyrrole is strictly limited to be methyl and the acetyl N-heterocycle has to be used in excess in order to obtain good yields.

Scheme 103. Synthesis of 2-heteroaryl substituted 4-methyl pyroles by Yamamoto.
Although many approaches exist toward 3-(hetero)aryl substituted indoles, there are only a few leading to the structurally related 2,4-diarly substituted pyroles.\textsuperscript{[392]} For example, 2,4-disubstituted pyroles with aryl substituents at the β-position could be obtained by a Rh-catalyzed hydroformylation of propargyl amines (Scheme 104).\textsuperscript{[393]}

\begin{align*}
\text{R}^1 &= \text{Ph, p-MeC}_6\text{H}_4 \\
\text{R}^2 &= \text{H, Ph, Me}
\end{align*}

Scheme 104. Pyroles via Rh-catalyzed reaction of propargyl amines with H$_2$/CO.

A Sm(II)-mediated synthesis of 2,4-diaryl pyroles from phenacyl azides with a quite complex mechanistic rationale was described in 2002 (Scheme 105).\textsuperscript{[394]} Besides the need for the preparation of azides as starting materials and for an excess of the Kagan’s reagent, this synthesis is strongly limited to give pyroles bearing two identical aryl substituents.

\begin{align*}
\text{Sml}_2 (2.5 \text{ equiv}) &\rightarrow \\
\text{Aryl} &\xrightarrow{\text{THF, rt, 5-10 min}}
\end{align*}

\begin{align*}
\text{Aryl} &= \text{Ph, p-MeC}_6\text{H}_4 \\
&\quad p-\text{MeOC}_6\text{H}_4, p-\text{BrC}_6\text{H}_4 \\
&\quad p-\text{ClC}_6\text{H}_4, 2-\text{Naphth}
\end{align*}

Scheme 105. Sml$_2$-mediated synthesis of 2,4-diarylpyroles.

In 2006, Carreira described a synthesis of 2,4-diaryl pyroles via a four-step synthesis from an alkene proceeding though an azirine as a key intermediate (Scheme 106).\textsuperscript{[395]} Using this method pyroles with an electron rich 2-aryl substituent and phenyl substituent on C-4 of the pyrrole can be obtained in moderate yields.
Scheme 106. Synthesis of 2,4-diaryl pyrroles according to Carreira.

Recently, a Au(I)-catalyzed synthesis of 2,4-diaryl pyrroles from alkynyl aziridines was reported by Davies (Scheme 107).\textsuperscript{396} However, the starting materials are not readily available, and the formation of the desired products is accompanied by the formation of the corresponding 2,5-disubstituted pendants, even under the optimized reaction conditions.

Scheme 107. Au(I)-catalyzed synthesis of 2,4-diaryl pyrroles by Davies.

2,4-Diheteroaryl substituted pyrroles are even less common. Chalcones were shown to be used in an approach delivering only two examples of pyrroles bearing 2-furyl and 2-thienyl substituents (Scheme 108).\textsuperscript{397}
Scheme 108. Preparation of 2,4-diheteroaryl substituted pyrroles from chalcones.

In conclusion, prior to this work there were no general and practically useful methods for the construction of 2,4-di(hetero)aryl pyrroles, especially those bearing N-heterocyclic moieties. Nevertheless, this substitution pattern could represent an yet underexplored class of biologically active compounds.\textsuperscript{[398]}
In the framework of this thesis, (hetero)aryl, alkenyl, and selected alkyl substituted acid chlorides can be efficiently coupled with N-Boc protected propargyl amine to produce ynones, which are converted in a one-pot fashion into 2-substituted 4-iodo N-Boc pyrroles, valuable synthetic building blocks (Scheme 109).[^399]

\[
\text{Sonogashira Coupling-Addition-Cyclocondensation Sequence}
\]

\[
\begin{align*}
\text{R'Cl} + \text{H-N-Boc} & \quad \xrightarrow{\text{[Pd/Cu] NET}_3 (1.0 \text{ equiv})} \quad \text{then: "I"} \\
\text{then:} & \quad \text{then:} \\
\text{then:} & \quad \text{I} \\
\end{align*}
\]

Scheme 109. One-pot synthesis of 2,4-disubstituted pyrroles.[^399]

Upon addition of a further alkyne, a second Sonogashira coupling could be carried out still in a one-pot fashion. This sequentially Pd/Cu-catalyzed process represents a very mild, preparatively simple, and efficient entry to 2,4-disubstituted N-Boc pyrroles, which represent a rare substitution pattern. The obtained 2-substituted 4-iodo N-Boc pyrroles were shown to be excellent substrates for a borylation – coupling sequence, also developed in the course of this work, to give 2,4-di(hetero)aryl pyrroles.[^464]

These results are part of this cumulative dissertation (publication 3.6).
2.10 Indole Alkaloids

“The marine environment, covering 70 % of the earth’s surface and 95 % of its tropical biosphere, represents 34 of the 36 phyla of life and provides a fascinating variety of biodiversity exceeding that of the terrestrial environment. Not surprising is that marine organisms produce an unprecedented molecular diversity by the incorporation of elements like bromine that are not readily available to terrestrial species. Partially responsible for the unique secondary metabolism of marine life are the ecological pressures in the marine ecosystem including significant competition for space, deterrence of predation, and a high level of symbiosis between different species. Due to the biogenetic origin, marine organism secondary metabolites possess a number of structural differences as compared to terrestrial natural products. In addition, marine organisms are not closely related to their terrestrial counterparts. Over 12,000 compounds from marine invertebrates, algae, and microorganisms have been discovered by a relative few marine research groups.”[^400]

Marine organisms represent one of the most promising sources of bioactive molecules.[^401][^402] “They produce natural products from a variety of structural classes exhibiting activity against numerous disease targets. Historically, marine natural products have largely been explored as anticancer agents. The indole alkaloids are a class of marine natural products that show unique promise in the development of new drug leads. A variety of marine sources including sponges, tunicates, red algae, acorn worms, and symbiotic bacteria have been shown to generate indole alkaloids, which represent the largest number and most complicated of marine alkaloids (1/4 of total alkaloids). Alkaloids obtained from marine organisms frequently possess novel frameworks, while in other cases terrestrially related compounds clearly exist. Their structure elucidation, chemical modification, stereochemistry, synthesis, and pharmacology have received a considerable interdisciplinary attention from areas of research other than chemistry and include pharmacology, physiology, and medicine. Specific biological activities of indole alkaloids include cytotoxic, antiviral, antimicrobial, antiparasitic, antiinflammatory, serotonin antagonistic, Ca$^{2+}$-releasing, calmodulin antagonistic, antitopoiso merase-I, and other pharmacological activities.”[^400]
Total synthesis of natural products and especially of indole alkaloids remains a tremendously important area of chemical research. It is still the ultimate prove of correct structure determination as has been recently demonstrated by Baker who reassigned the structures of psammopemmins (for a discussion, see chapter 2.10.1.5 Other 3-heteroaryl substituted indole alkaloids). Moreover, total synthesis is the only economically and ecologically bearable alternative to the isolation of natural products from their natural sources. For instance, there was not enough material available from the natural source to allow a full investigation of biological properties of variolin B. The combination of “high cost and difficulties of accessing the sponge Kirkpatrickia varialosa from Antarctica with the 1991 Madrid Protocol to the Antarctic treaty, which prohibits any person from removing flora and fauna from the region without the authorization of the government and which came into force in 1998, limits the possibility of obtaining more variolin B from its natural source”. As a consequence, there has been significant interest in the synthesis of variolin B and related compounds, so that access to these interesting materials could be restored and full biological studies could be carried out. Finally, total synthesis remains the touchstone of new synthetic methods and gives the inspiration for the development of novel elegant and efficient synthetic routes.
2.10.1 Meridianins, variolins, and related compounds

Numerous biologically active indole alkaloids have been discovered. Among them, 3-substituted indoles constitute a huge structural class of compounds with remarkable biological activity. The substituent in 3-position is frequently another heterocyclic ring: imidazole (nortopsentins\textsuperscript{[403]} and topsentins\textsuperscript{[404]}); imidazolone;\textsuperscript{[405],[406]} imidazoline (discodermindoles,\textsuperscript{[407]} spongotines,\textsuperscript{[408]} trachycladindoles\textsuperscript{[409]}); maleimide (didemnimides\textsuperscript{[410]}); oxazole (diazonamides,\textsuperscript{[411]} martefragin A,\textsuperscript{[412]} almazoles,\textsuperscript{[413]} pimprinine,\textsuperscript{[414]} and labradorins\textsuperscript{[415]}); oxazoline (JBIR-34 and JBIR-35),\textsuperscript{[416]} pyrrole (chromopyrrolic acid,\textsuperscript{[417]} lymbinamides\textsuperscript{[418]}); pyrrolinone (violacein\textsuperscript{[419]}); thiazole (camalexins\textsuperscript{[420]}, BE-10988\textsuperscript{[421]}); oxazinone (oxazinins\textsuperscript{[422]}); oxadiazinone (alboinon\textsuperscript{[423]}); benzoxazinone (cephalandole A\textsuperscript{[424]}); piperazine and (dihydro)pyrazine (dragmacidins,\textsuperscript{[425]} hamacanthins\textsuperscript{[426]}); pyrimidine (hyrtinadine A,\textsuperscript{[479]} meridianins,\textsuperscript{[432],[433]}); tetrahydropyrimidine (aplicyanins\textsuperscript{[477]}); azepine (hyrtiazepine\textsuperscript{[427]}); isoquinolinequinone (mensouramycin D\textsuperscript{[428]}); β-carboline (eudistomin U,\textsuperscript{[429]} hyrtioerectine A\textsuperscript{[430]}); and another indole.\textsuperscript{[431]}
2.10.1.1 Meridianins

“To date, more than 18,000 compounds have been reported from marine sources. However, only about 300 marine natural products originate from organisms collected in Antarctic habitats. Thus, cold-water marine habitats represent a source of natural products that has yet to be fully explored”. A class of indole alkaloids are meridianins A-E (Figure 7), isolated and identified first in 1998 by the group of Palermo from the tunicate Aplidium meridianum (Ascidiae, Polyclinidae family), collected at a depth of 100 m in the vicinity of the South Georgia Islands (South Atlantic). This Antarctic tunicate, first described by Sluiter in 1906, has various coloration, often forming green or gray colonies.

![Figure 7. Structures of meridianins.](image)

Later, the same group identified two further compounds, meridianins F and G, from a sample of another population of Aplidium meridianum. Just recently, meridianins A, B, C, and E have been isolated from the Antarctic tunicate Synoicum sp.

All compounds possess a brominated and/or hydroxylated indole core structure connected with a 2-amino pyrimidine substituent through a C-3/C-4' linkage. Only the simplest member of this family, meridianin G, has no substituents on the indole nucleus.

These alkaloids are cytotoxic toward cancer cell lines and inhibit protein kinases such as cyclin dependent kinases (CDKs), glycogen synthase kinase-3, cyclic nucleotide dependent kinases, and casein kinase 1. Meridianins display moderate cytotoxicity toward LMM3 (murine mammary adenocarcinoma cell line) and human cancer cell lines with IC<sub>50</sub> values in low micromolar range. Certainly, exhibiting micromolar inhibi-
tion of protein kinases meridianins constitute a new scaffold, from which more potent and selective inhibitors can be designed. Meridianins penetrate into cells and interfere with the activity of kinases which are responsible for cell division and apoptosis. The structure-activity studies show analogies with ATP-competitive CDK inhibitors. The “isomeridianins”, bearing the 2-amino pyrimidine substituent at the C-2-position of indole, are biologically inactive, which underlines the importance of the C-3 substitution.

The first synthesis of meridianins was reported in 2000 by Jiang. The key step was the Suzuki coupling of 3-indolyl boronic acids with 2-amino-4-chloropyrimidine (Scheme 110). The boronic acids had to be prepared from the corresponding bromides via bromine-lithium exchange with tBuLi at -78 °C followed by the reaction of the indolyl lithium reagents with trimethoxyborane and aqueous workup. After the Suzuki coupling step, the Ts protective group remained uncleaved and had to be removed in a separate step.

Scheme 110. Synthesis of meridianins according to Jiang.

In the meantime, several groups have reported syntheses of meridianins and their analogs as well as biological activities of these compounds: (1) synthesis of meridianins A–E via reaction of β-enaminones with guanidinium salts by Fresneda and Molina in 2001; (2) preparation of N-alkylated derivatives using the approach of Fresneda and Molina; (3) synthesis of derivatives with aryl substitution at C-5 and their in vitro antiproliferative activities; (4) synthesis of indolyluracils; (5) derivatives via alkenylation of indoles with α-oxo ketene dithioacetals; (6) new antimalarial agents via reaction of chalcones with guanidinium salts; and (7) me-
ridianins C and G with analogs via one-pot indolization of nitrosoarenes.\textsuperscript{[444]} Syntheses of meridianins have been reviewed.\textsuperscript{[445],[459]}

An intriguing issue is the biological role of meridianins. "Tunicates are subject to little predation, and this is often attributed to chemical compounds".\textsuperscript{[446]} Meridianins from Antarctic colonial ascidians \textit{Aplidium meridianum} and \textit{Aplidium falklandicum} have been shown to serve as chemical defence against predation.\textsuperscript{[446]} Crude extracts as well as isolated meridianins were tested for ecological activity against sympatric generalist predator, the Antarctic sea star \textit{Odontaster validus}. The experiments showed significant feeding repellant. However, none of the isolated meridianins showed activity in laboratory assays against cosmopolitan bacteria and yeasts.

Prior to this investigations, a sole total synthesis of meridianin A was reported by \textit{Molina} and \textit{Fresneda} in 2001 (Scheme 111).\textsuperscript{[447]}

![Scheme 111. Synthesis of meridianin A according to Molina and Fresneda.](image-url)
The natural product (19 mg) was obtained in 7 % total yield over 10 linear steps via a β-enaminone as a key intermediate (Bredereck pyrimidine synthesis). This synthesis can hardly be regarded as a useful approach since the objective was not to prepare meridianan A in a targeted fashion, but rather to prepare a common precursor for both meridianins A and E. Therefore, no efficient synthesis of this natural product was known prior to the presented work.

In 2005, we reported a short and elegant synthesis of several meridianins and a simplified variolin B analog (Scheme 112),[448] which was later called meriolin 1.[463] The key step was the carbonylative Sonogashira coupling of N-Boc 3-iodo (7-aza)indoles, which proceeded under mild conditions. The coupling was performed under ambient pressure of carbon monoxide at room temperature. It is worth mentioning that triethylamine was used as a base in the carbonylative Sonogashira step, whereas aqueous ammonia,[108] used in the procedure described by Mori, failed in our hands to give the desired products.

![Scheme 112. Synthesis of meridianins by the carbonylative Sonogashira coupling as a key step.](image)

The desired products were obtained in four steps and 28-41 % overall yields from the commercially available indoles. This total synthesis represents the first application of the carbonylative alkynylation in the synthesis of natural products.
Regarding the biological activity of the natural meridianins, kinase inhibition tests of the synthesized compounds have been performed revealing moderate micromolar activities. However, meridianins display only modest antiproliferative activities.

The synthesis and the biological activity of the 7-azaindole analog (meriolin 1), prepared by the same approach, will be discussed in chapter 2.10.1.3 Meriolins.
Meridianins show structural similarities with the alkaloid family of variolins, which have been extracted in 1994 from the rare and difficult-to-access red Antarctic sponge *Kirkpatrickia variolosa* by Blunt and Munro and have been shown to possess antitumor and antiviral activities (Figure 8).[^449] The isolated compounds included variolin A, variolin B, *N*-3'-methyl tetrahydrovariolin B, and variolin D, the latter of which was reported to be an artifact of the extraction process produced by aerial oxidation of the variolins.

![Structures of variolins](image)

**Figure 8.** Structures of variolins.

Strikingly, variolin B possesses the same heterocyclic substituent on C-5 of the tricycles as meridianins on C-3 of the indole core.

Variolins are the first example of either terrestrial or marine natural products with a fused tricyclic pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidine heteroaromatic core. This unprecedented tricyclic skeleton has made variolins an interesting class of alkaloids from both structural and biogenetic points of view. Preliminary investigations established that variolin B displayed the highest biological activity, whereas variolin D was inactive in all assays, again indicating the importance of the 2-amino pyrimidine ring. Variolin B inhibited the growth of P388 murine leukemia tumor cell line in micromolar concentrations (IC$_{50}$ value of 210 ng/mL) and was a very fast inducer of apoptosis. Moreover, it was active against *Herpes Simplex* type I and polio virus but inactive
against a range of bacteria and fungi. Further investigations have been hampered by a lack of material.

Therefore, there has been considerable interest in the synthesis of variolins due to the novelty of their structures, not to mention their biological properties and low natural occurrence. Several groups have reported syntheses of the variolin core\cite{450} as well as synthetic manipulations on the core.\cite{451}

To date, four total syntheses of variolin B have been reported in the literature: (1) the first successful total synthesis via tandem deoxygenation and cyclization of a triaryl-methanol was reported by Morris in 2001, elegantly taking advantage of a hidden symmetry element in the molecule;\cite{452} (2) Molina and Fresneda used a sequential approach with the Bredereck synthesis of the 2-amino pyrimidine ring;\cite{453} Álvarez and Joule reported an approach based on the Stille coupling of the iodo tricycle with the pyridylstannane to introduce the C-5 substituent;\cite{454} and finally Vaquero used Pd-mediated C–C, C–O, and C–N couplings to install substituents on a trihalo substituted tricyclic core.\cite{455} Preparation of the synthetic deoxyvariolin B, which showed higher stability and solubility compared to the natural product, has also been described.\cite{456,452b,454b} Syntheses and biological evaluation of simplified bicyclic analogs as well as of various derivatives such as 7-isovariolin B having the 2-amino pyrimidine ring at C-7 instead of C-5 and derivatives with the 2-amino pyrimidine at both positions have been reported as well.\cite{457,453b} However, none of the derivatives has shown improved activity compared to the natural product.

In different human cancer cell lines variolin B and deoxyvariolin B inhibited colony formation, caused cell cycle perturbations, and induced apoptosis at concentrations ranging from 0.1 to 2 μM. They prevent the cells from entering S phase, blocking cells in G1, and cause accumulation already evident 4 h after the beginning of treatment. Although intercalation of deoxyvariolin B in DNA has been demonstrated, neither variolin B nor deoxyvariolin B produce detectable breaks in DNA. In vitro biochemical assays also demonstrated that deoxyvariolin B is not a topoisomerase I or II poison. Instead, variolin B was identified as a potent inhibitor of all CDKs in micromolar concentrations, whereas deoxyvariolin B was 5- to 10-fold less potent. Both are a new class of CDK inhibitors that activate apoptosis in a p53-independent fashion, and thus they may be effective against tumors with p53 mutations or deletions.\cite{458}
Additionally, variolin B was found to be the most potent inhibitor of CK1, a significant therapeutic target in both Alzheimer’s disease and cancer.

In conclusion, the unique heterocyclic framework of variolins has emerged as a new scaffold for the design of new inhibitors of CDKs. Indeed, the Spanish pharmaceutical company PharmaMar has been investigating the potential of variolin B and its analogs as antitumor agents.

Isolation, structure determination, synthesis, and biological activity of variolins and related compounds such as meridianins and meriolins have been recently comprehensively reviewed by Morris in 2009\textsuperscript{[459]} and by Januário in 2010\textsuperscript{[460]} An earlier review on syntheses of variolins and bicyclic analogs was provided by Álvarez in 2004\textsuperscript{[461]}
2.10.1.3 Meriolins

Through a combination of the common features of meridianins and variolins, a new class of 7-azaindole containing analogs known as meriolins has been designed. Due to the 7-azaindole core with its pronounced inherent ability to bind to the hinge region of kinases, these compounds are predestined for investigations as kinase inhibitors.\textsuperscript{[372],[374]} The first synthesis of the simplest member of this class was performed by Molina and Fresnedo in 2001,\textsuperscript{[447]} followed by our synthesis in 2005.\textsuperscript{[448]} Later, Meijer reported a comprehensive study on synthesis, kinase inhibitory activity, cellular effects, and structure of a CDK2/cyclin A/meriolin complex, and coined the term “meriolins” to describe these hybride structures (Figure 9).\textsuperscript{[462],[463]}

![Meriolins](image)

Figure 9. Some members of the meriolin family.

The above mentioned synthesis by Molina and Fresnedo relies on the same synthetic strategy as used for the synthesis of meridianin A. The desired product was obtained in 4 linear steps and 16 % total yield (Scheme 113).\textsuperscript{[447]} The major drawback of this synthesis is the difficult Friedel-Crafts acylation of 7-azaindole resulting in the poor yield of 3-acetyl 7-azaindole.
Scheme 113. Synthesis of meriolin 1 according to Molina and Fresneda.

Merieolins display enhanced specificity toward CDKs (from 32 kinases tested), with marked potency on CDK2 and CDK9. Indeed, meriolins have proved to be even more potent CDK inhibitors than variolin B. This class of compounds also exhibits better antiproliferative and proapoptotic properties in human tumor cell cultures compared with their “inspirational parent” molecules, meridianins and variolins. SAR studies complemented with the crystal structure have provided some clarification on the action mechanisms of these molecules on their CDK target. Meriolin 3 and variolin B bind within the ATP binding site of the kinase, but in different orientations and via different binding modes, as could be determined by the X-ray crystallography. Meriolins induce cell death at submicromolecular concentrations in all cell lines tested, with the noticeable exception of normal fibroblasts, which were rather resistant. Moreover, meriolin 3 potently inhibits tumor growth in two mouse xenograft cancer models, namely, Ewing’s sarcoma and LS174T colorectal carcinoma. Meriolins thus constitute a new CDK inhibitory scaffold with promising antitumor activity, derived from molecules initially isolated from marine organisms.

Huang reported the synthesis of 7-azaindolyl pyrimidines with substituents on the amino group (described in chapter 2.3.6 Miyaura and Masuda borylations) (Figure 10).[182]
Some of the obtained compounds were shown to be very potent CDK1 inhibitors (IC$_{50}$ value of 3 nM for R = o-MeC$_6$H$_4$), and exhibited high antiproliferation activity on the HeLa (cervical carcinoma) cell line (IC$_{50}$ value of 28 nM for the same compound). The unsubstituted nitrogen atom of the indole nucleus was found to be essential for both CDK1 and antiproliferation activity. When screened against a panel of 100 kinases with 2 mM of ATP, the above mentioned compound displayed > 50 % inhibition of 61 kinases, and > 80 % inhibition of 33 kinases in the panel, thus representing a family of very potent multikinase inhibitors.

Our synthesis was based on the carbonylative Sonogashira coupling as described in chapter 2.10.1.1 Meridianins (Scheme 114). The desired product was obtained in 4 steps and 25 % total yield from the commercially available 7-azaindole.
Scheme 114. Synthesis of meriolin 1 according to Müller.

The compound was tested against a panel of 121 kinases displaying an inhibitory activity of > 50 % on 25 and > 90 % on 4 kinases at a concentration of 1 µM. Moreover, a significant improvement of antiproliferative activity on cancer cell lines was determined. In contrast to meridianin G displaying essentially no activity, meriolin 1 showed a sub-µM activity on HCT116 and A2780 cancer cell lines with IC₅₀ values of 0.18 µM and 0.14 µM, respectively.

In conclusion, meriolins display better antiproliferative and proapoptotic properties in human tumor cell cultures than their parent natural products, as determined by us and others, and therefore represent a very promising 7-azaindole based scaffold for development of potent kinase inhibitors.
In the framework of this thesis, a practical *Masuda* borylation – *Suzuki* coupling sequence was developed for the direct preparation of (7-aza)indoles bearing diverse 5- and 6-membered aryl and heteroaryl substituents starting from the corresponding iodides (Scheme 115).[^464]

![Masuda Borylation-Suzuki Coupling Sequence](image)

Scheme 115. One-pot synthesis of (hetero)aryl substituted heterocycles.[^464]

Besides iodo indoles and 7-azaindoles, iodo pyrroles[^399] were found to be excellent substrates to furnish 2,4-di(hetero)aryl pyrroles as a rare substitution pattern. Other electron rich (hetero)aryls could be reacted as well, and the scope of this sequence is remarkable. Even free hydroxy and amino groups as well as notoriously difficult 2-amino pyridine and pyrimidine motifs on both substrate and (hetero)aryl halide are well tolerated.

An an illustration of the utility of the developed sequence, concise total syntheses of marine natural products meridianin G, meridianin A, as well as of the variolin B analog, meriolin 1, were performed (Scheme 116 and Scheme 117).[^464] This strategy represents the most efficient and convenient approach to these alkaloids.
Scheme 116. Total syntheses of meridianin G and meriolin 1.\textsuperscript{[464]}

Again, a single commercially available Pd-precatalyst has been used for both couplings. No exotic ligands or additives were required.
Scheme 117. Total syntheses of meridianin A and isomeridianin A.\cite{464,481}

Meridianin A was prepared in 65 % total yield, representing the first targeted synthesis of this natural product. In a similar way, literature unknown isomeridianin A bearing the hydroxy group at C-5 was prepared in 77 % total yield.

Whereas the precursor to meridianin A, O-Me-meridianin A, was essentially inactive in the viability and kinase inhibition assays (> 50 % inhibition of 3 from 102 kinases at a concentration of 1 μM), the natural product displayed a micromolar activity on the A2780 (ovarian tumor) cancer cell line (IC_{50} = 3.9 μM).

In contrary, isomeridianin A and its precursor, O-Me-isomeridianin A, were only weak kinase inhibitors (> 50 % inhibition of 8 and 7 from 110 kinases at a concentration of 1 μM, respectively) and showed no essential activity on the cancer cell lines tested (A2780 and HCT116 (colon tumor)).

These results are part of this cumulative dissertation (publication 3.7).
2.10.1.4 Camalexins

Two indole phytoalexins, camalexin and methoxycamalexin, were isolated for the first time in 1991 from *Camelina sativa* leaves.[465] These compounds are fungitoxic to *Alternaria brassicae* and are produced after exposure and in response to this fungus. Later, the compounds were found to possess antitumor activity as well. They bear a thiazol-2-yl substituent at C-3 of the indole core (Figure 11).

$$
\begin{align*}
R = H: \text{Camalexin} \\
R = \text{OMe}: \text{Methoxycamalexin}
\end{align*}
$$

Figure 11. Structures of camalexin and methoxycamalexin.

The main phytoalexin camalexin attracted considerable interest, and extensive studies dealing with its biosynthesis[466] and biological role have been undertaken.[467]

The synthesis of camalexins and an analog, 5-methoxycamalexin, by an organometallic approach was reported in 1992 by Ayer (Scheme 118).[468]

$$
\text{1) CH}_3\text{MgI} \quad \text{Et}_2\text{O} \xrightarrow{1)} \quad \begin{cases}
R^1 &= R^2 = H: \text{Camalexin} \\
R^1 &= H; R^2 = \text{OMe}: \text{Methoxycamalexin} \\
R^1 &= \text{OMe}; R^2 = H: 5\text{-Methoxycamalexin}
\end{cases}
$$

Scheme 118. Synthesis of camalexins by an organometallic approach.
The reaction is well suitable for the preparation of natural products but has a limitation of functional group intolerance typical for organometallic approaches, which may be an obstacle for the preparation of further analogs.

The biological activity of camalexin is not restricted to microorganisms and plants. The natural product and some analogs, prepared according to Ayer’s method, were tested on the human breast cancer cell line SKBr3 with camalexin showing an IC_{50} value of 2.7 μM.[469]

Analogs of camalexin such as 1-methylcamalexin, 5-methyl-, and 5-fluorocamalexin were prepared according to Ayer’s method, and studies concerning detoxification and antifungal activity of these compounds were performed.[470] 5-Fluorocamalexin was found to be the best designer phytoalexin against fungus *Rhizoctonia solani* due to a slow metabolisation.

Another organometallic approach was described by Sakamoto using active Zn to produce indolylzinc iodide as the key intermediate that was coupled with 2-iodothiazole in a *Negishi* coupling to give camalexin in 2 steps and 61 % total yield (Scheme 119).[471] The method has a drawback of relatively tedious preparation of the active Zn reagent.

![Scheme 119. Synthesis of camalexin according to Sakamoto.](image-url)
A short synthetic route to camalexin was presented by Fürstner in 1995 based on a low-valent titanium induced reductive coupling of an oxo-amide, currently known as Fürstner indole synthesis (Scheme 120).\textsuperscript{[472]} This synthesis gave the desired product in 61 % yield and is suitable for the synthesis of C-2 substituted analogs.

Scheme 120. Synthesis of camalexin according to Fürstner.

A biomimetic approach according to the proposed biosynthetic scheme was demonstrated in 2001 by Dzurilla (Scheme 121).\textsuperscript{[473]} This synthesis gave only 10 mg of substance, which corresponds to 2.6 % total yield.

Scheme 121. Biomimetic synthesis of camalexin.
2-Aryl and 2-alkyl substituted camalexin derivatives were prepared using the Pd-catalyzed Cacchi indole synthesis.\cite{474} However, no extensive SAR studies of camalexin analogs have been conducted yet.
Psammopemmins were described in 1992 by Capon to represent an unusual group of natural products isolated as an amine salt from an Antarctic marine sponge *Psammopemma* sp. (Figure 12).\[475\] Three structurally related compounds designated psammopemmins A–C have been assigned. Unfortunately, a recent study of Baker, who also performed the first total synthesis of the proposed psammopemmin A, revealed the incorrect structure assignment in the original report.\[476\] According to the comparison of NMR data of meridianin A with the reported data of psammopemmin A, the molecules are identical.

![Psammopemmins](image)

*Figure 12. Erroneously assigned structures of psammopemmins.*

A new family of indole alkaloids was recently isolated from the Antarctic tunicate *Ap- lidi um cyaneum* by Reyes (Figure 13).\[477\] The aplicyanins A–F contain a bromoindole nucleus and a 6-tetrahydropyrimidine substituent at C-3. The aplicyanins share a common 3-(pyrimid-4-yl)indole structure with meridianins and variolins. The tetrahydropyrimidine system of the aplicyanins has a stereocenter at C-4', in contrast to the planar pyrimidine ring of the meridianins.
Aplicyanins B, D, and F have been found to possess significant cytotoxic and antimitotic activities, with IC$_{50}$ values in the low to sub-$\mu$M range.

Indoles with 5-membered heterocyclic substituents at C-3 represent another widespread group of natural products. Some representatives are depicted in Figure 14.
2.10.2 Marine bisindole alkaloids

Certain bisindole alkaloids possess unique structures with a 5- or 6-membered central ring which is shared by two indole units (Figure 15). These compounds display a broad spectrum of biological activities.\textsuperscript{[478]}

![Structures of naturally occurring bisindole alkaloids](image)

Figure 15. Structures of naturally occurring bisindole alkaloids (representative examples).

In 2007, Kobayashi reported the isolation and structural elucidation of the new bisindole alkaloid hyrtinadine A (Figure 16).\textsuperscript{[479]}
Figure 16. Structure of hyrtinadine A.

The compound was isolated from an Okinawan marine sponge *Hyrtios* sp. and contains two 5-hydroxyindole moieties connected by a 2,5-pyrimidyl ring. This structural element is unprecedented. It is worth mentioning that only 1 mg of this alkaloid could be obtained from 1.13 kg (!) sponge (wet weight), which corresponds to 0.0046 % yield. Hyrtinadine A exhibited cytotoxicity against murine leukemia L1210 cells (IC$_{50}$ = 1 µg/mL) and human epidermoid carcinoma KB cells (IC$_{50}$ = 3 µg/mL) in vitro.

The sole total synthesis of hyrtinadine A, described in 2008 by Sestelo and Sarandeses, was achieved by a two-fold cross-coupling reaction between a tris(3-indolyl)indium reagent and 5-bromo-2-chloropyrimidine as a key step (Scheme 122).[480]
Scheme 122. Total synthesis of hyrtinadine A via Pd-catalyzed coupling of an organoindium compound.

The starting material was prepared in a one-pot procedure and 90 % yield from the commercially available 5-methoxyindole by N-silylation with TBSCI, followed by bromination with NBS at a low temperature. The natural product was obtained in 46 % overall yield (31 mg were prepared). Despite the elegance and novelty of the key step, the major drawback of this synthesis is the required excess of the core indolylindium reagent, which has to be prepared and which is therefore a precious compound. In terms of the concept of atom economy, the key step is not efficient.
In the framework of this thesis, the developed *Masuda* borylation – *Suzuki* coupling sequence\(^{[464]}\) working with a simple catalytic system could be successfully applied for a concise one-pot synthesis of heteroaryl bridged (aza)indoles as demonstrated for the total synthesis of the marine natural product hyrtinadine A (Scheme 123).\(^{[481]}\)

![Scheme 123. Total synthesis of hyrtinadine A.\(^{[481]}\)](image)

Although hyrtinadine A was found to be essentially inactive in viability assays and in kinase assays (> 50 % inhibition of 3 from 121 kinases at a concentration of 1 \(\mu\)M), its synthetic precursor, \(O,O'\)-dimethyl hyrtinadine A, possessed an antiproliferative activity in a low micromolar range in assays with two cancer cell lines (IC\(_{50}\) (HCT116) = 3.7 \(\mu\)M; IC\(_{50}\) (A2780) = 4.5 \(\mu\)M). However, none of the 110 kinases tested were inhibited, indicating that the cytotoxic activity is presumably not correlated to the kinase inhibition activity of these compounds.

These results are part of this cumulative dissertation (publication 3.8).
2.11 Kinases and kinase inhibitors

The human genome encodes some 518 protein kinases (human kinome), which constitute one of the largest protein families in humans. The majority of small-molecule kinase inhibitors target the ATP-binding site of the enzymes.\cite{482} The ATP-binding site in protein kinases, placed between the two lobes of the kinase fold and called the hinge region, is highly conserved, and therefore, the development of highly ATP-competitive kinase inhibitors is a difficult task. Moreover, these inhibitors usually lack selectivity. However, there are regions within the binding cleft that are not occupied by ATP, and these regions (hydrophobic pockets) show a higher degree of structural diversity between members of the kinase family than the ATP-binding regions. This provides opportunities for the discovery or design of selective and small molecule ATP-competitive inhibitors.\cite{483,484}

Although a few kinase inhibitors such as staurosporine (Figure 17), a natural indolo[2,3-\(\alpha\)]carbazole alkaloid originally isolated in 1977 from Streptomyces staurosporeus, are unselective, many display a definite specificity profile, but all inhibit several kinases. Multitarget inhibitors may find appropriate medicinal use because they are less likely to allow resistance to develop.

Interestingly, certain indirubin dyes, which are the active ingredients in an ancient Chinese herbal remedy that has been used for centuries to treat diseases such as cancer, are potent CDK inhibitors (Figure 17).\cite{485}

![Staurosporine and Indirubin](image)

Figure 17. Structures of the multikinase inhibitor staurosporine and of CDK inhibitor indirubin, an isomer of indigo.
The anticancer drug Gleevec® (imatinib mesylate, Glivec®)[486] is one of the most interesting developments in the pharmaceutical industry in the last two decades. It is a 2-phenylamino pyrimidine[487] containing drug and belongs to the class of kinase inhibitors (Figure 18). The drug was developed by Novartis and is indicated for the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumors (GISTs).

![Structure of imatinib mesylate (gleevec). The pharmacophore is drawn in bold.](image)

Gleevec, which was approved for clinical use in May 2001, is the first important drug to be developed by targeting a protein kinase specifically. Gleevec does not attack all proliferating cells, but blocks selectively the ATP-binding site of Bcr-Abl tyrosin kinase protein, which is a constitutively active fusion protein version of the protein kinase c-Abl and plays the key role in the occurrence of CML. The structure-activity-relationship shows the phenylamino pyrimidine unit to be essential for the biological activity. Further substituents enhance the selectivity and bioavailability. The impact of imatinib on the field of cancer therapy has been dramatic and can not be overestimated. As the first successful targeted drug to treat cancer, imatinib opened the era of molecular targeted therapy and established a model for the development of future drugs.

The compound has been rationally designed, in contrast to another kinase inhibitor drug sorafenib (Nexavar®, Bayer), which has been developed by a combinatorial approach (Figure 19).[488],[489] This compound inhibits Raf kinase, a key mediator of signal-transduction pathways from cell surface receptors to the cell nucleus.
Due to the outstanding properties of imatinib, there has been an enormous interest in improvements of its synthesis.\[^{490}\] In 2008, imatinib and its analogs were reported to be prepared in an improved procedure using a Cu-catalyzed Ullmann-type coupling as a key step to synthesize the pharmacophore. The amino pyrimidine intermediate, however, was prepared by the reaction of β-enaminone and guanidine nitrate in a classical stepwise fashion (Scheme 124).\[^{491}\]

\[\text{Imatinib base} \rightarrow \text{6 main steps, 46\%}\]

Scheme 124. Improved synthetic route to imatinib and its analogs.

In 2010, Lu presented a new synthesis of imatinib using a stepwise preparation of the key phenylamino pyrimidine intermediate via reaction of the enaminone with thiourea, followed by a nucleophilic aromatic substitution of the 2-(methylthio)pyrimidine with an aniline derivative. However, this approach required even more steps to construct the pharmacophore.\[^{492}\] Also in 2010, Ley reported a concise flow-based synthesis of imatinib. Despite obvious advantages of this convergent approach, the pharma-
cophore is still built up via Buchwald-Hartwig amination using a large excess (4 equivs) of 4-(pyridine-3-yl)pyrimidine-2-amine for the ultimate construction of the phenylamino pyrimidine motif.[493]

Nilotinib[494] (Tasigna®, Novartis) possesses the same and bafetinib[495] a very similar pharmacophore as imitinib. They belong to the “second generation” inhibitors of Bcr-Abl for the treatment of imatinib-resistant CML (Figure 20).[496]

![Figure 20. Kinase inhibitors as drugs.](image)

It is worth mentioning that imatinib, sorafenib, and other kinase inhibitors which reached the market have been developed as selective inhibitors but turned out to be inhibitors of at least several kinases, which can also display cooperative effects.[484] For example, besides being a relatively specific inhibitor of Bcr-Abl, gleevec also inhibits the c-kit and PDGF-receptor tyrosin kinases with similar potency. It has been undergoing clinical trials for the treatment of gastrointestinal stromal tumors and other cancers in which c-kit or PDGF-receptor signalling is deregulated. Therefore, although achieving high selectivity is possible, it can often be an advantage to simultaneously inhibit several therapeutically relevant and complementary kinases at the same time (selectivity profile rather than absolute selectivity).[497] Thus, developing oligokinase inhibitors that inhibit a range of protein kinases is a valid approach.

To summarize, prior to this work the pharmacophore of imitinib and nilotinib had to be prepared in several steps rather than in a one-pot manner.
3 General Part – Publications

Publications relevant for this cumulative dissertation are enrolled and the estimated contributions are discussed.

Complete publication manuscripts with supporting information including characterization of all compounds can be found in the appendix.

3.1 Catalytic syntheses of $N$-heterocyclic yrones and ynediones by in situ activation of carboxylic acids with oxalyl chloride


Contribution

In the framework of this thesis, I developed the idea to establish this method, performed first orienting experiments that demonstrated its feasibility, was involved in the planning of the experiments, contributed to the writing of the first draft of the manuscript, assisted in the compilation of the supporting information, and was involved in the discussions. The experimental work was performed by M. Sc. Christina Boersch.

My contribution as a co-author of this paper is approximately 20 %.
3.2 Consecutive one-pot Sonogashira-Glaser coupling sequence – direct preparation of symmetrical diynes by sequential Pd/Cu-catalysis


**Contribution**

In the framework of this thesis, I developed the idea to work out this reaction as a preparative method, planned the experiments and performed approximately 55 % of the experimental work including the optimization. The remaining examples were prepared by Dipl.-Chem. Dominik Urselmann. I compiled the supporting information, contributed to the writing of the first draft of the manuscript, and was involved in the discussions.

My contribution as a co-author of this paper is approximately 70 %.
3.3 Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence


Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments and performed most of the experimental and optimization work. Several examples and the optimization of one sequence were performed by Fabian Klukas in the course of his organic chemistry research practicum under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. Dr. Dieter Dorsch and Dr. Hartmut Greiner were responsible for the biological evaluation of the compounds and the discussion of the obtained data. Dr. Ulrich Grädler performed the X-ray structure analysis of the complex of the compound 8f with the kinase PDK1 and discussed the crystallographic data.

My contribution as a co-author of this paper is approximately 80%.
3.4 Three-component synthesis of ynediones by a glyoxyla-
tion/Stephens-Castro coupling sequence

Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, Thomas J. J. Müller, 

**Contribution**

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, performed approximately 50 % of the experimental work and parts of the optimization studies. The remaining examples and additional optimization trials were performed by Janis Dohe in the course of his bachelor thesis and by B. Sc. Charlotte Gers in the course of her master thesis, both under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. Dr. Frank Rominger performed the X-ray structure analysis.

My contribution as a co-author of this paper is approximately 80 %.
3.5 Consecutive three-component synthesis of ynones by decarbonylative Sonogashira coupling


**Contribution**

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, performed the experimental work, compiled the supporting information, wrote the first draft of the manuscript, and was involved in the discussions. Dr. Thomas Oeser performed the X-ray structure analysis.

My contribution as a co-author of this paper is approximately 95 %.
3.6 Three-component synthesis of N-Boc-4-iodopyrroles and sequential one-pot alkynylation


Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, and performed approximately 55 % of the experimental work including the optimization. The remaining examples were prepared by Christina Boersch in the course of her bachelor thesis under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. The X-ray structure analysis was performed by Prof. Dr. Walter Frank.

My contribution as a co-author of this paper is approximately 80 %.
3.7 Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation – Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G


**Contribution**

In the framework of this thesis, I developed the idea to adapt this one-pot method to our synthetic problem, planned the experiments and performed most of the experimental work including the optimization. The total synthesis of meridianin A was performed by Elisabeth Schäfer in the course of her organic chemistry internship under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions.

My contribution as a co-author of this paper is approximately 95 %. 
3.8 One-pot synthesis of diazine-bridged bisindoles and concise synthesis of marine alkaloid hyrtinadine A


**Contribution**

In the framework of this thesis, I developed the idea to perform this synthesis, planned the experiments and performed approximately 50 % of the experimental work including the initial total synthesis of the natural product hyrtinadine A. The remaining examples were prepared by Dipl.-Chem. Boris Tasch and he improved the yield in the last step of the synthesis of hyrtinadine A. I contributed in parts to the writing of the first draft of the manuscript, to the compilation of the supporting information, and was involved in discussions.

My contribution as a co-author of this paper is approximately 70 %.
4 General Part – Outlook

4.1 Oxazol-2-ones

When the synthesis of 2,5-disubstituted 4-iodo pyrrroles in analogy to the presented one-pot three-component synthesis of 2-(hetero)aryl 4-iodo pyrrroles was attempted, unexpectedly 4,5-disubstituted oxazol-2-ones were obtained in moderate yields.\[^{[498]}\]

Remarkably, no pyrrrole byproducts could be detected, indicating a high selectivity of this process (Scheme 125).

Scheme 125. Unexpected selective formation of oxazol-2-ones.
In one case, the structure was also confirmed by an X-ray structure analysis (Figure 21). The compound forms an unsymmetrical dimer via intermolecular H-bonding between the two conformers.

![Figure 21. X-Ray structure analysis of 5-[2-(4-methoxyphenyl)-2-oxo-ethyl]-4-(4-methoxyphenyl)-3H-oxazol-2-one (performed by Prof. Dr. Walter Frank).](image_url)

This new synthesis of oxazolones via coupling – isomerization should be further investigated to unravel substitution effects leading to the selective formation of oxazolones over pyrrroles.
4.2 Glyoxylation – cross-coupling sequences

The developed strategy based on the glyoxylation of electron rich heterocycles with oxalyl chloride as a surrogate for carbon monoxide followed by metal-catalyzed coupling reactions such as Sonogashira or Castro couplings has the potential to be further developed in two directions: the one-pot synthesis of diverse heterocycles and the implementation of further cross-coupling reactions as part of new sequences.

As an illustration, in 2010 we reported a new synthesis of ketones by a glyoxylation – decarbonylative Stille coupling sequence as another example of decarbonylative reaction of glyoxyl chloride proceeding in a one-pot fashion (Scheme 126).\[^{[499]}\]

![Scheme 126. Glyoxylation – Stille coupling sequence for the preparation of ketones.](image)

Further sequences based on the glyoxylation – cross-coupling strategy can be conceived.

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4.3 5-Acyl pyrazoles

The disclosed access to ynediones via glyoxylation – *Stephens-Castro* alkynylation opens numerous possibilities for designing one-pot syntheses of heterocycles that are difficult to access in a conventional way. The best example is a novel strategy toward a selective synthesis of 5-acyl pyrazoles discovered in the scope of this work (Scheme 127).

![Scheme 127. Selective formation of an indoloyl pyrazole using Boc hydrazine as a key reagent.](image)

After the ynedione was formed in the course of the glyoxylation – *Stephens-Castro* coupling sequence, one equivalent of the Boc-protected hydrazine (*tert*-butyl carbazate) as an easy-to-handle, nontoxic, and safe reagent was added, furnishing the *N*-Boc protected indoloyl pyrazole in a good yield. After a smooth deprotection, the in-
doloyl pyrazole can be obtained in 61 % overall yield. No formation of the corresponding indolyl pyridazinone was observed. In contrary, the reaction of the same ynedione with hydrazine hydrate gave a statistical mixture of the acyl pyrazole (5-membered ring) with the corresponding pyridazinone (6-membered ring) (Scheme 128).

Scheme 128. Mixture of indoloyl pyrazole and indolyl pyridazinone by reaction of indolyl ynedione with hydrazine hydrate.

For the pyridazinone compound, an X-ray structure analysis confirmed the correct structural assignment (Figure 22). Dotted lines indicate intermolecular H-bonding between the molecules.

Figure 22. X-Ray structure analysis of 3-(1-methyl-1H-indol-3-yl)-6-phenylpyridazin-4(1H)-one (performed by Prof. Dr. Walter Frank).
Since pyrazoles as metabolically stable compounds represent one of the most widely used classes of 5-membered heterocycles in medicinal chemistry, this unprecedented strategy toward 3(5)-aryl-5(3)-aroyl pyrazoles,[500] to which no preparatively useful general synthetic approaches exist to date, may turn out to be very useful in the synthesis of pharmaceutically important molecules. This strategy is now under investigation.
4.4 Camalexins

The developed Masuda borylation – Suzuki coupling sequence works efficiently for the installation of 6-membered nitrogen heterocycles on (aza)indoles, pyrroles, and some other heterocycles. However, the sequence is by far less efficient in the case of 5-membered heterocyclic halides. Nevertheless, camalexin, methoxycamalexin, and 5-methoxycamalexin could be prepared in moderate yields using the standard procedure (Scheme 129).

Scheme 129. Synthesis of camalexins by the developed Masuda borylation – Suzuki coupling sequence.

The prepared camalexins were tested on two cancer cell lines and on a broad panel of kinases. Camalexin showed inhibition of the ovarian tumor cell line A2780 (IC$_{50}$ = 3.6 μM) but inhibited none of the 103 kinases tested.

Prospective investigations could be focused on preparation of further analogs of these natural products and other derivatives with 5-membered heterocyclic rings at C-3 of indoles and related systems.
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Appendix

Genius is one percent inspiration and ninety-nine percent perspiration.

*Thomas Alva Edison*

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Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride**

Christina Boersch, Eugen Merkul, and Thomas J. J. Müller*

Dedicated to Professor Kenkichi Sonogashira on the occasion of his 80th birthday

Ynones are highly reactive Michael systems and can be smoothly reacted with various mono- and binucleophiles in addition and addition–cyclocondensation processes. Consequently, they have received considerable attention as valuable building blocks in heterocycle synthesis. Ynonediones contain a 1,2-dione motif and are even more densely functionalized electrophiles, thus enabling a more multifaceted transformation profile towards heterocycles. Despite their auspicious synthetic potential, ynonediones have remained scarcely explored owing to a lack of a general and practical preparative access. Therefore, a direct, simple, and efficient route to this class of compounds would be highly desirable.

Aryl-substituted ynonediones can be easily prepared by stoichiometric or catalytic acylation of organometallic reagents, especially by Sonogashira coupling. However, an essential limitation of this methodology to date is the lack of an efficient method for the preparation of ynonediones with N-heterocyclic substituents. N-Heteroarenes are pervasive in numerous natural products and in biologically active agents in medicinal chemistry, and the quest for nitrogen-containing building blocks is enormous. However, the often observed low reactivity in cross-coupling reactions resulting from substrate or product inhibition by coordination to transition metals has fostered the necessity to develop a convincing and robust methodology for breaking this bottleneck. For instance, pyridine or quinoline carboxylic acid chlorides, which are highly interesting building blocks in medicinal chemistry, are often not readily available and thus, their transformation to ynonediones under modified Sonogashira coupling conditions was not considered to be practical. On the other hand, N-heterocyclic carboxylic acids are the immediate precursors of acid chlorides. Therefore, a one-pot access to ynonediones starting directly from carboxylic acids could overcome the shortcomings of acid chloride preparation and isolation, and a valuable, conceptually new synthetic tool for ynone preparation could evolve.

Aromatic carboxylic acids have received considerable attention as aryl-nucleophile precursors in metal-catalyzed cross-couplings, which in most cases proceed under decarboxylation. Cross-couplings of carboxylic acids using an excess of anhydrides or carbonates for activation allow for the carbonyl group to be maintained but result in the formation of simple alkyl and aryl ketones.

At the same time, the activation of carboxylic acids with oxalyl chloride is a widespread, mild, and clean method for the preparation of acid chlorides, which produces only gaseous by-products (carbon monoxide, carbon dioxide, and hydrogen chloride). Thus, an in situ conversion of carboxylic acids to acid chlorides using oxalyl chloride followed by alkyne coupling in a one-pot fashion can be considered as an activation–alkynylation sequence to ynonediones and ynonediones. To our knowledge this straightforward alkynylation methodology is unprecedented to date.

Recently, we disclosed conceptually novel approaches to ynonediones initiated by glyoxylation of electron-rich heteroaromatic nucleophiles with oxalyl chloride and subsequent alkyne coupling. The Pd/Cu-catalyzed decarboxylative Sonogashira coupling gives rise to the formation of ynonediones, whereas the Cu-catalyzed Stephens–Castro coupling maintains both carbonyl groups and results in the generation of ynonediones (Scheme 1).

Inspired by the alkynylation of in situ generated glyoxyl chloride, we set out to design one-pot activation–alkynylation sequences that either start from α-keto carboxylic acids and apply Castro conditions for the synthesis of ynonediones or from carboxylic acids using Sonogashira conditions for the generation of ynonediones (Scheme 2), especially addressing notoriously difficult transformations of N-heterocyclic carboxylic acids.

For the optimization of the activation–alkynylation sequence phenylglyoxylic acid (1a) and phenylacetylene...
The addition of triethylamine in the first step for deprotonation of the carboxylic acid in the chlorination step or scavenging the generated hydrogen chloride is not necessary (Table 1, entries 1 and 2). The most significant increase of the yield of isolated product from 43 to 65% was necessary (Table 1, entries 1 and 2). The most significant increase of the yield of isolated product from 43 to 65% was observed upon changing the solvent from THF to 1,4-dioxane (entry 3). It is known that 1,4-dioxane and oxalyl chloride molecules by coordination of the oxygen atoms of 1,4-dioxane to the chlorine atoms of oxalyl chloride. Presumably, the enhanced reactivity is caused by an activation of the reagent by destabilization of the chlorine–carbon bond of oxalyl chloride. We also attempted to exploit the known catalytic effect of DMF on the chlorination with oxalyl chloride by addition of 2 mol% of DMF; however, the obtained yield was lower (entry 4). The variation of the CuI loading in the alkylation step from 2 to 10 mol% revealed an optimum with 5 mol% of the catalyst (entries 3, 5, and 6). These optimized conditions were successfully applied to one-pot syntheses of several ynediones, which were obtained in moderate to good yields (Scheme 3).[19]

With this new and mild activation–Stephens–Castro alkylation sequence it was possible to prepare aryl (3a–c), heteroaryl (3d,e), and alkynyl ynediones (3f,g) in moderate to good yields starting directly from α-keto carboxylic acids 1 or their carboxylates. This novel, valuable sequence convincingly complements the glyoxylation–Stephens–Castro coupling sequence,[14] because electron-neutral and even sterically hindered substrates (see formation of 3c) can be transformed unevenly.

Likewise, the one-pot situ activation–alkynylation scenario was transposed to carboxylic acids 4 in the presence of 2 mol% [PdCl2(PPh3)2] and 4 mol% CuI as a catalyst system, leading to the successful formation of ynones 5 in moderate to excellent yields (Scheme 4).[19] Expectedly, the reaction times under Sonogashira conditions are considerably shorter, and complete conversion was achieved after only 1 h at room temperature.

The activation–Sonogashira alkylation sequence starting from heterocyclic carboxylic acids and carboxylates 4 furnishes a broad variety of the corresponding ynones 5. Most remarkably, Sonogashira coupling of commercially available pyridine-3-carbonyl chloride hydrochloride (Merck KGaA) to give ynone 5a under identical reaction conditions failed completely, even if the reason for this strange observation is yet unknown.

For sodium nicotinate (4a) it was demonstrated that the variation of the alkyne 2 was feasible. Besides phenylacetylene, 1-hexyne, and TIPS-acetylene, also N-heterocyclic alkenes can be efficiently coupled to yield highly functionalized building blocks (see formation of 5d,e). The example of the ynone 5e shows that even the highly labile Boc protective group on the 7-azaindolyl moiety is preserved.

Substituents in 2-, 5-, and 6- as well as in 2,6-positions of the pyridine core are well tolerated (5f–i and 5l). Bromine in 3-position of pyridine (5g) remains untouched under these gentle conditions, ready for addressing this ynone in further functionalizations. It could also be shown that dinitocic acid can be activated and coupled to give a bis(ynone) (5j) in a good yield. In addition to pyridine-containing carboxylic acids, this method can be well applied to convert a whole...
variety of 6-membered N-heterocyclic carboxylic acids, such as isonicotine, pyrimidine, quinoline, and cinnoline carboxylic acid (see formation of 5k–q). Also azoles such as indole, pyrazole, and indazole carboxylic acids can be successfully carried through the sequence (see formation of 5r–t).

It is noteworthy that the indazole derivative 5t is accessible neither by the carbonylative Sonogashira coupling nor by the glyoxylation–decarbonylative alkynylation sequence. Therefore, it is quite remarkable that there is no limitation with respect to the electronic nature of the substrates. Electron-poor (5a–q) as well as electron-rich (5r–t) ynones are accessible. Interestingly, the antimicrobial nalidixic acid (4p) can also be functionalized (5u) as well as a chromone carboxylic acid (4q) to give a chromenyl ynone (5v), now opening access to heterocyclic derivatives of flavones.

Both activation–alkynylation sequences for the preparation of ynediones 3 and ynones 5 are preparatively very simple, mild, and straightforward to perform. In particular, they open an entry to derivatives that are not accessible or difficult or expensive to access with known methods. Carboxylic acids are easily available, stable, and generally nontoxic compounds. Moreover, oxalyl chloride is a liquid which can be conveniently handled. Both sequences use simple standard catalyst systems. Neither exotic ligands nor additives are required, and the alkynylation steps proceed smoothly at room temperature. Finally, all reactants and reagents are used in strictly equimolar amounts without the need for excess reagents.

As an illustration of the applicability of ynediones and ynones as intermediates, one-pot three-component heterocycle syntheses of N-Boc-5-acylpyrazoles 6 and 2-aminopyrimidines 8 were conceived. In a consecutive three-component fashion the in situ generated ynediones 3 can be selectively transformed to N-Boc-protected 5-acylpyrazoles 6 with N-Boc-hydrazine. After deprotection, the 5-acylpyrazoles 7a–c are isolated as analytically pure products (Scheme 5).

Likewise, the cyclocondensation of o-tolyl guanidinium nitrate with the in situ generated trimethylsilyl (TMS) ynones 5 leads to the rapid assembly of the phenylaminopyrimidine scaffold in a one-pot fashion using simple and cheap starting materials, whereas other known procedures take two or more steps and use more elaborate precursors. Most remarkably, the analogue 8b possesses two activated chlorine atoms that have remained untouched, again emphasizing the high compatibility with other functionalities and the mild reaction conditions of the presented methodology.

In conclusion, we have developed new one-pot activation–alkynylation sequences starting from α-keto carboxylic acids or carboxylic acids as versatile and efficient approaches to ynediones and N-heterocyclic ynones, respectively. The one-pot three-component syntheses of 5-acylpyrazoles and 2-α-tolylaminopyrimidines illustrate the implementation of this approach for the preparation of a wide range of heterocycles.

Scheme 4. One-pot synthesis of ynones 5 by an activation–Sonogashira alkynylation sequence. All reactions were carried out on a 2.00 mmol scale [c(4) = 0.2 m] and yields refer to isolated and purified compounds. [a] The sodium carboxylate was used as a substrate. nBu = n-butyl, Py = pyridyl, Boc = tert-butyloxycarbonyl.

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Experimental Section


Experimental Section

3a: Phenylglyoxylic acid (1a, 306 mg, 2.00 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxaly chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and then cooled to room temperature. Cul (20 mg, 0.10 mmol), phenylacetylene (2a, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture, and stirring at room temperature was continued for 24 h. After complete conversion, water (10 mL) was added and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1). [rac] PdCl₂(Ph₃P)₂ (28 mg, 0.14 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxaly chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and then cooled to room temperature. [PdCl₂(Ph₃P)₂] (28 mg, 0.14 mmol), Cul (15 mg, 0.08 mmol), phenylacetylene (2a, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. After complete conversion, water (10 mL) was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1). For the synthesis of marine alkaloids meridianins, see: A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, Angew. Chem. 2005, 117, 7112–7117; Angew. Chem. Int. Ed. 2005, 44, 6951–6956.


Keywords: alkylation · carboxylic acids · C-C coupling · heterocycles · one-pot reactions


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[19] All assigned structures were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis.


Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride

Breaking the bottleneck: α-Keto carboxylic acids and N-heterocyclic carboxylic acids are activated in situ with oxalyl chloride and subsequently catalytically alkynylated to furnish ynediones and N-heterocyclic ynones very efficiently in a one-pot fashion. 5-Acylpyrazoles and 2-phenylaminopyrimidines, potentially interesting for pharmaceutical applications, are readily synthesized in concise one-pot, three-component syntheses.
Supporting Information

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Catalytic Syntheses of N-Heterocyclic Yrones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride**

Christina Boersch, Eugen Merkul, and Thomas J. J. Müller*

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1 General considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. 1,4-Dioxane was dried using MBraun system MB-SPS-800 and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

Commercial grade reagents were used as supplied without further purification and were purchased from ABCR GmbH & Co. KG, Acros Organics, Alfa Aesar GmbH & Co. KG, Fluka AG, Maybridge, Merck KGaA, Darmstadt, and Sigma-Aldrich Chemie GmbH.

The content of palladium (4 µg/g) in copper(I) iodide was determined in the laboratory Elementaranalytik of Merck Serono, Darmstadt.

The purification of pyrazoles was performed on silica gel 60 M (0.04-0.063 mm) from Fluka Analytical using flash technique and under pressure of 2 bar. The purification of alkynediones and alkynones was performed on Biotage SP-1 system using cartridges filled with ca. 340 g silica gel 60 (0.015-0.040 mm) from Merck KGaA, Darmstadt. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from Merck Serono, Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F\textsubscript{254} 20 x 20 cm aluminium sheets obtained from Merck KGaA, Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

\textsuperscript{1}H-, \textsuperscript{13}C-, and 135-DEPT-\textsuperscript{13}C-NMR spectra were recorded on Bruker Advanced DRX 500, Bruker Advanced DRX 200 and Bruker AVIII-300. CDCl\textsubscript{3} and DMSO-d\textsubscript{6} were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards (CDCl\textsubscript{3}: \textsuperscript{1}H δ 7.26, \textsuperscript{13}C δ 77.4; DMSO-d\textsubscript{6}: \textsuperscript{1}H δ 2.50, \textsuperscript{13}C δ 39.5). The multiplicities of signals were abbreviated as follows:

s: singlet; d: doublet; dd: doublet of doublets; dt: doublet of triplets; ddd: doublet of doublets of doublets; t: triplet; tt: triplet of triplets; q: quartet; quin: quintet; sext: sextet; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT-NMR spectra. For the description of the \textsuperscript{13}C-NMR spectra
primary carbon atoms are abbreviated with CH$_3$, secondary carbon atoms with CH$_2$, tertiary carbon atoms with CH and quaternary carbon atoms with C$_{quat}$.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer.

IR spectra were obtained on Bruker Vector 22 FT-IR, where the solids were measured as potassium bromide pellets and oils as films on potassium bromide plates or on Shimadzu IRAffinity-1 which works with the attenuated total reflection (ATR) method. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak).

The melting points (uncorrected) were measured on Reichert Thermovar.

Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the micro analytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.
2 Optimization studies

For optimization of the activation-alkynylation sequence the following model reaction has been chosen (Scheme 1).

Scheme 1. Model reaction for the optimization.

The reaction was carried out on a 2.00 mmol scale. The yields refer to the isolated and pure product 3a. The optimization steps are summarized (Table 1).

Table 1. Optimization of the activation-alkynylation sequence.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1st Reaction step</th>
<th>2nd Reaction step</th>
<th>Yield ynedione 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEt₃</td>
<td>Solvent</td>
<td>T</td>
</tr>
<tr>
<td>1</td>
<td>1.0 equiv.</td>
<td>THF</td>
<td>0 °C → RT</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv.</td>
<td>THF</td>
<td>0 °C → RT</td>
</tr>
<tr>
<td>3</td>
<td>1.0 equiv.</td>
<td>THF</td>
<td>0 °C → 50 °C</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>THF</td>
<td>0 °C → 50 °C</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>THF</td>
<td>0 °C → 50 °C</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>THF</td>
<td>0 °C → 50 °C</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>THF</td>
<td>0 °C → 50 °C</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>1,4-dioxane</td>
<td>RT → 100 °C</td>
</tr>
</tbody>
</table>
2. Optimization studies

Table 1 (continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Reaction step</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Reaction step</th>
<th>Yield ynedione 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt; Solvent T t</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt; [CuI]</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-  DMF 0 °C → 80 °C 4 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>39 %</td>
</tr>
<tr>
<td>10</td>
<td>-  diglyme&lt;sup&gt;[d]&lt;/sup&gt; 0 °C → 120 °C 4 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>n. i.</td>
</tr>
<tr>
<td>11</td>
<td>-  1,4-dioxane RT → 100 °C 4 h</td>
<td>3.0 equivs. 2 mol %</td>
<td>44 %</td>
</tr>
<tr>
<td>12</td>
<td>-  1,4-dioxane RT → 100 °C 1 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>56 %</td>
</tr>
<tr>
<td>13</td>
<td>-  1,4-dioxane RT → 50 °C 4 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>65 %&lt;sup&gt;[e]&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>-  1,4-dioxane 2 mol % DMF RT → 50 °C 4 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>51 %</td>
</tr>
<tr>
<td>15</td>
<td>-  1,4-dioxane RT → 50 °C 2 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>59 %</td>
</tr>
<tr>
<td>16</td>
<td>-  1,4-dioxane RT 4 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>56 %</td>
</tr>
<tr>
<td>17</td>
<td>-  1,4-dioxane RT 3 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>63 %</td>
</tr>
<tr>
<td>18</td>
<td>-  1,4-dioxane RT → 50 °C 4 h</td>
<td>3.0 equivs. 2 mol %</td>
<td>47 %</td>
</tr>
<tr>
<td>19</td>
<td>-  1,4-dioxane RT → 50 °C 4 h</td>
<td>3.0 equivs. 10 mol %</td>
<td>64 %</td>
</tr>
<tr>
<td>20</td>
<td>1.0 equiv.&lt;sup&gt;[b]&lt;/sup&gt; 1,4-dioxane RT → 50 °C 4 h</td>
<td>2.0 equivs. 5 mol %</td>
<td>59 %</td>
</tr>
<tr>
<td>21</td>
<td>-  1,4-dioxane RT → 50 °C 24 h</td>
<td>3.0 equivs. 5 mol %</td>
<td>49 %</td>
</tr>
</tbody>
</table>

[a] Addition of oxalyl chloride, then addition of NEt<sub>3</sub>
[b] Addition of NEt<sub>3</sub>, then addition of oxalyl chloride
[c] Hünig’s base (N,N-diisopropylethylamine) was used instead of NEt<sub>3</sub>
[d] 1-Methoxy-2-(2-methoxyethoxy)ethane
[e] On a 5.00 mmol scale, 61 % yield was obtained
n. i.: not isolated
3 Preparation of ynediones 3

3.1 General procedure

![Chemical reaction diagram](attachment:image.png)

2.00 mmol of glyoxylic acid 1 in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. CuI (20 mg, 0.10 mmol, 5 mol %), alkyne 2 (2.00 mmol, 1.00 equiv.) and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically (Biotage SP-1 apparatus, 100 g SNAP cartridge) on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give ynediones 3.

The experimental details for the synthesis of ynediones 3 are given in Table 2.
Table 2. Experimental details for the synthesis of ynediones 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylic acid</th>
<th>Alkyne 2</th>
<th>Ynedione 3</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(2.00 mmol)</td>
<td>(isolated yield)</td>
<td>R_f (eluent)</td>
</tr>
<tr>
<td>1</td>
<td>Phenylglyoxylic acid (Merck)</td>
<td>2a (2.00 mmol)</td>
<td>3a (isolated yield)</td>
<td>PE/EtOAc = 50:1</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>0.23 mL</td>
<td>302 mg</td>
<td>R_f (PE/EtOAc = 50:1) = 0.14</td>
</tr>
<tr>
<td></td>
<td>306 mg</td>
<td>1.29 mmol</td>
<td>65 %</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>0.45 mL</td>
<td>3b</td>
<td>PE/EtOAc = 100:1</td>
</tr>
<tr>
<td></td>
<td>306 mg</td>
<td>0.23 mL</td>
<td>396 mg</td>
<td>R_f (PE/EtOAc = 100:1) = 0.19</td>
</tr>
<tr>
<td></td>
<td>Tiisopropylsilylethylene (Fluka)</td>
<td>0.45 mL</td>
<td>63 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.26 mmol</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mesiylglyoxylic acid (ABCR)</td>
<td>2a (2.00 mmol)</td>
<td>3c (isolated yield)</td>
<td>PE/EtOAc = 50:1</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>0.23 mL</td>
<td>237 mg</td>
<td>R_f (PE/EtOAc = 50:1) = 0.36</td>
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<tr>
<td></td>
<td>388 mg</td>
<td>0.86 mmol</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2-Thiophenyl glyoxylic acid (Alpha Aesar)</td>
<td>2a (2.00 mmol)</td>
<td>3d (isolated yield)</td>
<td>PE/EtOAc = 50:1</td>
</tr>
<tr>
<td></td>
<td>1c</td>
<td>0.23 mL</td>
<td>293 mg</td>
<td>R_f (PE/EtOAc = 50:1) = 0.15</td>
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<tr>
<td></td>
<td>319 mg</td>
<td>1.22 mmol</td>
<td>61 %</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2 (continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylic acid</th>
<th>Alkyne 2</th>
<th>Ynedione 3</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2.00 mmol)</td>
<td></td>
<td>(isolated yield)</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; (eluent)</td>
</tr>
<tr>
<td>5</td>
<td>2-Furanyl glyoxylic acid &lt;br&gt; <em>(Sigma Aldrich)</em></td>
<td><strong>2a</strong></td>
<td>3e</td>
<td>PE/EtOAc = 10:1 &lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 10:1) = 0.27</td>
</tr>
<tr>
<td></td>
<td>1d</td>
<td>0.23 mL</td>
<td>244 mg</td>
<td>54 %</td>
</tr>
<tr>
<td></td>
<td>289 mg</td>
<td></td>
<td>(1.09 mmol)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><em>(E)</em>-Benzylidene glyoxylic acid potassium salt</td>
<td><strong>2a</strong></td>
<td>3f</td>
<td>PE/EtOAc = 50:1 &lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 50:1) = 0.14</td>
</tr>
<tr>
<td></td>
<td>1e&lt;sup&gt;[a]&lt;/sup&gt;</td>
<td>0.23 mL</td>
<td>175 mg (0.67 mmol)</td>
<td>34 %</td>
</tr>
<tr>
<td></td>
<td>429 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><em>(E)</em>-p-Chlorobenzylidene glyoxylic acid</td>
<td><strong>2a</strong></td>
<td>3g</td>
<td>PE/EtOAc = 50:1 &lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 50:1) = 0.18</td>
</tr>
<tr>
<td></td>
<td>1f&lt;sup&gt;[b]&lt;/sup&gt;</td>
<td>0.23 mL</td>
<td>228 mg (0.77 mmol)</td>
<td>39 %</td>
</tr>
<tr>
<td></td>
<td>421 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>[a]</sup> The potassium salt was prepared according to the literature procedure: C. Allais, T. Constantieux, J. Rodriguez, *Synthesis* 2009, 15, 2523-2530. 2.00 equivs. of triethylamine in the 2<sup>nd</sup> reaction step were used.

<sup>[b]</sup> The potassium salt was prepared according to the literature procedure: C. Allais, T. Constantieux, J. Rodriguez, *Synthesis* 2009, 15, 2523-2530. The free acid was obtained after acidifying with hydrochlorid acid.
3.2 Spectroscopic data of compounds 3a-g

3.2.1 1,4-Diphenylbut-3-yne-1,2-dione (3a)

\[
\text{C}_{16}\text{H}_{10}\text{O}_{2}
\]

234.25

302 mg (1.29 mmol, 65 % yield) as a yellow oil. \(^1\)H-NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.33-7.47 (m, 2 H), 7.47-7.59 (m, 3 H), 7.61-7.74 (m, 3 H), 8.00-8.21 (m, 2 H). \(^13\)C-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 87.4 (C\text{quat}), 99.5 (C\text{quat}), 119.5 (C\text{quat}), 129.1 (CH), 129.3 (CH), 130.9 (CH), 131.9 (C\text{quat}), 132.1 (CH), 134.0 (CH), 135.3 (CH), 178.9 (C\text{quat}), 188.8 (C\text{quat}). EI + MS (m/z (%)): 234 (M\(^+\), 0.4), 206 ((M-CO\(^+\), 3), 178 ((M-C\(_2\)O\(_2\))\(^+\), 31), 129 (C\(_6\)H\(_5\)O\(^+\), 71), 106 (7), 105 (C\(_7\)H\(_5\)O\(^+\), 100), 85 (11), 77 (C\(_6\)H\(_5\)), 75 (11), 71 (15), 57 (13). IR (film): \(\tilde{\nu}\) 3065 (w) cm\(^{-1}\), 2927 (w), 2593 (w), 2361 (w), 2191 (s), 1656 (s), 1595 (m), 1489 (w), 1449 (m), 1249 (m), 1182 (w), 1108 (s), 1025 (w), 1000 (w), 924 (m), 816 (w), 778 (m), 759 (m), 738 (m), 685 (s), 611 (w), 538 (w). Anal. calcd. for C\(_{16}\)H\(_{10}\)O\(_2\) (234.3): C 82.04, H 4.30. Found: C 82.13, H 4.31.


\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.41 (t, \(J = 7.74\) Hz, 2 H), 7.46-7.55 (m, 3 H), 7.64-7.69 (m, 3 H), 8.08 (d, \(J = 7.74\) Hz, 2 H). \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 87.05, 99.14, 119.24, 128.73, 128.92, 130.50, 131.66, 133.63, 134.86, 178.53, 188.43. MS (EI, 70 eV): 234 (M\(^+\), 27), 129 (44), 105 (100). \(R_f\) (EtOAc/hexanes = 1:15) = 0.37.
3.2.2 1-Phenyl-4-[tris(propan-2-yl)silyl]but-3-yn-1,2-dione (3b)

![Chemical Structure](image)

C<sub>19</sub>C<sub>26</sub>O<sub>2</sub>Si

314.49

396 mg (1.26 mmol, 63 % yield) as a yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.06-1.19 (m, 21 H), 7.44-7.54 (m, 2 H), 7.59-7.68 (m, 1 H), 7.98-8.06 (m, 2 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): δ 11.2 (CH), 18.7 (CH<sub>3</sub>), 102.8 (C<sub>quat</sub>), 106.5 (C<sub>quat</sub>), 129.1 (CH), 130.6 (CH), 131.8 (C<sub>quat</sub>), 135.1 (CH), 178.4 (C<sub>quat</sub>), 188.5 (C<sub>quat</sub>). EI + MS (m/z (%)): 286 ((M-CO)<sup>+</sup>, 0.1), 258 ((M-C<sub>2</sub>O<sub>2</sub>)<sup>+</sup>, 0.4), 271 ((M-C<sub>3</sub>H<sub>7</sub>)<sup>+</sup>, 3), 243 ((M-C<sub>3</sub>H<sub>7</sub>-CO)<sup>+</sup>, 3), 106 (8), 106 (7), 105 (C<sub>7</sub>H<sub>5</sub>O<sup>+</sup>, 100), 77 (C<sub>6</sub>H<sub>5</sub><sup>+</sup>, 16). IR (ATR): ν 2945 (w) cm<sup>-1</sup>, 2666 (w), 2145 (w), 1665 (s), 1597 (w), 1462 (w), 1450 (w), 1385 (w), 1319 (w), 1279 (w), 1125 (s), 1072 (w), 1018 (w), 999 (w), 916 (s), 881 (s), 812 (w), 756 (w), 733 (m), 681 (s), 662 (s). Anal. calcd. for C<sub>19</sub>H<sub>26</sub>O<sub>2</sub>Si (314.5): C 72.56, H 8.33. Found: C 72.20, H 8.62.
3.2.3 4-Phenyl-1-(2,4,6-trimethylphenyl)but-3-yn-1,2-dione (3c)

237 mg (0.86 mmol, 43 % yield) as a yellow oil. $^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 2.26 (s, 6 H), 2.32 (s, 3 H), 6.91 (s, 2 H), 7.39-7.48 (m, 2 H), 7.50-7.58 (m, 1 H), 7.60-7.73 (m, 2 H). $^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta$ 20.4 (CH$_3$), 21.6 (CH$_3$), 86.8 (C$_{quat}$), 99.8 (C$_{quat}$), 119.6 (C$_{quat}$), 129.1 (CH), 129.3 (CH), 132.0 (CH), 132.6 (C$_{quat}$), 134.1 (CH), 136.6 (C$_{quat}$), 141.4 (C$_{quat}$), 177.1 (C$_{quat}$), 194.8 (C$_{quat}$). EI + MS ($m/z$ (%)): 276 (M$^+$, 0.2), 220 ((M-C$_2$O$_2$)$^+$, 1), 148 (12), 147 (C$_{10}$H$_{11}$O$^+$, 100), 129 (C$_9$H$_5$O$^+$, 6), 119 (C$_9$H$_{11}$$^+$, 24), 57 (10). IR (film): $\tilde{\nu}$ 3299 (w) cm$^{-1}$, 2923 (m), 2561 (w), 2181 (s), 1661 (s), 1610 (m), 1489 (m), 1444 (m), 1379 (m), 1295 (w), 1234 (w), 1101 (m), 1027 (m), 959 (m), 905 (s), 853 (m), 760 (m), 687 (m), 611 (m), 543 (m). Anal. calcd. for C$_{19}$H$_{16}$O$_2$ (276.3): C 82.58, H 5.84. Found: C 82.60, H 5.98.
3. Preparation of ynediaones

3.2.4 4-Phenyl-1-(thiophen-2-yl)but-3-yne-1,2-dione (3d)

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{Ph} \\
&\text{S} \\
&\text{C} \\
&\text{14} \\
&\text{H} \\
&\text{8} \\
&\text{O} \\
&\text{2} \\
&\text{S} \\
&\text{240.28} \\
&\text{C}_{14}\text{H}_8\text{O}_2\text{S} \\
&\text{293 mg (1.22 mmol, 61 % yield) as a yellow solid. Mp 84 °C.} \\
&\text{\textsuperscript{1}H-NMR (CDCl}_3, 500 MHz):} \ \delta 7.15-7.25 (m, 1 H), 7.35-7.46 (m, 2 H), 7.47-7.58 (m, 1 H), 7.62-7.75 (m, 2 H), 7.79-7.92 (m, 1 H), 8.13-8.25 (m, 1 H). \ \text{\textsuperscript{13}C-NMR (CDCl}_3, 125 MHz):} \ \delta 87.2 (\text{C}_{\text{quat}}), 99.6 (\text{C}_{\text{quat}}), 119.6 (\text{C}_{\text{quat}}), 129.1 (\text{CH}), 132.0 (\text{CH}), 134.1 (\text{CH}), 137.5 (\text{C}_{\text{quat}}), 137.9 (\text{CH}), 138.2 (\text{CH}), 176.5 (\text{C}_{\text{quat}}), 178.9 (\text{C}_{\text{quat}}). \ \text{EI + MS (m/z (%))}: 240 (M\textsuperscript{+}, 2), 212 ((M-\text{CO})\textsuperscript{+}, 11), 184 ((M-\text{C}_2\text{O}_2)\textsuperscript{+}, 31), 130 (10), 129 (\text{C}_6\text{H}_5\text{O}\textsuperscript{+}, 100), 111 (\text{C}_6\text{H}_3\text{OS}\textsuperscript{+}, 97), 83 (\text{C}_4\text{H}_2\text{S}\textsuperscript{+}, 9), 75 (12). \ \text{IR (KBr):} \ \bar{\nu} 2181 (s) \ \text{cm}^{-1}, 1650 (s), 1592 (m), 1501 (m), 1487 (m), 1443 (w), 1405 (m), 1363 (m), 1298 (w), 1248 (m), 1111 (m), 1072 (w), 1040 (m), 909 (m), 858 (m), 763 (m), 732 (s), 684 (m), 624 (w), 567 (w), 540 (w). \ \text{Anal. calcd. for C}_{14}\text{H}_8\text{O}_2\text{S (240.3)}: C 69.98, H 3.36. Found: C 69.79, H 3.34.
\end{align*}
\]
3. Preparation of ynediones

3.2.5 1-(Furan-2-yl)-4-phenylbut-3-yne-1,2-dione (3e)

\[
\begin{align*}
\text{C}_{14}\text{H}_8\text{O}_3 & \quad 224.21 \\
\end{align*}
\]

244 mg (1.09 mmol, 54 % yield) as a yellow solid. Mp 84 °C. \(^1\)H-NMR (CDCl\(_3\), 500 MHz): \(\delta\) 6.59-6.69 (m, 1 H), 7.35-7.48 (m, 2 H), 7.49-7.54 (m, 1 H), 7.63-7.73 (m, 2 H), 7.74-7.82 (m, 1 H). \(^13\)C-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 87.1 (C\(_{quat}\)), 99.5 (C\(_{quat}\)), 113.5 (CH), 119.6 (C\(_{quat}\)), 125.5 (CH), 129.1 (CH), 132.0 (CH), 134.1 (CH), 148.1 (C\(_{quat}\)), 150.0 (CH), 173.8 (C\(_{quat}\)), 175.9 (C\(_{quat}\)). EI + MS (m/z (%)): 224 (M\(^+\), 0.1), 196 ((M-CO\(^+\)), 7), 168 ((M-C\(_2\)O\(_2\))\(^+\)), 15), 130 (10), 129 (C\(_9\)H\(_5\)O\(^+\), 100), 95 (C\(_5\)H\(_3\)O\(_2\))\(^+\), 15). IR (KBr): \(\tilde{\nu}\) 3117 (m) cm\(^{-1}\), 2191 (s), 1654 (s), 1596 (m), 1552 (m), 1489 (w), 1459 (s), 1367 (m), 1323 (m), 1272 (m), 1186 (w), 1129 (s), 1084 (m), 1030 (s), 999 (w), 950 (s), 892 (s), 757 (s), 685 (s), 591 (m), 538 (m), 515 (w). Anal. calcd. for C\(_{14}\)H\(_8\)O\(_3\) (224.2): C 75.00, H 3.60. Found: C 74.82, H 3.68.
3.2.6 (1E)-1,6-Diphenylhex-1-en-5-yne-3,4-dione (3f)

\[
\begin{array}{c}
\text{C}_{18}\text{H}_{12}\text{O}_{2} \\
260.29
\end{array}
\]

170 mg (0.65 mmol, 34 % yield) as a yellow solid. Mp 104 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.37-7.57 (m, 7 H), 7.63-7.75 (m, 4 H), 7.93 (d, \(J = 16.1\) Hz, 1 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 87.0 (C\text{quat}), 99.4 (C\text{quat}), 118.2 (CH), 119.8 (C\text{quat}), 129.1 (CH), 129.4 (CH), 131.9 (CH), 132.0 (CH), 134.1 (CH), 134.6 (C\text{quat}), 148.9 (CH), 177.4 (C\text{quat}), 184.8 (C\text{quat}). EI + MS (m/z (%)): 260 (M\(^+\), 2), 232 ((M-CO)\(^+\), 2), 204 ((M-C\(_2\)O\(_2\))\(^+\), 3), 132 (10), 131 ((M-C\(_9\)H\(_5\)O)\(^+\), 100), 129 (C\(_9\)H\(_5\)O\(^+\), 33), 103 (C\(_9\)H\(_7\)\(^+\), 28), 77 (C\(_6\)H\(_5\)\(^+\), 12). IR (KBr): \(\tilde{\nu}\) 2200 (m) cm\(^{-1}\), 1719 (w), 1701 (w), 1685 (m), 1654 (s), 1608 (s), 1572 (m), 1561 (m), 1544 (m), 1509 (w), 1490 (w), 1459 (w), 1440 (m), 1273 (w), 1180 (w), 1033 (m), 1011 (m), 993 (s), 736 (s), 681 (m), 566 (w), 540 (w). Anal. calcd. for C\(_{18}\)H\(_{12}\)O\(_2\) (260.3): C 83.06, H 4.65. Found: C 82.90, H 4.70.


Obtained as yellow needles, yield 85%, mp 103-105 °C; \(^1\)H NMR \(\delta\) 7.41-7.60 (m, 7 H), 7.62-7.82 (m, 4 H), 7.94 (d, 1 H, \(J = 16.2\) Hz); \(^{13}\)C NMR \(\delta\) 86.6, 99.0, 118.0, 119.4, 128.7, 129.0, 131.5, 131.6, 133.7, 134.2, 148.5, 177.1, 184.5. Anal. Calcd. for C\(_{18}\)H\(_{12}\)O\(_2\): C, 83.06; H, 4.65. Found: C, 83.20; H, 4.64.
3. Preparation of ynediones 3

3.2.7 (1E)-1-(4-Chlorophenyl)-6-phenylhex-1-en-5-yne-3,4-dione (3g)

![Chemical Structure](image)

170 mg (0.65 mmol, 39 % yield) as a yellow solid. Mp 144 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): δ 7.34-7.55 (m, 6 H), 7.56-7.63 (m, 2 H), 7.66-7.73 (m, 2 H), 7.86 (d, J = 16.1 Hz, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): δ 86.9 (C$_{quat}$), 99.7 (C$_{quat}$), 118.6 (CH), 119.7 (C$_{quat}$), 129.1 (CH), 129.8 (CH), 130.5 (CH), 132.0 (CH), 133.1 (C$_{quat}$), 134.1 (CH), 138.0 (C$_{quat}$), 147.2 (CH), 177.2 (C$_{quat}$), 184.6 (C$_{quat}$). EI + MS (m/z (%)): 296 (M$(^{37}$Cl)$^+$, 1), 294 (M$(^{35}$Cl)$^+$, 4), 265 ((M$(^{35}$Cl)-CO-H)$^+$, 5), 259 ((M-Cl)$^+$, 7), 167 ((M$(^{37}$Cl)-C$_9$H$_5$O+2H)$^+$, 33), 166 (9), 165 ((M$(^{35}$Cl)-C$_9$H$_5$O+2H)$^+$, 100), 139 (C$_8$H$_6^{37}$Cl$^+$, 6), 137 (C$_8$H$_6^{35}$Cl$^+$, 19), 129 (C$_9$H$_5$O$^+$, 77), 102 (C$_8$H$_6^+$, 17), 101 (18), 75 (13), 43 (24), 40 (10). IR (ATR): ν 2195 (m) cm$^{-1}$, 1682 (w), 1649 (w), 1630 (m), 1614 (m), 1595 (m), 1568 (m), 1489 (m), 1443 (w), 1368 (w), 1290 (m), 1209 (w), 1175 (m), 1146 (w), 1119 (w), 1026 (w), 1011 (m), 995 (w), 988 (w), 957 (m), 785 (m), 750 (s), 685 (s), 658 (w). Anal. calcd. for C$_{18}$H$_{11}$ClO$_2$ (294.7): C 73.35, H 3.76. Found: C 73.36, H 3.81.
4 Preparation of heterocyclic yrones 5

4.1 General procedure

\[ \begin{align*}
4 & \xrightarrow{1) COCl_2} \xrightarrow{2) [Pd/Cu]} 5
\end{align*} \]

2.00 mmol of carboxylic acid 4 in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. \( \text{PdCl}_2(\text{PPh}_3)_2 \) (28 mg, 0.04 mmol, 2 mol%), CuI (15 mg, 0.08 mmol, 4 mol%), alkyne 2 (2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 1 h. After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically (Biotage SP-1 apparatus, 100 g SNAP cartridge) on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give yrones 5.

The experimental details for the synthesis of yrones 5 are given in Table 3.
Table 3. Experimental details for the synthesis of ynones 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2 (2.00 mmol)</th>
<th>Ynone 5 (isolated yield)</th>
<th>Chromatographic purification Rf (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-Pyridyl carboxylic acid sodium salt (ABCR) 4a[a]</td>
<td>Phenylacetylene (Merck) 2a</td>
<td>377 mg (1.82 mmol)</td>
<td>PE/EtOAc = 3:1, Rf (PE/EtOAc = 3:1) = 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.23 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4a[a] 296 mg</td>
<td>1-Hexyne (Acros Organics) 2c</td>
<td>299 mg (1.60 mmol)</td>
<td>PE/EtOAc = 5:1, Rf (PE/EtOAc = 5:1) = 0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.24 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4a[a] 296 mg</td>
<td>Ethynyltriisopropylsilane (Fluka) 2b</td>
<td>558 mg (1.94 mmol)</td>
<td>PE/EtOAc = 15:1, Rf (PE/EtOAc = 15:1) = 0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.45 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4a[a] 296 mg</td>
<td>3-Ethynylpyridine (Sigma Aldrich) 2d</td>
<td>238 mg (1.14 mmol)</td>
<td>PE/EtOAc = 1:1, Rf (PE/EtOAc = 1:1) = 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>210 mg</td>
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### Table 3 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2 (2.00 mmol)</th>
<th>Ynone 5 (isolated yield)</th>
<th>Chromatographic purification R&lt;sub&gt;f&lt;/sub&gt; (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4a&lt;sup&gt;a&lt;/sup&gt; 296 mg</td>
<td>tert-Butyl 3-ethynylpyrrolo[2,3-b]pyridine-1-carboxylate&lt;sup&gt;b&lt;/sup&gt; 485 mg</td>
<td>5e 491 mg (1.41 mmol) 71 %</td>
<td>PE/EtOAc= 1:1 R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 1:1) = 0.06</td>
</tr>
<tr>
<td>6</td>
<td>2-Chloronicotinic acid&lt;sup&gt;c&lt;/sup&gt; 315 mg</td>
<td>2a 0.23 mL</td>
<td>5f 297 mg (1.23 mmol) 62 %</td>
<td>PE/EtOAc= 7:1 R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 7:1) = 0.16</td>
</tr>
<tr>
<td>7</td>
<td>5-Bromonicotinic acid&lt;sup&gt;c&lt;/sup&gt; 404 mg</td>
<td>2a 0.23 mL</td>
<td>5g 349 mg (1.22 mmol) 61 %</td>
<td>PE/EtOAc = 20:1 R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 20:1) = 0.16</td>
</tr>
</tbody>
</table>
### Table 3 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2 (2.00 mmol)</th>
<th>Ynone 5 (isolated yield)</th>
<th>Chromatographic purification Rf (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5-(4-Fluoro-phenyl)-nicotinic acid[\textsuperscript{c}]</td>
<td>2a</td>
<td>0.23 mL</td>
<td>5h</td>
</tr>
<tr>
<td></td>
<td>4d</td>
<td>495 mg (1.64 mmol)</td>
<td>82 %</td>
<td>PE/EtOAc = 4:1 Rf (PE/EtOAc = 4:1) = 0.25</td>
</tr>
<tr>
<td></td>
<td>313 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>6-Methoxy-nicotinic acid (\textit{Matrix Scientific})</td>
<td>2a</td>
<td>0.23 mL</td>
<td>5i</td>
</tr>
<tr>
<td></td>
<td>4e</td>
<td>197 mg (0.83 mmol)</td>
<td>41 %</td>
<td>PE/EtOAc = 25:1 Rf (PE/EtOAc = 25:1) = 0.13</td>
</tr>
<tr>
<td></td>
<td>313 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dinicotinic acid (\textit{Alfa Aesar})</td>
<td>2a</td>
<td>0.23 mL</td>
<td>5j</td>
</tr>
<tr>
<td></td>
<td>4f</td>
<td>449 mg (1.34 mmol)</td>
<td>67 %[\textsuperscript{d}]</td>
<td>PE/EtOAc = 6:1 Rf (PE/EtOAc = 6:1) = 0.30</td>
</tr>
<tr>
<td></td>
<td>341 mg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>Isonicotinic acid (\textit{Sigma Aldrich})</td>
<td>2a</td>
<td>0.23 mL</td>
<td>5k</td>
</tr>
<tr>
<td></td>
<td>4g</td>
<td>143 mg (0.69 mmol)</td>
<td>35 %</td>
<td>PE/EtOAc = 2:1 Rf (PE/EtOAc = 2:1) = 0.35</td>
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</table>
## Table 3 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2 (2.00 mmol)</th>
<th>Ynone 5 (isolated yield)</th>
<th>Chromatographic purification R&lt;sub&gt;f&lt;/sub&gt; (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>2,6-Dichloroisonicotinic acid (ABCR)&lt;br&gt;4h</td>
<td>2a&lt;br&gt;0.23 mL&lt;br&gt;396 mg</td>
<td>5l&lt;br&gt;379 mg&lt;br&gt;(1.37 mmol)&lt;br&gt;69 %</td>
<td>PE/EtOAc = 50:1&lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 50:1) = 0.19</td>
</tr>
<tr>
<td>13</td>
<td>Pyrimidine-5-carboxylic acid&lt;sup&gt;[c]&lt;/sup&gt;&lt;br&gt;4i</td>
<td>2a&lt;br&gt;0.23 mL&lt;br&gt;248 mg</td>
<td>5m&lt;br&gt;242 mg&lt;br&gt;(1.16 mmol)&lt;br&gt;58 %</td>
<td>PE/EtOAc = 4:1&lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 4:1) = 0.20</td>
</tr>
<tr>
<td>14</td>
<td>Quinoline-3-carboxylic acid (Alfa Aesar)&lt;br&gt;4j</td>
<td>2a&lt;br&gt;0.23 mL&lt;br&gt;353 mg</td>
<td>5n&lt;br&gt;425 mg&lt;br&gt;(1.65 mmol)&lt;br&gt;83 %</td>
<td>PE/EtOAc = 6:1&lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 6:1) = 0.24</td>
</tr>
<tr>
<td>15</td>
<td>Quinoline-4-carboxylic acid (Maybridge)&lt;br&gt;4k</td>
<td>2a&lt;br&gt;0.23 mL&lt;br&gt;357 mg</td>
<td>5o&lt;br&gt;505 mg&lt;br&gt;(1.98 mmol)&lt;br&gt;98 %</td>
<td>PE/EtOAc = 6:1&lt;br&gt;R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 6:1) = 0.22</td>
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</table>
### Table 3 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2 (2.00 mmol)</th>
<th>Ynone 5 (isolated yield)</th>
<th>Chromatographic purification</th>
<th>R&lt;sub&gt;f&lt;/sub&gt; (eluent)</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>2-Phenyl-quinoline-4-carboxylic acid&lt;sup&gt;[cl]&lt;/sup&gt; 4l</td>
<td>2a 0.23 mL</td>
<td>5p 584 mg (1.75 mmol) 88 %</td>
<td>PE/EtOAc = 25:1</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 25:1) = 0.20</td>
</tr>
<tr>
<td></td>
<td>499 mg</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>17</td>
<td>Cinnoline-4-carboxylic acid (Sigma Aldrich) 4m</td>
<td>2a 0.23 mL</td>
<td>5q 134 mg (0.52 mmol) 26 %</td>
<td>PE/EtOAc = 4:1</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 4:1) = 0.21</td>
</tr>
<tr>
<td></td>
<td>359 mg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td>1-Methylindole-2-carboxylic acid (Acros Organics) 4n</td>
<td>2a 0.23 mL</td>
<td>5r 190 mg (0.73 mmol) 37 %</td>
<td>PE/EtOAc = 30:1</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 30:1) = 0.19</td>
</tr>
<tr>
<td></td>
<td>350 mg</td>
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<tr>
<td>19</td>
<td>2-Methyl-pyrazole-3-carboxylic acid (ABCR) 4o</td>
<td>2a 0.23 mL</td>
<td>5s 168 mg (0.80 mmol) 40 %</td>
<td>PE/EtOAc = 20:1</td>
<td>R&lt;sub&gt;f&lt;/sub&gt; (PE/EtOAc = 20:1) = 0.09</td>
</tr>
<tr>
<td></td>
<td>363 mg</td>
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Table 3 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid 4 (2.00 mmol)</th>
<th>Alkyne 2a (2.00 mmol)</th>
<th>Ynone 5t (isolated yield)</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1-Methylindazole-3-carboxylic acid (Alfa Aesar)</td>
<td>2a</td>
<td>0.23 mL</td>
<td>PE/EtOAc = 5:1</td>
</tr>
<tr>
<td></td>
<td>4p</td>
<td></td>
<td>325 mg</td>
<td>Rf (PE/EtOAc = 5:1) = 0.18</td>
</tr>
<tr>
<td></td>
<td>363 mg</td>
<td></td>
<td>(1.25 mmol)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Nalidixic acid (Sigma Aldrich)</td>
<td>2a</td>
<td>0.23 mL</td>
<td>PE/EtOAc = 3:1</td>
</tr>
<tr>
<td></td>
<td>4q</td>
<td></td>
<td>117 mg</td>
<td>Rf (PE/EtOAc = 3:1) = 0.07</td>
</tr>
<tr>
<td></td>
<td>464 mg</td>
<td></td>
<td>(0.37 mmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 %</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>4-Oxo-chromene-2-carboxylic acid (Acros Organics)</td>
<td>2a</td>
<td>0.23 mL</td>
<td>PE/EtOAc = 6:1</td>
</tr>
<tr>
<td></td>
<td>4r</td>
<td></td>
<td>470 mg</td>
<td>Rf (PE/EtOAc = 6:1) = 0.22</td>
</tr>
<tr>
<td></td>
<td>392 mg</td>
<td></td>
<td>(1.06 mmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53%</td>
<td></td>
</tr>
</tbody>
</table>

[a] 2.00 equivs. of triethylamine in the 2nd reaction step

[b] The alkyne 2e was prepared by Sonogashira coupling of tert-butyl 3-iodopyrrolo[2,3-b]pyridine-1-carboxylate with trimethylsilylacetylene. The trimethylsilyl group was removed by adding tetra-n-butylammonium fluoride solution (1 M in THF, Aldrich).

[c] The carboxylic acid was prepared in the laboratories of Merck Serono KGaA, Darmstadt.

[d] Differing from the general procedure 0.36 mL (4.00 mmol, 2.00 equivs.) of (COCl)_2, 56 mg PdCl_2(PPh_3)_2 (0.08 mmol, 4 mol %), 30 mg Cul (0.16 mmol, 8 mol %), 0.46 mL (4.00 mmol, 2.00 equivs.) of phenylacetylene 2a, and 1.65 mL (12.0 mmol, 6.00 equivs.) of triethylamine were used.
4. Preparation of heterocyclic yrones

4.2 Spectroscopic data of compounds 5a-u

4.2.1 3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one (5a)

\[
\text{C}_{14}\text{H}_{9}\text{NO}
\]

207.23

377 mg (1.82 mmol, 91 % yield) as a pale brown solid. Mp 73 °C. ¹H-NMR (CDCl₃, 300 MHz): δ 7.40-7.60 (m, 4 H), 7.65-7.74 (m, 2 H), 8.34-8.48 (m, 1 H), 8.80-8.88 (m, 1 H), 9.40-9.47 (m, 1 H). ¹³C-NMR (CDCl₃, 75 MHz): δ 86.6 (Cₙ), 95.1 (Cₙ), 119.9 (Cₙ), 123.9 (CH), 129.1 (CH), 131.6 (CH), 132.5 (Cₙ), 133.6 (CH), 136.6 (CH), 151.7 (CH), 154.5 (CH), 176.7 (Cₙ). El + MS (m/z (%)): 208 ((M+H)⁺, 7), 207 (M⁺, 46), 206 (12), 179 ((M-CO)⁺, 29), 178 ((M-CO-H)⁺, 14), 130 (10), 129 (C₉H₅O⁺, 100), 101 (C₈H₆⁺, 8), 75 (12). IR (KBr): ν 3063 (w) cm⁻¹, (w), 2200 (s), 1650 (s), 1584 (s), 1488 (m), 1443 (m), 1421 (s), 1328 (s), 1304 (s), 1215 (s), 1193 (m), 1156 (w), 1115 (m), 1080 (w), 1044 (s), 1030 (m), 1014 (m), 995 (s), 918 (w), 838 (w), 820 (w), 756 (s), 719 (s), 694 (m), 684 (s), 636 (m), 616 (m), 533 (m). Anal. calc'd. for C₁₄H₉NO (207.2): C 81.14, H 4.38, N 6.76. Found: C 80.94, H 4.53, N 6.59.


Mp 73-75 °C. ¹H-NMR (CDCl₃, 400 MHz) δ 7.42-7.54 (m, 4 H), 7.69-7.71 (dd, J = 8.2, 1.4 Hz, 2 H), 8.42-8.45 (m, 1 H), 8.84-8.86 (dd, J = 4.8, 1.6 Hz, 1 H), 9.45 (t, J = 0.8, 1 H). ¹³C-NMR δ 86.4, 94.8, 119.6, 123.7, 128.9, 131.4, 132.3, 133.4, 136.3, 151.5, 154.3, 176.5. HRMS Calcd. for C₁₄H₉NO: 207.0684; Found: 207.0689.
4.2.2 1-(Pyridin-3-yl)hept-2-yne-1-one (5b)

274 mg (1.46 mmol, 73 % yield) as an orange oil. $^1$H-NMR (CDCl$_3$, 500 MHz): δ 0.93 (t, $J = 7.3$ Hz, 3 H), 1.47 (sext, $J = 7.6$ Hz, 2 H), 1.64 (quin, $J = 7.3$ Hz, 2 H), 2.50 (t, $J = 7.3$ Hz, 2 H), 7.40 (ddd, $J = 8.2$ Hz, $J = 5.0$ Hz, $J = 0.5$ Hz, 1 H), 8.31 (dt, $J = 7.9$ Hz, $J = 1.9$ Hz, 1 H), 8.77 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 9.30 (d, $J = 1.6$ Hz, 1 H). $^{13}$C-NMR (CDCl$_3$, 125 MHz): δ 13.8 (CH$_3$), 19.2 (CH$_2$), 22.4 (CH$_2$), 30.0 (CH$_2$), 79.5 (C$_{quat}$), 99.0 (C$_{quat}$), 123.7 (CH), 132.5 (C$_{quat}$), 136.5 (CH), 151.8 (CH), 154.3 (CH), 176.9 (C$_{quat}$). EI + MS (m/z (%)): 187 (M$^+$, 5), 186 (20), 172 ((M-CH$_3$)$^+$, 10), 159 ((M-CO)$^+$, 23), 158 ((M-CO-H)$^+$, 49), 146 (29), 145 ((M-CO-CH$_3$+H)$^+$, 100), 144 ((M-CO-CH$_3$)$^+$, 14), 131 (14), 130 ((M-CO-C$_2$H$_5$)$^+$, 22), 117 (18), 116 ((M-CO-C$_3$H$_7$)$^+$, 9), 109 ((M-C$_5$H$_4$N)$^+$, 42), 106 (62), 90 (10), 89 (11), 79 (C$_5$H$_5$N$^+$, 50), 78 (C$_5$H$_4$N$^+$, 40), 77 (11), 53 (16), 51 (19), 43 (10), 41 (13). IR (ATR): $\tilde{\nu}$ 2959 (w) cm$^{-1}$, 2934 (w), 2872 (w), 2251 (w), 1645 (s), 1584 (s), 1572 (w), 1464 (w), 1416 (m), 1327 (w), 1267 (s), 1234 (w), 1194 (w), 1125 (w), 1084 (w), 1024 (w), 984 (w), 961 (w), 910 (m), 845 (w), 826 (w), 721 (s), 698 (m), 625 (w). Anal. calcd. for C$_{12}$H$_{13}$NO (187.2): C 76.98, H 7.00, N 7.48. Found: C 77.15, H 7.18, N 7.18.
4.2.3 1-(Pyridin-3-yl)-3-[tris(propan-2-yl)silyl]prop-2-yn-1-one (5c)

\[
\begin{align*}
\text{C}_{17}\text{H}_{25}\text{NOSi} \\
287.47
\end{align*}
\]

558 mg (1.94 mmol, 97 % yield) as a colorless oil. \( ^1 \)H-NMR (CDCl\(_3\), 500 MHz): \( \delta \) 1.11-1.22 (m, 21 H), 7.36-7.50 (m, 1 H), 8.36 (dt, \( J = 8.0 \) Hz, \( J = 2.0 \) Hz, 1 H), 8.80 (dd, \( J = 4.8 \) Hz, \( J = 1.7 \) Hz, 1 H), 9.32-9.44 (m, 1 H). \( ^{13} \)C-NMR (CDCl\(_3\), 125 MHz): \( \delta \) 11.4 (CH), 18.9 (CH\(_3\)), 100.5 (C\(_{\text{quat}}\)), 102.5 (C\(_{\text{quat}}\)), 123.8 (CH), 132.4 (C\(_{\text{quat}}\)), 136.5 (CH), 151.7 (CH), 154.4 (CH), 176.2 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 287 (M\(^+\), 2), 245 (21), 244 ((M-C\(_3\)H\(_7\))\(^+\), 100), 217 (9), 216 ((M-CO-C\(_3\)H\(_7\))\(^+\), 45), 202 ((M-C\(_6\)H\(_{13}\))\(^+\), 17), 189 (13), 188 (77), 173 ((M-CO-C\(_6\)H\(_{13}\))\(^+\), 23), 160 ((M-C\(_9\)H\(_{19}\))\(^+\), 13), 158 (11), 156 (11), 142 (10), 130 (M-Si(C\(_3\)H\(_7\))\(^+\), 9), 106 (24), 78 (C\(_5\)H\(_4\)N\(^+\), 21), 75 (11). IR (ATR): \( \tilde{\nu} \) 2943 (w) cm\(^{-1}\), 2866 (w), 2149 (w), 1647 (s), 1584 (m), 1460 (w), 1418 (m), 1248 (s), 1192 (w), 1107 (w), 1076 (w), 1051 (s), 1009 (s), 920 (w), 881 (m), 824 (w), 785 (m), 715 (s), 677 (s), 660 (s), 602 (s). Anal. calcd. for C\(_{17}\)H\(_{25}\)NOSi (287.5): C 71.03, H 8.77, N 4.87. Found: C 70.94, H 8.53, N 4.73.
4.2.4 Bis(pyridin-3-yl)prop-2-yn-1-one (5d)

238 mg (1.14 mmol, 57 % yield) as a pale brown solid. Mp 131 °C. ¹H-NMR (CDCl₃, 300 MHz): δ 7.35-7.42 (m, 1 H), 7.44-7.50 (m, 1 H), 7.96 (dt, J = 7.9 Hz, J = 1.9 Hz, 1 H), 8.40 (dt, J = 8.0 Hz, J = 2.0 Hz, 1 H), 8.70 (dd, J = 4.9 Hz, J = 1.7 Hz, 1 H), 8.84 (dd, J = 4.8 Hz, J = 1.7 Hz, 1 H), 8.87-8.93 (m, 1 H), 9.34-9.45 (m, 1 H). ¹³C-NMR (CDCl₃, 75 MHz): δ 89.0 (Cquat), 90.8 (Cquat), 117.3 (Cquat), 123.7 (CH), 124.0 (CH), 132.2 (Cquat), 136.6 (CH), 140.4 (CH), 151.5 (CH), 151.8 (CH), 153.8 (CH), 154.9 (CH), 176.3 (Cquat). EI + MS (m/z (%)): 208 (M⁺, 65), 207 (19), 180 ((M-CO)⁺, 33), 179 (22), 131 (9), 130 ((M-C₅H₅N)⁺, 100), 102 (17), 77 (14), 75 (13), 74 (10), 51 (11). IR (ATR): ν 2203 (m) cm⁻¹, 1641 (s), 1582 (s), 1479 (m), 1422 (w), 1410 (m), 1329 (m), 1302 (s), 1323 (m), 1192 (m), 1121 (m), 1080 (w), 1047 (w), 1026 (m), 1007 (s), 826 (w), 802 (m), 719 (s), 694 (s), 642 (m). Anal. calcd. for C₁₃H₈N₂O (208.2): C 74.99, H 3.87, N 13.45. Found: C 74.97, H 4.12, N 13.27.
4. Preparation of heterocyclic yrones

4.2.5 tert-Butyl 3-[3-oxo-3-(pyridin-3-yl)prop-1-yn-1-yl]-1H-pyrrolo[2,3-b]-pyridine-1-carboxylate (5e)

![Chemical Structure](image)

C_{20}H_{17}N_{3}O_{3}  
347.37

491 mg (1.41 mmol, 71 % yield) as a pale brown solid. Mp 148 °C. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 1.69 (s, 9 H), 7.35 (dd, \(J = 7.8\) Hz, \(J = 4.8\) Hz, 1 H), 7.49 (dd, \(J = 7.9\) Hz, \(J = 4.8\) Hz, 1 H), 8.13 (dd, \(J = 7.8\) Hz, \(J = 1.5\) Hz, 1 H), 8.19 (s, 1 H), 8.43 (dt, \(J = 8.0\) Hz, \(J = 1.9\) Hz, 1 H), 8.61 (dd, \(J = 4.8\) Hz, \(J = 1.6\) Hz, 1 H), 8.85 (dd, \(J = 4.8\) Hz, \(J = 1.6\) Hz, 1 H), 9.39-9.58 (m, 1 H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 28.4 (CH\textsubscript{3}), 86.2 (C\textsubscript{quat}), 87.7 (C\textsubscript{quat}), 91.1 (C\textsubscript{quat}), 97.9 (C\textsubscript{quat}), 120.1 (CH), 122.9 (C\textsubscript{quat}), 124.0 (CH), 129.1 (CH), 132.5 (CH), 134.6 (CH), 136.4 (C\textsubscript{quat}), 147.0 (C\textsubscript{quat}), 147.3 (CH), 147.9 (C\textsubscript{quat}), 151.8 (CH), 154.6 (CH), 176.2 (C\textsubscript{quat}). EI + MS (m/z (%)): 347 (M\textsuperscript{+}, 2), 248 (17), 247 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}+H\textsuperscript{+}), 100), 246 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2})\textsuperscript{+}, 67), 219 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}-CO\textsuperscript{+}, 52), 218 (19), 19 (12), 191 (10), 170 (11), 169 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}-C\textsubscript{5}H\textsubscript{9}N\textsuperscript{+}, 99), 164 (13), 141 (44), 114 (30), 110 (11), 88 (10), 87 (15), 78 (C\textsubscript{5}H\textsubscript{4}N\textsuperscript{+}, 12), 57 (C\textsubscript{4}H\textsubscript{9}, 66), 56 (15), 51 (10), 44 (14), 41 (26), 39 (12). IR (ATR): \textnu\textsuperscript{max} 2195 (m) cm\textsuperscript{-1}, 1765 (s), 1634 (s), 1584 (w), 1541 (m), 1477 (w), 1412 (m), 1365 (m), 1333 (m), 1296 (s), 1246 (s), 1233 (m), 1182 (m), 1148 (s), 1140 (s), 1096 (m), 1057 (m), 1034 (m), 980 (m), 854 (w), 775 (s), 748 (w), 719 (s), 696 (m), 646 (s), 629 (m), 617 (m). Anal. calcd. for C\textsubscript{20}H\textsubscript{17}N\textsubscript{3}O\textsubscript{3} (347.4): C 69.15, H 4.93, N 12.10. Found: C 69.01, H 5.14, N 12.14.
4.2.6 1-(2-Chloropyridin-3-yl)-3-phenylprop-2-yn-1-one (5f)

297 mg (1.23 mmol, 62 % yield) as a pale brown solid. Mp 72 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 7.37-7.46 (m, 3 H), 7.47-7.55 (m, 1 H), 7.61-7.70 (m, 2 H), 8.34 (dd, $J = 7.1$ Hz, $J = 2.0$ Hz, 1 H), 8.56 (dd, $J = 4.8$ Hz, $J = 2.0$ Hz, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ 88.3 (C$^{\text{quat}}$), 96.1 (C$^{\text{quat}}$), 120.0 (C$^{\text{quat}}$), 122.8 (CH), 129.2 (CH), 131.7 (CH), 133.0 (C$^{\text{quat}}$), 133.6 (CH), 141.1 (CH), 149.9 (C$^{\text{quat}}$), 152.7 (CH), 175.9 (C$^{\text{quat}}$). EI + MS (m/z (%)): 243 ((M$^{(37)\text{Cl}}$)$^+$, 7), 241 ((M$^{(35)\text{Cl}}$)$^+$, 21), 215 ((M$^{(37)\text{Cl}}$-CO)$^+$, 6), 213 ((M$^{(35)\text{Cl}}$-CO)$^+$, 17), 178 ((M-CO-Cl)$^+$, 6), 130 (10), 129 (C$_9$H$_7$O$^+$, 100), 75 (11). IR (ATR): $\tilde{\nu}$ 2195 (m) cm$^{-1}$, 1634 (s), 1572 (m), 1489 (w), 1443 (w), 1400 (m), 1312 (m), 1260 (w), 1088 (s), 1065 (m), 1028 (w), 1015 (m), 995 (m), 822 (m), 750 (s), 710 (m), 681 (s), 658 (m), 627 (m), 619 (m). Anal. calcd. for C$_{14}$H$_8$ClNO (241.7): C 69.58, H 3.34, N 5.80. Found: C 69.33, H 3.55, N 5.54.

Yellowish-brown crystals, mp 69–71 °C (MeOH); $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 8.56 (dd, $^3$J(H5,H6) = 4.7 Hz, $^4$J = 1.9 Hz, 1H, H-6), 8.34 (dd, $^3$J = 7.7 Hz, $^4$J = 1.9 Hz, 1H, H-4), 7.65 (m, 2H, Ph H-2,6), 7.51 (m, 1H, Ph H-4), 7.42 (m, 3H, H-5, Ph H-3,5); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 175.5 (C=O, $^3$J(CO,H4) = 5.3 Hz), 152.3 (C-6, $^1$J(C6,H6) = 183.7 Hz, $^2$J(C6,H5) = 3.8 Hz, $^3$J(C6,H4) = 8.2 Hz), 149.5 (C-2, $^3$J(C2,H4) = 8.8 Hz, $^3$J(C2,H6) = 13.8 Hz, $^4$J(C2,H5) = 1.5Hz), 140.7 (C-4, $^1$J(C4,H4) = 166.2 Hz, $^2$J(C4,H5) = 1.9 Hz, $^3$J(C4,H6) = 6.7 Hz), 132.6 (C-3), 133.2 (Ph C-2,6), 131.3 (Ph C-4), 128.8 (Ph C-3,5), 122.4 (C-5, $^1$J(C5,H5) = 168.2 Hz, $^2$J(C5,H6) = 8.2 Hz), 119.5 (Ph C-1, $^3$J(Ph C1,Ph H3,5) = 8.6 Hz, $^4$J(Ph C1,Ph H4) = 1.4 Hz), 95.7 (COC=CC$_6$H$_5$, $^3$J(C,Ph H2,6) = 5.3 Hz), 87.9 (COC=CC$_6$H$_5$); $^{15}$N-NMR (50 MHz): $\delta$ –70.3 (N-1); IR: 2199 (C≡C), 1636 (C=O) cm$^{-1}$; MS m/z (%): 243/241 (M$^+$, 6/15), 215/213 ([M – C≡O]$^+$, 6/21), 129 ([COC=CC$_6$H$_5$]$^+$, 100), 101 ([C≡CC$_6$H$_5$]$^+$, 13). Calcd. for C$_{14}$H$_8$ClNO: C, 69.58; H, 3.34; N, 5.80. Found: C, 69.59; H, 3.16; N, 5.67.
4. Preparation of heterocyclic ynone 5

4.2.7 1-(5-Bromopyridin-3-yl)-3-phenylprop-2-yn-1-one (5g)

![Chemical Structure](image)

\[C_{14}H_8BrNO\]

349 mg (1.22 mmol, 61 % yield) as a pale brown solid. Mp 127 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.31-7.58 (m, 3 H), 7.59-7.86 (m, 2 H), 8.53 (t, \(J = 2.1\) Hz, 1 H), 8.89 (d, \(J = 2.3\) Hz, 1 H), 9.33 (d, \(J = 1.8\) Hz, 1 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 86.4 (C\(_{\text{quat}}\)), 96.0 (C\(_{\text{quat}}\)), 119.6 (C\(_{\text{quat}}\)), 121.5 (C\(_{\text{quat}}\)), 129.2 (CH), 131.9 (CH), 133.7 (CH), 138.9 (CH), 149.6 (CH), 155.6 (CH), 175.3 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 287 (M\(^{81}\)Br\(^+\), 40), 286 (11), 285 (M\(^{79}\)Br\(^+\), 40), 259 ((M\(^{81}\)Br-CO)\(^+\), 16), 257 ((M\(^{79}\)Br-CO)\(^+\), 15), 206 ((M-Br)\(^+\), 3), 130 (10), 129 (C\(_9\)H\(_5\)O\(^+\), 100), 101 (C\(_8\)H\(_5\)\(^+\), 6), 77 (C\(_6\)H\(_5\)\(^+\), 3), 75 (11). IR (ATR): \(\tilde{\nu}\) 2201 (m) cm\(^{-1}\), 1628 (m), 1570 (w), 1489 (w), 1416 (m), 1290 (m), 1213 (m), 1153 (m), 1140 (w), 1092 (w), 1040 (m), 1013 (m), 964 (w), 928 (w), 905 (w), 839 (m), 764 (s), 739 (s), 685 (s), 660 (m), 619 (m). Anal. calcd. for C\(_{14}\)H\(_8\)BrNO (286.1): C 58.77, H 2.82, N 4.90. Found: C 58.99, H 2.95, N 4.69.
4. Preparation of heterocyclic ynone 5

4.2.8 1-[5-(4-Fluorophenyl)pyridin-3-yl]-3-phenylprop-2-yn-1-one (5h)

![Structure of 1-[5-(4-Fluorophenyl)pyridin-3-yl]-3-phenylprop-2-yn-1-one (5h)](image)

495 mg (1.64 mmol, 82% yield) as a bright yellow solid. Mp 136 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 7.21-7.34 (m, 2 H), 7.45-7.61 (m, 3 H), 7.62-7.71 (m, 2 H), 7.72-7.84 (m, 2 H), 8.59 (t, $J = 2.1$ Hz, 1 H), 9.03-9.12 (m, 1 H), 9.42-9.50 (m, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ 86.8 (C$_{quat}$), 95.4 (C$_{quat}$), 116.8 (d, $J = 21.8$ Hz, CH), 119.8 (C$_{quat}$), 129.2 (CH), 129.4 (d, $J = 8.3$ Hz, CH), 131.7 (CH), 132.6 (C$_{quat}$), 133.0 (d, $J = 3.3$ Hz, C$_{quat}$), 133.7 (CH), 134.2 (CH), 136.2 (C$_{quat}$), 150.5 (CH), 152.8 (CH), 163.7 (d, $J = 249.1$ Hz, C$_{quat}$), 176.6 (C$_{quat}$). El + MS (m/z (%)): 302 (11), 301 (M$^+$, 52), 300 (6), 273 ((M-CO)$^+$, 26), 272 (10), 130 (10), 129 (C$_9$H$_5$O$^+$, 100), 75 (8). IR (ATR): $\bar{v}$ 2197 (m) cm$^{-1}$, 1638 (m), 1605 (w), 1585 (w), 1566 (w), 1512 (m), 1489 (w), 1445 (m), 1431 (m), 1329 (w), 1308 (m), 1271 (m), 1225 (m), 1198 (m), 1155 (m), 1099 (w), 1072 (m), 1018 (m), 995 (m), 860 (w), 833 (s), 812 (m), 758 (s), 745 (s), 702 (m), 685 (s), 673 (m), 617 (m). Anal. calcd. for C$_{20}$H$_{12}$FNO (301.3): C 79.72, H 4.01, N 4.65. Found: C 79.51, H 3.92, N 4.59.
4.2.9 1-(6-Methoxypyridin-3-yl)-3-phenylprop-2-yn-1-one (5i)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{C}_{15}\text{H}_{11}\text{NO}_2 \\
237.25
\end{align*}
\]

197 mg (0.83 mmol, 41 % yield) as a colorless solid. Mp 86 °C. \( ^1 \)H-NMR (CDCl\(_3\), 300 MHz): \( \delta \) 4.04 (s, 3 H), 6.83 (d, \( J = 8.7 \) Hz, 1 H), 7.36-7.54 (m, 3 H), 7.63-7.72 (m, 2 H), 8.29 (dd, \( J = 8.7 \) Hz, \( J = 2.4 \) Hz, 1 H), 9.09 (d, \( J = 2.3 \) Hz, 1 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \( \delta \) 54.6 (CH\(_3\)), 86.7 (C\(_{\text{quat}}\)), 93.6 (C\(_{\text{quat}}\)), 111.7 (CH), 120.3 (C\(_{\text{quat}}\)), 127.5 (C\(_{\text{quat}}\)), 129.1 (CH), 131.3 (CH), 133.5 (CH), 138.8 (CH), 152.1 (CH), 167.8 (C\(_{\text{quat}}\)), 175.8 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 238 (16), 237 (M\(^+\), 100), 236 (76), 209 (10), 208 ((M-CO\(^+\), 39), 207 (14), 180 (23), 178 ((M-C\(_9\)H\(_5\)N\(^+\)), 10), 139 (14), 130 (7), 129 (C\(_9\)H\(_5\)O\(^+\), 68), 75 (13). IR (ATR): \( \tilde{\nu} \) 2195 (s) cm\(^{-1}\), 1632 (s), 1597 (s), 1560 (m), 1495 (m), 1375 (s), 1300 (m), 1285 (s), 1213 (m), 1117 (m), 1032 (m), 1022 (m), 1007 (s), 993 (m), 939 (w), 912 (w), 833 (s), 787 (w), 772 (s), 750 (s), 706 (m), 679 (s), 625 (m), 615 (s). Anal. calcd. for C\(_{15}\)H\(_{11}\)NO\(_2\) (237.3): C 75.94, H 4.67, N 5.90. Found: C 76.00, H 4.83, N 5.81.
4.2.10 3-Phenyl-1-[5-(3-phenylprop-2-ynoyl)pyridin-3-yl]prop-2-yn-1-one (5j)

![Chemical Structure](image.png)

C<sub>23</sub>H<sub>13</sub>NO<sub>2</sub>

335.35

449 mg (1.34 mmol, 67 % yield) as a yellow solid. Mp 153 °C. ¹H-NMR (CDCl₃, 500 MHz): δ 7.35 (tt, J = 7.5 Hz, J = 1.1 Hz, 2 H), 7.39-7.44 (m, 4 H), 7.68-7.72 (m, 4 H), 9.16 (t, J = 2.1 Hz, 1 H), 9.60 (d, J = 2.1 Hz, 2 H). ¹³C-NMR (CDCl₃, 125 MHz): δ 86.5 (C<sub>quat</sub>), 96.2 (C<sub>quat</sub>), 119.6 (C<sub>quat</sub>), 129.2 (CH), 131.9 (CH), 132.4 (C<sub>quat</sub>), 133.7 (CH), 137.4 (CH), 155.0 (CH), 175.6 (C<sub>quat</sub>). El + MS (m/z (%)): 336 (8), 335 (M⁺, 29), 334 (3), 307 ((M-CO)⁺, 4), 280 ((M-C<sub>2</sub>O₂+H)⁺, 1), 279 ((M-C<sub>2</sub>O₂⁺, 6), 130 (9), 129 (C<sub>9</sub>H₅O⁺, 100). IR (ATR): ʋ 3028 (w) cm⁻¹, 2922 (w), 2851 (w), 2199 (m), 2174 (w), 1732 (w), 1636 (s), 1582 (m), 1441 (w), 1423 (w), 1279 (m), 1240 (w), 1165 (m), 1067 (m), 1018 (w), 918 (w), 872 (w), 791 (w), 752 (s), 729 (s), 700 (s), 632 (m), 617 (m). Anal. calcd. for C<sub>23</sub>H<sub>13</sub>NO<sub>2</sub> (335.4): C 82.37, H 3.91, N 4.18. Found: C 82.61, H 4.18, N 4.08.
4.2.11 3-Phenyl-1-(pyridin-4-yl)prop-2-yn-1-one (5k)

\[
\text{C}_{14}\text{H}_9\text{NO}
\]

143 mg (0.69 mmol, 35 % yield) as a pale brown solid. Mp 81 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.40-7.56 (m, 3 H), 7.66-7.74 (m, 2 H), 7.95-8.02 (m, 2 H), 8.84-8.90 (m, 2 H). \(^1^3\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 86.7 (C\(_{\text{quat}}\)), 95.4 (C\(_{\text{quat}}\)), 119.7 (C\(_{\text{quat}}\)), 122.3 (CH), 129.2 (CH), 131.7 (CH), 133.6 (CH), 142.8 (C\(_{\text{quat}}\)), 151.2 (CH), 177.2 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 207 (M\(^+\), 27), 179 ((M-CO)\(^+\), 10), 130 (10), 129 (C\(_8\)H\(_5\)O\(^+\), 100), 101 (C\(_8\)H\(_5\)\(^+\), 6), 75 (8). IR (KBr): \(v\) 2197 (s) cm\(^{-1}\), 1645 (s), 1555 (m), 1491 (w), 1449 (w), 1404 (m), 1324 (m), 1290 (m), 1218 (m), 1200 (m), 1058 (w), 1035 (m), 995 (m), 839 (m), 760 (s), 745 (m), 686 (s), 627 (m), 535 (m). Anal. calcd. for C\(_{14}\)H\(_9\)NO (207.2): C 81.14, H 4.38, N 6.76. Found: C 80.92, H 4.58, N 6.87.


UV (CH\(_2\)Cl\(_2\)): \(\lambda_{\text{max}}\) (\(\epsilon\)) 233 (9300), 301 (7200). IR (CH\(_2\)Cl\(_2\)): 1264, 1421, 1551, 1604, 1650, 1961 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.41 (m, 2H), 7.48 (m, 1H), 7.66 (m, 2H), 7.96 (d, \(J = 5.8\) Hz, 2H), 8.83 (d, \(J = 5.8\) Hz, 2H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 86.2, 95.2, 119.3, 122.1, 128.8, 131.4, 133.3, 142.5, 150.6, 176.7. MS (FAB\(^+\)): m/z 208 [M + H]\(^+\). Anal. Calcd for C\(_{14}\)H\(_9\)NO (207.2): C, 81.14; H, 4.38; N, 6.76. Found: C, 81.02; H, 4.42; N, 6.69%.
4. Preparation of heterocyclic yrones 5

4.2.12 1-(2,6-Dichloropyridin-4-yl)-3-phenylprop-2-yn-1-one (5l)

\[
\text{C}_14\text{H}_7\text{Cl}_2\text{NO}
\]

379 mg (1.37 mmol, 69 % yield) as a pale yellow solid. Mp 121 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.43-7.51 (m, 2 H), 7.52-7.60 (m, 1 H), 7.67-7.74 (m, 2 H), 7.92 (s, 2 H).

\(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 86.3 (C\(_{\text{quat}}\)), 97.1 (C\(_{\text{quat}}\)), 119.2 (C\(_{\text{quat}}\)), 122.3 (CH), 129.2 (CH), 132.3 (CH), 133.9 (CH), 147.8 (C\(_{\text{quat}}\)), 152.2 (C\(_{\text{quat}}\)), 174.0 (C\(_{\text{quat}}\)).

EI + MS (m/z (%)): 279 (M\(^{37}\text{Cl}^{37}\text{Cl})^+, 2), 277 (M\(^{37}\text{Cl}^{35}\text{Cl})^+, 7), 275 (M\(^{35}\text{Cl}^{35}\text{Cl})^+, 13), 251 ((M\(^{37}\text{Cl}^{37}\text{Cl})-\text{CO})^+, 0.4), 249 ((M\(^{37}\text{Cl}^{35}\text{Cl})-\text{CO})^+, 3), 247 ((M\(^{35}\text{Cl}^{35}\text{Cl})-\text{CO})^+, 5), 130 (10), 129 (C\(_6\text{H}_5\text{O}^+\), 100), 101 (C\(_6\text{H}_5^+\), 5), 75 (9). IR (ATR): \(\tilde{\nu}\) 2197 (m) cm\(^{-1}\), 1643 (s), 1578 (w), 1541 (m), 1489 (w), 1443 (w), 1406 (w), 1350 (m), 1296 (s), 1283 (m), 1211 (s), 1175 (w), 1153 (m), 1105 (m), 1074 (w), 1053 (m), 1022 (w), 937 (w), 883 (m), 858 (w), 806 (m), 762 (s), 735 (s), 691 (s), 637 (s). Anal. calcd. for C\(_{14}\)H\(_7\)Cl\(_2\)NO (276.1): C 60.90, H 2.56, N 5.07. Found: C 61.07, H 2.84, N 4.96.
4.2.13 3-Phenyl-1-(pyrimidin-5-yl)prop-2-yn-1-one (5m)

\[
\begin{align*}
O & \quad \equiv \\
\text{Ph} & \\
\text{C}_{13}\text{H}_8\text{N}_2\text{O} & \\
208.22
\end{align*}
\]

242 mg (1.16 mmol, 58 % yield) as a pale yellow solid. Mp 99 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.40-7.49 (m, 2 H), 7.50-7.58 (m, 1 H), 7.66-7.74 (m, 2 H), 9.08-9.83 (m, 3 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 86.1 (C\(_{\text{quat}}\)), 96.7 (C\(_{\text{quat}}\)), 119.4 (C\(_{\text{quat}}\)), 129.3 (CH), 130.1 (C\(_{\text{quat}}\)), 132.1 (CH), 133.8 (CH), 158.1 (CH), 162.1 (CH), 174.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 208 (M\(^+\), 43), 207 (28), 181 ((M-CO+H\(^+\), 12), 180 ((M-CO)\(^+\), 21), 153 (11), 130 (10), 129 (C\(_8\)H\(_5\)O\(^+\), 100), 126 (24), 101 (C\(_9\)H\(_5\)\(^+\), 8), 75 (12). IR (ATR): \(\nu\) 2197 (m) cm\(^{-1}\), 1632 (s), 1574 (s), 1557 (m), 1487 (w), 1433 (m), 1408 (m), 1348 (w), 1300 (m), 1221 (m), 1196 (m), 1113 (m), 1043 (m), 1009 (m), 993 (m), 925 (w), 827 (w), 764 (s), 731 (s), 712 (m), 689 (s), 632 (s), 621 (m). Anal. calcd. for C\(_{13}\)H\(_8\)N\(_2\)O (208.2): C 74.99, H 3.87, N 13.45. Found: C 74.99, H 4.07, N 13.21.
4.2.14 3-Phenyl-1-(quinolin-3-yl)prop-2-yn-1-one (5n)

302 mg (1.18 mmol, 59 % yield) as a pale brown solid. Mp 125 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): δ 7.40-7.58 (m, 3 H), 7.62-7.70 (m, 1 H), 7.70-7.78 (m, 2 H), 7.84-7.93 (m, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 8.21 (d, J = 8.2 Hz, 1 H), 8.97 (s, 1 H), 9.62-9.68 (m, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): δ 86.6 (C$_\text{quat}$), 95.1 (C$_\text{quat}$), 112.0 (C$_\text{quat}$), 127.1 (C$_\text{quat}$), 128.2 (CH), 129.2 (CH), 129.7 (C$_\text{quat}$), 129.8 (CH), 130.0 (CH), 131.6 (CH), 133.0 (CH), 133.6 (CH), 139.5 (CH), 149.9 (CH), 150.3 (C$_\text{quat}$), 176.6 (C$_\text{quat}$). EI + MS (m/z (%)): 258 (18), 257 (M$^+$, 91), 256 (31), 229 ((M-CO)$^+$, 41), 228 (26), 155 (10), 130 (10), 129 (C$_9$H$_5$O$^+$, 100), 128 (C$_9$H$_6$N$^+$, 9), 127 (15), 114 (23), 101 (C$_8$H$_5^+$, 27), 75 (18), 43 (13). IR (ATR): ν 2195 (w) cm$^{-1}$, 1651 (m), 1609 (m), 1585 (m), 1568 (m), 1487 (m), 1443 (w), 1410 (w), 1287 (w), 1271 (w), 1180 (w), 1086 (w), 1007 (m), 986 (s), 951 (w), 897 (w), 822 (m), 772 (m), 750 (s), 687 (s), 646 (w). Anal. calcd. for C$_{18}$H$_{11}$NO (257.3): C 84.03, H 4.31, N 5.44. Found: C 83.94, H 4.28, N 5.41.
4.2.15 3-Phenyl-1-(quinolin-4-yl)prop-2-yn-1-one (5o)

354 mg (1.37 mmol, 69 % yield) as a pale brown solid. Mp 93 °C. \( ^1 \)H-NMR (CDCl\(_3\), 300 MHz): \( \delta \) 7.38-7.56 (m, 3 H), 7.65-7.76 (m, 3 H), 7.76-7.85 (m, 1 H), 8.16-8.28 (m, 2 H), 8.98 (d, \( J = 9.0 \) Hz, 1 H), 9.16 (d, \( J = 9.2 \) Hz, 1 H). \( ^{13} \)C-NMR (CDCl\(_3\), 75 MHz): \( \delta \) 88.4 (C_{quat}), 94.1 (C_{quat}), 119.9 (C_{quat}), 124.3 (C_{quat}), 124.4 (CH), 125.9 (CH), 129.1 (CH), 129.4 (CH), 130.3 (CH), 131.6 (CH), 133.6 (CH), 139.9 (C_{quat}), 149.6 (C_{quat}), 150.3 (CH), 179.3 (C_{quat}). EI + MS (m/z (%)): 258 (13), 257 (M\(^+\), 74), 256 (49), 229 ((M-CO\(^+\), 31), 228 (36), 202 (33), 201 (14), 200 (11), 130 (10), 129 (C\(_9\)H\(_5\)O\(^+\), 100), 114 (18), 101 (C\(_9\)H\(_5\)\(^+\), 26), 100 (12), 75 (22). IR (KBr): \( \nu \) 3045 (w) cm\(^{-1}\), 2199 (s), 1638 (s), 1578 (m), 1506 (m), 1492 (m), 1460 (m), 1443 (m), 1349 (w), 1288 (s), 1210 (w), 1162 (m), 1141 (w), 1108 (s), 1069 (m), 963 (m), 930 (w), 878 (w), 858 (m), 789 (m), 774 (s), 759 (s), 688 (s), 629 (m), 620 (m), 570 (w), 538 (m), 514 (w). Anal. calcld. for C\(_{18}\)H\(_{11}\)NO (257.3): C 84.03, H 4.31, N 5.44. Found: C 83.86, H 4.40, N 5.51.


UV (CH\(_2\)Cl\(_2\)): \( \lambda_{\text{max}} (\varepsilon) \) 230 (25200), 309 (13200). IR (CH\(_2\)Cl\(_2\)): 1605, 2354, 3679 cm\(^{-1}\).

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.43-7.47 (m, 2H), 7.50 (m, 1H), 7.69-7.74 (m, 3H), 7.78-7.83 (m, 1H), 8.21 (d, \( J = 8.5 \) Hz, 1H), 8.25 (d, \( J = 4.4 \) Hz, 1H), 8.98 (d, \( J = 8.5 \) Hz, 1H), 9.15 (d, \( J = 4.4 \) Hz, 1H). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 88.2, 93.8, 119.7, 124.1, 125.7, 128.9, 129.1, 130.2, 131.4, 133.3, 139.7, 149.4, 150.1, 179.1. MS (FAB\(^+\)): m/z 258 [M+H\(^+\)]. Anal. Calcd for C\(_{18}\)H\(_{11}\)NO: C, 84.03; H, 4.31; N, 5.44. Found: C, 84.11; H, 4.23; N, 5.49%.
4.2.16 3-Phenyl-1-(2-phenylquinolin-4-yl)prop-2-yn-1-one (5p)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \\
C_{24}H_{15}NO & \quad 333.38
\end{align*}
\]

584 mg (1.75 mmol, 88 % yield) as a yellow solid. Mp 101 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.41-7.63 (m, 6 H), 7.64-7.75 (m, 3 H), 7.77-7.84 (m, 1 H), 8.22-8.30 (m, 3 H), 8.72 (s, 1 H), 8.95 (dd, \(J = 8.5\) Hz, \(J = 0.9\) Hz, 1 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\delta\) 88.6 (C\(_{\text{quat}}\)), 94.2 (C\(_{\text{quat}}\)), 120.0 (C\(_{\text{quat}}\)), 122.6 (CH), 123.3 (C\(_{\text{quat}}\)), 125.7 (CH), 127.8 (CH), 129.0 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 130.6 (CH), 130.7 (CH), 131.7 (CH), 133.7 (CH), 139.2 (C\(_{\text{quat}}\)), 141.0 (C\(_{\text{quat}}\)), 149.8 (C\(_{\text{quat}}\)), 157.2 (C\(_{\text{quat}}\)), 179.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 334 (29), 333 (M\(^+\), 100), 332 (38), 305 (M-CO\(^+\), 38), 304 (89), 303 (11), 256 (M-C\(_6\)H\(_5\))\(^+\), 5), 203 (12), 202 (47), 152 (11), 151 (11), 130 (5), 129 (C\(_9\)H\(_5\)O\(^+\), 47). IR (ATR): \(\tilde{\nu}\) 2922 (w) cm\(^{-1}\), 2197 (m), 1645 (m), 1580 (w), 1543 (w), 1491 (m), 1443 (w), 1333 (m), 1288 (m), 1269 (m), 1236 (m), 1219 (m), 1163 (m), 1139 (m), 1101 (s), 1063 (w), 1026 (w), 999 (w), 951 (m), 887 (w), 757 (s), 756 (s), 731 (m), 685 (s), 667 (m), 629 (m), 617 (m). Anal. calcd. for C\(_{24}\)H\(_{15}\)NO (333.4): C 86.46, H 4.54, N 4.20. Found: C 86.35, H 4.75, N 4.11.
4.2.17 1-(Cinnolin-4-yl)-3-phenylprop-2-yn-1-one (5q)

C<sub>17</sub>H<sub>10</sub>N<sub>2</sub>O  
258.27

134 mg (0.52 mmol, 26 % yield) as a yellow solid. Mp 131 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.41-7.60 (m, 3 H), 7.70-7.79 (m, 2 H), 7.91-8.01 (m, 2 H), 8.63-8.74 (m, 1 H), 9.01-9.10 (m, 1 H), 10.04 (s, 1 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): δ 87.9 (C<sub>quat</sub>), 95.6 (C<sub>quat</sub>), 119.5 (C<sub>quat</sub>), 121.9 (C<sub>quat</sub>), 125.1 (CH), 126.0 (C<sub>quat</sub>), 129.3 (CH), 131.1 (CH), 131.5 (CH), 132.1 (CH), 133.9 (CH), 134.6 (CH), 145.5 (CH), 152.1 (C<sub>quat</sub>), 178.4 (C<sub>quat</sub>). EI + MS (m/z (%)): 259 (7), 258 (M<sup>+</sup>, 39), 230 (M-CO<sup>+</sup>)<sup>+</sup>, 2), 202 (12), 130 (10), 129 (C<sub>9</sub>H<sub>6</sub>O<sup>+</sup>, 100), 101 (10), 75 (11). IR (ATR): ν 3057 (w) cm<sup>-1</sup>, 2201 (m), 1632 (m), 1522 (w), 1497 (w), 1443 (w), 1377 (w), 1302 (m), 1182 (w), 1163 (m), 1115 (m), 1061 (m), 980 (w), 930 (w), 777 (s), 750 (s), 685 (s), 633 (m). Anal. calcd. for C<sub>17</sub>H<sub>10</sub>N<sub>2</sub>O (258.3): C 79.06, H 3.90, N 10.85. Found: C 78.92, H 4.00, N 10.83.
4.2.18  1-(1-Methyl-1H-indol-2-yl)-3-phenylprop-2-yn-1-one (5r)

![Chemical Structure](image)

C\textsubscript{18}H\textsubscript{13}NO  
259.30

190 mg (0.73 mmol, 37 % yield) as a yellow solid. Mp 97 °C. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 4.13 (s, 3 H), 7.12-7.24 (m, 1 H), 7.32-7.56 (m, 5 H), 7.60-7.83 (m, 4 H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 32.5 (CH\textsubscript{3}), 88.3 (C\textsubscript{quat}), 90.0 (C\textsubscript{quat}), 110.8 (CH), 116.8 (CH), 120.8 (C\textsubscript{quat}), 121.4 (CH), 123.7 (CH), 126.3 (C\textsubscript{quat}), 127.2 (CH), 129.0 (CH), 130.9 (CH), 133.3 (CH), 136.5 (C\textsubscript{quat}), 141.4 (C\textsubscript{quat}), 170.0 (C\textsubscript{quat}). EI + MS (m/z (%)): 260 (19), 259 (M\textsuperscript{+}, 100), 258 (47), 231 ((M-CO)\textsuperscript{+}, 19), 230 (79), 201 (11), 182 (17), 154 (20), 143 (18), 142 (18), 130 (6), 129 (C\textsubscript{9}H\textsubscript{5}O\textsuperscript{+}, 28), 128 (14), 116 (14), 115 ((M-C\textsubscript{9}H\textsubscript{5}O-CH\textsubscript{3})\textsuperscript{+}, 41), 102 (10), 101 (C\textsubscript{8}H\textsubscript{5}\textsuperscript{+}, 11), 89 (16). IR (ATR): \(\tilde{\nu}\) 2197 (m) cm\textsuperscript{-1}, 1603 (s), 1506 (m), 1466 (m), 1423 (m), 1395 (m), 1273 (m), 1186 (m), 1146 (w), 1128 (s), 1096 (w), 1028 (m), 1015 (m), 993 (s), 818 (w), 756 (s), 737 (s), 685 (s), 644 (m). Anal. calcd. for C\textsubscript{18}H\textsubscript{13}NO (259.3): C 83.37, H 5.05, N 5.40. Found: C 83.38, H 5.28, N 5.30.
4.2.19 1-(1-Methyl-1H-pyrazol-5-yl)-3-phenylprop-2-yn-1-one (5s)

\[
\begin{align*}
\text{O} & \quad \text{Ph} \\
\text{C}_13\text{H}_{10}\text{N}_2\text{O} & \quad 210.23
\end{align*}
\]

168 mg (0.80 mmol, 40 % yield) as a pale yellow solid. Mp 107 °C. \(^1\)H-NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 4.21 (s, 3 H), 7.13 (d, \(J = 2.1\) Hz, 1 H), 7.36-7.55 (m, 4 H), 7.60-7.68 (m, 2 H). \(^{13}\)C-NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 40.5 (CH\textsubscript{3}), 87.7 (C\textsubscript{quat}), 91.8 (C\textsubscript{quat}), 115.2 (CH), 120.1 (C\textsubscript{quat}), 129.1 (CH), 131.4 (CH), 133.4 (CH), 138.3 (CH), 139.9 (C\textsubscript{quat}), 167.4 (C\textsubscript{quat}). EI + MS (\(m/z\) %): 211 (3), 210 (M\textsuperscript{+}, 25), 209 (47), 182 ((M-CO)\textsuperscript{+}, 6), 181 (8), 154 (23), 130 (3), 129 (C\textsubscript{9}H\textsubscript{5}O\textsuperscript{+}, 25). IR (ATR): \(\tilde{\nu}\) 2199 (m) cm\textsuperscript{-1}, 1643 (s), 1503 (m), 1489 (w), 1462 (m), 1441 (m), 1422 (m), 1395 (w), 1314 (m), 1296 (m), 1269 (m), 1209 (m), 1157 (w), 1069 (m), 1024 (w), 982 (s), 926 (m), 806 (m), 791 (m), 762 (s), 745 (3), 719 (m), 689 (s), 637 (m). Anal. calcd. for C\textsubscript{13}H\textsubscript{10}N\textsubscript{2}O (210.2): C 74.27, H 4.79, N 13.33. Found: C 74.00, H 4.94, N 13.33.


Mp. 76.5-77.5 °C, Anal. calcd.: C 74.06, H 4.61, N 13.44. Found: C 74.27, H 4.79, N 13.44. \(^1\)H NMR: \(\delta\) 4.08 (s, 3H, CH\textsubscript{3}), 6.73 (d, 1H, C\textsuperscript{4}H), 7.59 (d, 1H, C\textsuperscript{3}H), 7.53-7.57 and 8.12-8.22 (m, 5H, Ph).
4. Preparation of heterocyclic ynone 5

4.2.20 1-(1-Methyl-1H-indazol-3-yl)-3-phenylprop-2-yn-1-one (5t)

\[ \text{C}_{17}\text{H}_{12}\text{N}_{2}\text{O} \]

325 mg (1.25 mmol, 62 % yield) as a pale brown solid. Mp 83 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 4.22 (s, 3 H), 7.32-7.52 (m, 6 H), 7.70-7.78 (m, 2 H), 8.40 (dt, $J = 8.1$ Hz, $J = 1.0$ Hz, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ 37.0 (CH$_3$), 88.1 (C$_{\text{quat}}$), 92.1 (C$_{\text{quat}}$), 109.8 (CH), 120.9 (C$_{\text{quat}}$), 122.9 (CH), 123.4 (C$_{\text{quat}}$), 124.4 (CH), 127.6 (CH), 128.9 (CH), 130.9 (CH), 133.5 (CH), 141.6 (C$_{\text{quat}}$), 143.2 (C$_{\text{quat}}$), 172.6 (C$_{\text{quat}}$). EI + MS (m/z (%)): 261 (18), 260 (M$^+$, 90), 233 ((M-CO+H)$^+$, 14), 232 ((M-CO)$^+$, 82), 231 (48), 130 (11), 129 (C$_9$H$_5$O$^+$, 100), 116 (C$_7$H$_4$N$_2$$^+$, 22), 101 (C$_8$H$_5^+$, 15), 94 (17), 93 (29), 77 (10), 75 (18). IR (ATR): $\tilde{\nu}$ 2195 (w) cm$^{-1}$, 1607 (m), 1474 (m), 1443 (w), 1423 (m), 1391 (m), 1304 (m), 1275 (w), 1242 (m), 1150 (m), 1084 (s), 1042 (m), 1005 (w), 961 (m), 799 (m), 777 (s), 746 (s), 691 (s), 644 (m), 629 (s). Anal. calcd. for C$_{17}$H$_{12}$N$_2$O (260.3): C 78.44, H 4.65, N 10.76. Found: C 78.22, H 4.56, N 10.88.
4.2.21 1-Ethyl-7-methyl-3-(3-phenylprop-2-ynoyl)-1,4-dihydro-1,8-naphthyridin-4-one (5u)

![Chemical structure of 1-Ethyl-7-methyl-3-(3-phenylprop-2-ynoyl)-1,4-dihydro-1,8-naphthyridin-4-one (5u)](image)

C_{20}H_{16}N_{2}O_{2}

$\text{m/z (\%)}$: 317 (23), 316 (M$^+$, 100), 315 (5), 288 ((M-CO)$^+$, 25), 287 (19), 273 ((M-CO-CH$_3$)$^+$, 22), 261 (11), 260 (57), 259 (21), 245 (16), 232 (15), 231 (11), 144 (14), 129 (C$_3$H$_5$O$^+$, 14). IR (ATR): $\tilde{\nu}$ 2193 (m) cm$^{-1}$, 1641 (s), 1614 (m), 1591 (s), 1568 (m), 1531 (s), 1489 (m), 1439 (s), 1369 (m), 1337 (s), 1300 (m), 1263 (m), 1252 (m), 1221 (m), 1173 (s), 1157 (m), 1115 (s), 1061 (s), 1042 (s), 997 (m), 930 (m), 791 (s), 770 (s), 748 (s), 691 (s), 656 (s), 619 (m). Anal. calcd. for C$_{20}$H$_{16}$N$_2$O$_2$ (316.4): C 75.93, H 5.10, N 8.86. Found: C 75.82, H 5.31, N 8.64.
4.2.22 2-(3-Phenylprop-2-ynoyl)-4'H-chromen-4-one (5v)

![Chemical structure of 2-(3-Phenylprop-2-ynoyl)-4'H-chromen-4-one (5v)]

C_{18}H_{10}O_{3}

274.27

470 mg (1.06 mmol, 53 % yield) as a yellow solid. Mp 153 °C. $^1$H-NMR (CDCl$_3$, 300 MHz): δ 7.34 (s, 1 H), 7.42-7.59 (m, 4 H), 7.62-7.81 (m, 4 H), 8.22 (dd, $J = 8.0$ Hz, $J = 1.7$ Hz, 1 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): δ 81.1 (C$_{quat}$), 97.0 (C$_{quat}$), 116.1 (CH), 119.2 (C$_{quat}$), 119.3 (CH), 125.0 (C$_{quat}$), 126.2 (CH), 126.5 (CH), 129.3 (CH), 132.3 (CH), 133.9 (CH), 135.5 (CH), 156.1 (C$_{quat}$), 156.8 (C$_{quat}$), 171.2 (C$_{quat}$), 179.1 (C$_{quat}$). EI + MS (m/z (%)): 276 (2), 275 (4), 274 (M$^+$, 15), 246 ((M-CO)$^+$, 10), 130 (9), 129 (C$_9$H$_5$O$^+$, 100), 75 (7). IR (ATR): ν 2922 (w) cm$^{-1}$, 2851 (w), 2193 (m), 1641 (s), 1614 (m), 1570 (w), 1462 (m), 1443 (w), 1396 (m), 1335 (w), 1308 (m), 1271 (m), 1219 (w), 1180 (w), 1121 (s), 1049 (s), 997 (m), 961 (w), 930 (w), 856 (m), 777 (m), 752 (s), 685 (s), 671 (m). Anal. calcd. for C$_{18}$H$_{10}$O$_3$ (274.3): C 78.82, H 3.67. Found: C 78.71, H 3.76.
5 Preparation of 2-acylpyrazoles 7

5.1 General procedure

2.00 mmol of glyoxylic acid 1 in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. CuI (20 mg, 0.10 mmol, 5 mol %), phenylacetylene (2a) (0.23 mL, 2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 24 h. Afterwards, tert-butyl carbazate (267 mg, 2.00 mmol, 1.00 equiv.) and 2 mL of 2-methoxyethanol were added. This mixture was stirred for 24 h at 100 °C (preheated oil bath). After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the N-Boc protected acylpyrazoles 6 as pale brown solids which were used as obtained in the subsequent step.
For deprotection the N-Boc protected acylpyrazoles 6 were dissolved in methanol (0.2 M), 2.5 equivs. of potassium carbonate were added, and the mixture was stirred for 2 h at 50 °C (preheated oil bath). After complete deprotection (monitored by TLC) the mixture was adsorbed on Celite® and chromatographed on silica gel with dichloromethane (DCM)/methanol/aqueous ammonia to give 2-acylpyrazoles 7.

The experimental details for the synthesis of the 2-acylpyrazoles 7 are given in Table 4.

Table 4. Experimental details for the synthesis of 2-acylpyrazoles 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylic acid</th>
<th>2-Acylpyrazole 7 (isolated yield)</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenylglyoxylic acid (Merck) 1a</td>
<td>306 mg 7a (0.81 mmol) 201 mg (41%)</td>
<td>DCM/methanol/aqueous ammonia = 100:1:1</td>
</tr>
<tr>
<td>2</td>
<td>Mesiylglyoxylic acid (ABCR) 1b</td>
<td>388 mg 7b (0.80 mmol) 232 mg (41%)</td>
<td>DCM/methanol/aqueous ammonia = 100:1:1</td>
</tr>
</tbody>
</table>
Table 4 (Continuation).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylic acid</th>
<th>2-Acylpyrazole 7</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>(isolated yield)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(2.00 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2-Thiophenyl</td>
<td></td>
<td>DCM/methanol/aqueous ammonia = 100:1:1&lt;sup&gt;[a]&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>glyoxylic acid</td>
<td>7c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Alpha Aesar)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>319 mg</td>
<td>256 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.08 mmol)</td>
<td>(1.08 mmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Additionally purified by dissolving in hydrogen chloride solution in ethanol (1.25 M, Fluka).
5.2 Spectroscopic data of compounds 7a-c

5.2.1 5-Benzoyl-3-phenyl-1H-pyrazole (7a)

![Structure of 5-Benzoyl-3-phenyl-1H-pyrazole (7a)](image)

201 mg (0.81 mmol, 41 % yield) as a colorless solid. Mp 167-170 °C. 1H-NMR (DMSO-d$_6$, 200 MHz, 100 °C): $\delta$ 6.71-6.81 (m, 1 H), 6.85-7.25 (m, 6 H), 7.33-7.44 (m, 2 H), 7.52-7.88 (m, 2 H), 13.2 (brs, NH). El + MS (m/z (%)): 249 (19), 248 (M$^+$, 100), 247 (3), 220 (11), 219 (13), 191 (10), 171 ((M-C$_6$H$_5$)$^+$, 14), 149 (10), 114 (13), 105 (C$_7$H$_5$O$^+$, 58), 77 (C$_6$H$_5^+$, 50), 71 (13), 57 (12). IR (KBr): $\tilde{v}$ 3223 (m) cm$^{-1}$, 1719 (w), 1636 (s), 1573 (m), 1492 (w), 1466 (m), 1397 (m), 1277 (m), 1257 (m), 1183 (m), 1065 (w), 1025 (w), 960 (w), 901 (m), 831 (m), 798 (m), 764 (m), 729 (s), 686 (m), 512 (w). Anal. calcd. for C$_{16}$H$_{12}$N$_2$O (248.3): C 77.40, H 4.87, N 11.28. Found: C 77.20, H 5.04, N 11.06.


Mp 174-175 °C. 1H NMR (CDCl$_3$): $\delta$ 14.01 (bs, NH), multipletts near 7-8 ppm due to aromatic protons are omitted. IR (KBr): $\tilde{v}$ 3221 cm$^{-1}$ (NH), 1636 (C=O), 1397, 1256 (pyrazole ring). Anal. calcd.: C 77.40, H 4.87, N 11.28. Found: C 77.31, H 4.84, N 11.44.
5.2.2  3-Phenyl-5-[(2,4,6-trimethylphenyl)carbonyl]-1H-pyrazole (7b)

\[
\begin{align*}
\text{C}_{19}\text{H}_{18}\text{N}_{2}\text{O} \\
290.36
\end{align*}
\]

232 mg (0.80 mmol, 41 % yield) as a colorless solid. Mp 71 °C. \(^1\)H-NMR (DMSO-d\(_6\), 200 MHz, 100 °C): \(\delta\) 1.65 (s, 6 H), 1.85 (s, 3 H), 6.47 (s, 2 H), 6.54 (s, 1 H), 6.80-7.12 (m, 3 H), 7.27-7.41 (m, 2 H), 13.2 (brs, NH). EI + MS (m/z (%)): 291 (19), 290 (M\(^+\), 100), 289 (30), 273 (21), 262 ((M-CO)\(^+\), 23), 261 (24), 247 (14), 187 (17), 172 (17), 158 (22), 157 (15), 147 (C\(_{10}\)H\(_{11}\)O\(^+\), 20), 146 (24), 145 (12), 144 (26), 119 (C\(_9\)H\(_{11}\)\(^+\), 26), 117 (18), 116 (15), 115 (24), 104 (16), 103 (13), 91 (36), 77 (C\(_6\)H\(_5\)\(^+\), 25), 43 (14).

IR (KBr): \(\tilde{\nu}\) 1661 (m) cm\(^{-1}\), 1611 (w), 1462 (m), 1429 (m), 1398 (m), 1375 (m), 1273 (w), 1242 (m), 1177 (m), 1142 (w), 1061 (w), 1032 (w), 1016 (w), 961 (w), 953 (w), 883 (s), 849 (m), 829 (m), 762 (s), 739 (m), 691 (s), 627 (m). Anal. calcd. for C\(_{19}\)H\(_{18}\)N\(_2\)O (290.4): C 78.59, H 6.25, N 9.65. Found: C 78.53, H 6.44, N 9.41.
5.2.3 3-Phenyl-5-[thiophen-2-yl]carbonyl]-1H-pyrazole (7c)

\[
\begin{align*}
\text{O} & \quad \begin{array}{c} \text{HN-N} \\ \text{Ph} \end{array} \\
\text{C}_{14}H_{10}N_{2}OS & \quad 254.31
\end{align*}
\]

256 mg (1.08 mmol, 54 % yield) as a colorless solid. Mp 187 °C. $^1$H-NMR (DMSO-d$_6$, 200 MHz, 100 °C): $\delta$ 6.63-6.87 (m, 2 H), 6.87-7.06 (m, 3 H), 7.27-7.42 (m, 2 H), 7.42-7.58 (m, 1 H), 7.91 (brs, 1 H), 13.30 (brs, 1 H). EI + MS (m/z (%)): 256 (6), 255 (17), 254 (M$^+$, 100), 253 (8), 226 ((M-CO)$^+$, 7), 225 (6), 171 (15), 123 (11), 115 (13), 114 (49), 113 (10), 111 (C$_5$H$_3$OS$^+$, 90), 83 (C$_4$H$_3$S$^+$, 12), 77 (C$_6$H$_5^+$, 10). IR (ATR): $\tilde{\nu}$ 3204 (w) cm$^{-1}$, 2980 (w), 2361 (w), 1603 (m), 1516 (w), 1472 (w), 1396 (w), 1258 (w), 1192 (w), 1155 (w), 997 (w), 961 (w), 914 (w), 858 (w), 820 (s), 772 (m), 756 (s), 716 (s), 680 (s), 673 (m), 642 (w), 617 (w). Anal. calcd. for C$_{14}$H$_{10}$N$_2$OS (254.3): C 66.12, H 3.96, N 11.02. Found: C 65.89, H 4.13, N 11.27.
6 Preparation of 2-phenylaminopyrimidines 8

6.1 General procedure

2.00 mmol of carboxylic acid 1 in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. PdCl$_2$(PPh$_3$)$_2$ (28 mg, 0.04 mmol, 2 mol %), Cul (15 mg, 0.08 mmol, 4 mol %), trimethylsilylacetylene ($ABCR$) (2f) (0.27 mL, 2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 1 h. Afterwards, 1-(2-methylphenyl)guanidinium nitrate$^{[a]}$ (424 mg, 2.00 mmol, 1.00 equiv.), potassium carbonate (698 mg, 5.00 mmol, 2.50 equivs.), and 2 mL of 2-methoxyethanol were added. This mixture was stirred for 24 h at 120 °C (preheated oil bath). After complete conversion the residue was adsorbed on Celite$^\circledR$ and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia to give 2-phenylaminopyrimidines 8 as analytically pure compounds.

The experimental details for the synthesis of 2-phenylaminopyrimidines 8 are given in Table 5.
Table 5. Experimental details for the synthesis of 2-phenylaminopyrimidines 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid</th>
<th>2-Phenylaminopyrimidine 8</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-Pyridyl carboxylic acid sodium salt (ABCR)</td>
<td><img src="image" alt="8a" /></td>
<td>DCM/methanol/aqueous ammonia = 100:1:1</td>
</tr>
<tr>
<td></td>
<td>296 mg</td>
<td>279 mg</td>
<td>(1.06 mmol)</td>
</tr>
<tr>
<td>2</td>
<td>2,6-Dichloroisonicotinic acid (ABCR)</td>
<td><img src="image" alt="8b" /></td>
<td>DCM/methanol/aqueous ammonia = 100:1:1</td>
</tr>
<tr>
<td></td>
<td>396 mg</td>
<td>282 mg</td>
<td>(0.85 mmol)</td>
</tr>
</tbody>
</table>

[a] 2.00 equivs. of triethylamine in the 2<sup>nd</sup> reaction step
6.2 Spectroscopic data of compounds 8a-b

6.2.1 *N*-(2-Methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (8a)

![Chemical structure of 8a]

279 mg (1.06 mmol, 53 % yield) as an orange solid. Mp 84 °C. \(^1\)H-NMR (CDCl\(_3\), 300 MHz): δ 2.36 (s, 3 H), 7.01-7.12 (m, 2 H), 7.14 (d, \(J = 5.2\) Hz, 1 H), 7.20-7.32 (m, 2 H), 7.36-7.44 (m, 1 H), 8.07 (d, \(J = 8.1\) Hz, 1 H), 8.29-8.37 (m, 1 H), 8.49 (d, \(J = 5.2\) Hz, 1 H), 8.67-8.74 (m, 1 H), 9.23-9.29 (m, 1 H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz):

\(\delta\) 18.5 (CH\(_3\)), 108.4 (CH), 122.3 (CH), 124.0 (CH), 124.2 (CH), 127.0 (CH), 129.2 (C\(_{\text{quat}}\)), 130.9 (CH), 133.0 (C\(_{\text{quat}}\)), 134.8 (CH), 137.6 (C\(_{\text{quat}}\)), 148.9 (CH), 151.8 (CH), 159.5 (CH), 161.2 (C\(_{\text{quat}}\)), 162.9 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 263 (12), 262 (M\(^+\), 66), 261 (49), 248 (18), 247 ((M-CH\(_3\)-H)+, 100), 246 (21), 130 (11). IR (ATR): \(\tilde{\nu}\) 1591 (m) cm\(^{-1}\), 1557 (s), 1530 (m), 1483 (m), 1445 (s), 1373 (m), 1333 (m), 1319 (m), 1287 (m), 1240 (m), 1196 (m), 1140 (w), 1120 (w), 1107 (w), 1080 (w), 1024 (m), 989 (w), 935 (w), 853 (w), 791 (s), 748 (s), 718 (s), 702 (s), 642 (s), 613 (m). Anal. calcd. for C\(_{16}\)H\(_{14}\)N\(_4\) (262.3): C 73.26, H 5.38, N 21.36. Found: C 73.19, H 5.60, N 21.16.


\(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ ppm 2.26 (s, 3 H), 7.19-7.26 (m, 2 H), 7.41 (d, \(J=5.2\) Hz, 1 H), 7.52-7.57 (m, 2 H), 8.38-8.42 (m, 1 H), 8.50 (d, \(J=5.0\) Hz, 1 H), 8.70 (dd, \(J=4.8, 1.8\) Hz, 1 H), 8.94 (s, 1 H), 9.25 (dd, \(J=2.3, 0.7\) Hz, 1 H). MS (ESI) m/z 263.1.
6.2.2 4-(2,6-Dichloropyridin-4-yl)-N-(2-methylphenyl)pyrimidin-2-amine (8b)

C_{16}H_{12}Cl_{2}N_{4}  
331.20

282 mg (0.85 mmol, 43 % yield) as a yellow solid. Mp 155 °C. ^1H-NMR (DMSO-d$_6$, 300 MHz): δ 2.25 (s, 3 H), 7.05-7.15 (m, 1 H), 7.15-7.30 (m, 2 H), 7.45-7.60 (m, 2 H), 8.13 (s, 2 H), 8.59 (m, 1 H), 9.12 (s, 1 H). ^13C-NMR (DMSO, 75 MHz): δ 18.1 (CH$_3$), 108.3 (CH), 120.7 (CH), 124.8 (CH), 125.2 (CH), 125.9 (CH), 130.3 (CH), 132.5 (C$_{quat}$), 137.5 (C$_{quat}$), 150.2 (C$_{quat}$), 150.5 (C$_{quat}$), 160.4 (CH), 161.2 (C$_{quat}$). El + MS (m/z (%)): 333 ((M($^{37}$Cl$^{37}$Cl)-H)$^+$, 12), 332 ((M($^{37}$Cl$^{35}$Cl)$^+$, 39), 331 ((M($^{37}$Cl$^{35}$Cl)-H)$^+$, 37), 330 (M($^{35}$Cl$^{35}$Cl)$^+$, 61), 329 ((M($^{35}$Cl$^{35}$Cl)-H)$^+$, 45), 319 ((M($^{37}$Cl$^{37}$Cl)-CH$_3$)$^+$, 11), 318 ((M($^{37}$Cl$^{35}$Cl)-CH$_3$-H)$^+$, 14), 317 ((M($^{37}$Cl$^{35}$Cl)-CH$_3$)$^+$, 64), 316 ((M($^{37}$Cl$^{35}$Cl)-CH$_3$-H)$^+$, 33), 315 ((M($^{35}$Cl$^{35}$Cl)-CH$_3$)$^+$, 100), 314 ((M($^{35}$Cl$^{35}$Cl)-CH$_3$-H)$^+$, 24), 165 (10), 164 (11), 132 (14), 130 (10), 129 (15), 116 (16), 106 (C$_7$H$_8$N$^+$, 17), 104 (12), 91 (C$_7$H$_7^+$, 16), 89 (12), 77 (C$_6$H$_5^+$, 17), 65 (C$_5$H$_5^+$, 13), 43 (13). IR (ATR): ν 2920 (w) cm$^{-1}$, 1601 (w), 1570 (w), 1528 (w), 1487 (w), 1452 (s), 1400 (m), 1373 (m), 1354 (m), 1321 (w), 1285 (w), 1271 (w), 1252 (m), 1238 (m), 1196 (w), 1171 (m), 1146 (s), 1111 (w), 1049 (w), 1020 (w), 874 (m), 793 (s), 741 (s), 714 (m), 689 (m), 652 (m), 615 (w). Anal. calcd. for C$_{16}$H$_{12}$Cl$_2$N$_4$ (331.2): C 58.02, H 3.65, N 16.92. Found: C 57.80, H 3.77, N 16.75.
7. 1H- and 13C-NMR Spectra of compounds 3a-g

$^1$H-NMR (500 MHz) of 3a (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
7. 1H- and 13C-NMR Spectra of compounds 3a-g

13C-NMR (125 MHz) of 3a (30 mg) in CDCl₃ at 295 K (δ in ppm).

13C-DEPT 135-NMR (125 MHz) of 3a (30 mg) in CDCl₃ at 295 K (δ in ppm).
$^1$H-NMR (300 MHz) of 3b (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm).
13C-NMR (75 MHz) of 3b (30 mg) in CDCl₃ at 295 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 3b (30 mg) in CDCl₃ at 295 K (δ in ppm).
$^1$H-NMR (500 MHz) of 3c (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C-NMR (125 MHz) of 3c (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C-DEPT 135-NMR (125 MHz) of 3c (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H-NMR (300 MHz) of 3d (30 mg) in CDCl$_3$ at 294 K ($\delta$ in ppm). *Impurities from residual solvents.
13C-NMR (75 MHz) of 3d (30 mg) in CDCl₃ at 295 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 3d (30 mg) in CDCl₃ at 296 K (δ in ppm).
$^1$H-NMR (500 MHz) of 3e (30 mg) in CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
7. 1H- and 13C-NMR Spectra of compounds 3a-g

13C-NMR (125 MHz) of 3e (30 mg) in CDCl$_3$ at 297 K ($\delta$ in ppm).

13C-DEPT 135-NMR (125 MHz) of 3e (30 mg) in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H-NMR (300 MHz) of 3f (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
1H- and 13C-NMR Spectra of compounds 3a-g

13C-NMR (75 MHz) of 3f (30 mg) in CDCl₃ at 295 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 3f (30 mg) in CDCl₃ at 295 K (δ in ppm).
$^1$H-NMR (300 MHz) of 3g (30 mg) in CDCl$_3$ at 295 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C-NMR (75 MHz) of 3g (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C-DEPT 135-NMR (75 MHz) of 3g (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm).
$^1$H-NMR (500 MHz) of 5a (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (125 MHz) of 5a (30 mg) in CDCl₃ at 296 K (δ in ppm).

13C-DEPT 135-NMR (125 MHz) of 5a (30 mg) in CDCl₃ at 296 K (δ in ppm).
$^1$H-NMR (500 MHz) of 5b (30 mg) in CDCl$_3$ at 299 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C-NMR (125 MHz) of 5b (30 mg) in CDCl$_3$ at 299 K (δ in ppm).

$^{13}$C-DEPT 135-NMR (125 MHz) of 5b (30 mg) in CDCl$_3$ at 299 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5c (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
13C-NMR (75 MHz) of 5c (30 mg) in CDCl$_3$ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5c (30 mg) in CDCl$_3$ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5d (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
13C-NMR (75 MHz) of 5d (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5d (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5e (30 mg) in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C-NMR (75 MHz) of 5e (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C-DEPT 135-NMR (75 MHz) of 5e (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H-NMR (300 MHz) of 5f (30 mg) in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5f (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5f (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5g (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
13C-NMR (75 MHz) of 5g (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5g (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5h (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5h (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5h (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5i (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^{13}$C-NMR (75 MHz) of 5i (30 mg) in CDCl$_3$ at 298 K (δ in ppm).

$^{13}$C-DEPT 135-NMR (75 MHz) of 5i (30 mg) in CDCl$_3$ at 298 K (δ in ppm).
$^1$H-NMR (500 MHz) of 5j (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
13C-NMR (125 MHz) of 5j (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (125 MHz) of 5j (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5k (30 mg) in CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
13C-NMR (75 MHz) of 5k (30 mg) in CDCl₃ at 297 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5k (30 mg) in CDCl₃ at 297 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5I (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$\text{13C-NMR (75 MHz) of 5l (30 mg) in CDCl}_3 \text{ at 298 K (}\delta\text{ in ppm).}$

$\text{13C-DEPT 135-NMR (75 MHz) of 5l (30 mg) in CDCl}_3 \text{ at 298 K (}\delta\text{ in ppm).}$
$^1$H-NMR (300 MHz) of 5m (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
\[ \text{\textsuperscript{13}C-DEPT 135-NMR (75 MHz) of 5m (30 mg) in CDCl}_3 \text{ at 298 K (\(\delta\) in ppm).} \]
$^1$H-NMR (300 MHz) of 5n (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5n (30 mg) in CDCl₃ at 295 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5n (30 mg) in CDCl₃ at 296 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5o (30 mg) in CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

\[\text{\(13\)C-NMR (75 MHz) of } 5o \text{ (30 mg) in CDCl}_3 \text{ at 297 K (\(\delta\) in ppm).}\]

\[\text{\(13\)C-DEPT 135-NMR (75 MHz) of } 5o \text{ (30 mg) in CDCl}_3 \text{ at 297 K (\(\delta\) in ppm).}\]
$^1$H-NMR (300 MHz) of 5p (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C-NMR (75 MHz) of 5p (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C-DEPT 135-NMR (75 MHz) of 5p (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
\(^1\)H-NMR (300 MHz) of 5q (30 mg) in CDCl\(_3\) at 298 K (\(\delta\) in ppm). *Impurities from residual solvents.
\[ \text{\(^{13}\)C-NMR (75 MHz) of 5q (30 mg) in CDCl}_3 \text{ at 298 K (\(\delta\) in ppm).} \]

\[ \text{\(^{13}\)C-DEPT 135-NMR (75 MHz) of 5q (30 mg) in CDCl}_3 \text{ at 298 K (\(\delta\) in ppm).} \]
"\(^1\)H-NMR (300 MHz) of 5r (30 mg) in CDCl\(_3\) at 298 K (\(\delta\) in ppm). *Impurities from residual solvents."
8. 1H- and 13C-NMR Spectra of compounds 5a-u

1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5r (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5r (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5s (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
13C-NMR (75 MHz) of 5s (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5s (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5t (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5t (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5t (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5u (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
8. 1H- and 13C-NMR Spectra of compounds 5a-u

13C-NMR (75 MHz) of 5u (30 mg) in CDCl₃ at 298 K (δ in ppm).

13C-DEPT 135-NMR (75 MHz) of 5u (30 mg) in CDCl₃ at 298 K (δ in ppm).
$^1$H-NMR (300 MHz) of 5v (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
1H- and 13C-NMR Spectra of compounds 5a-u

$1^3$C-NMR (75 MHz) of 5v (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).

$1^3$C-DEPT 135-NMR (75 MHz) of 5v (30 mg) in CDCl$_3$ at 298 K ($\delta$ in ppm).
9. 1H- and 13C-NMR Spectra of compounds 7a-c

$^1$H-NMR (200 MHz) of 7a (30 mg) in DMSO-$d_6$ at 373 K (δ in ppm). *Impurities from residual solvents.
$^1$H-NMR (200 MHz) of 7b (30 mg) in DMSO-d$_6$ at 373 K ($\delta$ in ppm). *Impurities from residual solvents.
$^1$H-NMR (200 MHz) of 7c (30 mg) in DMSO-$_6$ at 373 K ($\delta$ in ppm).
10 $^1$H- and $^{13}$C-NMR Spectra of compounds 8a-b

$^1$H-NMR (300 MHz) of 8a (30 mg) in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
10. 1H- and 13C-NMR Spectra of compounds 8a-b

\[ \text{CDCl}_3 \]

\[ 13\text{C-NMR (75 MHz) of } 8a \text{ (30 mg) in CDCl}_3 \text{ at 296 K (}\delta \text{ in ppm).} \]

\[ 13\text{C-DEPT 135-NMR (75 MHz) of } 8a \text{ (30 mg) in CDCl}_3 \text{ at 296 K (}\delta \text{ in ppm).} \]
$^1$H-NMR (300 MHz) of 8b (30 mg) in DMSO-d$_6$ at 298 K (δ in ppm). *Impurities from residual solvents.
10. 1H- and 13C-NMR Spectra of compounds 8a-b

13C-NMR (75 MHz) of 8b (30 mg) in DMSO-d$_6$ at 298 K ($\delta$ in ppm).

13C-DEPT 135-NMR (75 MHz) of 8b (30 mg) in DMSO-d$_6$ at 298 K ($\delta$ in ppm).
11 Full Reference


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Consecutive One-Pot Sonogashira–Glaser Coupling Sequence – Direct Preparation of Symmetrical Diynes by Sequential Pd/Cu Catalysis

Eugen Merkul,[a] Dominik Urselmann,[a] and Thomas J. J. Müller*[a]

Dedicated to Prof. Dr. Henning Hopf on the occasion of his 70th birthday

Keywords: Alkynes / C–C coupling / Copper / Multicomponent reactions / Palladium

Sonogashira coupling and the catalytic Glaser coupling are both catalyzed by the Pd–Cu complex couple and can be concatenated to a consecutive sequentially Pd/Cu-catalyzed process in a one-pot fashion, and air oxygen serves as the only oxidant in the second step. In a pseudo-four-component synthesis, a broad variety of symmetrically substituted 1,4-bis(hetero)aryl-1,3-butadiynes are obtained in good to excellent yields. Interestingly, the presence of iodide ions has been found to be advantageous over other halides to trigger the Pd/Cu-catalyzed Glaser step, and Pd and Cu species, as well as triethylamine as a base, are prerequisite for both couplings, which proceed with higher efficiency if performed in a one-pot sequence.

Introduction

1,4-Disubstituted 1,3-butadiynes are recurring building blocks in natural products and analogues,[1] molecular electronic devices,[2] or optical materials[3] and serve as intermediates in the synthesis of a variety of heterocycles.[4] Traditionally, copper(I)- or copper(II)-catalyzed Glaser,[5] Eglington,[6] or Hay[7] coupling reactions and their numerous modifications[8] utilizing terminal alkynes as substrates are applied for the synthesis of symmetrical 1,3-diynes. Even more efficient transformations rely on catalytic systems consisting of combined palladium(0) or palladium(II) and copper(I) sources.[9] Recently, a ligand-, palladium-, amine- and even oxidant-free procedure, which uses copper nanoparticles as a catalyst, has been reported.[8a] Despite numerous efficient strategies developed for Glaser-type acetylene dimerizations,[10] the major drawback of utilizing terminal alkynes as substrates is their sensitivity towards polymerization and their occasionally tedious purification. Moreover, some of the terminal alkynes proved to be quite unstable, which limits their shelf life and complicates their synthesis. Therefore, a synthetic route that avoids the isolation of these compounds would be highly desirable.

In the past years some methodologies for the preparation of 1,3-butadiynes starting from alkynyltrifluoroborates,[11a] alkynylboronates,[11b] or alkynylsilanes[11c–11e] have been published. Although these transformations avoid the use of free terminal alkynes, they still require the application of sophisticated organoboron or organosilicon substrates.

A reliable, quick and general approach to generate terminal alkynes starting from easily available (hetero)aryl halides employs the Pd/Cu-cocatalyzed Sonogashira–Hagihara cross coupling, followed by subsequent deprotection.[12] Since this catalytic system matches with the conditions of the Glaser-type couplings mentioned above,[9] the development of a sequentially catalyzed route for the synthesis of 1,4-disubstituted 1,3-butadiynes utilizing the same catalyst couple for alkylation and oxidative coupling lies at hand (Scheme 1). The isolation of intermediate terminal alkynes becomes dispensable. To the best of our knowledge, this obvious and straightforward concept has never been realized.

Scheme 1. Concept of a Sonogashira–Glaser coupling sequence.

Concatenating the Sonogashira and the Glaser coupling reactions into a one-pot sequence is especially advantageous from an economical point of view but also because of practical considerations. Herein, we report a sequence of a Pd/Cu-cocatalyzed Sonogashira coupling of iodo arenes with trimethylsilylacetylene (TMSA), followed by in-situ cleavage of the silyl protective group and subsequent Glaser-type homocoupling of the generated terminal alkynes.
to form symmetrical 1,4-disubstituted 1,3-butadiynes under aerobic conditions in a one-pot fashion. This resulting sequence represents another unique showcase for sequentially Pd/Cu-catalyzed processes.$^{[13]}$

**Results and Discussion**

At the outset of our investigations, we reacted iodo-benzene (1a) with TMSA (1.5 equiv.) under standard Sonogashira conditions [PdCl₂(PPh₃)₂, CuI, and NEt₃] as a base$^{[14]}$ to form trimethyl(phenylethynyl)silane in a smooth reaction within 1 h at ambient temperature. After the reaction vessel was opened, potassium fluoride and methanol were added to cleave the TMS protective group. Simultaneously, upon subjecting to aerobic atmosphere and further stirring at room temperature, the Glaser-type coupling proceeded smoothly. The desired 1,4-diphenylbuta-1,3-diyne (2a) was isolated in 81% yield [Equation (1)].

\[
\text{Ph} \equiv \equiv \equiv \text{Ph} \quad (1)
\]

To gain insight into the mode of action of the catalytic system in the final Glaser coupling step, we subjected commercially available phenylacetylene to different combinations of precatalysts and additives used for the entire sequence to form the diyne 2a in a single step [Equation (2), Table 1].

\[
\text{Ph} \equiv \equiv \equiv \text{Ph} \quad (2)
\]

**Table 1. Influence of precatalysts and additives in the Glaser-type coupling step.$^{[a]}$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time [h]</th>
<th>Yield of 2a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no additives</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>no PdCl₂(PPh₃)₂, no additives</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>no CuI, no additives</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>1.0 equiv. KF</td>
<td>26</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>1.0 equiv. NH₄Cl</td>
<td>26</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>1.0 equiv. NaBr</td>
<td>26</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>1.0 equiv. NaI</td>
<td>26</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1.0 equiv. NaI, no NEt₃</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>1.0 equiv. NaI, no CuI</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>1.0 equiv. NaI, no PdCl₂(PPh₃)₂</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

[a] All reactions were carried out on a 2-mmol scale with 2 mol-% PdCl₂(PPh₃)₂, 4 mol-% CuI, and NEt₃ (1.0 equiv.) in a mixture of THF (5 mL) and methanol (5 mL). The mixture was stirred at room temperature for the indicated time. The conditions were varied or adjusted by additives as indicated. [b] Yield of isolated and purified compound 2a.

Whilst use of Cu¹ iodide as a single catalyst gave only very low amounts of the desired compound 2a (Entry 2), application of the palladium precatalyst led to the formation of an increased amount of diyne 2a (Entry 3). Upon combination of both precatalysts, a slight increase in the isolated yield of product 2a could be observed (Entry 1). Another experiment, which uses 2 mol-% PdCl₂(PPh₃)₂, 4 mol-% CuI, and 1.5 equiv. KF starting from commercially available trimethyl(phenylethynyl)silane, gave 55% of diyne 2a within 28 h of reaction time. This implies that no fluorosilane complexes are involved in the transmetalation step. Surprisingly, the yields of the Glaser coupling step alone were much lower than those from the complete sequence, which additionally includes Sonogashira and deprotection steps. Bearing in mind that the apparent difference between the conditions applied in the sequence and in the separated Glaser coupling step is the generation of 1 equiv. triethylammonium iodide in the Sonogashira coupling step, we scrutinized the influence of halide anions on the Glaser coupling step. Thus, upon addition of 1.0 equiv. potassium fluoride, the yield of the isolated diyne 2a increased dramatically relative to the yield obtained without additives (Entries 1 and 4). Furthermore, the yield continuously increased from fluoride (82%) through chloride (86%) and bromide (92%) to iodide (95%) (Entries 4–7). To the best of our knowledge, the effect of halide anions on the Glaser coupling has neither been observed nor investigated. Although the reason for this behavior is not clear at this stage, the high yield obtained by the addition of iodide may explain the high efficiency of the developed sequence, since ammonium iodide generated in the Sonogashira step could promote the Glaser coupling step. Moreover, this preliminary investigation shows that the catalytic system PdCl₂(PPh₃)₂/CuI/NEt₃ is essential for both Sonogashira and Glaser coupling reactions to proceed efficiently, since the absence of one of these components diminishes the yield dramatically (Entries 8–10). These findings clearly emphasize the benefits of combining Sonogashira and Glaser couplings into a one-pot sequence.

The presented sequence is preparatively strikingly simple and utilizes commercially available and stable reagents and precatalysts without fancy ligands or additives. The use of air as an oxidant additionally supports the sustainable aspect of the method (Scheme 2). With these mild conditions for the sequence in hand, the substrate scope was examined and a novel pseudo-four-component synthesis of symmetrical 1,3-butadiynes 2 was established (Figure 1). All reactions were carried out on a 2-mmol scale with respect to (hetero)aryl iodide 1. The structures of compounds 2 were unambiguously supported by combustion analysis, NMR spectroscopy, and mass spectrometry.
The substituent pattern of the obtained 1,4-bis(hetero)aryl-1,3-butadiynes 2 (Figure 1) clearly supports that the precursor (hetero)aryl halides 1 can be electroneutral, electron rich, as well as electron poor. Substituents in the ortho-, meta- and para position, as well as the higher-substituted trimethoxyphenyl group or the dimethyluracil derivative, are tolerated. Overall, a large variety of functional groups in the (hetero)aryl iodides 1, such as halides, nitro, cyano, ester, amide, carbamate, urea, and, even unprotected hydroxy and amino groups, can be carried through the sequence without difficulties. The functional group tolerance and the possibility to react different types of electronically diverse six- and five-membered heterocyclic iodides are remarkable for such a simple sequence. In most cases, the isolated target compounds 2 are stable crystalline solids that can be conveniently purified by column chromatography or recrystallization. The crude reaction mixtures obtained by the described sequence showed no notable amounts of by-products in the TLC in nearly all examples mentioned above. Thus, isolation of the desired 1,3-butadiynes 2 turned out to be remarkably quick and easy. It should be noted that the reaction times (see Supporting Information, Table S2) are not optimized and might be considerably shorter than indicated. The yields of the isolated diynes 2 are fair to excellent regardless of the electronic nature or substituent pattern of the applied iodides. The whole sequence is performed at ambient temperature. Indeed, many applications in medicinal chemistry and material science can be envisioned.

By considering the results obtained from our preliminary studies (vide supra), the mechanistic rationale of this Sonogashira–Glaser coupling sequence can be outlined as follows (Scheme 3). In the Sonogashira cycle, driven by the catalytic Pd⁰/CuI pair, the cross-coupling of (hetero)aryl iodides 1 and trimethylsilane (TMS) affords the corresponding (hetero)aryltrimethylsilanes 2. The subsequent functionalization of 2 with CuI and F⁻ in the presence of base NEt₃ yields the (hetero)arylfluorides 3. Finally, the Glaser cycle, driven by the catalytic Pd⁰/CuI pair in the presence of O₂ and H⁺, converts the (hetero)arylfluorides 3 into the (hetero)arylbutadiynes 2.
dide 1 and TMSA furnishes the TMS-protected (hetero)aryl alkyne 3, which is deprotected with fluoride to give the corresponding terminal alkyne 4. Alkyne 4 (2 equiv.) now enters the Glaser cycle, which is triggered by the catalytic PdII/CuI pair. CuI ions are involved in transmetalation to PdI, and thus a dialkynyl PdII complex is generated, which furnishes the desired 1,3-butadiyne 2 on reductive elimination. Moreover, CuI is readily oxidized to CuII by atmospheric oxygen. In analogy to the Wacker oxidation,[15] an intercepting CuII/CuI cycle fueled by oxygen is ultimately responsible for reoxidizing PdII back to PdI. Interestingly, the same mechanism that leads to the unwanted by-product of the Sonogashira coupling in the initial activation step[16] now becomes the modus operandi to form the desired diynes 2.

Conclusions

In conclusion, we have disclosed a general, efficient and economical sequentially Pd/Cu-catalyzed one-pot reaction for transforming (hetero)aryl iodides into symmetrical 1,4-disubstituted 1,3-butadiynes. The commercially available or easily accessible starting materials,[17] the wide range of tolerated functional groups, and the simplicity of the described sequence render it a practical method for routine applications. Methodological extension to aryl bromides and chlorides as substrates and studies taking advantage of the versatility of 1,3-butadiynes in a variety of catalytic and non-catalytic conversions are currently under investigation.

Experimental Section

Synthesis of 2m: A mixture of methyl 2-iodobenzoate (1m) (535 mg, 2.00 mmol), PdCl2(PPh3)2 (28 mg, 0.04 mmol, 2 mol-%) and CuI (16 mg, 0.08 mmol, 4 mol-%) was dissolved in dry degassed THF (5.00 mL) in a screw-cap Schlenk vessel with septum. After addition of TMSA (0.43 mL, 3.00 mmol) and dry triethylamine (0.55 mL, 4.00 mmol), the solution was stirred at room temperature (water bath) for 1 h until complete conversion (monitored by TLC). KF (236 mg, 4.00 mmol) and methanol (5.00 mL) were then added, and the reaction mixture was stirred in air (the reaction vessel was opened) for 22 h. After completion of the reaction, as indicated by TLC, the mixture was filtered and adsorbed on Celite®, and after removal of the solvents in vacuo, the residue was purified by column chromatography on silica gel by using petroleum ether (boiling range 40–60 °C)/ethyl acetate = 10:1 as eluent to give, after drying in vacuo, 1,4-bis(2-methylbenzyl)buta-1,3-diyne (2m) (296 mg; 93%) as a yellow oil. Upon suspension in anisole, sonication in ultrasound bath, filtration and drying in vacuo, 1,4-bis(2-methylbenzoyl)buta-1,3-diyne (2m) was obtained. M.p. 59–60 °C.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for the compounds prepared are presented.

Acknowledgments

The authors cordially thank Merck Serono KGaA, Darmstadt for the financial support of this research.


[14] Although numerous precatalysts have been described for the Sonogashira-type reactions, this standard catalytic system is still by far the most-widely used one. For a recent review, see: R. Chinchilla, C. Nájera, Chem. Rev. 2007, 107, 874–922.


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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using MBraun system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

tert-Butyl 3-iodo-1H-indole-1-carboxylate (1u)\(^1\) and tert-butyl 4-iodo-2-(4-methoxy-phenyl)-1H-pyrrole-1-carboxylate (1v)\(^2\), 1-benzyl-5-iodo-1H-imidazole (1x)\(^3\) and 2-ethyl-3-iodo-5-(thiophen-2-yl)furan (1z)\(^4\) were prepared according to the literature procedures. Commercial grade reagents were used as supplied without further purification and were purchased from Sigma-Aldrich Chemie GmbH, Fluka AG, ABCR GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, Riedel-de Haën, EGA-Chemie-Gesellschaft, and Merck Serono KGaA. Trimethylsilylacetylene (TMSA) and potassium fluoride were obtained from Merck Serono KGaA.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite\(^\text{®} 545\) (0.02-0.10 mm) from Merck Serono KGaA Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F\(_{254}\) 5 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.
$^1$H, $^{13}$C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. CDCl$_3$ and DMSO-d$_6$ were used as deuterated solvents. TMS was used as reference ($\delta$ = 0.0) or the resonances of the solvents were locked as internal standards (CDCl$_3$: $^1$H $\delta$ 7.24, $^{13}$C $\delta$ 77.2; DMSO-d$_6$: $^1$H $\delta$ 2.50, $^{13}$C $\delta$ 39.5). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, td: triplet of doublets, q: quartet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.
2. Preparation of Starting Materials

2.1. Preparation of tert-butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1v)[2]

\[
\begin{align*}
\text{MeO-} & \quad \text{Cl} \\
\text{MeO-} & \quad \text{I}
\end{align*}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (425 mg, 0.60 mmol, 2 mol %) and Cul (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature (water bath). Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and tert-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 ml of tert-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite\(^\circledR\) and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (1v) as a colorless solid.

2.2. Preparation of 2-ethyl-3-iodo-5-(thiophen-2-yl)furan \((1z)\)[4]

\[
\text{Cl} \quad \text{O} \quad \text{THP} \\
\text{Cl} \quad \text{I} \\
\text{Furan} \\
\text{OTHP} \\
1z
\]

\(\text{PdCl}_2(\text{PPh}_3)_2\) (142 mg, 0.20 mmol, 2 mol \%) and \(\text{CuI}\) (78 mg, 0.40 mmol, 4 mol \%) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature (water bath). Then, 50 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol), thiophene-2-carbonyl chloride (1.50 g, 10.0 mmol), and tetrahydro-2-(pent-1-yn-3-yloxy)-2\(H\)-pyran (4.66 g, 10.0 mmol) were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). Then, sodium iodide (7.57 g, 50.0 mmol), toluene-4-sulfonic acid monohydrate (2.14 g, 11.0 mmol) and 30 ml of methanol were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE = 10:1) to give 2.72 g (8.93 mmol, 89 \% yield) of the desired product \((1z)\) as an orange oil.


3. Sonogashira-Glaser Coupling Sequence

3.1. General Procedure

\[
\begin{array}{c}
\text{(Het)Ar} \rightarrow \text{I} & \xrightarrow{\text{TMSA}} & \text{(Het)Ar} \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{TMS} & \xrightarrow{\text{KF} \text{ air}} & \text{(Het)Ar} \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{(Het)Ar}
\end{array}
\]

A mixture of (hetero)aryl iodide 1 (2.00 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (28 mg, 0.04 mmol, 2 mol %) and CuI (16 mg, 0.08 mmol, 4 mol %) was dissolved in degassed THF (5.00-10.0 mL) in a dry screw-cap Schlenk vessel with septum. After addition of trimethylsilylacetylene (0.43 mL, 3.00 mmol) and dry triethylamine (0.55 mL, 4.00 mmol) the solution was stirred at room temperature (water bath) until the complete conversion (monitored by TLC). Then, KF (236 mg, 4.00 mmol) and methanol (5.00 mL) were added subsequently and the reaction mixture was stirred under air atmosphere (the reaction vessel was opened) overnight at room temperature (water bath) or 50 °C (for compounds \(2v, 2w, 2x\) and \(2z\) in a preheated oil bath). After completion of the reaction, as indicated by TLC, the mixture was filtered (for compounds purified chromatographically; scarcely soluble \(2s\) was transferred directly into a flask and adsorbed onto Celite\textsuperscript{®} for chromatographic purification) or diluted with THF and filtered through neutral aluminium oxide (for compounds purified by recrystallisation). After removal of the solvents in vacuo the residue was either absorbed onto Celite\textsuperscript{®} and purified by column chromatography on silica gel using petrolether (boiling range 40-60 °C)/ethyl acetate or it was purified by recrystallisation from the appropriate solvent to give the analytically pure diynes 2.

The experimental details are depicted in Table 1.
<table>
<thead>
<tr>
<th>Entry</th>
<th>(Hetero) Aryl iodide 1</th>
<th>Diyne 2</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(isolated yield %)[a]</td>
<td></td>
<td>R_f (eluent) or recrystallisation (solvent)</td>
</tr>
<tr>
<td>1</td>
<td>412 mg (2.00 mmol) 1-iodo-benzene (Merck) 1a</td>
<td>Pale yellow solid 157 mg (0.78 mmol, 78 %)</td>
<td>PE (eluent) R_f (PE) : 0.44</td>
</tr>
<tr>
<td></td>
<td>Pale brown needles 163 mg (0.81 mmol, 81 %)</td>
<td>Recrystallisation from n-pentane</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>468 mg (2.00 mmol) 1-iodo-4-methoxy-benzene (Merck) 1b</td>
<td>Yellow crystals 191 mg (0.73 mmol, 73 %)</td>
<td>'PrOH/H_2O (solvents)</td>
</tr>
<tr>
<td>3</td>
<td>600 mg (2.00 mmol) 5-iodo-1,2,3-trimethoxy-benzene (Alfa Aesar) 1c</td>
<td>Pale yellow solid 259 mg (0.68 mmol, 68 %)</td>
<td>DCM (eluent) R_f (DCM) : 0.24</td>
</tr>
<tr>
<td>4</td>
<td>477 mg (2.00 mmol) 1-iodo-4-chloro-benzene (ABCR) 1d</td>
<td>Colorless solid 137 mg (0.51 mmol, 51 %)</td>
<td>EE (solvent)</td>
</tr>
<tr>
<td>5</td>
<td>444 mg (2.00 mmol) 1-fluoro-4-iodobenzene (ABCR) 1e</td>
<td>Colorless crystals 212 mg (0.89 mmol, 89 %)</td>
<td>PE (eluent) R_f (PE) : 0.50</td>
</tr>
</tbody>
</table>

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.
Table 1 (continuation). Experimental details for the synthesis of diynes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Hetero)Aryl iodide 1</th>
<th>Diyne 2 (isolated yield %)[a]</th>
<th>Chromatographic purification or recrystallisation (solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>544 mg (2.00 mmol) 1-(Trifluoromethyl)-4-iodobenzene (Alfa Aesar) 1f</td>
<td>Colorless solid 241 mg (0.71 mmol, 71 %)</td>
<td>PE (eluent) Rf (PE) : 0.64</td>
</tr>
<tr>
<td>7</td>
<td>458 mg (2.00 mmol) 4-Iodo-benzonitrile (ABCR) 1g</td>
<td>Pale brown crystals 141 mg (0.56 mmol, 56 %)</td>
<td>EE (solvent)</td>
</tr>
<tr>
<td>8</td>
<td>502 mg (2.00 mmol) 1-(4-Iodo-phenyl)-ethanone (Alfa Aesar) 1h</td>
<td>Blue solid 211 mg (0.74 mmol, 74 %)</td>
<td>PE-EE = 5:1 Rf (PE-EE = 5:1) : 0.23</td>
</tr>
<tr>
<td>9</td>
<td>477 mg (2.00 mmol) 1-Iodo-3-chloro-benzene (ABCR) 1i</td>
<td>Pale yellow crystals 183 mg (0.67 mmol, 67 %)</td>
<td>PE (eluent) Rf (PE) : 0.61</td>
</tr>
<tr>
<td>10</td>
<td>449 mg (2.00 mmol) 3-Iodophenol (Alfa Aesar) 1j</td>
<td>Pale beige solid 189 mg (0.81 mmol, 81 %)</td>
<td>DCM-MeOH-NH3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1</td>
</tr>
</tbody>
</table>

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.
### Table 1 (continuation). Experimental details for the synthesis of diynes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Hetero)Aryl iodide 1</th>
<th>Diyne 2 (isolated yield %)[a]</th>
<th>Chromatographic purification Rₚ (eluent) or recrystallisation (solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>447 mg (2.00 mmol) 3-iodobenzenamine (Merck) 1k</td>
<td>Pale yellow solid[b] 204 mg (0.88 mmol, 88 %)</td>
<td>PE-EE = 2:1 → 1:1 Rₚ (PE-EE = 2:1) : 0.14 Suspended in 1.25 M HCl in EtOH[b] (Fluka) DCM (solvent)</td>
</tr>
<tr>
<td>12</td>
<td>498 mg (2.00 mmol) 1-iodo-2-nitrobenzene (ABCR) 1l</td>
<td>Yellow solid 150 mg (0.51 mmol, 51 %)</td>
<td>PE-EE = 10:1 Rₚ (PE-EE = 10:1) : 0.16</td>
</tr>
<tr>
<td>13</td>
<td>535 mg (2.00 mmol) Methyl 2-iodobenzoate (ABCR) 1m</td>
<td>Yellow solid 296 mg (0.93 mmol, 93 %)</td>
<td>PE-EE = 20:1 Rₚ (PE-EE = 20:1) : 0.32</td>
</tr>
<tr>
<td>14</td>
<td>658 mg (2.00 mmol) tert-Butyl 2-iodophenylcarbamate (Aldrich) 1n</td>
<td>Yellow solid 387 mg (0.90 mmol, 90 %)</td>
<td>PE-EE = 20:1 Rₚ (PE-EE = 20:1) : 0.32</td>
</tr>
<tr>
<td>15</td>
<td>519 mg (2.00 mmol) 1-iodonaphthalene (Alfa Aesar) 1o</td>
<td>Yellow solid 235 mg (0.78 mmol, 78 %)</td>
<td>PE (eluent) Rₚ (PE) : 0.21</td>
</tr>
</tbody>
</table>

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.

[b] The solid was unstable as a free base. It was characterized as the corresponding dihydrochloride.
Table 1 (continuation). Experimental details for the synthesis of diynes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Hetero)Aryl iodide 1</th>
<th>Diyne 2 (isolated yield %)[a]</th>
<th>Chromatographic purification or recrystallisation (solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>410 mg (2.00 mmol) 2-iodopyridine (ABCR) 1p</td>
<td>Colorless solid 124 mg (0.61 mmol, 61 %)</td>
<td>PE-EE = 1:1 R_f (PE-EE = 1:1) : 0.38</td>
</tr>
<tr>
<td>17</td>
<td>410 mg (2.00 mmol) 3-iodopyridine (EGA) 1q</td>
<td>Colorless solid 148 mg (0.72 mmol, 72 %)</td>
<td>PE-EE = 1:1 R_f (PE-EE = 1:1) : 0.31</td>
</tr>
<tr>
<td>18</td>
<td>410 mg (2.00 mmol) 4-iodopyridine (ABCR) 1r</td>
<td>Colorless solid 139 mg (0.68 mmol, 68 %)</td>
<td>DCM-MeOH-NH_3 = 100:2:1 R_f (PE-EE = 1:1) : 0.18</td>
</tr>
<tr>
<td>19</td>
<td>537 mg (2.00 mmol) 5-iodo-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (5-iodo-1,3-dimethyluracil) (Aldrich) 1s</td>
<td>Yellow solid 170 mg (0.52 mmol, 52 %)</td>
<td>DCM-MeOH-NH_3 = 100:1:1</td>
</tr>
<tr>
<td>20</td>
<td>496 mg (2.00 mmol) 5-iodo-1H-indole (ABCR) 1t</td>
<td>Brown solid 238 mg (0.85 mmol, 85 %)</td>
<td>PE-EE = 3:1 R_f (PE-EE = 2:1) : 0.20</td>
</tr>
</tbody>
</table>

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.
Table 1 (continuation). Experimental details for the synthesis of diynes 2.

| Entry | (Hetero)Aryl iodide 1 | Diyne 2 (isolated yield %)[a] | Chromatographic purification
|-------|-----------------------|-----------------------------|-------------------------------
|       |                       |                             | R<sub>f</sub> (eluent) or recrystallisation (solvent) |
| 21    | 686 mg (2.00 mmol)    | Pale yellow solid 315 mg (0.66 mmol, 66 %) | PE-EE = 50:1 R<sub>f</sub> (PE-EE = 50:1) : 0.15 |
|       | tert-Butyl 3-iodo-1H-indole-1-carboxylate[b] | | Crystallisation in n-pentane |
| 22    | 798 mg (2.00 mmol)    | Pale yellow solid 341 mg (0.58 mmol, 58 %) | PE-EE = 10:1 R<sub>f</sub> (PE-EE = 10:1) : 0.15 |
|       | tert-Butyl 4-iodo-2-(4-methoxy-phenyl)-1H-pyrrole-1-carboxylate[c] | | |
| 23    | 568 mg (2.00 mmol)    | Yellow solid 244 mg (0.67 mmol, 67 %) | PE-EE = 3:1 R<sub>f</sub> (PE-EE = 3:1) : 0.30 |
|       | 1-Benzyl-4-iodo-1H-pyrazole (Aldrich) | | |

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.


Table 1 (continuation). Experimental details for the synthesis of diynes 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Hetero)Aryl iodide 1</th>
<th>Diyne 2 (isolated yield %)[a]</th>
<th>Chromatographic purification R_f (eluent) or recrystallisation (solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>568 mg (2.00 mmol) 1-Benzyl-5-iodo-1H-imidazole[^b] 1x</td>
<td>Colorless solid[^c] 183 mg (0.51 mmol, 51 %)</td>
<td>DCM-MeOH-NH_3 = 100:1:1 Suspended in 1.25 M HCl in EtOH[^c] (Fluka)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>420 mg (2.00 mmol) 2-Iodothiophene (Aldrich) 1y</td>
<td>Pale brown solid 151 mg (0.71 mmol, 71 %)</td>
<td>PE (eluent) R_f (PE) : 0.48</td>
</tr>
<tr>
<td>26</td>
<td>608 mg (2.00 mmol) 2-Ethyl-3-iodo-5-(thiophen-2-yl)furan[^d] 1z</td>
<td>Yellow solid 204 mg (0.51 mmol, 51 %)</td>
<td>PE-PE-EE = 100:1 R_f (PE) : 0.17</td>
</tr>
</tbody>
</table>

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide 1.
[b] 1x was obtained along with isomeric 1-benzyl-4-iodo-1H-imidazole as a separable mixture from 4(5)-iodo-1H-imidazole according to a procedure described for the synthesis of 1-benzyl 4-iodo-1H-pyrazole from 4-iodo-1H-pyrazole: W. Holzer, I. Pöcher, J. Het. Chem. 1995, 32, 189-194. For a similar procedure and characterisation of both isomers, see: C. J. Lovely, H. Du, R. Sivappa, M. R. Bhandari, Y. He, H. V. R. Dias, J. Org. Chem. 2007, 72, 3741-3749.
[c] The compound was characterized as its dihydrochloride salt.
Table 2. Reaction times\textsuperscript{[a]} in the synthesis of diynes 2.

<table>
<thead>
<tr>
<th>Diyne 2</th>
<th>Sonogashira coupling step</th>
<th>Deprotection/ Glaser coupling step</th>
<th>Diyne 2</th>
<th>Sonogashira coupling step</th>
<th>Deprotection/ Glaser coupling step</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1 h</td>
<td>18 h</td>
<td>2o</td>
<td>1 h</td>
<td>16 h</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>17 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>3 h</td>
<td>16 h</td>
<td>2p</td>
<td>3 h</td>
<td>16 h</td>
</tr>
<tr>
<td>2c</td>
<td>1 h</td>
<td>18 h</td>
<td>2q</td>
<td>3 h</td>
<td>16 h</td>
</tr>
<tr>
<td>2d</td>
<td>2 h</td>
<td>17 h</td>
<td>2r</td>
<td>3 h</td>
<td>16 h</td>
</tr>
<tr>
<td>2e</td>
<td>2 h</td>
<td>17 h</td>
<td>2s</td>
<td>1 h</td>
<td>15 h</td>
</tr>
<tr>
<td>2f</td>
<td>2 h</td>
<td>17 h</td>
<td>2t</td>
<td>1 h</td>
<td>27 h</td>
</tr>
<tr>
<td>2g</td>
<td>2 h</td>
<td>17 h</td>
<td>2u</td>
<td>1.5 h</td>
<td>73 h</td>
</tr>
<tr>
<td>2h</td>
<td>1 h</td>
<td>19 h</td>
<td>2v</td>
<td>2 h</td>
<td>25 h\textsuperscript{[b]}</td>
</tr>
<tr>
<td>2i</td>
<td>2 h</td>
<td>17 h</td>
<td>2w</td>
<td>1 h</td>
<td>22 h\textsuperscript{[b]}</td>
</tr>
<tr>
<td>2j</td>
<td>1 h</td>
<td>16 h</td>
<td>2x</td>
<td>9 h</td>
<td>16 h\textsuperscript{[b]}</td>
</tr>
<tr>
<td>2k</td>
<td>1 h</td>
<td>24 h</td>
<td>2y</td>
<td>2 h</td>
<td>17 h</td>
</tr>
<tr>
<td>2l</td>
<td>2 h</td>
<td>17 h</td>
<td>2z</td>
<td>1 h</td>
<td>52 h\textsuperscript{[b]}</td>
</tr>
<tr>
<td>2m</td>
<td>1 h</td>
<td>22 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2n</td>
<td>1 h</td>
<td>24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} The reaction times for both steps are not optimized. The actual reaction times might be much shorter than indicated.

\textsuperscript{[b]} The deprotection-Glaser coupling step was performed at 50 °C.
3.2 Spectroscopic Data of Compounds 2a-2aa

3.2.1. 1,4-Diphenylbuta-1,3-diyne (2a)

\[
\begin{array}{c}
\text{C}_{16}\text{H}_{10} \\
202.25
\end{array}
\]

157 mg (0.78 mmol, 78 % yield) as a pale yellow solid. Mp 82-85 °C (n-pentane). \(^1H\) NMR (CDCl\(_3\), 500 MHz): \(\delta 7.28-7.40 (m, 6 \text{ H}), 7.46-7.56 (m, 4 \text{ H})\). \(^{13}\text{C} \) NMR (CDCl\(_3\), 125 MHz): \(\delta 74.1 \text{ (C}_{\text{quat}}\), 81.8 (C}_{\text{quat}}\), 122.0 (C}_{\text{quat}}\), 128.7 (CH), 129.4 (CH), 132.7 (CH). El + MS (m/z (%)): 203 (17), 202 (M\(^+\), 100), 201 ((M-H\(^+\), 11), 200 (23), 101 (C\(_8\)H\(_5\)^{+}, 19), 88 (13). IR (KBr): \(\nu 3049 \text{ (w) cm}^{-1}\), 2148 (w), 1655 (w), 1638 (w), 1483 (w), 1439 (w), 1067 (w), 1024 (w), 915 (w), 755 (s), 685 (s), 524 (m). Anal. calcd for C\(_{16}\)H\(_{10}\) (202.3): C 95.02, H 4.98. Found: C 94.96, H 5.10.

Alternatively, the product can be isolated by crystallisation from \(^1\text{PrOH/H}_2\text{O} \) as pale brown needles (163 mg; 0.81 mmol, 81 % yield). Mp 84-86 °C (\(^1\text{PrOH/H}_2\text{O})

Product from the studies concerning the influence of halide anions upon the Glaser coupling step (Table 1 in manuscript) was obtained as a colorless solid. Mp 83-86 °C.


White solid. Mp 86-87 °C. \(^1H\) NMR (CDCl\(_3\), 200 MHz): \(\delta 7.31-7.35 (m, 6 \text{ H}), 7.53 (d, J = 7.3 \text{ Hz}, 4 \text{ H})\). \(^{13}\text{C} \) NMR (CDCl\(_3\), 50 MHz): \(\delta 73.9, 81.0, 121.8, 128.4, 129.1, 132.5\).
3.2.2. 1,4-Bis(4-methoxyphenyl)buta-1,3-diyne (2b)

![Chemical Structure]

191 mg (0.73 mmol, 73 % yield) as yellow crystals. Mp 142 °C (PrOH). $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.80 (s, 6 H), 7.80-7.87 (m, 4 H), 7.41-7.47 (m, 4 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 55.6 (CH$_3$), 73.2 ($C_{quat}$), 81.4 ($C_{quat}$), 114.3 ($C_{quat}$), 114.4 (CH), 134.3 (CH), 160.4 ($C_{quat}$). EI + MS (m/z (%)): 263 (19), 262 (M$^+$, 100), 248 (10), 247 ((M-CH$_3$)$^+$, 51), 219 (13), 176 (16), 149 (12), 131 (23), 111 (14), 109 (13), 99 (10), 97 (20), 95 (14), 85 (18), 83 (17), 81 (13), 71 (25), 69 (15), 57 (27), 55 (14), 43 (12). IR (KBr): $\tilde{\nu}$ 3003 (w) cm$^{-1}$, 2975 (w), 2936 (w), 2841 (w), 2138 (w), 1599 (s), 1561 (w), 1504 (s), 1461 (m), 1439 (w), 1294 (s), 1256 (s), 1182 (w), 1168 (s), 1108 (w), 1028 (m), 842 (m), 821 (m), 691 (w), 538 (w). Anal. calcd for C$_{18}$H$_{14}$O$_2$ (262.3): C 82.42, H 5.38. Found: C 82.58, H 5.57.


White solid. Mp 141-142 °C. $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 3.82 (s, 6 H), 6.85 (d, $J = 8.7$ Hz, 4 H), 7.46 (d, $J = 8.7$ Hz, 4 H). $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$ 55.3, 73.0, 81.2, 113.9, 114.1, 134.0, 160.2.
3.2.3. 1,4-Bis(3,4,5-trimethoxyphenyl)buta-1,3-diyne (2c)

![Chemical structure image]

C\textsubscript{22}H\textsubscript{22}O\textsubscript{6}  
382.41

259 mg (0.68 mmol, 68 % yield) as a pale yellow solid. Mp 199-201 °C. \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 3.86 (s, 12 H), 3.87 (s, 6 H), 6.76 (s, 4 H). \(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 56.1 (CH\textsubscript{3}), 61.0 (CH\textsubscript{3}), 73.0 (C\textsubscript{quat}), 81.6 (C\textsubscript{quat}), 109.6 (CH), 116.5 (C\textsubscript{quat}), 139.8 (C\textsubscript{quat}), 153.0 (C\textsubscript{quat}). EI + MS (m/z (%)): 382 (M\textsuperscript{+}, 5), 279 (7), 167 (34), 150 (12), 149 (C\textsubscript{8}H\textsubscript{5}O\textsubscript{3}\textsuperscript{+}, 100), 113 (11), 95 (10), 94 (98), 84 (12), 83 (14), 71 (27), 70 (17), 69 (11), 57 (28), 55 (15), 43 (14). IR (KBr): \(\tilde{\nu}\) 3014 (w) cm\textsuperscript{-1}, 2941 (w), 2838 (w), 2143 (w), 1573 (s), 1504 (s), 1464 (m), 1436 (w), 1410 (s), 1331 (s), 1236 (s), 1186 (w), 1128 (s), 993 (s), 963 (w), 887 (m), 821 (m), 774 (w), 739 (w), 675 (w), 624 (w), 564 (w), 526 (w). Anal. calcd for C\textsubscript{22}H\textsubscript{22}O\textsubscript{6} (382.4): C 69.10, H 5.80. Found: C 68.96, H 5.73.
3.2.4. 1,4-Bis(4-chlorophenyl)buta-1,3-diyne (2d)

\[
\begin{array}{c}
\text{Cl} \\
\text{C} \\
\text{H} \\
\text{Cl}
\end{array}
\]

\[\text{C}_{16}\text{H}_8\text{Cl}_2\]

271.14

137 mg (0.51 mmol, 51 % yield) as a colorless solid. Mp 253 °C (dec., ethyl acetate). EI + MS (m/z (%)): 274 (M(\text{37Cl})_{37Cl})^{+}, 11), 272 (M(\text{37Cl35Cl})^{+}, 64), 270 (M(\text{35Cl35Cl})^{+}, 100), 236 (14), 200 (26), 71 (23). IR (KBr): \(\tilde{\nu}\) 1890 (w) cm\(^{-1}\), 1639 (w), 1587 (w), 1544 (w), 1509 (w), 1485 (s), 1466 (m), 1396 (m), 1095 (s), 1013 (m), 823 (s), 592 (w), 521 (m).

Anal. calcd for C\(_{16}\)H\(_8\)Cl\(_2\) (271.1): C 70.88, H 2.97. Found: C 71.09, H 2.85.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.


\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.32 (d, \(J = 8.1\) Hz, 4 H), 7.46 (d, \(J = 8.1\) Hz, 4 H). Very insoluble in common organic solvents.
3.2.5. 1,4-Bis(4-fluorophenyl)buta-1,3-diyne (2e)

\[
\begin{align*}
\text{C}_{16}\text{H}_8\text{F}_2 \\
238.23
\end{align*}
\]

212 mg (0.89 mmol, 89 % yield) as colorless crystals. Mp 187-188 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.00-7.06 (m, 4 H), 7.46-7.52 (m, 4 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 73.7 (C\(_{\text{quat}}\)), 80.6 (C\(_{\text{quat}}\)), 116.1 (d, \(J = 22.2\) Hz, CH), 118.0 (d, \(J = 3.6\) Hz, C\(_{\text{quat}}\)), 134.8 (d, \(J = 8.6\) Hz, CH), 163.3 (d, \(J = 251.7\) Hz, C\(_{\text{quat}}\)). EI + MS (m/z (%)): 239 (26), 238 (M\(^+\), 100), 236 (17), 119 (22). IR (KBr): \(\tilde{\nu}\) 2143 (w) cm\(^{-1}\), 1888 (w), 1639 (w), 1596 (s), 1502 (s), 1404 (w), 1275 (w), 1228 (s), 1159 (s), 1094 (m), 1013 (w), 829 (s), 697 (m), 525 (s).


White solid. Mp 187-189 °C. \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 7.04 (dd, \(J = 8.6\) Hz, \(J = 8.6\) Hz, 4 H), 7.51 (dd, \(J = 8.6\) Hz, \(J = 2.2\) Hz, 4 H). \(^{13}\)C NMR (CDCl\(_3\), 50 MHz): \(\delta\) 73.6, 80.4, 115.9 (d, \(J = 22.2\) Hz), 117.9 (d, \(J = 3.8\) Hz), 134.5 (d, \(J = 8.4\) Hz), 163.0 (d, \(J = 250.3\) Hz).
3.2.6. 1,4-Bis(4-(trifluoromethyl)phenyl)buta-1,3-diyne (2f)

\[
\begin{array}{c}
\text{F}_3\text{C} & \equiv & \equiv & \equiv & \text{CF}_3 \\
\text{C}_{18}\text{H}_8\text{F}_6 \\
338.25
\end{array}
\]

241 mg (0.71 mmol, 71 % yield) as a colorless solid. Mp 163 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.56-7.66 (m, 8 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 75.8 (C$_{quat}$), 81.2 (C$_{quat}$), 123.9 (q, $J = 272.3$ Hz, C$_{quat}$), 125.4-125.5 (m, C$_{quat}$), 125.7 (q, $J = 3.7$ Hz, CH), 131.3 (q, $J = 32.9$ Hz, C$_{quat}$), 133.0 (CH). EI + MS ($m/z$ (%)): 339 (19), 338 (M$^+$, 100), 319 (14), 143 (12), 119 (12). IR (KBr): $\tilde{\nu}$ 2219 (w) cm$^{-1}$, 1925 (w), 1802 (w), 1611 (m), 1561 (m), 1408 (m), 1318 (s), 1234 (w), 1177 (s), 1134 (s), 1107 (s), 1065 (s), 1015 (m), 841 (s), 734 (m), 596 (m), 551 (w), 522 (w). Anal. calcd for C$_{18}$H$_8$F$_6$ (338.3): C 63.92, H 2.38. Found: C 63.70, H 2.56.


White solid. Mp 166-168 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.62 (d, $J = 8.4$ Hz, 4 H), 7.65 (d, $J = 8.4$ Hz, 4 H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 75.6, 81.0, 122.3, 125.0, 125.2, 125.4, 125.5, 130.9, 131.2, 132.8. MS ($m/z$ (%)): 338 (M$^+$, 100).
3.2.7. 1,4-Bis(4-cyanophenyl)buta-1,3-diyne (2g)

\[
\text{NC} \equiv \equiv \equiv \text{CN} \\
\text{C}_{18}\text{H}_8\text{N}_2 \\
252.27
\]

141 mg (0.56 mmol, 56 % yield) as pale brown crystals. Mp 292 °C (dec., ethyl acetate). EI + MS \((m/z\)%): 253 (20), 252 (M\(^+\), 100). IR (KBr): 3092 (w) cm\(^{-1}\), 2227 (s), 1689 (w), 1599 (w), 1546 (w), 1493 (m), 1404 (m), 1269 (w), 1172 (w), 1104 (w), 1014 (w), 840 (s), 826 (s), 652 (w), 553 (s). Anal. calcd for C\(_{18}\)H\(_8\)N\(_2\) (252.3): C 85.70, H 3.20, N 11.10. Found: C 85.64, H 3.28, N 11.15.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.


Light brown solid. Mp 183-185 °C. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.48-7.51 (d, J = 8.6 Hz, 4 H), 7.60-7.63 (d, J = 8.8 Hz, 4 H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 74.6, 76.9, 112.3, 115.7, 127.0, 131.8, 133.0. MS \((m/z\)%): 252 (M\(^+\)). Anal. calcd for C\(_{18}\)H\(_8\)N\(_2\) (252.3): C 85.70, H 3.20, N 11.10. Found: C 85.89, H 2.98, N 11.13.
3.2.8. 1,4-Bis(4-acetylphenyl)buta-1,3-diyne (2h)

\[
\begin{align*}
\text{O} & \quad \text{\textbf{C}}_{20}\text{H}_{14}\text{O}_2 \\
& \\
286.32
\end{align*}
\]

211 mg (0.74 mmol, 74 % yield) as a blue solid. Mp 172-174 °C. El + MS \((m/z (\%))\): 287 (14), 286 (M\(^+\), 64), 272 (21), 271 ((M-CH\(_3\))\(^+\), 100), 243 ((M-C\(_2\)H\(_3\))\(^+\), 11), 228 ((M-C\(_3\)H\(_6\))\(^+\), 24), 200 ((M-C\(_4\)H\(_6\)O\(_2\))\(^+\), 23), 199 (10), 149 (12), 128 (C\(_9\)H\(_4\)O\(^+\), 26), 114 (15), 100 (12), 94 (11), 43 (C\(_2\)H\(_3\)O\(^+\), 15). IR (KBr): \(\tilde{\nu}\) 1668 (s) cm\(^{-1}\), 1598 (m), 1402 (w), 1285 (w), 1264 (m), 1180 (w), 962 (w), 835 (m), 652 (w), 595 (w). Anal. calcd for C\(_{20}\)H\(_{14}\)O\(_2\) (286.3): C 83.90, H 4.93. Found: C 84.03, H 4.66.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.


Blue solid. Mp 178-180 °C. \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 2.62 (s, 6 H), 7.62 (d, \(J = 8.3\) Hz, 4 H), 7.94 (d, \(J = 8.3\) Hz, 4 H). \(^{13}\)C NMR (CDCl\(_3\), 50 MHz): \(\delta\) 26.6, 76.5, 81.9, 126.1, 128.2, 132.6, 137.0, 196.8. HRMS calcd for C\(_{20}\)H\(_{14}\)O\(_2\), 286.0994; found, 286.0998.
3.2.9. 1,4-Bis(3-chlorophenyl)buta-1,3-diyne (2i)

\[ \text{C}_{16}\text{H}_8\text{Cl}_2 \]

271.14

183 mg (0.67 mmol, 67 % yield) as pale yellow crystals. Mp 73 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.19-7.24 (m, 2 H), 7.29-7.33 (m, 2 H), 7.34-7.38 (m, 2 H), 7.44-7.47 (m, 2 H).

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 74.9 (C\(_{\text{quat}}\)), 80.8 (C\(_{\text{quat}}\)), 123.5 (C\(_{\text{quat}}\)), 129.9 (CH), 130.9 (CH), 132.5 (CH), 134.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 274 (M\(^{37}\text{Cl}^{37}\text{Cl}\)+, 10), 273 (11), 272 (M\(^{37}\text{Cl}^{35}\text{Cl}\)+, 66), 271 (17), 270 (M\(^{35}\text{Cl}^{35}\text{Cl}\)+, 100), 243 (24), 217 (16), 200 (38), 199 (11), 135 (14), 100 (17), 99 (12), 85 (12), 71 (13). IR (KBr): \(\tilde{\nu}\) 1584 (m) cm\(^{-1}\), 1557 (m), 1471 (m), 1454 (m), 1402 (m), 1202 (w), 1165 (w), 1094 (m), 1077 (m), 907 (w), 890 (s), 854 (m), 793 (s), 683 (s), 523 (w). Anal. calcd for C\(_{16}\)H\(_8\)Cl\(_2\) (271.1) : C 70.88, H 2.97. Found: C 70.84, H 2.95.


\(^1\)H NMR (CDCl\(_3\), 270 MHz): \(\delta\) 7.18-7.26 (m, 2 H), 7.28-7.36 (m, 4 H), 7.44-7.46 (m, 2 H).

\(^{13}\)C NMR (CDCl\(_3\), 67.8 MHz): \(\delta\) 75.2, 81.0, 123.7, 130.2, 131.1, 132.7, 134.8. EI + MS (m/z (%)): 274 (11), 273 (12), 272 (64), 271 (M\(^+\), 18), 270 (100), 200 (31).
3.2.10. 3-(4-(3-Hydroxyphenyl)buta-1,3-diynyl)phenol (2j)

\[
\text{C}_{16}\text{H}_{10}\text{O}_2 \\
234.25
\]

189 mg (0.81 mmol, 81 % yield) as a pale beige solid. Mp 200 °C. \( ^1 \text{H} \) NMR (DMSO-d\textsubscript{6}, 500 MHz): \( \delta \) 6.90 (dd, \( J = 8.2 \) Hz, \( J = 1.9 \) Hz, 2 H), 6.94-6.96 (m, 2 H), 7.02-7.05 (m, 2 H), 7.24 (t, \( J = 7.9 \) Hz, 2 H), 9.86 (s, 2 H, OH). \( ^{13} \text{C} \) NMR (DMSO-d\textsubscript{6}, 125 MHz): \( \delta \) 72.9 (C\textsubscript{quat}), 81.8 (C\textsubscript{quat}), 117.6 (CH), 118.5 (CH), 121.2 (C\textsubscript{quat}), 123.2 (CH), 130.1 (CH), 157.4 (C\textsubscript{quat}). EI + MS (m/z (%)): 235 (17), 234 (M\textsuperscript{+}, 100), 176 (13), 149 (11), 117 (C\textsubscript{8}H\textsubscript{5}O\textsuperscript{+}, 9). IR (KBr): \( \tilde{\nu} \) 3224 (s) cm\textsuperscript{-1}, 1603 (w), 1590 (s), 1448 (s), 1364 (w), 1308 (w), 1262 (m), 1244 (m), 1149 (m), 1081 (w), 997 (w), 932 (m), 856 (m), 785 (s), 721 (w), 680 (s), 563 (w), 527 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{10}O\textsubscript{2} (234.3): C 82.04, H 4.30. Found: C 82.15, H 4.33.
3.2.11. 3-(4-(3-Aminophenyl)buta-1,3-diynyl)benzenamine dihydrochloride (2k)

\[
\text{C}_{16}\text{H}_{14}\text{Cl}_{2}\text{N}_{2}
\]

204 mg (0.88 mmol, 88 % yield) as a pale brown solid (free base). For characterisation, it was suspended in 1.25 \( M \) HCl in EtOH, stirred at the room temperature, filtered and washed with \( n \)-pentane. Pale brown solid. Mp 150-155 °C. El + MS (\( m/z \) (%)): 233 (19), 232 ((M-2 HCl)+, 100), 116 (C_8H_6N^+, 11). IR (KBr): \( \tilde{\nu} \) 3054 (m) cm\(^{-1}\), 2878 (s), 2551 (m), 1590 (w), 1561 (m), 1516 (m), 1481 (w), 1440 (w), 1098 (w), 1074 (w), 998 (w), 917 (w), 889 (w), 795 (s), 681 (s), 531 (m). Anal. calcd for C\(_{16}\)H\(_{14}\)Cl\(_{2}\)N\(_{2}\) (305.2): C 62.97, H 4.62, N 9.18. Found: C 62.79, H 4.59, N 9.13.

The dihydrochloride was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

Data reported in the literature for the free base: L. Yin, J. Liebscher, Synthesis 2005, 131-135.

Grey-green solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 3.70 (br s, 4 H), 6.69 (m, 2 H), 6.81 (t, \( J = 1.9 \) Hz, 2 H), 6.93 (dt, \( J = 7.5 \) Hz, \( J = 1.2 \) Hz, 2 H), 7.11 (t, \( J = 7.9 \) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta \) 73.4, 81.7, 116.3, 118.4, 122.4, 123.0, 129.4, 146.3. Anal. calcd for C\(_{16}\)H\(_{12}\)N\(_2\) (232.3): C 82.73, H 5.21, N 12.06. Found: C 82.84, H 5.40, N 12.01.
3.2.12. 1,4-Bis(2-nitrophenyl)buta-1,3-diyne (2l)

\[
\begin{align*}
\text{NO}_2 & \quad \equiv \quad \equiv \quad \text{O}_2N \\
\text{C}_{16}\text{H}_8\text{N}_2\text{O}_4 & \\
292.25
\end{align*}
\]

150 mg (0.51 mmol, 51 % yield) as a yellow solid. Mp 204 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.53 (t, \(J = 7.8\) Hz, 2 H), 7.63 (t, \(J = 7.6\) Hz, 2 H), 7.76 (d, \(J = 7.7\) Hz, 2 H), 8.13 (d, \(J = 8.2\) Hz, 2 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 79.4 (C\(_{\text{quat}}\)), 81.1 (C\(_{\text{quat}}\)), 100.2 (C\(_{\text{quat}}\)), 117.5 (C\(_{\text{quat}}\)), 125.3 (CH), 130.1 (CH), 133.4 (CH), 136.2 (CH). MALDI MS (m/z (%)): 292.4 (M\(^+\)). IR (KBr): \(\tilde{\nu}\) 3105 (w) cm\(^{-1}\), 2850 (w), 1836 (w), 1602 (m), 1564 (m), 1518 (s), 1474 (m), 1437 (m), 1381 (w), 1340 (s), 1301 (m), 1254 (m), 1207 (w), 1143 (m), 1080 (m), 991 (w), 957 (w), 858 (s), 781 (s), 739 (s), 687 (s), 660 (s). Anal. calcd for C\(_{16}\)H\(_8\)N\(_2\)O\(_4\) (292.3) : C 65.76, H 2.76, N 9.59. Found: C 65.61, H 2.88, N 9.36.


Dark brown solid. Mp 204-205 °C. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.19-7.54 (m, 2 H), 7.59-7.63 (dt, \(J = 7.7\) Hz, \(J = 1.3\) Hz, 2 H), 7.39-7.76 (dd, \(J = 7.7\) Hz, \(J = 1.5\) Hz, 2 H), 8.10-8.13 (dd, \(J = 8.2\) Hz, \(J = 1.2\) Hz, 2 H). MS (m/z (%)): 292 (M\(^+\)). Anal. calcd for C\(_{16}\)H\(_8\)N\(_2\)O\(_4\) (292.3) : C 65.76, H 2.76, N 9.59. Found: C 65.55, H 2.65, N 9.03.
3.2.13. 1,4-Bis(2-methylbenzoyl)buta-1,3-diyne (2m)

![Chemical structure of 1,4-Bis(2-methylbenzoyl)buta-1,3-diyne (2m)]

296 mg (0.93 mmol, 93 % yield) as a yellow oil. Suspending in n-pentane, sonication in ultrasound bath, filtration and drying gave a yellow solid. Mp 59-60 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.97 (s, 6 H), 7.40-7.44 (m, 2 H), 7.48-7.52 (m, 2 H), 7.65-7.69 (m, 2 H), 7.97-8.00 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 52.4 (CH$_3$), 78.9 (C$_{quat}$), 81.5 (C$_{quat}$), 122.5 (C$_{quat}$), 128.8 (CH), 130.6 (CH), 131.8 (CH), 132.7 (C$_{quat}$), 135.2 (CH), 166.1 (C$_{quat}$). EI + MS (m/z (%)): 318 (M$^+$, 46), 303 ((M-CH$_3$)$^+$, 32), 285 (61), 275 (25), 272 (28), 259 ((M-C$_2$H$_3$O$_2$)$^+$, 74), 258 (34), 257 (40), 204 (28), 202 (C$_{16}$H$_{10}$$^+$, 49), 200 (C$_{18}$H$_8$$^+$, 25), 189 (35), 188 (31), 187 (60), 176 (41), 144 (100), 133 (25), 127 (32), 114 (37), 105 (27), 101 (35), 100 (51), 88 (48), 87 (35). IR (KBr): $\nu$ 3011 (w) cm$^{-1}$, 2961 (w), 1715 (s), 1593 (w), 1562 (w), 1479 (w), 1442 (m), 1426 (w), 1294 (s), 1251 (m), 1185 (w), 1124 (m), 1088 (w), 1044 (w), 956 (w), 839 (w), 798 (w), 774 (w), 751 (s), 696 (m), 656 (w), 573 (w), 539 (w). Anal. calcd for C$_{20}$H$_{14}$O$_4$ (318.3) : C 75.46, H 4.43. Found: C 75.22, H 4.70.
3.2.14. 1,4-Bis(2-tert-buty carbamoylphenyl)buta-1,3-diyne (2n)

![Chemical Structure](image)

\[ C_{26}H_{28}N_2O_4 \]

432.51

387 mg (0.90 mmol, 90 % yield) as a yellow solid (purification by suspending in \( n \)-pentane and sonication in ultrasound bath). Mp 134 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \)

- 1.56 (s, 18 H), 6.98 (td, \( J = 7.6 \) Hz, \( J = 0.9 \) Hz, 2 H), 7.20 (s, 2 H, NH), 7.33-7.38 (m, 2 H), 7.48 (dd, \( J = 7.6 \) Hz, \( J = 1.3 \) Hz, 2 H), 8.17 (d, \( J = 8.5 \) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \)

- 28.3 (CH\(_3\)), 78.9 (C\(_{quat}\)), 79.7 (C\(_{quat}\)), 81.2 (C\(_{quat}\)), 109.4 (C\(_{quat}\)), 118.0 (CH), 122.3 (CH), 130.9 (CH), 133.2 (CH), 141.1 (C\(_{quat}\)), 152.3 (C\(_{quat}\)). EI + MS (m/z (%)): 432 (M\(^+\), 1), 332 ((M-C\(_5\)H\(_9\)O\(_2\))\(^+\), 5), 302 (17), 285 (10), 284 (50), 276 (23), 259 (12), 258 (42), 233 (16), 232 ((M-C\(_{10}\)H\(_{10}\)O\(_4\))\(^+\), 92), 231 ((M-C\(_{10}\)H\(_{19}\)O\(_4\))\(^+\), 100), 230 ((M-C\(_{10}\)H\(_{20}\)O\(_4\))\(^+\), 16), 229 (51), 228 (12), 204 (38), 203 (14), 201 (12), 146 (12), 102 (13), 101 (11), 89 (14), 88 (14), 59 (27), 57 (C\(_4\)H\(_9\)^+\), 50), 56 (13), 44 (CO\(_2\)^+\), 12), 41 (25). IR (KBr): \( \tilde{\nu} \) 3408 (w) cm\(^{-1}\), 2979 (w), 2933 (w), 2146 (w), 1735 (s), 1578 (m), 1516 (s), 1446 (m), 1393 (w), 1368 (w), 1305 (m), 1280 (w), 1232 (m), 1155 (s), 1051 (w), 1024 (w), 945 (w), 899 (w), 836 (w), 754 (m), 578 (w), 550 (w). Anal. calcd for C\(_{26}\)H\(_{28}\)N\(_2\)O\(_4\) (432.5): C 72.20, H 6.53, N 6.48. Found: C 72.18, H 6.69, N 6.48.
3.2.15. 1,4-Di(naphthalen-1-yl)buta-1,3-diyne (2o)

![Chemical Structure](image)

235 mg (0.78 mmol, 78 % yield) as a yellow solid. Mp 175-177 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.43-7.48 (m, 2 H), 7.52-7.57 (m, 2 H), 7.60-7.65 (m, 2 H), 7.81-7.84 (m, 2 H), 7.85-7.90 (m, 4 H), 8.42 (d, \(J = 8.5\) Hz, 2 H). \(^1^3\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 78.7 (C\(_{quart}\)), 119.5 (C\(_{quart}\)), 125.2 (CH), 126.1 (CH), 126.7 (CH), 127.2 (CH), 128.5 (CH), 129.8 (CH), 132.1 (CH), 133.1 (C\(_{quart}\)), 133.9 (C\(_{quart}\)). EI + MS (m/z (%)): 303 (19), 302 (M\(^+\), 74), 300 (30), 167 (28), 151 (C\(_{12}\)H\(_7^+\), 17), 150 (100), 94 (21), 71 (19), 70 (13), 57 (15). IR (KBr): \(\tilde{\nu}\) 3055 (w) cm\(^{-1}\), 2137 (w), 1812 (w), 1638 (w), 1584 (w), 1504 (w), 1390 (m), 1332 (w), 1267 (w), 1155 (w), 1012 (w), 905 (w), 862 (w), 796 (s), 769 (s), 694 (w), 561 (w). Anal. calcd for C\(_{24}\)H\(_{14}\) (302.4) : C 95.33, H 4.67. Found: C 95.22, H 4.44.


Yellow solid. Mp 177-180 °C. \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 7.43-7.68 (m, 6 H), 7.82-7.92 (m, 6 H), 8.44 (d, \(J = 8.0\) Hz, 2 H). \(^1^3\)C NMR (CDCl\(_3\), 50 MHz): \(\delta\) 78.7, 81.0, 119.5, 125.2, 126.1, 126.7, 127.2, 128.4, 129.7, 132.0, 133.1, 133.9.
3.2.16. 2-(4-(Pyridin-2-yl)buta-1,3-diynyl)pyridine (2p)

\[
\begin{align*}
\text{C}_{14}\text{H}_8\text{N}_2 \\
204.23
\end{align*}
\]

124 mg (0.61 mmol, 61 % yield) as a colorless solid. Mp 119 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.25-7.30 (m, 2 H), 7.53 (d, \(J = 7.8\) Hz, 2 H), 7.67 (td, \(J = 7.7\) Hz, \(J = 1.6\) Hz, 2 H), 8.60 (d, \(J = 4.8\) Hz, 2 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 73.4 (C\(_{quat}\)), 81.1 (C\(_{quat}\)), 124.0 (CH), 128.6 (CH), 136.4 (CH), 142.1 (C\(_{quat}\)), 150.6 (CH). EI + MS (m/z (%)): 205 (18), 204 (M\(^+\), 100), 203 ((M-H)\(^+\), 21), 177 (10), 176 (10), 151 (12). IR (KBr): \(\tilde{\nu}\) 1655 (m) cm\(^{-1}\), 1638 (m), 1577 (m), 1561 (m), 1544 (w), 1459 (m), 1425 (m), 1240 (w), 1047 (w), 987 (w), 887 (w), 774 (s), 734 (m), 629 (w), 532 (w). Anal. calcd for C\(_{14}\)H\(_8\)N\(_2\) (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.35, H 3.94, N 13.50.


Pale yellow crystalline solid. Mp 121-122 °C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.63 (br d, \(J = 4.7\) Hz, 2 H), 7.70 (dt, \(J = 1.7\) Hz, 7.7 2 H), 7.56 (br dt, \(J = 1.0\) Hz, 7.9 Hz, 2 H), 7.31 (ddd, \(J = 1.2\) Hz, 4.8 Hz, 7.6 Hz, 2 H). \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 150.3, 141.8, 136.2, 128.4, 123.8, 80.8, 73.3. MS (EI, 70 eV): m/z (%): 204 (M\(^+\), 100), 176 (14), 152 (9), 99 (9), 50 (15). IR (ATR): \(\tilde{\nu}\) = 1560 cm\(^{-1}\), 1424, 1230, 990, 770, 733. Anal. calcd for C\(_{14}\)H\(_8\)N\(_2\) (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.11, H 4.08, N 13.63.
3.2.17. 3-(4-(Pyridin-3-yl)buta-1,3-diynyl)pyridine (2q)

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{14} \\
\text{H} \\
\text{8} \\
\text{N} \\
\text{2} \\
\end{array}
\]

C\textsubscript{14}H\textsubscript{8}N\textsubscript{2}  
204.23

148 mg (0.72 mmol, 72 % yield) as a colorless solid. Mp 153 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 7.28 (dd, \(J = 7.9\) Hz, \(J = 4.9\) Hz, 2 H), 7.80 (dt, \(J = 7.9\) Hz, \(J = 1.8\) Hz, 2 H), 8.58 (dd, \(J = 4.9\) Hz, \(J = 1.5\) Hz, 2 H), 8.75 (d, \(J = 1.6\) Hz, 2 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 76.9 (C\textsubscript{quat}), 79.3 (C\textsubscript{quat}), 119.1 (C\textsubscript{quat}), 123.3 (CH), 139.7 (CH), 149.6 (CH), 153.2 (CH). EI + MS (m/z (%)): 205 (17), 204 (M\(^+\), 100), 203 ((M-H)\(^+\), 12), 151 (17), 98 (12). IR (KBr): \(\tilde{\nu}\) 3054 (w) cm\(^{-1}\), 3006 (w), 2150 (w), 1638 (w), 1579 (m), 1560 (m), 1474 (m), 1413 (s), 1329 (m), 1189 (m), 1121 (w), 1065 (w), 1038 (m), 1022 (s), 957 (w), 804 (s), 699 (s), 626 (m), 515 (m). Anal. calcd for C\textsubscript{14}H\textsubscript{8}N\textsubscript{2} (204.2): C 82.33, H 3.95, N 13.72. Found: C 82.11, H 3.66, N 13.46.


White solid. Mp 144-146 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.34 (t, \(J = 4.8\) Hz, 2 H), 7.86 (d, \(J = 8.0\) Hz, 2 H), 8.62 (d, \(J = 4.0\) Hz, 2 H), 8.79 (s, 2 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 79.1, 119.1, 123.3, 139.9, 149.0, 152.7.
3.2.18. 4-(4-(Pyridin-4-yl)buta-1,3-diylnyl)pyridine (2r)

![Chemical structure of 4-(4-(Pyridin-4-yl)buta-1,3-diylnyl)pyridine (2r)]

\[\text{C}_{14}\text{H}_8\text{N}_2\]

204.23

139 mg (0.68 mmol, 68 % yield) as a colorless solid. Mp 206 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.31 (dd, \(J = 4.5\) Hz, \(J = 1.5\) Hz, 4 H), 8.57 (dd, \(J = 4.5\) Hz, \(J = 1.5\) Hz, 4 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 77.4 (C\(_{\text{quat}}\)), 80.4 (C\(_{\text{quat}}\)), 126.3 (CH), 129.6 (C\(_{\text{quat}}\)), 150.2 (CH). EI + MS (m/z (%)): 205 (16), 204 (M\(^+\), 100), 203 ((M-H)\(^+\), 11), 177 (11), 151 (12). IR (KBr): \(\tilde{\nu}\) 3026 (w) cm\(^{-1}\), 1671 (w), 1584 (s), 1538 (m), 1486 (w), 1398 (m), 1217 (w), 1062 (w), 987 (w), 815 (s), 778 (s), 671 (w), 542 (m), 513 (w). Anal. calcd for C\(_{14}\)H\(_8\)N\(_2\) (204.2): C 82.33, H 3.95, N 13.72. Found: C 82.30, H 4.02, N 13.49.


Brown solid. Mp 198-201 °C. \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 7.41 (d, \(J = 7.2\) Hz, 4 H), 8.67 (br s, 4 H). \(^13\)C NMR (CDCl\(_3\), 200 MHz): \(\delta\) 76.9, 79.9, 125.7, 128.9, 149.6. MS (m/z (%)): 204 (M\(^+\), 100), 177 (13), 151 (14), 124 (6). IR (nujol): \(\tilde{\nu}\) 1580 cm\(^{-1}\), 980, 810.
3.2.19. 5-(4-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)buta-1,3-diynyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (2s)

![Chemical Structure]

\[ C_{16}H_{14}N_4O_4 \]

326.31

170 mg (0.52 mmol, 52 % yield) as a yellow solid. Mp 319-321 °C. EI + MS (m/z (%)):

- 327 (20), 326 (M⁺, 100), 228 (58), 212 (11), 200 (34), 156 (19), 155 (11), 143 (18), 115 (22), 114 (14), 86 (13), 84 (13).

IR (KBr): \( \tilde{\nu} \) 3061 (w) cm\(^{-1}\), 2952 (w), 2152 (w), 1704 (s), 1655 (s), 1620 (m), 1451 (m), 1392 (w), 1343 (m), 1263 (w), 1177 (w), 1077 (m), 930 (w), 764 (w), 752 (m), 553 (w).


The compound was not sufficiently soluble in DMSO-d\(_6\) to obtain NMR spectra.
3.2.20. 5-(4-(1H-Indol-5-yl)buta-1,3-diynyl)-1H-indole (2t)

238 mg (0.85 mmol, 85 % yield) as a yellow solid. Suspending in dichloromethane, sonication in ultrasound bath, filtration and drying gave a brown solid. Mp 250 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 6.48-6.51 (m, 2 H), 7.29 (dd, $J = 8.2$ Hz, $J = 1.6$ Hz, 2 H), $7.43$-$7.47$ (m, 4 H), 7.85-7.86 (m, 2 H), 11.41 (s, 2 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 71.8 (C$_{quat}$), 83.0 (C$_{quat}$), 101.5 (CH), 110.7 (C$_{quat}$), 112.0 (CH), 124.9 (CH), 125.1 (CH), 127.0 (CH), 127.5 (C$_{quat}$), 136.0 (C$_{quat}$). EI + MS (m/z (%)): 281 (22), 280 (M$^+$, 100), 279 (10), 251 (6), 140 (C$_{10}$H$_6$N$^+$, 20), 125 (10). IR (KBr): $\tilde{\nu}$ 3399 (s) cm$^{-1}$, 2146 (w), 1719 (w), 1655 (w), 1609 (w), 1561 (w), 1543 (w), 1509 (w), 1460 (m), 1412 (m), 1342 (w), 1310 (w), 1093 (w), 896 (w), 881 (w), 813 (m), 764 (w), 729 (m), 603 (m), 506 (m). Anal. calcd for C$_{20}$H$_{12}$O$_2$ (280.3) : C 85.69, H 4.31, N 9.99. Found: C 85.80, H 4.07, N 10.00.
3.2.21. tert-Butyl 3-(4-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)buta-1,3-diynyl)-1H-indole-1-carboxylate (2u)

![Chemical Structure](image)

C₃₀H₂₈N₂O₄

480.55

315 mg (0.66 mmol, 66 % yield) as a yellow oil. Upon crystallisation in n-pentane, a pale yellow solid was obtained. Mp 120-121 °C. ¹H NMR (CDCl₃, 500 MHz): δ 1.68 (s, 18 H), 7.30-7.35 (m, 2 H), 7.35-7.40 (m, 2 H), 7.73-7.76 (m, 2 H), 7.89 (s, 2 H), 8.15 (d, J = 7.9 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz): δ 28.1 (CH₃), 74.1 (C quat), 77.4 (C quat), 84.6 (C quat), 102.1 (C quat), 115.3 (CH), 120.2 (CH), 123.4 (CH), 125.4 (CH), 130.4 (C quat), 131.1 (CH), 134.5 (C quat), 148.8 (C quat). EI + MS (m/z (%)): 480 (M⁺, 2), 368 (C₂₂H₁₂N₂O₄⁺, 10), 324 (C₂₁H₁₂N₂O₂⁺, 7), 280 (C₂₀H₁₂N₂⁺, 40), 279 (10), 140 (C₁₀H₇N⁺, 10), 57 (C₄H₉⁺, 27), 56 (64), 55 (28), 44 (CO₂⁺, 100), 43 (27), 42 (16), 41 (82). IR (KBr): ν 3158 (w) cm⁻¹, 2974 (w), 2149 (w), 1724 (s), 1616 (w), 1544 (m), 1475 (m), 1453 (s), 1369 (s), 1305 (m), 1288 (m), 1260 (m), 1226 (s), 1156 (s), 1106 (m), 1087 (m), 1053 (m), 1014 (w), 938 (w), 857 (w), 810 (w), 744 (m), 613 (w), 579 (w), 503 (w). Anal. calcd for C₃₀H₂₈N₂O₄ (480.6): C 74.98, H 5.87, N 5.83. Found: C 75.15, H 5.93, N 5.80.
3.2.22. tert-Butyl 2-(4-methoxyphenyl)-4-(4-(2-(4-methoxyphenyl))-1-(tert-butoxycarbonyl)-1H-pyrrol-3-yl)buta-1,3-diylnyl)-1H-pyrrole-1-carboxylate (2v)

![Chemical Structure](image)

C$_{36}$H$_{36}$N$_2$O$_6$

592.68

341 mg (0.58 mmol, 58 % yield) as a pale yellow solid. Mp 143-145 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.39 (s, 18 H), 3.82 (s, 6 H), 6.21 (d, $J = 1.9$ Hz, 2 H), 6.87-6.91 (m, 4 H), 7.23-7.26 (m, 4 H), 7.57 (d, $J = 1.9$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 27.6 (CH$_3$), 55.2 (CH$_3$), 74.2 (C$_{quat}$), 75.2 (C$_{quat}$), 84.4 (C$_{quat}$), 105.5 (C$_{quat}$), 113.1 (CH), 116.3 (CH), 125.5 (C$_{quat}$), 127.5 (CH), 130.5 (CH), 135.1 (C$_{quat}$), 148.3 (C$_{quat}$), 159.3 (C$_{quat}$). EI + MS ($m/z$ (%)): 592 (M$^+$, 0.2), 392 (C$_{26}$H$_{20}$N$_2$O$_2^+$, 6), 310 (3), 197 (4), 57 (C$_4$H$_9^+$, 14), 56 (77), 55 (31), 44 (CO$_2^+$, 94), 41 (100). IR (KBr): $\tilde{\nu}$ 3147 (w) cm$^{-1}$, 2981 (w), 2836 (w), 2150 (w), 1742 (s), 1614 (w), 1571 (w), 1524 (w), 1488 (s), 1361 (s), 1331 (s), 1287 (m), 1249 (s), 1205 (w), 1177 (m), 1151 (s), 1108 (w), 1035 (w), 991 (w), 847 (m), 766 (w), 608 (w). Anal. calcd for C$_{36}$H$_{36}$N$_2$O$_6$ (592.7): C 72.95, H 6.12, N 4.73. Found: C 72.70, H 6.05, N 4.75.
3.2.23. 1-Benzyl-4-(4-(1-benzyl-1H-pyrazol-4-yl)buta-1,3-diynyl)-1H-pyrazole (2w)

\[
\text{C}_{24}\text{H}_{18}\text{N}_4
\]

362.43

244 mg (0.67 mmol, 67 % yield) as a yellow solid. Mp 182-184 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 5.26 (s, 4 H), 7.19-7.23 (m, 4 H), 7.29-7.37 (m, 6 H), 7.53 (s, 2 H), 7.66 (s, 2 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 56.3 (CH\(_2\)), 72.5 (C\(_{\text{quat}}\)), 74.8 (C\(_{\text{quat}}\)), 102.4 (C\(_{\text{quat}}\)), 127.9 (CH), 128.4 (CH), 129.0 (CH), 133.3 (CH), 135.4 (C\(_{\text{quat}}\)), 143.1 (CH). EI + MS (m/z (%)):

- 363 (14), 362 (M\(^+\), 47), 271 ((M-C\(_7\)H\(_7\))^+, 5), 91 (C\(_7\)H\(_7\)^+, 100), 65 (C\(_5\)H\(_5\)^+, 8). IR (KBr): \(\tilde{\nu}\) 3103 (w) cm\(^{-1}\), 2147 (m), 1638 (w), 1536 (s), 1493 (w), 1451 (m), 1435 (m), 1373 (s), 1343 (m), 1200 (w), 1162 (m), 1076 (m), 1005 (m), 988 (m), 856 (s), 820 (w), 721 (s), 695 (m), 656 (w), 632 (m), 586 (w). Anal. calcd for C\(_{24}\)H\(_{18}\)N\(_4\) (362.4): C 79.54, H 5.01, N 15.46. Found: C 79.40, H 4.94, N 15.27.
3.2.24. 1-Benzyl-5-(4-(1-benzyl-1H-imidazol-5-yl)buta-1,3-diylnyl)-1H-imidazole dihydrochloride (2x)

183 mg (0.51 mmol, 51 % yield) as a colorless solid (free base). For characterisation, it was suspended in 1.25 M HCl in EtOH, stirred at the room temperature, filtered and washed with n-pentane. Colorless solid. Mp 160-162 °C. EI + MS (m/z (%)): 362 ((M-2 HCl)\(^+\), 4), 277 (14), 158 (C\(_{10}\)H\(_{10}\)N\(_2\)\(^+\), 44), 91 (C\(_7\)H\(_7\)\(^+\), 100), 65 (C\(_5\)H\(_5\)\(^+\), 8). IR (KBr): \(\tilde{\nu}\) 3445 (w) cm\(^{-1}\), 3131 (m), 3088 (m), 3029 (w), 2974 (w), 2639 (w), 2332 (s), 1904 (m), 1638 (w), 1572 (w), 1497 (w), 1458 (w), 1437 (w), 1395 (w), 1377 (w), 1306 (s), 1262 (w), 1188 (m), 1098 (w), 971 (w), 898 (m), 866 (m), 819 (m), 727 (s), 695 (w), 625 (m), 520 (w). Anal. calcd for C\(_{24}\)H\(_{20}\)Cl\(_2\)N\(_4\) (435.4) : C 66.21, H 4.63, N 12.87. Found: C 65.95, H 4.61, N 12.85.

The dihydrochloride was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.
3.2.25. 2-(4-((Thiophen-2-yl)buta-1,3-diynyl)thiophene (2y)

![Chemical structure]

C_{12}H_6S_2

214.31

151 mg (0.71 mmol, 71 % yield) as a pale brown solid. Mp 86-88 °C. ¹H NMR (CDCl₃, 500 MHz): δ 6.98 (dd, J = 5.1 Hz, J = 3.7 Hz, 2 H), 7.31 (dd, J = 5.1 Hz, J = 1.1 Hz, 2 H), 7.33 (dd, J = 3.7 Hz, J = 1.1 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz): δ 76.8 (C_quat), 78.0 (C_quat), 122.1 (C_quat), 127.4 (CH), 129.1 (CH), 134.6 (CH). El + MS (m/z (%)): 216 (10), 215 (15), 214 (M⁺, 100), 170 (19). IR (KBr): ν 3104 (w) cm⁻¹, 2140 (m), 1655 (w), 1544 (w), 1408 (m), 1368 (w), 1226 (m), 1208 (w), 1148 (m), 1130 (m), 1080 (w), 1038 (w), 836 (s), 711 (s), 569 (w), 508 (m). Anal. calcd for C_{12}H_6S_2 (214.3) : C 67.25, H 2.82. Found: C 67.02, H 2.94.


Light sensitive pale yellow solid. Mp 92-93 °C. ¹H NMR (CDCl₃, 200 MHz): δ 7.00 (dd, J = 5.1 Hz, J = 3.7 Hz, 2 H), 7.32 (dd, J = 5.1 Hz, J = 1.2 Hz, 2 H), 7.34 (dd, J = 3.7 Hz, J = 1.2 Hz, 2 H). ¹³C NMR (CDCl₃, 50.3 MHz): δ 76.6, 77.8, 122.0, 127.2, 128.9, 134.4. IR (neat): ν 3106 cm⁻¹, 2141, 1408, 714. Anal. calcd for C_{12}H_6S_2 (214.3) : C 67.25, H 2.82. Found: C 67.12, H 2.69.
3.2.26. 2-Ethyl-3-(4-(2-ethyl-5-(thiophen-2-yl)furan-3-yl)buta-1,3-diynyl)-5-(thiophen-2-yl)furan (2z)

204 mg (0.51 mmol, 51 % yield) as a yellow solid. Mp 122 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.32 (t, $J = 7.6$ Hz, 6 H), 2.84 (q, $J = 7.6$ Hz, 4 H), 6.46 (s, 2 H), 7.01-7.04 (m, 2 H), 7.21-7.24 (m, 4 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 12.4 (CH$_3$), 21.1 (CH$_2$), 73.7 (C$_{quat}$), 76.8 (C$_{quat}$), 103.3 (C$_{quat}$), 107.4 (CH), 122.9 (CH), 124.4 (CH), 127.6 (CH), 132.8 (C$_{quat}$), 147.3 (C$_{quat}$), 163.2 (C$_{quat}$). EI + MS (m/z (%)): 404 (14), 403 (28), 402 (M$^+$, 100), 389 (12), 388 (25), 387 ((M-CH$_3$)$^+$, 98), 201 (C$_{12}$H$_{10}$OS$^+$, 12), 193 (18), 187 (19), 186 (C$_{11}$H$_{8}$OS$^+$, 66), 135 (20), 111 (43), 43 (11). IR (KBr): $\bar{\nu}$ 2973 (w) cm$^{-1}$, 2933 (m), 2143 (w), 1655 (m), 1638 (m), 1561 (m), 1543 (w), 1509 (w), 1450 (w), 1422 (w), 1376 (w), 1251 (w), 1203 (m), 1114 (w), 1050 (s), 1037 (m), 996 (w), 895 (w), 849 (m), 819 (w), 785 (s), 689 (s), 635 (w), 579 (m). Anal. calcd for C$_{24}$H$_{18}$O$_2$S$_2$ (402.5): C 71.61, H 4.51. Found: C 71.65, H 4.46.
4. $^1$H and $^{13}$C NMR Spectra of Compounds 2a-2z

$^1$H NMR of 2a in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^{13}$C NMR of 2a in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2a in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 2b in CDCl$_3$ at 296 K (δ in ppm).
$^{13}$C NMR of 2b in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2b in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 2c in CDCl₃ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2c in CDCl$_3$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2c in CDCl$_3$ at 296 K (δ in ppm).
$^1$H NMR of 2e in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2e in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 2e in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 2f in CDCl$_3$ at 296 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2f in CDCl$_3$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2f in CDCl$_3$ at 297 K (δ in ppm).
$^1$H NMR of 2i in CDCl$_3$ at 298 K (δ in ppm).
$^{13}$C NMR of \(2i\) in CDCl$_3$ at 298 K (\(\delta\) in ppm).

$^{13}$C DEPT 135-NMR of \(2i\) in CDCl$_3$ at 298 K (\(\delta\) in ppm).
$^1$H NMR of 2j in CDCl$_3$ at 296 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2j in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2j in CDCl$_3$ at 296 K ($\delta$ in ppm).
\(^1\text{H NMR of 2l in CDCl}_3\) at 295 K (\(\delta\) in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2I in CDCl$_3$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2I in CDCl$_3$ at 296 K (δ in ppm).
$^1$H NMR of 2m in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 2m in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2m in CDCl$_3$ at 296 K (δ in ppm).
$^1$H NMR of 2n in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 2n in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2n in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 2o in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2o in CDCl$_3$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2o in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 2p in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2p in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2p in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 2q in CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2q in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2q in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 2r in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2r in CDCl$_3$ at 298 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2r in CDCl$_3$ at 298 K (δ in ppm).
$^1$H NMR of 2t in CDCl$_3$ at 299 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2t in CDCl$_3$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2t in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 2u in CDCl$_3$ at 296 K (δ in ppm).
$^{13}$C NMR of 2u in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2u in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 2v in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of 2v in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2v in CDCl$_3$ at 297 K ($\delta$ in ppm).
'H NMR of 2w in CDCl₃ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2w in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 2w in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 2y in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 2y in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 2y in CDCl$_3$ at 297 K (δ in ppm).
$^1$H NMR of 2z in CDCl$_3$ at 299 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of $2z$ in CDCl$_3$ at 299 K (δ in ppm).

$^{13}$C DEPT 135-NMR of $2z$ in CDCl$_3$ at 299 K (δ in ppm).
5. References


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Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence†‡

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The one-pot, three-component Sonogashira coupling–TMS-deprotection–CuAAC (“click”) sequence is the key reaction for the rapid synthesis of triazolyl substituted N-Boc protected NH-heterocycles, such as indole, indazole, 4-, 5-, 6-, and 7-azaindoles, 4,7-diazaindole, 7-deazapurines, pyrrole, pyrazole, and imidazole. Subsequently, the protective group was readily removed to give the corresponding triazolyl derivatives of these tremendously important NH-heterocycles. All compounds have been tested in a broad panel of kinase assays. Several compounds, 8f, 8h, 8k, and 8l, have been shown to inhibit the kinase PDK1, a target with high oncology relevance, and thus they are promising lead structures for the development of more active derivatives. The X-ray structure analysis of compound 8f in complex with PDK1 has revealed the detailed binding mode of the molecule in the kinase.

Introduction

Indoles represent one of the most prominent privileged structures1 because they are widespread in nature2 and pharmaceutically relevant compounds.3 Among them, indoles bearing 5- and 6-membered heterocycles as substituents in the 3-position represent a conspicuously frequently occurring substitution pattern. In particular, the heterocyclic ring found in natural products or their bioactive analogues can be pyrimidine (meridianins,4 hyrtinadine A5), tetrahydropyrimidine (aplicyanins6), piperazine and (dihydro)pyprazine (dragmacidins7, hamacanthins8), oxazinone (oxazinins9), oxadiazinone (alboinons10), imidazole (nortopsentins,11,12 topsentins12), imidazolone,13,14 oxazole (diazonamides,15 martefragin A,16 almazoles,17 pinprinine,18 and labradorins19), thiazole (camalexins,20 BE-1098821), imidazoline (spongotines,22 discoderminolides,23 trachycladinolides24), oxazoline,25 maleimide (didemnimides26), isouquinolinequinoxone (mensouramycin D27), β-carboline (eudistomin U,28 hyrtioerectine A29), pyrrole (chromopyrrolic acid,30 lynamicins31), pyrroline (violacein32), or another indole.33 Besides indoles, their aza analogues, i.e. indazole and azaindoles, apparently play an increasingly important role as scaffolds for biologically active molecules.34 In particular, 7-azaindoles are predestined to be promising scaffolds for investigations as kinase inhibitors due to their pronounced ability to bind to the hinge region of kinases.35 Again, heterocyclic substituents at the C-3 position are very common. The most prominent examples are the marine natural products variolins36 and the simplified synthetic analogues of variolin B, i.e. the meriolins37 (Fig. 1).

Fig. 1 Biologically active (aza)indoles with 5- and 6-membered heterocycles at C-3 (corresponds to C-5 in variolin B).

Recently, we reported a practical approach to indoles and 7-azaindoles substituted with azines38 via a one-pot Masuda borylation–Suzuki coupling sequence.38 Using this approach,
Results and discussion

The Sonogashira coupling–TMS-deprotection–CuAAC sequence

The Sonogashira–Hagihara cross-coupling is among the most reliable C–C bond forming reactions and has become the method of choice for the construction of internal alkynes from heteroaryl halides and terminal alkynes. Upon coupling halides with trimethylsilylacetylene (TMSA), TMS-protected alkynes are formed, which can be easily deprotected to give (hetero)aromatic groups. All these features render this reaction highly practical, reliable, mild, general, and highly tolerant to diverse functional groups.

Surprisingly, triazoyl substituted indoles have hardly been explored, although the 1,2,3-triazole ring as an electron-poor meta-stable 5-membered heterocyclic substituent has attracted considerable attention in bioconjugate chemistry, medicinal chemistry, and drug discovery. In addition to its function as a convenient linker, the 1,4-disubstituted 1,2,3-triazole is a peptidomimetic, has a large dipole moment and is an H-acceptor over N-2 and N-3 atoms. Here, we report a diversity-oriented synthetic concept to access 3-triazolyl-substituted (aza)indole scaffolds in a one-pot fashion. In addition, the potential of the title compounds as kinase inhibitors and cytotstatics is explored.

Scheme 1 Synthetic concept for triazoyl N-Boc protected heterocycles (X = CH or N; R = alkyl or aryl, may be generated in situ).

Easily introduced on the nitrogen atoms of 5-membered NH-heterocycles or it can be installed directly in the course of their synthesis. If not further required, this group can be removed easily and cleanly under various conditions. Previously, we have demonstrated the enormous utility and versatility of 3-iodo N-Boc protected indoles, 7-azaindoles, and pyroles as easily accessible synthetic building blocks.

The Sonogashira coupling of iodo N-Boc NH-heterocycles with TMSA proceeded smoothly under standard Sonogashira conditions (PdCl₂(PPh₃)₃/CuI/NEt₃). The obtained TMS-alkynes were not isolated but directly deprotected with TBAF and subsequently reacted with one equivalent of the commercially available and stable benzyl azide to furnish N-Boc 3-triazolyl (aza)indoles and azoles in a one-pot fashion (Scheme 2). The yields were very similar for (aza)indoles and pyrole regardless of the number and position of nitrogen atoms.

Scheme 2 Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of N-Boc 3-triazolyl (aza)indoles and azoles (X = CH or N; R = alkyl, aryl, Me, OMe, O(CH₂)₃OMe, p-MeOC₆H₄).

No further addition of CuI was required in the CuAAC step. The reaction progress can be conveniently monitored by TLC and the steps cleanly proceed as “spot-to-spot” reactions without noticeable amounts of byproducts. No Glaser-type homodimerization products were detected because the CuAAC reaction was performed under an argon atmosphere. It is worth mentioning that the electron-withdrawing Boc protective group renders the (aza)indolyl iodides stable to storage, whereas the unprotected iodoles are frequently sensitive to light and temperature and therefore inconvenient to handle.

Moreover, the Sonogashira coupling is greatly facilitated, or even becomes feasible, due to the diminished electron density of these heterocycles.

For the synthesis of triazoles with different substituents on the N-1 atom of the triazole moiety, the sequence was extended.
to a four-component reaction with N-Boc protected 3-iodo 7-azaindole (1f) as a substrate. This sequence additionally includes the in situ generation of the azide 5 via nucleophilic substitution of a halide with caesium azide (Scheme 3). Hence, not only electronically diverse benzyl substituents (2p and 2q), and even α-phenylethyl substituents (2s), but also the homobenzyl group can be introduced with a comparable yield (2r).

Scheme 3 Four-component Sonogashira coupling–TMS-deprotection–Finkelstein-type reaction–CuAAC sequence for the synthesis of N-Boc protected triazolyl 7-azaindoles 2p–s (R = alkyl; Hal = Br, Cl).

For 4- and 5-bromo 7-azaindoles (6a and 6b), which are commercially available and stable compounds, a four-component Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to give N-Boc protected 4- and 5-triazolyl azaindoles (7a and 7b) in very good yields (Scheme 4). The Sonogashira coupling was performed at room temperature using Fu’s catalytic system.73

Scheme 4 Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of N-Boc 4- and 5-triazolyl 7-azaindoles 7a and 7b.

The possibility to easily adopt the whole synthesis to a specific substrate and a flexible incorporation of additional steps into the sequence is an additional advantage of this one-pot methodology. The obtained N-Boc protected triazolyl NH-heterocycles 2 and 7 were readily deprotected under extremely mild conditions using potassium carbonate in methanol at room temperature or slightly above (Scheme 5). It should be mentioned that although the Boc protective group could be removed after the completed sequence in a one-pot fashion, we preferred to perform the Boc-deprotection in a separate step to ensure the high purity of the final products (as determined by HT-LC-MS analysis, the UV purity was 99.9–100% for all presented compounds). The content of Pd and Cu in compound 8f was determined to be < 1 μg g⁻¹ (< 3 ppm) and < 2 μg g⁻¹ (< 9 ppm), respectively. Thus, no additional removal of these heavy metals is required.74

The scope of the presented methodology includes indole (8a) and its bioisosters such as indazole (8b), all azaindoles (8c–i, 8p–s, and 9), diazaindole (8j), deazapurines (8k–l), as well as pyrrole (8m), pyrazole (8n), and imidazole (8o) (Fig. 2).

Fig. 2 Scope of the synthetic strategy towards triazolyl NH-heterocycles 8 and 9 (isolated yields over two steps).

The yields are fair to good and are very similar for all indole analogues 8a–l. They are little affected by the position and number of additional nitrogen atoms, which is not self-evident (according to personal observations experienced with other coupling reactions of these substrates) and emphasizes the synthetic power gained from the combination of two very general methods, Sonogashira coupling and CuAAC. Only the azoles 8n and 8o gave poor yields due to the increased lability of the Boc protective group in the corresponding starting materials. Moreover, with tert-butyl1-iodo-1H-imidazole-1-carboxylate (1n) the Sonogashira coupling proceeded very sluggish and required
15 d reaction time. The structures of the obtained triazoles 8 and 9 were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound 8f, cocrystallized with kinase PDK1 (vide infra).

The sequences are very straightforward and preparatively extremely simple to perform. Generally, all steps proceed at room temperature, which is especially important if less stable azides are to be used. However, they can even be generated in situ with comparable efficiency. It should be noted that while these studies were in progress two reports appeared in the literature which described the same synthetic approach with simple aryl iodides. However, we used this strategy to synthesize triazolyl NH-heterocycles, which are more sophisticated chemical targets and show promising biological activity, thus illustrating the synthetic utility of this practical synthesis. Since a variety of diverse NH-heterocycles, which are of paramount importance in many areas of research, can be decorated with triazoles in a very straightforward fashion, the sequence is quite general. Starting from these small lead structures, more potent derivatives can be readily developed using this synthetic approach.

Biological data

All compounds 8 and 9 were tested for inhibition of a broad panel of kinases at the Division of Signal Transduction Therapy (DSTT) at the University of Dundee, UK. The compounds were screened against 95–121 kinases at a concentration of 1 µM. In addition, for all compounds, IC<sub>50</sub> values for the inhibition of the kinase PDK1, a target of high relevance for oncology, were determined. The results for compounds that showed submicromolar activity on at least one kinase are summarized in Table 1.

For the compounds described here, a hydrogen donor/acceptor pattern of the 7-azaindole core that can interact with the hinge region of kinases, is a prerequisite for kinase inhibitory activity. All compounds in this table possess such a pattern whereas the great majority of the inactive compounds 8a, 8c, 8d, 8e, 8m, 8n, and 8o, lack this peculiar structural feature. In particular, compounds with a benzyltriazole group in the 3-position of a 7-azaindole-like template turned out to be broad kinase inhibitors with 8h, 8k, and 8l having the broadest activity. In contrast, compounds 9a and 9b, which possess a benzyltriazole substituent at C-4 and C-5 of the 7-azaindole, are much less active, thus emphasizing the importance of C-3 substitution. Furthermore, substitution at C-6 or a nitrogen atom in the para-position to N-7 of the 7-azaindole seem to reduce the biological activity of compounds 8i and 8j.

For determining whether the triazole unit is merely a linker or possesses an additional function, an analogue of compound 8f was prepared via the recently reported Masuda borylation–Suzuki coupling sequence. This compound bears a pyrazole moiety instead of a triazole. Interestingly, the triazole unit seems to be important for the biological activity, since the pyrazole compound 11 was significantly less active with an IC<sub>50</sub> value of 2.6 µM for PDK1 compared with 0.8 µM for the triazole 8f. Therefore, triazole does not simply seem to be a linker, as in many applications of this heterocycle, but rather displays a pharmacophore character. However, even more exciting was the observation that the isomeric compound 10, differing from 8f only in the permutation of substituents on N-1 and C-4 of the triazole unit, showed no activity on kinases, including PDK1 (Table 2).

X-ray structure of 8f in complex with PDK1

For further characterization of the binding mode, compound 8f was soaked in crystals of the kinase domain of PDK1. Broad kinase activity of triazole derivatives is related to PDK1 activity (Table 1), which suggests that the binding mode in this kinase may be representative for several other kinases. The crystal structure was solved at 1.7 Å (Table 3) and reveals the detailed binding mode of 8f within the ATP-binding site (Fig. 3).

Compound 8f shows two canonical hydrogen bonds to the hinge region, an H-bond donor contact from azaindole N-1 to Ser160, and an H-bond acceptor contact from azaindole N-7 to Ala162. The triazole nitrogen atoms are also involved in hydrogen bonding interactions: N-3 to the Thr222 side chain (which may explain the lower activity of the pyrazole 11) and N-2 to a water molecule. This water molecule is also in the H-bond distance to the catalytic amino acids Lys111 and Asp223. The molecule binds in an overall bent conformation with the benzyl group forming hydrophobic interactions with the glycine-rich region (GC-loop). The reason for the inactivity of compound 10, which is a bioisostere of compound 8f and differs only in the relative position of the substituents on N-1 and C-4 of the triazole unit and consequently in the dipole moment.

Table 1  Biological data of selected compounds 8 and 9

<table>
<thead>
<tr>
<th>Number of kinases with &gt;50% inhibition @ 1 µM/number of kinases tested</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;[PDK1] (µM)</th>
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<tr>
<td>8b</td>
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<tr>
<td>8f</td>
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<tr>
<td>9a</td>
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</tr>
<tr>
<td>9b</td>
<td>4/110</td>
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</table>

IC<sub>50</sub>: concentration inhibiting kinase activity or reducing cell proliferation by 50%.

Table 2  Comparison of IC<sub>50</sub> values of PDK1 inhibition between isomeric 3-triazolyl 7-azaindole compounds 8f and 10, as well as 3-pyrazolyl 7-azaindole 11

<table>
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<tr>
<th>PDK1 inhibition/IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
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<tr>
<td></td>
</tr>
<tr>
<td>8f</td>
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<tr>
<td>0.8</td>
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<td></td>
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<td>10</td>
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<td>&gt;10</td>
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<td>11</td>
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<td>2.6</td>
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of the molecule, cannot be deduced from this X-ray structure and still remains obscure.

Conclusions

A practical and preparatively simple one-pot three-component Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to synthetically access a variety of triazolyl NH-heterocycles 8 and 9 in high purity and a very concise fashion. The sequence works very reliably for substrates with nitrogen atoms in different positions of various indole isosters, arising from the robustness, the versatility, and the generality of both Sonogashira coupling and CuAAC. The title compounds were tested for inhibition of a broad panel of kinases to reveal their kinase inhibitory activities. Compounds 8f, 8h, 8k, and 8l were found to inhibit PDK1 kinase with IC_{50} values below 1 μM. The X-ray structure analysis of compound 8f in complex with PDK1 reveals the importance of the benzyl substituent for the binding. The phenyl and homobenzyl derivatives 8g and 8r were considerably less active, indicating a suboptimal position of their aromatic rings for favorable interaction towards the GC-loop compared with the benzyl substituent in 8f. Since all synthesized compounds are small molecules, more potent analogues can be envisioned by derivatization, which can be achieved easily with the presented method.

Experimental

Synthesis of 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8f)

(Compound 2f): PdCl₂(PPh₃)₂ (71 mg, 0.10 mmol, 2 mol%) and CuI (39 mg, 0.20 mmol, 4 mol%) were placed in a dry screw-cap Schlenk vessel with a septum. Then, tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f) (1.72 g, 5.00 mmol) was added in 25 mL of dry tetrahydrofuran under an argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylethylene (1.08 mL, 7.50 mmol, 1.50 equiv.) and dry triethylamine (1.39 mL, 10.0 mmol, 2.00 equiv.) were added and the mixture was stirred at room temperature (in a water bath) for 1 h until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (7.50 mL, 1.50 mmol, 1.50 equiv.) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (5a) (679 mg, 5.00 mmol, 1.00 equiv.) in 5 mL of dry methanol was added and the mixture was stirred at room temperature for 40 h until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40–60°C)–ethyl acetate PE–EtOAc = 2:1 (R_ν = 0.20) to give 1.56 g (4.15 g, 83%) tert-butyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (2f) as a yellow foam. The obtained compound was deprotected without characterization and further purification.

(Compound 8f): tert-Butyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (2f) (1.56 g, 4.15 mmol) was placed in 21 mL of methanol. Then, potassium carbonate (1.45 g, 10.4 mmol, 2.50 equiv.) and dry triethylamine (1.39 mL, 10.0 mmol, 2.00 equiv.) were added and the mixture was stirred at room temperature (in a water bath) for 1 h (monitored by TLC). A precipitate formed after a few min. The mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane–methanol–aqueous ammonia DCM–MeOH–NH₃ = 100:3:1 (stepwise gradient). After drying in vacuo overnight, 930 mg (3.38 mmol, 81%) of a pale yellow solid were obtained. The product was additionally purified by suspension in dichloromethane, sonication in ultrasonic bath for 0.5 h, filtration and drying in vacuo at 70°C overnight to obtain the analytically pure 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8f) as a colorless solid. UV purity (HT-LC-MS): 100%. M.p. 234–237°C. H NMR (DMSO-d₆, 500 MHz): δ (ppm) 5.66 (s, 2 H), 7.17 (dd, J = 7.9 Hz, J = 4.7 Hz, 1 H), 7.32–7.43 (m, 5 H), 7.92 (d, J = 2.5 Hz, 1 H), 8.29 (dd, J = 4.7 Hz, J = 1.6 Hz, 1 H), 8.44 (dd, J = 7.9 Hz, J = 1.6 Hz, 1 H), 8.54 (s, 1 H), 11.9 (br, 1 H, NH). ¹³C NMR (DMSO-d₆, 125 MHz): δ (ppm) 52.8 (CH₃), 105.0 (C quat), 115.9 (CH), 116.9 (C quat), 119.8 (CH), 123.2 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 136.1 (C quat), 142.4 (C quat), 143.1 (CH), 148.5

---

**Table 3 Crystallographic data of compound 8f**

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**Fig. 3** X-ray structure of the complex of 8f with PDK1 at 1.7 Å resolution. The 7-azaindole ring forms H-bonds to the hinge region (Ser160 & Ala162); two of the triazole N-atoms form H-bonds to Thr222 and a water molecule. The benzyl ring is oriented towards the GC-loop.
The diffraction data were collected at the PXIII beamline equipped of 50 peptide/protein substrate for 5 min before initiation of the reaction termination by the addition of 50 mM orthophosphoric acid) and dried in air. The dry assay plates were then harvested onto P81 Unifilter Plates (wash 0.25 M. Guyot and M. Meyer, Can. J. Chem. 1994, 72, 1233.


PKD1 biochemical kinase assay

The PKD1 (3-phosphoinositide-dependent protein kinase-1) assay was carried out in 384-well streptavidin-coated FlashPlates (PerkinElmer). 3.4 mM His6-PDK1(Δ1-50), 400 nM biotinylated PKD1kde (Biotin-βA-βA-KTFCGTPYEALPEVRREPRILS-EEEQEMFRDFDY1ADWC), and 4 µM ATP (spiked with 0.25 µCi 32P-ATP per well) were incubated in a total volume of 50 µL (50 mM TRIS, 10 mM magnesium acetate, 0.1% mercaptoethanol, 0.02% Brij35, 0.1% bovine serum albumin, pH 7.5) with or without test compound (7–10 concentrations) for 60 min at 30 °C. The reaction was stopped by the addition of 25 µL 200 mM EDTA. After 30 min at room temperature the liquid was removed and each well washed three times with 100 µL 0.9% sodium chloride solution. Nonspecific reaction was determined in the presence of 100 nM staurosporine. Radioactivity was measured in a Topcount (PerkinElmer). Results (IC50 values) were calculated with e.g. AssayExplorer (Symyx).

DSTT kinase assays

The kinase assay was carried out at room temperature. Compounds were pre-incubated in the presence of the enzyme and peptide/protein substrate for 5 min before initiation of the reaction by adding ATP. Assays were incubated at room temperature before termination by the addition of 5 µL orthophosphoric acid. The assay plates were then harvested onto P81 Unifilter Plates (wash buffer was 50 mM orthophosphoric acid) and dried in air. The dry Unifilter plates were then sealed on the presence of MicroSci O and were counted in Packard Topcount NXT scintillation counters.

Cocrystallization of compound 8f with PKD1 and X-ray structure determination

Cocrystallization of PKD1 was performed as previously described and crystals were used for soaking with compound 8f. X-Ray diffraction data were collected at the PXIII beamline equipped of a Pilatus detector at the Paul Scherrer Institut in Villingen, Switzerland. With the detector set at 270 mm, data were collected in 720 contiguous 0.25° oscillation images at 1 Å wavelength. The data for compound 8f extends to 1.7 Å resolution, has an Rwork of 7.2% and 3.31-fold multiplicity. The structure was refined using CNS (Accelrys Inc.) to an Rfactor of 19.8%.

Acknowledgements

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For recent reviews on CuAAC, see: V. V. Fokin, Angew. Chem., Int. Ed., 2007, 46, 1018.


For recent reviews, see: T. J. J. Müller,  


Compounds 1a, 1d–k, and in were prepared as described in: B. Willy, U. Ragnarsson, Tetrahedron, 2000, 56, 8473.

Although numerous efficient catalytic systems have been described for the Sonogashira-type alknylations, this standard catalytic system is still by far the most widely used one: H. Plenio, Angew. Chem. Int. Ed., 2008, 47, 6954; R. R. Tykwinski, Angew. Chem., Int. Ed., 2003, 42, 1566.


Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence**


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[**] This work was supported by Merck Serono, Darmstadt
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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using MBraun system MB-SPS-800, and triethylamine was refluxed under argon atmosphere over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from Sigma-Aldrich Chemie GmbH.

7-, 6-, and 5-Azaindoles were obtained commercially from Biosynth. 4-Azaindole, 4-chloro-7-azaindole, and 4-chloro-deazapurine were synthesized in laboratories of Merck Serono, Darmstadt. 4,7-Diazaindole and 2-methyl-7-azaindole were obtained from Ark Pharm, Inc. 4(5)-lodo-1H-imidazole and tert-butyl 4-iodo-1H-pyrazole-1-carboxylate (1m) were purchased from ABCR GmBH & Co. 4-Bromo-7-azaindole (6a) and 5-bromo-7-azaindole (6b) were obtained from Sigma-Aldrich Chemie GmbH.

Trimethylsilylacetylene was obtained from Sigma-Aldrich Chemie GmbH. Tetrabutylammonium fluoride (1 M in THF) was obtained from Sigma-Aldrich Chemie GmbH. Benzyl azide (5a) was obtained from ABCR GmBH & Co. Azidobenzene solution (~ 0.5 M in tert-butylmethylether) was obtained from Sigma-Aldrich Chemie GmbH. Cesium azide was obtained from Sigma-Aldrich Chemie GmbH. Cp*RuCl(PPh3)2 was obtained from ABCR GmBH & Co.

Commercial grade reagents were used as supplied without further purification and were purchased from Acros Organics, Sigma-Aldrich Chemie GmbH, Fluka AG, ABCR GmBH & Co. KG, AppliChem, and Merck KGaA.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck KGaA using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from Merck KGaA before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F254 5 x 7.5 cm aluminium sheets obtained by Merck KGaA. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.
$^1$H, $^{13}$C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. CDCl$_3$ and DMSO-d$_6$ were used as deuterated solvents. TMS was used as reference ($\delta = 0.0$) or the resonances of the solvents were locked as internal standards (CDCl$_3$: $^1$H $\delta$ 7.26, $^{13}$C $\delta$ 77.0; DMSO-d$_6$: $^1$H $\delta$ 2.50, $^{13}$C $\delta$ 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, q: quartet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf. HT-LC-MS spectra were measured in the Molecule Analytics laboratory of Central Analytical Services, Merck KGaA Darmstadt. The content of Pd and Cu in the compound 8f was determined in the Element Analytics laboratory of Central Analytical Services, Merck KGaA Darmstadt.
2. Preparation of Starting Materials 1a-l and 1n

2.1. Preparation of N-Boc 3-iodo (aza)indoles 1a, 1d-k, and 1n (shown for tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f))

A solution of iodine (25.7 g, 101 mmol, 1.01 equiv) in 180 mL of DMF was dropped to the solution of 7-azaindole (12.1 g, 100 mmol) and potassium hydroxide (16.5 g, 250 mmol, 2.50 equiv) in 180 mL of DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poured on 1 L ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 23.7 g (97.2 mmol, 97 % yield) of a yellow solid. The obtained iodide was used without further purification in the next step. It was suspended in 180 mL of dichloromethane, 4-dimethylaminopyridine (1.21 g, 9.72 mmol, 10 mol %) was added and di-tert-butyl dicarbonate (32.8 g, 146 mmol, 1.50 equiv), dissolved in 180 mL of dichloromethane, was added dropwise over 30 min. The mixture was stirred for 30 min at room temperature, washed with 200 mL of 0.1 N HCl, and the aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 20:1, Rf (PE-EtOAc = 20:1): 0.14) to give 31.6 g (91.8 mmol, 94 % yield; 92 % total yield over two steps) of tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f) as an orange oil, which solidifies upon storage in refrigerator.

Compounds 1a, 1d-e, 1g-k, and 1n were obtained analogously.

The experimental details are depicted in Table 1.
2.2. Preparation of tert-butyl 3-iodo-1H-indazole-1-carboxylate (1b)

A solution of iodine (13.8 g, 54.3 mmol, 2.00 equiv) in 50 mL of DMF was dropped to the solution of 1H-indazole (3.34 g, 27.1 mmol) and potassium hydroxide (5.70 g, 102 mmol, 3.76 equiv) in 50 mL of DMF at room temperature and the mixture was stirred for 4 h. The reaction mixture was then poured onto 200 mL of saturated sodium silfite solution and extracted with diethylether (2 x 50 mL). The combined organic layers were washed with water and brine and dried with sodium sulphate. After the solvents were removed under reduced pressure, 6.09 g (24.9 mmol, 92 % yield) of a yellow solid were obtained.

The obtained iodide was used without further purification for the next step. 3-Iodo-1H-indazole (5.09 g, 20.9 mmol) was dissolved in 100 mL of dichloromethane, then triethylamine (27.2 mL, 196 mmol, 9.39 equiv) and 4-dimethylaminopyridine (261 mg, 2.09 mmol, 10 mol %) were added, and di-tert-butyl dicarbonate (14.1 g, 62.6 mmol, 3.00 equiv), dissolved in 50 mL of dichloromethane, was slowly added dropwise. The mixture was stirred for 4 h at room temperature, washed with saturated sodium sulfite solution (3 x 20 mL), dried with sodium sulphate, and the solvents were removed under reduced pressure. The residue was adsorbed onto Celite® and purified chromatographically on basic Alox with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 20:1, Rf (PE-EtOAc = 20:1): 0.31) to give 6.26 g (18.2 mmol, 87 % yield; 80 % total yield over two steps) of tert-butyl 3-iodo-1H-indazole-1-carboxylate (1b) as a pale yellow solid.
2.3. Preparation of tert-butyl 3-iodo-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (1c)[2]

4-Azaindole (11.8 g, 100 mmol) was dissolved in 200 mL of pyridine and the solution was cooled with an ice bath. Then, 220 mL of a 0.5 M solution of iodomonochloride (17.9 g, 110 mmol, 1.10 equiv) in dichloromethane was added over 5 min. After 15 min the cooling bath was removed, and after another 30 min the solution was diluted with 2 L of ethyl acetate. The mixture was washed successively with 1 N HCl and 1 N NaOH, dried with sodium sulphate, and the solvents were removed in vacuo. The residue was dried in vacuo to give 18.3 g (75.0 mmol, 75 %) of an orange solid. The obtained iodide was used without further purification for the next step. 3-Iodo-1H-pyrrolo[3,2-b]pyridine (1.82 g, 7.45 mmol) was dissolved in 30 mL of dichloromethane, then triethylamine (6.62 mL, 47.8 mmol, 6.41 equiv) and 4-dimethylaminopyridine (91 mg, 0.75 mmol, 10 mol %) were added, and di-tert-butyl dicarbonate (3.25 g, 14.9 mmol, 2.00 equiv), dissolved in 25 mL of dichloromethane, was slowly added dropwise. The mixture was stirred for 4 h at room temperature, washed with saturated sodium sulfite solution (2 x 20 mL), dried with sodium sulphate, and the solvents were removed under reduced pressure. The residue was adsorbed onto Celite® and purified chromatographically on neutral Alox with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1, Rf (PE-EtOAc = 5:1): 0.41) to give 1.88 g (5.45 mmol, 73 % yield; 55 % total yield over two steps) of tert-butyl 3-iodo-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (1c) as a colorless solid.
### Table 1. Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles 1a-k and N-Boc 4-iodo imidazole 1n.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(Aza)Indole</th>
<th>3-Iodo (aza)indole</th>
<th>N-Boc 3-Iodo (aza)indole 1 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
<th>Rf (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0 g (171 mmol) 1H-Indole (Acros)</td>
<td>Yellow solid 32.8 g (135 mmol, 79 %)</td>
<td>Brown oil 11.3 g (32.9 mmol, 80 %)</td>
<td>PE-EtOAc = 50:1</td>
<td>Rf (PE-EtOAc = 50:1): 0.38</td>
</tr>
<tr>
<td></td>
<td>11.3 g (32.9 mmol, 80 %)</td>
<td>Total yield: 63 %</td>
<td>For Boc-protection: 10.0 g (41.1 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.34 g (27.1 mmol) 1H-Indazole (ABCR)</td>
<td>Yellow solid 6.09 g (24.9 mmol, 92 %)</td>
<td>Colorless solid 6.26 g (18.2 mmol, 87 %)</td>
<td>PE-EtOAc = 20:1</td>
<td>Rf (PE-EtOAc = 20:1): 0.31</td>
</tr>
<tr>
<td></td>
<td>6.26 g (18.2 mmol, 87 %)</td>
<td>Total yield: 80 %</td>
<td>For Boc-protection: 5.09 g (20.9 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11.8 g (100 mmol) 1H-Pyrrolo[3,2-b]pyridine (4-Azaindole) (Biosynth)</td>
<td>Orange solid 18.3 g (75.0 mmol, 75 %)</td>
<td>Colorless solid 1.88 g (5.45 mmol, 73 %)</td>
<td>PE-EtOAc = 5:1</td>
<td>Rf (PE-EtOAc = 5:1): 0.41</td>
</tr>
<tr>
<td></td>
<td>1.88 g (5.45 mmol, 73 %)</td>
<td>Total yield: 55 %</td>
<td>For Boc-protection: 1.82 g (7.45 mmol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (continuation). Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles 1a-k and N-Boc 4-iodo imidazole 1n.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azaindole</th>
<th>3-Iodo azaindole</th>
<th>N-Boc 3-Iodo azaindole 1 (isolated yield %)</th>
<th>Chromatographic purification (elucent)</th>
<th>Rf (elucent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.00 g</td>
<td>Pale yellow solid</td>
<td>Colorless solid 1.85 g (5.36 mmol, 87 %)</td>
<td>PE-EtOAc = 2:1</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>(8.47 mmol)</td>
<td>1.50 g (6.14 mmol, 73 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>1d</strong></td>
<td></td>
<td>Total yield: 64 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.00 g</td>
<td>Yellow solid</td>
<td>Pale yellow solid 7.52 g (21.9 mmol, 75 %)</td>
<td>PE-EtOAc = 2:1</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(42.3 mmol)</td>
<td>8.10 g (33.2 mmol, 78 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>1e</strong></td>
<td></td>
<td>Total yield: 59 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.1 g</td>
<td>Yellow solid</td>
<td>Yellow-orange oil[a] 31.6 g (91.8 mmol, 94 %)</td>
<td>PE-EtOAc = 20:1</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(100 mmol)</td>
<td>23.7 g (97.2 mmol, 97 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>1f</strong></td>
<td></td>
<td>Total yield: 92 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Solidifies upon storage in refrigerator.
Table 1 (continuation). Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles 1a-k and N-Boc 4-iodo imidazole 1n.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azaindole</th>
<th>3-Iodo azaindole</th>
<th>N-Boc 3-Iodo azaindole</th>
<th>Chromatographic purification (eluent)</th>
<th>Rf (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>284 mg (1.92 mmol) 4-Methoxy-1H-pyrrolo[2,3-b]pyridine[a]</td>
<td>Yellow solid 420 mg (1.53 mmol, 80 %)</td>
<td>Colorless solid 428 mg (1.14 mmol, 82 %)</td>
<td>PE-EtOAc = 1:1</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Boc- protection: 385 mg (1.40 mmol)</td>
<td>Total yield: 65 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.50 g (18.0 mmol) 2-Methyl-1H-pyrrolo[2,3-b]pyridine (Ark Pharm)</td>
<td>Beige solid 4.33 g (16.8 mmol, 93 %)</td>
<td>Yellow oil[b] 5.58 g (15.6 mmol, 95 %)</td>
<td>PE-EtOAc = 20:1 → 15:1</td>
<td>Rf (PE-EtOAc = 15:1): 0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Boc- protection: 4.25 g (16.5 mmol)</td>
<td>Total yield: 88 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.25 g (10.0 mmol) 5H-Pyrrolo[2,3-b]pyrazine (4,7-Diaza-indole) (Ark Pharm)</td>
<td>Yellow solid 2.00 g (8.18 mmol, 82 %)</td>
<td>Pale yellow solid 2.53 g (7.33 mmol, 92 %)</td>
<td>PE-EtOAc = 5:1</td>
<td>Rf (PE-EtOAc = 5:1): 0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Boc- protection: 1.96 g (7.99 mmol)</td>
<td>Total yield: 75 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Preparation from 4-chloro-1H-pyrrolo[2,3-b]pyridine is described in S. Benoit, S. Gingras, N. Soundararajan, PCT Int. Appl. 2003, WO 2003082289 A1 20031009. The beige solid was obtained in 78 % yield.
[b] Solidifies upon storage in refrigerator.
**Table 1 (continuation).** Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles 1a-k and N-Boc 4-iodo imidazole 1n.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azaindole</th>
<th>3-Iodo azaindole</th>
<th>N-Boc 3-Iodo azaindole 1 (isolated yield %)</th>
<th>Chromatographic purification (eluent) R_f (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>611 mg (4.10 mmol) 4-Methoxy-7H-pyrrolo[2,3-d]pyrimidine [a]</td>
<td>Pale yellow solid</td>
<td>Colorless solid 1.12 g (2.98 mmol, 91 %) Total yield: 73 %</td>
<td>PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1): 0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>966 mg (5.00 mmol) 4-(2-Methoxyethoxy)-7H-pyrrolo[2,3-d]pyrimidine [b]</td>
<td>Pale yellow solid 1.33 g (4.15 mmol, 83 %) For Boc-protection: 1.26 g (3.95 mmol)</td>
<td>Pale yellow oil 1.55 g (3.70 mmol, 94 %) Total yield: 78 %</td>
<td>PE-EtOAc = 5:1 → 4:1 R_f (PE-EtOAc = 5:1): 0.22</td>
</tr>
<tr>
<td>12</td>
<td>2.06 g (10.0 mmol) 4(5)-Iodo-1H-imidazole (ABCR) [c]</td>
<td>Yellow oil 2.71 g (9.23 mmol, 92 %) [c]</td>
<td>PE-EtOAc = 20:1 R_f (PE-EtOAc = 20:1): 0.16</td>
<td></td>
</tr>
</tbody>
</table>

[a] Preparation from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine as described for 4-methoxy-7-azaindole in S. Benoit, S. Gingras, N. Soundararajan, PCT Int. Appl. 2003, WO 2003082289 A1 20031009. The colorless solid was obtained in 76 % yield.

[b] Preparation from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine upon refluxing with 2.5 equivs of Cs₂CO₃ in 2-methoxyethanol (c = 0.2 M) as a colorless solid in 85 % yield.

[c] The isomer, tert-butyl 5-iodo-1H-imidazole-1-carboxylate, was obtained along with 1n as a yellow solid in 4 % yield (123 mg, 0.42 mmol).
2.4. Spectroscopic data of compounds 1a-k and 1n

2.4.1. tert-Butyl 3-iodo-1H-indole-1-carboxylate (1a)

**Structural formula:**

![Structure](image)

C<sub>13</sub>H<sub>14</sub>INO<sub>2</sub>

343.16

11.3 g (32.9 mmol, 63 % yield over two steps) as a pale brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 1.66 (s, 9 H), 7.28-7.32 (m, 1 H), 7.33-7.36 (m, 1 H), 7.36-7.40 (m, 1 H), 7.72 (s, 1 H), 8.12 (d, J = 7.3 Hz, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 28.1 (CH<sub>3</sub>), 65.4 (C<sub>quat</sub>), 84.2 (C<sub>quat</sub>), 115.0 (CH), 121.4 (CH), 123.3 (CH), 125.3 (CH), 130.0 (CH), 132.0 (C<sub>quat</sub>), 134.8 (C<sub>quat</sub>), 148.6 (C<sub>quat</sub>). El + MS (m/z (%)): 343 (M<sup>+</sup>, 14), 287 ((M-C<sub>4</sub>H<sub>9</sub>+H)<sup>+</sup>, 59), 270 ((M-C<sub>4</sub>H<sub>5</sub>O+H)<sup>+</sup>, 6), 243 ((M-C<sub>5</sub>H<sub>9</sub>O<sub>2</sub>+H)<sup>+</sup>, 79), 116 (C<sub>4</sub>H<sub>9</sub>N<sup>+</sup>, 30), 115 (C<sub>4</sub>H<sub>5</sub>N<sup>+</sup>, 22), 88 (10), 57 (C<sub>4</sub>H<sub>5</sub>CH<sup>+</sup>, 100), 41 (13). Anal. calcd for C<sub>13</sub>H<sub>14</sub>INO<sub>2</sub> (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.24, H 4.30, N 3.89.

Data reported in the literature:


Colorless solid (n-pentane). Mp 36-40 ºC. <sup>1</sup>H NMR (400 MHz): δ 1.68 (s, 9 H), 7.29-7.43 (m, 3 H), 7.73 (s, 1 H), 8.13 (d, J = 8.1 Hz, 1 H). <sup>13</sup>C NMR (100 MHz): δ 28.1 (q), 65.4 (s), 115.1 (d), 121.5 (d), 123.3 (d), 125.3 (d), 130.1 (d), 132.1 (s), 134.9 (s), 148.7 (s). El + MS (m/z (%)): 343 (M<sup>+</sup>, 69), 287 (100), 270 (13), 243 (98), 116 (28), 57 (98). Anal. calcd for C<sub>13</sub>H<sub>14</sub>INO<sub>2</sub> (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.37, H 3.66, N 3.96.


<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.69 (s, 9 H), 7.20-7.41 (m, 3 H), 7.72 (s, 1 H), 8.15 (d, J = 5.0 Hz, 1 H).
2.4.2. tert-Butyl 3-iodo-1H-indazole-1-carboxylate (1b)

![Structural formula]

C_{12}H_{13}IN_{2}O_{2}  
344.15

6.26 g (18.2 mmol, 80% yield over two steps) as a colorless solid. Mp 117 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.73 (s, 9 H), 7.34-7.39 (m, 1 H), 7.47-7.51 (m, 1 H), 7.56-7.61 (m, 1 H), 8.11 (d, $J = 8.5$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 28.1 (CH$_3$), 85.4 (C$_{quat}$), 102.9 (C$_{quat}$), 114.5 (CH), 121.9 (CH), 124.1 (CH), 129.9 (CH), 130.1 (C$_{quat}$), 139.5 (C$_{quat}$), 148.3 (C$_{quat}$). EI + MS (m/z (%)): 344 (M$^+$, 21), 244 ((M-C$_4$H$_9$+H-CO$_2$)$^+$, 100), 117 (C$_7$H$_5$N$_2^+$, 13), 58 (11), 57 (C$_4$H$_9^+$, 61), 43 (14). Anal. calcd for C$_{12}$H$_{13}$IN$_2$O$_2$ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.11, H 4.03, N 8.01.

Data reported in the literature:

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.72 (s, 9 H), 7.37 (t, $J = 8.1$ Hz, 1 H), 7.49 (d, $J = 8.1$ Hz, 1 H), 7.58 (t, $J = 7.5$ Hz, 1 H), 8.11 (d, $J = 8.7$ Hz, 1 H). MS (m/z): 367 (M+Na)$^+$, 345 (M+H)$^+$, 310, 289, 244, 124, 74, 56. HRMS calcd for C$_{12}$H$_{14}$IN$_2$O$_2$ (M+H): 345.0100. Found 345.0095.
2.4.3. tert-Butyl 3-iodo-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (1c)

\[ 
\text{C}_{12}\text{H}_{13}\text{IN}_{2}\text{O}_2 
\]

1.88 g (5.45 mmol, 55 % yield over two steps) as a colorless solid. Mp 125 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.68 (s, 9 H), 7.30 (dd, \(J = 8.5\) Hz, \(J = 4.7\) Hz, 1 H), 7.98 (s, 1 H), 8.4 (br, 1 H), 8.62 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 28.1 (CH\(_3\)), 67.7 (C\(_{\text{quat}}\)), 85.2 (C\(_{\text{quat}}\)), 119.9 (CH), 122.6 (CH), 128.3 (C\(_{\text{quat}}\)), 132.8 (CH), 146.4 (CH), 147.9 (C\(_{\text{quat}}\)), 148.2 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 344 (M\(^+\), 33), 288 ((M-C\(_4\)H\(_9\)+H\(^+\)), 85), 244 ((M-C\(_4\)H\(_9\)+H-CO\(_2\))\(^+\), 81), 57 (C\(_4\)H\(_9\)+, 100). Anal. calcd for C\(_{12}\)H\(_{13}\)IN\(_2\)O\(_2\) (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.04, H 4.06, N 8.04.
2.4.4. tert-Butyl 3-iodo-1H-pyrrolo[3,2-c]pyridine-1-carboxylate (1d)

![Chemical Structure](image)

C₁₂H₁₃Iₙ₂O₂

344.15

1.85 g (5.36 mmol, 64 % yield over two steps) as a colorless solid. Mp 119 °C. ¹H NMR (CDCl₃, 500 MHz): δ 1.68 (s, 9 H), 7.73 (s, 1 H), 7.95 (br, 1 H), 8.54 (d, J = 5.7 Hz, 1 H), 8.71 (s, 1 H). ¹³C NMR (CDCl₃, 125 MHz): δ 28.0 (CH₃), 62.1 (C_quat), 85.5 (C_quat), 109.5 (CH), 128.1 (C_quat), 130.8 (CH), 139.7 (C_quat), 144.5 (CH), 145.1 (CH), 148.0 (C_quat). EI + MS (m/z %): 344 (M⁺, 11), 288 ((M-C₄H₉+H)⁺, 36), 244 ((M-C₄H₉+H-CO₂)⁺, 65), 117 (C₇H₅N₂⁺, 15), 116 (C₇H₄N₂⁺, 7), 57 (C₄H₉⁺, 100), 41 (13). Anal. calcd for C₁₂H₁₃Iₙ₂O₂ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.13, H 3.82, N 8.13.

Data reported in the literature:


White solid. Rₜ (PE-EtOAc = 6:4): 0.3. Mp 127-128 °C. ¹H NMR (CDCl₃, 250 MHz): δ 1.68 (s, 9 H, C(CH₃)₃), 7.73 (s, 1 H, H-2), 7.95 (dd, J = 5.7 Hz, J = 0.9 Hz, 1 H, H-6), 8.55 (d, J = 5.7 Hz, 1 H, H-7), 8.71 (d, J = 0.9 Hz, 1 H, H-4). ¹³C NMR (CDCl₃, 62.5 MHz): δ 28.2 (C(CH₃)₃), 62.2 (C-I), 85.7 (C(CH₃)₃), 109.7 (CH-6), 128.3 (C_quat), 131.0 (CH-2), 139.8 (C_quat), 144.6 (CH-4), 145.1 (CH-7), 148.2 (t-BuOOC). EI + MS (m/z (%)): 345 (MH⁺, 92), 289 ((MH-t-Bu)⁺, 100), 245 ((MH-Boc)⁺, 29). IR (KBr): ν 2982 cm⁻¹, 1746, 1168. HRMS (El) m/z calcd for C₁₂H₁₃Iₙ₂O₂: 344.00218; found: 344.0021.
2.4.5. tert-Butyl 3-iodo-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (1e)

![Chemical Structure]

C\textsubscript{12}H\textsubscript{13}IN\textsubscript{2}O\textsubscript{2}  
344.15

7.52 g (21.9 mmol, 59 % yield over two steps) as a pale yellow solid. Mp 149-150 °C.  
\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 1.70 (s, 9 H), 7.38 (d, \(J = 5.4\) Hz, 1 H), 7.90 (s, 1 H), 8.51 (d, \(J = 5.4\) Hz, 1 H), 9.37 (s, 1 H).  
\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 28.0 (CH\textsubscript{3}), 63.4 (C\textsubscript{quat}), 85.9 (C\textsubscript{quat}), 115.8 (CH), 131.8 (C\textsubscript{quat}), 133.5 (CH), 136.8 (CH), 138.3 (C\textsubscript{quat}), 141.8 (CH), 147.7 (C\textsubscript{quat}). EI + MS (m/z (%)): 344 (M\textsuperscript{+}, 13), 288 ((M-C\textsubscript{4}H\textsubscript{9}+H\textsuperscript{+}, 27), 244 ((M-C\textsubscript{4}H\textsubscript{9}+H-CO\textsubscript{2}\textsuperscript{+}, 100), 117 (C\textsubscript{7}H\textsubscript{5}N\textsubscript{2}\textsuperscript{+}, 22), 116 (C\textsubscript{7}H\textsubscript{4}N\textsubscript{2}\textsuperscript{+}, 11), 90 (10), 57 (C\textsubscript{4}H\textsubscript{9}\textsuperscript{+}, 100), 41 (13). Anal. calcd for C\textsubscript{12}H\textsubscript{13}IN\textsubscript{2}O\textsubscript{2} (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.13, H 3.93, N 8.01.
2.4.6. tert-Butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f)

\[
\text{C}_{12}\text{H}_{13}\text{I}\text{N}_{2}\text{O}_{2}
\]

344.15

31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 79 °C. \(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz): \(\delta\) 1.66 (s, 9 H), 7.22 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.61 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 7.78 (s, 1 H), 8.50 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H). \(^{13}\text{C NMR}\) (CDCl\(_3\), 125 MHz): \(\delta\) 27.4 (CH\(_3\)), 61.3 (C\(_\text{quat}\)), 83.8 (C\(_\text{quat}\)), 118.5 (CH), 124.3 (C\(_\text{quat}\)), 128.9 (CH), 129.9 (CH), 145.3 (CH), 146.0 (C\(_\text{quat}\)), 146.6 (C\(_\text{quat}\)). EI + MS \((m/z \%)\): 344 (M\(^+\), 4), 245 (8), 244 ((M-\text{C}_5\text{H}_9\text{O}_2+\text{H})\(^+\), 100), 117 (\text{C}_7\text{H}_5\text{N}_2\(^+\), 23), 116 (\text{C}_7\text{H}_4\text{N}_2\(^+\), 10), 90 (10), 57 (\text{C}_4\text{H}_9\(^+\), 26).

Data reported in the literature:


\(^1\text{H NMR}\) (CDCl\(_3\)): \(\delta\) 1.70 (s, 9 H), 7.28 (dd, \(J = 8.5\) Hz, 1 H), 7.72 (dd, \(J = 8.1\) Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, \(J = 5.1\) Hz, 1 H).
2.4.7. tert-Butyl 3-iodo-4-methoxy-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1g)

![Chemical Structure](image)

C$_{13}$H$_{15}$IN$_2$O$_3$

374.17

428 mg (1.14 mmol, 65 % yield over two steps) as a colorless solid. Mp 122 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.65 (s, 9 H), 3.99 (s, 3 H), 6.67 (d, $J = 5.7$ Hz, 1 H), 7.63 (s, 1 H), 8.40 (d, $J = 5.7$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 28.0 (CH$_3$), 54.6 (C$_{quat}$), 55.5 (CH$_3$), 84.6 (C$_{quat}$), 101.0 (CH), 112.8 (C$_{quat}$), 129.7 (CH), 146.8 (C$_{quat}$), 147.8 (CH), 149.0 (C$_{quat}$), 160.1 (C$_{quat}$). EI + MS (m/z (%)): 374 (M$^+$, 5), 301 ((M-C$_4$H$_9$O)$^+$, 2), 274 ((M-C$_5$H$_9$O$_2$+H)$^+$, 61), 273 ((M-C$_5$H$_9$O$_2$)$^+$, 13), 259 ((M-C$_5$H$_9$O$_2$+H-CH$_3$)$^+$, 9), 243 ((M-C$_5$H$_9$O$_2$+H-OCH$_3$)$^+$, 2), 231 ((M-I-CH$_3$)$^+$, 8), 131 (C$_7$H$_3$N$_2$O$_+^+$, 15), 117 (C$_7$H$_5$N$_2^+$, 18), 116 (C$_7$H$_4$N$_2^+$, 21), 77 (11), 57 (C$_4$H$_9^+$, 100), 43 (C$_2$H$_3$O$^+$, 12), 41 (C$_2$H$_3$N$^+$, 53), 39 (C$_3$H$_3^+$, 13). Anal. calcd for C$_{13}$H$_{15}$IN$_2$O$_3$ (374.2): C 41.73, H 4.04, N 7.49. Found: C 41.89, H 3.91, N 7.23.
2.4.8. tert-Butyl 3-iodo-2-methyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1h)

5.58 g (15.6 mmol, 88% yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 47 °C. \( ^1H \) NMR (CDCl\(_3\), 500 MHz): \( \delta \) 1.69 (s, 9 H), 2.69 (s, 3 H), 7.21 (dd, \( J = 7.9 \) Hz, \( J = 4.7 \) Hz, 1 H), 7.61 (dd, \( J = 7.9 \) Hz, \( J = 1.9 \) Hz, 1 H), 8.43 (dd, \( J = 5.0 \) Hz, \( J = 1.6 \) Hz, 1 H).\(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) 17.9 (CH\(_3\)), 28.1 (CH\(_3\)), 67.1 (C\(_{\text{quat}}\)), 84.8 (C\(_{\text{quat}}\)), 119.1 (CH), 124.4 (C\(_{\text{quat}}\)), 128.7 (CH), 138.3 (C\(_{\text{quat}}\)), 145.0 (CH), 148.1 (C\(_{\text{quat}}\)), 148.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 358 (M\(^+\), 19), 285 ((M-C\(_4\)H\(_9\)O\(^+\), 4), 258 ((M-C\(_5\)H\(_9\)O\(_2\)H\(^+\)), 100), 158 ((M-C\(_4\)H\(_9\)O-I\(^+\)), 2), 131 (C\(_8\)H\(_7\)N\(_2\)\(^+\), 13), 57 (C\(_4\)H\(_9\)\(^+\), 55), 41 (C\(_2\)H\(_3\)N\(^+\), 11). Anal. calcd for C\(_{13}\)H\(_{15}\)I\(_2\)N\(_2\)O\(_2\) (358.2): C 43.59, H 4.22, N 7.82. Found: C 43.59, H 4.45, N 7.63.
2.4.9. tert-Butyl 7-iodo-5H-pyrrolo[2,3-b]pyrazine-5-carboxylate (1i)

![Chemical Structure](image)

C_{11}H_{12}IN_3O_2

345.14

2.53 g (7.33 mmol, 75 % yield over two steps) as a pale yellow solid. Mp 128 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.69 (s, 9 H), 8.12 (s, 1 H), 8.46 (d, \(J = 2.5\) Hz, 1 H), 8.60 (d, \(J = 2.5\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 28.0 (CH\(_3\)), 64.2 (C\(_{quat}\)), 85.8 (C\(_{quat}\)), 134.4 (CH), 139.8 (CH), 141.1 (C\(_{quat}\)), 141.3 (CH), 141.8 (C\(_{quat}\)), 146.4 (C\(_{quat}\)).

EI + MS (m/z (%)): 345 (M\(^+\), 23), 245 ((M-C_4H_9+H-CO_2)^+, 100), 57 (C_4H_9^+, 85), 41 (13). Anal. calcd for C_{11}H_{12}IN_3O_2 (345.1): C 38.28, H 3.50, N 12.17. Found: C 38.31, H 3.62, N 12.11.
2.4.10. tert-Butyl 5-iodo-4-methoxy-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (1j)

![Chemical Structure Image]

C_{12}H_{14}IN_{3}O_{3}  
375.16

1.12 g (2.98 mmol, 73 % yield over two steps) as a colorless solid. Mp 98-99 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.67 (s, 9 H), 4.15 (s, 3 H), 7.63 (s, 1 H), 8.65 (s, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 27.9 (CH\(_3\)), 53.9 (CH\(_3\)), 54.9 (C\(_\text{quat}\)), 85.6 (C\(_\text{quat}\)), 109.1 (C\(_\text{quat}\)), 129.4 (CH), 146.2 (C\(_\text{quat}\)), 152.4 (C\(_\text{quat}\)), 153.6 (CH), 163.1 (C\(_\text{quat}\)). EI + MS (m/z (%)): 375 (M\(^+\), 7), 276 (9), 275 ((M-C\(_5\)H\(_9\)O\(_2\)+H\(^+\)), 100), 274 ((M-C\(_6\)H\(_9\)O\(_2\))^+) (15), 246 (10), 234 (10), 148 (C\(_7\)H\(_8\)N\(_3\)O\(^+\), 7), 118 (C\(_8\)H\(_4\)N\(_3\)^+, 8), 57 (C\(_4\)H\(_5\)^+, 50). Anal. calcd for C\(_{12}\)H\(_{14}\)IN\(_3\)O\(_3\) (375.2): C 38.42, H 3.76, N 11.20. Found: C 38.46, H 3.85, N 11.32.
2.4.11. tert-Butyl 4-(2-methoxyethoxy)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (1k)

1.55 g (3.70 mmol, 78 % yield over two steps) as a pale yellow oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.67 (s, 9 H), 3.49 (s, 3 H), 3.84-3.88 (m, 2 H), 4.67-4.71 (m, 2 H), 7.62 (s, 1 H), 8.62 (s, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 27.9 (CH\(_3\)), 55.1 (C\(_{\text{quat}}\)), 59.3 (CH\(_3\)), 66.0 (CH\(_2\)), 70.4 (CH\(_2\)), 85.6 (C\(_{\text{quat}}\)), 109.0 (C\(_{\text{quat}}\)), 129.4 (CH), 146.2 (C\(_{\text{quat}}\)), 152.5 (C\(_{\text{quat}}\)), 153.5 (CH), 162.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 419 (M\(^+\), 1), 319 ((M-C\(_5\)H\(_9\)O\(_2\)+H\(^+\)), 3), 261 (C\(_6\)H\(_4\)I\(_3\)O\(^+\), 6), 88 (13), 70 (13), 61 (16), 45 (C\(_2\)H\(_5\)O\(^+\), 15), 43 (100). Anal. calcd for C\(_{14}\)H\(_{18}\)I\(_3\)O\(_4\) (419.2): C 40.11, H 4.33, N 10.02. Found: C 40.41, H 4.55, N 9.81.
2.4.12. tert-Butyl 4-iodo-1H-imidazole-1-carboxylate (1n)

![Chemical Structure]

C₈H₁₁IN₂O₂  
294.09

2.71 g (9.23 mmol, 92 % yield) as a yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 1.62 (s, 9 H), 7.47 (d, J = 1.3 Hz, 1 H), 7.95 (d, J = 1.3 Hz, 1 H). ¹³C NMR (CDCl₃, 125 MHz): δ 27.8 (CH₃), 84.3 (Cquat), 86.5 (Cquat), 122.8 (CH), 138.1 (CH), 145.7 (Cquat). El + MS (m/z (%)): 295 (8), 294 (M⁺, 62), 238 ((M-C₄H₉+H)⁺, 12), 221 ((M-C₄H₉O)⁺, 28), 194 ((M-C₅H₉O₂+H)⁺, 64), 166 ((M-I+H)⁺, 18), 59 (10), 58 (19), 57 (C₄H₅⁺, 100), 41 (64). Anal. calcd for C₈H₁₁IN₂O₂ (294.1): C 32.67, H 3.77, N 9.53. Found: C 32.95, H 4.07, N 9.35.
2.5. Preparation of tert-butyl 4-iodo-2-(4-methoxy-phenyl)-1H-pyrrole-1-carboxylate (1l)[3]

PdCl$_2$(PPh$_3$)$_2$ (425 mg, 0.60 mmol, 2 mol %) and Cul (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a dry screw-cap vessel. Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol, 1.00 equiv), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and tert-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol, 1.00 equiv) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol, 5.00 equiv), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol, 2.00 equiv) and 30 ml of tert-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (1l) as a colorless solid.
**tert-Butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1)**

![Chemical Structure](image)

1.46 g (3.66 mmol, 73 % yield) as a colorless solid. Mp 71-72 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, $J = 1.9$ Hz, 1 H), 6.88 (d, $J = 8.8$ Hz, 1 H), 7.24 (d, $J = 8.8$ Hz, 1 H), 7.39 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 27.6 (CH$_3$), 55.3 (CH$_3$), 64.4 (C$_{quat}$), 84.2 (C$_{quat}$), 113.1 (CH), 120.3 (CH), 125.3 (C$_{quat}$), 126.7 (CH), 130.4 (CH), 136.5 (C$_{quat}$), 147.9 (C$_{quat}$), 159.3 (C$_{quat}$). EI + MS (m/z (%)): 399 (M$^+$, 3), 343 ((M-C$_5$H$_9$+H)$^+$, 11), 299 ((M-C$_5$H$_9$O$_2$+H)$^+$, 16), 298 ((M-C$_5$H$_9$O$_2$)$^+$, 13), 171 ((M-C$_5$H$_9$O$_2$-I)$^+$, 6), 156 (12), 128 (11), 57 (C$_4$H$_9^+$, 100), 41 (34). IR (KBr): $\tilde{\nu}$ 3145 (m) cm$^{-1}$, 2986 (m), 2934 (w), 2832 (w), 2734 (s), 1609 (m), 1576 (w), 1557 (w), 1511 (s), 1476 (m), 1460 (m), 1435 (w), 1370 (s), 1337 (s), 1293 (s), 1251 (s), 1180 (s), 1151 (s), 1108 (m), 1032 (s), 985 (m), 904 (m), 847 (s), 833 (m), 808 (s), 771 (m), 675 (w), 629 (w), 615 (w), 594 (m), 528 (w), 511 (w). Anal. calcd for C$_{16}$H$_{18}$INO$_3$ (399.2): C 48.14, H 4.54, N 3.51. Found: C 48.36, H 4.37, N 3.34.
3 Multicomponent Syntheses of Triazolyl Substituted N-Boc protected NH-Heterocycles 2a-s

3.1. Three-component Sonogashira coupling □ TMS-deprotection □ CuAAC sequence

3.1.1. General procedure for the preparation of compounds 2a-o

PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol, 2 mol %) and CuI (8 mg, 0.04 mmol, 4 mol %) were placed in a dry screw-cap Schlenk vessel with septum. Then, 1.00 mmol of $N$-Boc iodo NH-heterocycle 1 was added in 5 mL of dry tetrahydrofuran under argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv) and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added and the mixture was stirred at room temperature (water bath) until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (5a) (136 mg, 1.00 mmol, 1.00 equiv) in 1 mL of dry methanol* was added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl...
acetate to give the N-Boc protected triazoles 2. The obtained compounds were not characterized but directly deprotected in the next step.

* For the synthesis of compound 2g 2 mL of phenyl azide solution (∼ 0.5 M in TBME) (5b) (1.00 mmol, 1.00 equiv) were added, followed by the addition of 1 mL of dry methanol.

The experimental details are depicted in Table 1.

Table 1. Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected (aza)indolyl triazoles 2a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo NH-heterocycle 1</th>
<th>Reaction time[a]</th>
<th>N-Boc protected (aza)indolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st step 2nd step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>343 mg (1.00 mmol)</td>
<td>1 h 4 d</td>
<td>Beige-yellow solid 280 mg (0.75 mmol, 75 %)</td>
<td>PE-EtOAc = 5:1</td>
</tr>
<tr>
<td><img src="image1.png" alt="1a" /></td>
<td><img src="image2.png" alt="2a" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 2     | 688 mg (2.00 mmol)          | 2 h 24 h         | Pale beige solid 538 mg (1.43 mmol, 72 %) | PE-EtOAc = 5:1  
Rf (PE-EtOAc = 5:1) = 0.13 |
| ![1b](image3.png) | ![2b](image4.png) | | | |

[a] The reaction times are not optimized and might be shorter than indicated.
Table 1 (continuation). Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected (aza)indolyl triazoles 2c-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo NH-heterocycle 1</th>
<th>Reaction time[a]</th>
<th>Chromatographic purification (eluent)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st step</td>
<td>2nd step</td>
</tr>
<tr>
<td>3</td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>3 d</td>
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<tr>
<td></td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>24 h</td>
</tr>
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<tr>
<td></td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="1e" /></td>
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</table>

[a] The reaction times are not optimized and might be shorter than indicated.
**Table 1 (continuation).** Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected (aza)indolyl triazoles 2f-h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo NH-heterocycle 1</th>
<th>Reaction time[a]</th>
<th>N-Boc protected (aza)indolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st step</td>
<td>2nd step</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.72 g (5.00 mmol)</td>
<td>1 h</td>
<td>40 h</td>
<td>Yellow foam 1.56 g (4.15 mmol, 83 %)[b]</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="1f" /></td>
<td><img src="image" alt="2f" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>66 h</td>
<td>Yellow foam 254 mg (0.70 mmol, 70 %)</td>
</tr>
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<td><img src="image" alt="2g" /></td>
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</tr>
<tr>
<td>8</td>
<td>374 mg (1.00 mmol)</td>
<td>1 h</td>
<td>64 h</td>
<td>Pale yellow solid 219 mg (0.54 mmol, 54 %)</td>
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<td><img src="image" alt="1g" /></td>
<td><img src="image" alt="2h" /></td>
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<td></td>
</tr>
</tbody>
</table>

[a] The reaction times are not optimized and might be shorter than indicated.

[b] On a 1.00 mmol scale, 295 mg (0.79 mmol, 79 % yield) of a yellow foam were obtained.
Table 1 (continuation). Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected (aza)indolyl triazoles 2i-k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo NH-heterocycle 1</th>
<th>Reaction time(^{[a]})</th>
<th>N-Boc protected (aza)indolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1(^{st}) step</td>
<td>2(^{nd}) step</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>716 mg (2.00 mmol)</td>
<td>23 h</td>
<td>119 h</td>
<td>Pale yellow solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>462 mg (1.19 mmol, 59 %)</td>
</tr>
<tr>
<td></td>
<td>1h</td>
<td><img src="image" alt="1h" /></td>
<td><img src="image" alt="2i" /></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>345 mg (1.00 mmol)</td>
<td>1 h</td>
<td>48 h</td>
<td>Colorless solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>211 mg (0.56 mmol, 56 %)</td>
</tr>
<tr>
<td></td>
<td>1i</td>
<td><img src="image" alt="1i" /></td>
<td><img src="image" alt="2j" /></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>375 mg (1.00 mmol)</td>
<td>1 h</td>
<td>72 h</td>
<td>Yellow solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>297 mg (0.73 mmol, 73 %)</td>
</tr>
<tr>
<td></td>
<td>1j</td>
<td><img src="image" alt="1j" /></td>
<td><img src="image" alt="2k" /></td>
<td></td>
</tr>
</tbody>
</table>

\(^{[a]}\) The reaction times are not optimized and might be shorter than indicated.
Table 1 (continuation). Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected (aza)indolyl triazole 2l and pyrrolyl triazole 2m.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo NH- heterocycle 1</th>
<th>Reaction time[a]</th>
<th>N-Boc protected (aza)indolyl or pyrrolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N-Boc protected (aza)indolyl or pyrrolyl triazole 2</td>
<td>1st step</td>
<td>2nd step</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>720 mg (1.72 mmol)</td>
<td>1 h</td>
<td>87 h</td>
<td>Pale yellow foam</td>
</tr>
<tr>
<td></td>
<td><img src="1k.png" alt="Image" /></td>
<td></td>
<td></td>
<td>341 mg (0.97 mmol, 57 %)</td>
</tr>
<tr>
<td>13</td>
<td>399 mg (1.00 mmol)</td>
<td>2 h</td>
<td>115 h</td>
<td>Yellow oil</td>
</tr>
<tr>
<td></td>
<td><img src="1l.png" alt="Image" /></td>
<td></td>
<td></td>
<td>224 mg (0.52 mmol, 52 %)</td>
</tr>
</tbody>
</table>

[a] The reaction times are not optimized and might be shorter than indicated.
Table 1 (continuation). Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of N-Boc protected azolyl triazoles 2n-o.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc iodo (NH)-heterocycle 1</th>
<th>Reaction time[^{[a]}]</th>
<th>N-Boc protected azolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>294 mg (1.00 mmol) tert-Butyl 4-iodo-1H-pyrazole-1-carboxylate (ABCR)</td>
<td>3 h 63 h</td>
<td>Yellow-orange oil 208 mg (0.64 mmol, 64 %)</td>
<td>PE-EtOAc = 1:1</td>
</tr>
<tr>
<td>15</td>
<td>294 mg (1.00 mmol) 1n</td>
<td>15 d 23 h</td>
<td>Yellow oil 99 mg (0.30 mmol, 30 %)</td>
<td>PE-EtOAc = 1:1</td>
</tr>
</tbody>
</table>

\[^{[a]}\] The reaction times are not optimized and might be shorter than indicated.
3.2. Four-component Sonogashira coupling □ TMS-deprotection □ Azide-Halide exchange □ CuAAC sequence

3.2.1. General procedure for the preparation of compounds 2p-s

PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol, 2 mol %) and Cul (8 mg, 0.04 mmol, 4 mol %) were placed in a dry screw-cap Schlenk vessel with septum. Then, tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f) (344 mg, 1.00 mmol) was added in 5 mL of dry tetrahydrofuran under argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv) and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added and the mixture was stirred at room temperature (water bath) until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, cesium azide (175 mg, 1.00 mmol, 1.00 equiv) and an organic halide (1.00 mmol, 1.00 equiv) in 1 mL of dry methanol were added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the N-Boc protected 7-azaindolyl triazoles 2p-s. The obtained compounds were not characterized but used as obtained in the subsequent deprotection step.
The experimental details are depicted in **Table 3**.

**Table 3.** Experimental details of the four-component Sonogashira coupling – TMS-deprotection – azide-halide exchange – CuAAC sequence for the synthesis of indolyl triazoles 2p-s.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc 3-iodo 7-azaindole 1f</th>
<th>Reaction time[^{[a]}]</th>
<th>N-Boc protected 7-azaindolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In situ generated azide 5</td>
<td>1st step 2nd step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>688 mg (2.00 mmol)</td>
<td>1 h 51 h</td>
<td>Pale yellow solid 444 mg (1.08 mmol, 54 %)</td>
<td>PE-EtOAc = 2:1</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>350 mg (2.00 mmol) CsN(_3) (Aldrich)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>322 mg (2.00 mmol) (Merck)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>344 mg (1.00 mmol) 1f</td>
<td>1 h 72 h</td>
<td>Yellow foam 295 mg (0.73 mmol, 73 %)</td>
<td>PE-EtOAc = 2:1</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>175 mg (1.00 mmol) CsN(_3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>163 mg (1.00 mmol) (ABCR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[^{[a]}\] The reaction times are not optimized and might be shorter than indicated.
Table 3. Experimental details of the three-component Sonogashira-CuAAC sequence for the synthesis of indolyl triazoles 2p-s.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc 3-iodo 7-azaindole 1</th>
<th>Reaction time(^{[a]})</th>
<th>N-Boc protected 7-azaindolyl triazole 2</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In situ generated azide 5</td>
<td>1st step</td>
<td>2nd step</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>111 h</td>
<td>Yellow oil 269 mg (0.69 mmol, 69 %)</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="1f" /></td>
<td></td>
<td></td>
<td>PE-EtOAc = 2:1</td>
</tr>
<tr>
<td></td>
<td>175 mg (1.00 mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsN(_3) (Aldrich)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>189 mg (1.00 mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Merck) <img src="image" alt="5e" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>344 mg (1.00 mmol)</td>
<td>1 h</td>
<td>64 h</td>
<td>Yellow oil 250 mg (0.64 mmol, 64 %)</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="1f" /></td>
<td></td>
<td></td>
<td>PE-EtOAc = 2:1</td>
</tr>
<tr>
<td></td>
<td>175 mg (1.00 mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsN(_3) (Aldrich)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>191 mg (1.00 mmol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ABCR) <img src="image" alt="5f" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{[a]}\) The reaction times are not optimized and might be shorter than indicated.
3.3. Four-component Boc-protection □ Sonogashira coupling □ TMS-deprotection □ CuAAC sequence

3.3.1. General procedure for the preparation of compounds 7a-b
1.00 mmol of a bromo-7-azaindole 6 was placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum. Then, di-tert-butyl dicarbonate (338 mg, 1.50 mmol, 1.50 equiv) in 1 mL of dry 1,4-dioxane and 4-dimethylaminopyridine (12 mg, 0.10 mmol, 10 mol %) were added under argon atmosphere and the reaction mixture was stirred at room temperature (water bath) for 15 min until the complete consumption of the starting material (evolution of a gas ceased, monitored by TLC). After that, 1 mL of dry methanol was added and the mixture was degassed with argon. Then, PdCl$_2$(PhCN)$_2$ (8 mg, 0.02 mmol, 2 mol %), [‘Bu$_3$PH]BF$_4$ (12 mg, 0.04 mmol, 4 mol %), CuI (8 mg, 0.04 mmol, 4 mol %), trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv), and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added subsequently and the mixture was stirred at room temperature until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (5a) (136 mg, 1.00 mmol, 1.00 equiv) in 1 mL of dry methanol was added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the N-Boc protected 7-azaindolyl triazole 7. The obtained compound was not characterized but used as obtained in the subsequent deprotection step.

The experimental details are depicted in Table 4.
Table 4. Experimental details for the four-component Boc-protection – Sonogashira coupling – TMS-deprotection – CuAAC sequence for the synthesis of N-Boc protected 7-azaindolyl triazoles 7a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromo-7-azaindole 6</th>
<th>Reaction time</th>
<th>N-Boc protected 7-azaindolyl triazole 7 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2nd step[b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>205 mg (1.00 mmol)</td>
<td>1 h</td>
<td>Yellow oil 311 mg (0.83 mmol, 83 %)</td>
<td>PE-EtOAc = 1:1</td>
</tr>
<tr>
<td></td>
<td>(4-Bromo-7-azaindole) (Aldrich)</td>
<td>18 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>203 mg (1.00 mmol)</td>
<td>5 h</td>
<td>Yellow oil 373 mg (0.99 mmol, 99 %)</td>
<td>PE-EtOAc = 2:1</td>
</tr>
<tr>
<td></td>
<td>(5-Bromo-7-azaindole) (Aldrich)</td>
<td>4 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] The reaction times are not optimized and might be shorter than indicated.
[b] 2nd step: Sonogashira coupling with TMSA.
[c] 3rd step: CuAAC with benzyl azide (5a).
4. Deprotection of *N*-Boc Protected Triazolyl *NH*-Heterocycles

4.1. General procedure for the preparation of compounds 8a-s and 9a-b

\[ 2a-s \xrightarrow{K_2CO_3/MeOH} 8a-s \]
\[ 7a-b \xrightarrow{K_2CO_3/MeOH} 9a-b \]

*N*-Boc protected triazolyl heterocycle 2 or 7 was placed in methanol (c = 0.2 M). Then, 2.50 equiv of potassium carbonate were added and the mixture was stirred at room temperature (water bath) or 50 °C (for compounds 2a and 2i, preheated oil bath) for 1 h* (monitored by TLC). Frequently, a precipitate was formed. The mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia. After drying in vacuo at 70 °C overnight, analytically pure triazoles 8 or 9 were obtained. The products can be further purified by suspension in dichloromethane and sonication in ultrasound bath for 0.5-1 h, filtration and drying in vacuo at 70 °C overnight.

* 5 h for compound 2m.

The experimental details are given in Table 5, Table 6, and Table 7.
Table 5. Experimental details for the deprotection of \(N\)-Boc (aza)indolyl triazoles 8a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(N)-Boc protected (aza)indolyl triazole 2</th>
<th>(Aza)indolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>280 mg (0.75 mmol)</td>
<td>Pale yellow solid[^{[a]}] 147 mg (0.54 mmol, 72 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1 (\rightarrow) 100:2:1 (\rightarrow) 100:3:1 (\rightarrow) 100:4:1</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2a" /></td>
<td><img src="image" alt="8a" /></td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>2</td>
<td>404 mg (1.08 mmol)</td>
<td>Colorless solid 264 mg (0.96 mmol, 89 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2b" /></td>
<td><img src="image" alt="8b" /></td>
<td>HT-LC-MS: 100 %[^{[b]}]</td>
</tr>
<tr>
<td>3</td>
<td>230 mg (0.61 mmol)</td>
<td>Colorless solid 137 mg (0.50 mmol, 81 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1 (\rightarrow) 100:2:1 (\rightarrow) 100:3:1 (\rightarrow) 100:4:1</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2c" /></td>
<td><img src="image" alt="8c" /></td>
<td>HT-LC-MS: 100 %</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Deprotection was performed at 50 °C for 1 h.
\[^{[b]}\] Additionally purified by suspension in DCM and sonication in ultrasound bath.
Table 5 (continuation). Experimental details for the deprotection of N-Boc (aza)indolyl triazoles 8d-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected (aza)indolyl triazole 2</th>
<th>(Aza)indolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>149 mg (0.40 mmol) Colorless solid</td>
<td>95 mg (0.35 mmol, 86 %) Total yield: 48 %</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2d" /></td>
<td><img src="image" alt="8d" /></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>149 mg (0.40 mmol) Pale yellow solid</td>
<td>93 mg (0.34 mmol, 85 %) Total yield: 50 %</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 99.9 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2e" /></td>
<td><img src="image" alt="8e" /></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.56 g (4.15 mmol) Colorless solid</td>
<td>930 mg (3.38 mmol, 81 %) Total yield: 67 %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 HT-LC-MS: 100 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2f" /></td>
<td><img src="image" alt="8f" /></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Additionally purified by suspension in DCM and sonication in ultrasound bath.

<sup>b</sup> On a 1.00 mmol scale, 179 mg (0.65 mmol, 65 % yield over two steps) were obtained as a colorless solid.
Table 5 (continuation). Experimental details for the deprotection of N-Boc (aza)indolyl triazoles 8g–i.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected (aza)indolyl triazole 2</th>
<th>(Aza)indolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>254 mg (0.70 mmol) Yellow solid 143 mg (0.55 mmol, 78 %) Total yield: 55 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 $\rightarrow$ 100:2:1 $\rightarrow$ 100:3:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2g" /></td>
<td><img src="image" alt="8g" /></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>162 mg (0.40 mmol) Yellow solid 109 mg (0.36 mmol, 89 %) Total yield: 48 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 $\rightarrow$ 100:2:1 $\rightarrow$ 100:3:1 $\rightarrow$ 100:4:1 $\rightarrow$ 100:5:1 $\rightarrow$ 100:6:1</td>
<td>HT-LC-MS: 100 %$^{[a]}$</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2h" /></td>
<td><img src="image" alt="8h" /></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>462 mg (1.19 mmol) Colorless solid$^{[b]}$ 300 mg (1.04 mmol, 87 %) Total yield: 52 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 $\rightarrow$ 100:2:1 $\rightarrow$ 100:3:1 $\rightarrow$ 100:4:1 $\rightarrow$ 100:5:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2i" /></td>
<td><img src="image" alt="8i" /></td>
<td></td>
</tr>
</tbody>
</table>

$^{[a]}$ Additionally purified by suspension in DCM and sonication in ultrasound bath.

$^{[b]}$ Deprotection was performed at 50 °C for 1 h.
Table 5 (continuation). Experimental details for the deprotection of \( N \)-Boc (aza)indolyl triazoles 8j-l.

<table>
<thead>
<tr>
<th>Entry</th>
<th>( N )-Boc protected (aza)indolyl triazole 2</th>
<th>(Aza)ndolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>152 mg (0.40 mmol)</td>
<td>Colorless solid 93 mg (0.34 mmol, 83 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total yield: 47 %</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2j" /></td>
<td><img src="image" alt="8j" /></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>297 mg (0.73 mmol)</td>
<td>Colorless solid 165 mg (0.54 mmol, 74 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total yield: 54 %</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2k" /></td>
<td><img src="image" alt="8k" /></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>197 mg (0.56 mmol)</td>
<td>Colorless solid 141 mg (0.40 mmol, 72 %)</td>
<td>DCM-MeOH-NH(_3) = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total yield: 41 %</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2l" /></td>
<td><img src="image" alt="8l" /></td>
<td></td>
</tr>
</tbody>
</table>

[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.
**Table 5 (continuation).** Experimental details for the deprotection of N-Boc azolyl triazoles 8m-o.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected azolyl triazole 2</th>
<th>Azolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td><img src="image" alt="2m" /> 224 mg (0.52 mmol)</td>
<td>Pale yellow solid[^a] 147 mg (0.44 mmol, 85 %) Total yield: 44 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="8m" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="2n" /> 208 mg (0.64 mmol)</td>
<td>Colorless solid 86 mg (0.38 mmol, 60 %) Total yield: 38 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="8n" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="2o" /> 99 mg (0.30 mmol)</td>
<td>Colorless solid 46 mg (0.20 mmol, 68 %) Total yield: 20 %</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="8o" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a]: Deprotection was performed at room temperature for 5 h.
Table 6. Experimental details for the deprotection of N-Boc 7-azaindolyl triazoles 8p-q.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected 7-azaindolyl triazole 2</th>
<th>7-Azaindolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>347 mg (0.85 mmol)</td>
<td>Colorless solid 218 mg (0.70 mmol, 83 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %$^{[a]}$</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2p" /></td>
<td><img src="image" alt="8p" /></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>295 mg (0.73 mmol)</td>
<td>Colorless solid 179 mg (0.58 mmol, 80 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="2q" /></td>
<td><img src="image" alt="8q" /></td>
<td></td>
</tr>
</tbody>
</table>

$^{[a]}$ Additionally purified by suspension in DCM and sonication in ultrasound bath.
Table 6 (continuation). Experimental details for the deprotection of N-Boc 7-azaindolyl triazoles 8r-s.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected 7-azaindolyl triazole 2</th>
<th>7-Azaindolyl triazole 8 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>269 mg (0.69 mmol)</td>
<td>Colorless solid 179 mg (0.62 mmol, 90 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total yield: 62 %</td>
<td>HT-LC-MS: 100 %(^{[a]})</td>
</tr>
<tr>
<td>19</td>
<td>250 mg (0.64 mmol)</td>
<td>Pale yellow solid 160 mg (0.55 mmol, 86 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total yield: 55 %</td>
<td>HT-LC-MS: 100 %(^{[a]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Additionally purified by suspension in DCM and sonication in ultrasound bath.
Table 7. Experimental details for the Boc-deprotection of 7-azaindolyl triazoles 9a-b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Boc protected 7-azaindolyl triazole 7</th>
<th>7-Azaindolyl triazole 9 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>311 mg ((0.83 \text{ mmol}))</td>
<td>Colorless solid 207 mg ((0.75 \text{ mmol, 91 %})) Total yield: 75 %</td>
<td>DCM-MeOH-NH3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>21</td>
<td>373 mg ((0.99 \text{ mmol}))</td>
<td>Colorless solid 182 mg ((0.66 \text{ mmol, 66 %})) Total yield: 66 %</td>
<td>DCM-MeOH-NH3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HT-LC-MS: 100 %</td>
</tr>
</tbody>
</table>
4.2. Spectroscopic data of compounds 8a-s and 9a-b

4.2.1. 3-(1-Benzyl-1H,2,3-triazol-4-yl)-1H-indole (8a)

![Chemical structure of 3-(1-Benzyl-1H,2,3-triazol-4-yl)-1H-indole (8a)]

C<sub>17</sub>H<sub>14</sub>N<sub>4</sub> 274.32

147 mg (0.54 mmol, 54 % yield over two steps) as a pale yellow solid. Mp 171 °C. ¹H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 5.64 (s, 2 H), 7.08-7.12 (m, 1 H), 7.13-7.18 (m, 1 H), 7.31-7.36 (m, 1 H), 7.36-7.41 (m, 4 H), 7.42-7.45 (m, 1 H), 7.79 (d, J = 2.5 Hz, 1 H), 8.03 (d, J = 7.9 Hz, 1 H), 8.49 (s, 1 H), 11.3 (br, 1 H, NH). ¹³C NMR (DMSO-d<sub>6</sub>, 125 MHz): δ 52.8 (CH<sub>2</sub>), 106.1 (C<sub>quat</sub>), 111.8 (CH), 119.5 (CH), 119.6 (CH), 119.9 (CH), 121.6 (CH), 123.1 (CH), 124.6 (C<sub>quat</sub>), 127.9 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C<sub>quat</sub>), 136.3 (C<sub>quat</sub>), 142.9 (C<sub>quat</sub>). EI + MS (m/z (%)): 275 (9), 274 (M<sup>+</sup>, 44), 246 (47), 245 (100), 219 (11), 218 (50), 217 (16), 169 (C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>+, 31), 155 (46), 129 (10), 128 (43), 127 (10), 117 (16), 115 (12), 101 (26), 91 (C<sub>7</sub>H<sub>7</sub>+, 43), 77 (C<sub>6</sub>H<sub>5</sub>+, 14), 65 (C<sub>5</sub>H<sub>5</sub>+, 12). IR (KBr): v 3397 (s) cm<sup>-1</sup>, 1624 (w), 1601 (w), 1497 (w), 1456 (m), 1337 (w), 1221 (m), 1099 (w), 1053 (w), 939 (w), 776 (w), 749 (m), 727 (m), 586 (w), 522 (w). Anal. calcd for C<sub>17</sub>H<sub>14</sub>N<sub>4</sub> (274.3): C 74.43, H 5.14, N 20.42. Found: C 74.31, H 4.91, N 20.36.
4.2.2. 3-(1-Benzyl-1H,2,3-triazol-4-yl)-1H-indazole (8b)

\[
\begin{align*}
\text{C}_{16}\text{H}_{13}\text{N}_5 \\
275.31
\end{align*}
\]

264 mg (0.96 mmol, 64 % yield over two steps) as a colorless solid. Further purified by suspension in DCM and sonication in ultrasound bath. Mp 164 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 5.70 (s, 2 H), 7.19-7.23 (m, 1 H), 7.31-7.43 (m, 6 H), 7.55-7.59 (m, 1 H), 8.29 (d, \(J = 8.2\) Hz, 1 H), 8.69 (d, \(J = 0.9\) Hz, 1 H), 13.24 (s, 1 H, NH).

\(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 52.9 (CH\(_2\)), 110.2 (CH), 120.2 (C\(_{\text{quat}}\)), 120.9 (CH), 121.4 (CH), 121.7 (CH), 126.4 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.0 (C\(_{\text{quat}}\)), 136.1 (C\(_{\text{quat}}\)), 140.9 (C\(_{\text{quat}}\)), 142.2 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 275 (M\(^+\), 79), 246 ((M-HN\(_2\))^+, 84), 219 (16), 156 (C\(_9\)H\(_6\)N\(_3\))^+, 79), 102 (21), 91 (C\(_7\)H\(_7^+\), 100), 65 (C\(_5\)H\(_5^+\), 20).

IR (KBr): \(\tilde{\nu}\) 3181 (s) cm\(^{-1}\), 1624 (w), 1597 (w), 1497 (w), 1478 (w), 1457 (m), 1431 (w), 1348 (m), 1299 (w), 1241 (m), 1228 (w), 1217 (w), 1152 (w), 1133 (w), 1098 (w), 1062 (m), 1046 (w), 1003 (w), 965 (w), 904 (w), 819 (w), 773 (w), 750 (s), 715 (s), 584 (w). Anal. calcd for C\(_{16}\)H\(_{13}\)N\(_5\) (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.68, H 4.63, N 25.50.
4.2.3. 3-(1-Benzyl-1H,2,3-triazol-4-yl)-1H-pyrrolo[3,2-b]pyridine (8c)

\[
\text{C}_{16}\text{H}_{13}\text{N}_{5}
\]

275.31

137 mg (0.50 mmol, 50 % yield over two steps) as a colorless solid. Mp 246 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 5.69 (s, 2 H), 7.18 (dd, \(J = 8.2\) Hz, \(J = 4.7\) Hz, 1 H), 7.30-7.36 (m, 1 H), 7.36-7.41 (m, 4 H), 7.83 (dd, \(J = 8.2\) Hz, \(J = 1.3\) Hz, 1 H), 8.1 (br, 1 H), 8.40 (dd, \(J = 4.7\) Hz, \(J = 1.3\) Hz, 1 H), 8.61 (s, 1 H), 11.6 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 52.7 (CH\(_2\)), 106.5 (C\(_{\text{quat}}\)), 116.9 (CH), 119.1 (CH), 120.5 (CH), 125.6 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.0 (C\(_{\text{quat}}\)), 136.4 (C\(_{\text{quat}}\)), 140.9 (C\(_{\text{quat}}\)), 142.5 (C\(_{\text{quat}}\)), 142.8 (CH). El + MS (m/z (%)): 275 (M\(^+\), 21), 247 (20), 246 ((M-HN\(_2\))\(^+\), 100), 219 (19), 156 (C\(_6\)H\(_6\)N\(_3\))\(^+\), 149 (23), 143 (20), 129 (26), 102 (16), 97 (11), 91 (C\(_7\)H\(_7\))\(^+\), 89 (13), 85 (11), 84 (14), 83 (11), 77 (C\(_6\)H\(_5\))\(^+\), 15), 71 (14), 69 (10), 65 (C\(_5\)H\(_5\))\(^+\), 11), 57 (18), 55 (11), 43 (13). IR (KBr): \(\nu\) 3163 (s) cm\(^{-1}\), 3047 (m), 1628 (s), 1561 (w), 1497 (w), 1457 (w), 1413 (s), 1362 (m), 1335 (w), 1314 (w), 1277 (w), 1221 (w), 1200 (w), 1123 (w), 1106 (w), 1085 (w), 1051 (s), 943 (w), 889 (w), 776 (s), 718 (s), 697 (w), 613 (w), 580 (w), 508 (w). Anal. calcd for C\(_{16}\)H\(_{13}\)N\(_5\) (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.85, H 4.94, N 25.34.
4.2.4. 3-(1-Benzyl-1H,1,2,3-triazol-4-yl)-1H-pyrrolo[3,2-c]pyridine (8d)

95 mg (0.35 mmol, 48 % yield over two steps) as a colorless solid. Mp 195 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta \) 5.66 (s, 2 H), 7.31-7.37 (m, 1 H), 7.37-7.41 (m, 4 H), 7.43 (d, \(J = 5.7\) Hz, \(J = 0.6\) Hz, 1 H), 7.89 (s, 1 H), 8.24 (d, \(J = 5.7\) Hz, 1 H), 8.60 (s, 1 H), 9.33 (s, 1 H), 11.7 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta \) 52.9 (CH\(_2\)), 106.0 (C\(_{\text{quat}}\)), 107.0 (CH), 120.3 (CH), 121.7 (C\(_{\text{quat}}\)), 124.0 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.1 (C\(_{\text{quat}}\)), 139.7 (C\(_{\text{quat}}\)), 140.5 (CH), 141.9 (C\(_{\text{quat}}\)), 143.0 (CH). EI + MS (m/z (%)): 276 (19), 275 (M\(^+\), 100), 248 (14), 247 (86), 246 ((M-HN\(_2\))^+, 87), 220 (19), 219 (53), 170 (27), 156 (C\(_9\)H\(_6\)N\(_3\))^+, 61), 129 (38), 102 (13), 91 (C\(_7\)H\(_7\))^+, 99), 75 (13), 65 (C\(_5\)H\(_5\))^+, 22). IR (KBr): \(\tilde{\nu} \) 3088 (s) cm\(^{-1}\), 2975 (s), 2912 (s), 1627 (s), 1597 (s), 1578 (s), 1494 (w), 1464 (s), 1341 (m), 1299 (w), 1244 (m), 1212 (m), 1167 (w), 1117 (w), 1053 (m), 1026 (m), 938 (w), 901 (w), 854 (w), 806 (m), 769 (w), 716 (s), 693 (m), 650 (w), 631 (w), 596 (w), 505 (w). Anal. calcd for C\(_{16}\)H\(_{13}\)N\(_5\) (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.85, H 4.77, N 25.31.
4.2.5. 3-(1-Benzyl-1H,1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-c]pyridine (8e)

93 mg (0.34 mmol, 50% yield over two steps) as a pale yellow solid. Further purified by suspension in DCM and sonication in ultrasound bath. Mp 226 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 5.66 (s, 2 H), 7.31-7.42 (m, 5 H), 7.98 (d, J = 5.4 Hz, 1 H), 8.03 (s, 1 H), 8.20 (d, J = 5.4 Hz, 1 H), 8.55 (s, 1 H), 8.80 (s, 1 H), 11.8 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 52.9 (CH$_2$), 105.9 (C$_{quat}$), 114.6 (CH), 120.0 (CH), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 128.8 (C$_{quat}$), 133.5 (C$_{quat}$), 134.8 (CH), 136.2 (C$_{quat}$), 138.3 (CH), 142.0 (C$_{quat}$). EI + MS (m/z (%)): 276 (7), 275 (M$^+$, 34), 247 (47), 246 ((M-HN$_2$)$^+$, 100), 220 (14), 219 (55), 170 (28), 156 (C$_9$H$_5$N$_3^+$, 50), 129 (39), 102 (21), 91 (C$_7$H$_7^+$, 68), 75 (13), 65 (C$_5$H$_5^+$, 18). IR (KBr): $\tilde{\nu}$ 3068 (m) cm$^{-1}$, 2901 (m), 1655 (w), 1628 (m), 1560 (w), 1499 (m), 1459 (s), 1340 (w), 1296 (w), 1225 (s), 1173 (w), 1125 (m), 1061 (m), 1041 (m), 1028 (m), 887 (w), 810 (m), 722 (m), 711 (w), 670 (w), 596 (w). Anal. calcd for C$_{16}$H$_{13}$N$_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.88, H 4.96, N 25.24.
4.2.6. 3-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8f)

\[ \text{C}_{16}\text{H}_{13}\text{N}_{5} \]

275.31

930 mg (3.38 mmol, 67 % yield over two steps) as a pale yellow solid. After suspension in dichloromethane, sonication in ultrasonic bath, filtration, and drying, a colorless solid was obtained. Mp 234-237 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 5.66 (s, 2 H), 7.17 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.32-7.43 (m, 5 H), 7.92 (d, \(J = 2.5\) Hz, 1 H), 8.29 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H), 8.44 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 8.54 (s, 1 H), 11.9 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 52.8 (CH\(_2\)), 105.0 (C\(_{\text{quat}}\)), 115.9 (CH), 116.9 (C\(_{\text{quat}}\)), 119.8 (CH), 123.2 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 136.1 (C\(_{\text{quat}}\)), 142.4 (C\(_{\text{quat}}\)), 143.1 (CH), 148.5 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 275 (M\(^+\), 100), 248 (13), 247 (74), 246 (87), 220 (11), 219 (35), 170 (15), 156 (24), 142 (10), 129 (17), 91 (C\(_7\)H\(_7\)^+\), 19), 44 (19). IR (KBr): \(\tilde{\nu}\) 3133 (w) cm\(^{-1}\), 1655 (w), 1626 (w), 1584 (s), 1498 (w), 1458 (m), 1420 (m), 1327 (w), 1286 (w), 1220 (m), 1130 (w), 1111 (w), 1058 (w), 941 (m), 897 (w), 799 (m), 771 (s), 722 (s), 587 (w). Anal. calcd for C\(_{16}\)H\(_{13}\)N\(_5\) (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.71, H 5.02, N 25.44.
4.2.7. 3-(1-Phenyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8g)

C_{15}H_{11}N_{5}  
261.28

143 mg (0.55 mmol, 55 % yield over two steps) as a yellow solid. Mp 260 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 7.23 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.50-7.55 (m, 1 H), 7.63-7.68 (m, 2 H), 8.01-8.04 (m, 3 H), 8.34 (dd, $J = 4.4$ Hz, $J = 0.9$ Hz, 1 H), 8.58 (d, $J = 7.9$ Hz, 1 H), 9.18 (s, 1 H), 12.0 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 104.6 (C$_{quat}$), 116.1 (CH), 116.9 (C$_{quat}$), 117.5 (CH), 119.9 (CH), 123.6 (CH), 128.3 (CH), 128.4 (CH), 129.8 (CH), 136.7 (C$_{quat}$), 142.9 (C$_{quat}$), 143.3 (CH), 148.6 (C$_{quat}$).

EI + MS (m/z (%)): 261 (M$^+$, 11), 234 (14), 233 (C$_5$H$_{11}$N$_3$+, 88), 232 (100), 205 (31), 156 (43), 130 (15), 129 (15), 103 (29), 102 (19), 77 (C$_6$H$_5$+, 13), 76 (11), 51 (C$_4$H$_3$+, 10).

IR (KBr): $\tilde{v}$ 3440 (s) cm$^{-1}$, 3080 (s), 2924 (w), 2852 (w), 1656 (w), 1623 (w), 1585 (s), 1545 (w), 1495 (m), 1460 (w), 1423 (s), 1322 (m), 1281 (m), 1236 (w), 1215 (m), 1157 (w), 1129 (w), 1113 (w), 1074 (w), 1044 (s), 993 (w), 933 (w), 895 (w), 832 (w), 799 (m), 757 (s), 692 (s), 647 (w), 626 (w), 584 (s), 538 (w), 518 (w). Anal. calcd for C$_{15}$H$_{11}$N$_5$ (261.3): C 68.95, H 4.24, N 26.80. Found: C 68.71, H 4.43, N 26.90.
4.2.8. 3-(1-Benzyl-1H,2,3-triazol-4-yl)-4-methoxy-1H-pyrrolo[2,3-b]pyridine (8h)

\[
\text{C}_{17}\text{H}_{15}\text{N}_{5}\text{O}
\]

109 mg (0.36 mmol, 48 % yield over two steps) as a yellow solid. Mp 253-258 °C (dec.). \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 3.92 (s, 3 H), 5.65 (s, 2 H), 6.68 (d, \(J = 5.4\) Hz, 1 H), 7.32-7.43 (m, 5 H), 7.74 (d, \(J = 2.2\) Hz, 1 H), 8.12 (d, \(J = 5.4\) Hz, 1 H), 8.24 (s, 1 H), 11.8 (br, 1 H, NH). \(^13\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 52.6 (CH\(_2\)), 55.3 (CH\(_3\)), 98.2 (CH), 104.7 (C\(_{quat}\)), 106.4 (C\(_{quat}\)), 121.5 (CH), 122.1 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.4 (C\(_{quat}\)), 142.0 (C\(_{quat}\)), 145.2 (CH), 150.3 (C\(_{quat}\)), 159.6 (C\(_{quat}\)).

EI + MS (m/z (%)): 306 (21), 305 (M\(^+\), 100), 278 (17), 277 (83), 276 (86), 262 (27), 261 (11), 250 (12), 249 (38), 234 (10), 200 (16), 186 (31), 159 (14), 156 (18), 131 (12), 129 (11), 91 (C\(_7\)H\(_7\)\(^+\)), 65 (C\(_5\)H\(_5\)\(^+\)), 12. IR (KBr): \(\tilde{\nu}\) 3091 (w) cm\(^{-1}\), 3007 (w), 2940 (w), 2842 (w), 1578 (s), 1512 (w), 1498 (w), 1459 (w), 1430 (w), 1410 (w), 1321 (m), 1308 (m), 1279 (m), 1222 (w), 1150 (w), 1098 (m), 1051 (w), 974 (w), 939 (w), 852 (w), 801 (m), 726 (m), 653 (w). Anal. calcd for C\(_{17}\)H\(_{15}\)N\(_5\)O (305.3): C 66.87, H 4.95, N 22.94. Found: C 66.74, H 5.15, N 22.96.
4.2.9. 3-(1-Benzyl-1H-1,2,3-triazol-4-yl)-2-methyl-1H-pyrrolo[2,3-b]pyridine (8i)

\[
\text{C}_{17}\text{H}_{15}\text{N}_5
\]

300 mg (1.04 mmol, 52 % yield over two steps) as a colorless solid. Mp 263 °C. \( ^1H \) NMR (DMSO-d\(_6\), 500 MHz): \( \delta \) 2.63 (s, 3 H), 5.67 (s, 2 H), 7.10 (dd, \( J = 7.9 \) Hz, \( J = 4.7 \) Hz, 1 H), 7.32-7.37 (m, 1 H), 7.38-7.41 (m, 4 H), 8.18 (dd, \( J = 4.7 \) Hz, \( J = 1.3 \) Hz, 1 H), 8.28 (dd, \( J = 7.6 \) Hz, \( J = 0.9 \) Hz, 1 H), 8.51 (s, 1 H), 11.8 (br, 1 H, NH). \(^{13}C\) NMR (DMSO-d\(_6\), 125 MHz): \( \delta \) 13.0 (CH\(_3\)), 52.8 (CH\(_2\)), 101.0 (C\(_{\text{quat}}\)), 115.7 (CH), 118.5 (C\(_{\text{quat}}\)), 120.4 (CH), 126.9 (CH), 127.8 (CH), 128.0 (CH), 128.7 (CH), 134.1 (C\(_{\text{quat}}\)), 136.2 (C\(_{\text{quat}}\)), 141.8 (CH), 142.2 (C\(_{\text{quat}}\)), 147.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 289 (M\(^+\), 64), 262 (18), 261 ((M-N\(_2\))^+\, 100), 260 (45), 246 (54), 233 (45), 232 (25), 231 (18), 219 (35), 184 (54), 170 (71), 157 (17), 156 (38), 155 (37), 143 (23), 132 (24), 131 (17), 130 (17), 129 (14), 116 (15), 103 (15), 102 (43), 91 (C\(_7\)H\(_7\)^+\, 55), 65 (C\(_5\)H\(_5\)^+\, 17). IR (KBr): \( \tilde{\nu} \) 3425 (m) cm\(^{-1}\), 3103 (w), 3035 (w), 2921 (w), 2850 (w), 1625 (w), 1585 (s), 1527 (m), 1494 (w), 1457 (m), 1417 (s), 1390 (w), 1279 (s), 1217 (s), 1138 (w), 1117 (w), 1070 (m), 1046 (w), 969 (w), 931 (s), 824 (w), 796 (m), 771 (s), 715 (s), 693 (w), 673 (m), 650 (w), 582 (w). Anal. calcd for C\(_{17}\)H\(_{15}\)N\(_5\) (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.33, H 5.20, N 24.25.
4.2.10. 7-(1-Benzyl-1\textsubscript{H}-1,2,3-triazol-4-yl)-5\textsubscript{H}-pyrrolo[2,3-b]pyrazine (8j)

93 mg (0.34 mmol, 47% yield over two steps) as a colorless solid. Mp 248-249 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \textdelta 5.70 (s, 2 H), 7.31-7.37 (m, 1 H), 7.37-7.41 (m, 4 H), 8.31-8.35 (m, 2 H), 8.47 (d, J = 2.5 Hz, 1 H), 8.59 (s, 1 H), 12.3 (br, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \textdelta 52.7 (CH\textsubscript{2}), 105.4 (C\textsubscript{quat}), 120.8 (CH), 127.1 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 135.6 (C\textsubscript{quat}), 136.2 (C\textsubscript{quat}), 137.5 (CH), 138.3 (CH), 139.8 (C\textsubscript{quat}), 141.7 (C\textsubscript{quat}). EI + MS (m/z (%)): 276 (M\textsuperscript{+}, 50), 248 ((M-N\textsubscript{2})\textsuperscript{+}, 44), 247 ((M-HN\textsubscript{2})\textsuperscript{+}, 100), 220 (14), 157 (C\textsubscript{8}H\textsubscript{5}N\textsubscript{4}\textsuperscript{+}, 48), 130 (12), 91 (C\textsubscript{7}H\textsubscript{7}\textsuperscript{+}, 39), 65 (C\textsubscript{5}H\textsubscript{5}\textsuperscript{+}, 8). IR (KBr): \texttilde 3151 (s) cm\textsuperscript{-1}, 1632 (m), 1590 (m), 1544 (w), 1492 (m), 1456 (s), 1409 (m), 1364 (m), 1336 (s), 1221 (s), 1180 (m), 1119 (m), 1054 (m), 1038 (m), 944 (m), 908 (w), 849 (w), 799 (m), 721 (s), 694 (w), 673 (w), 628 (w), 586 (m), 540 (w). Anal. calcd for C\textsubscript{15}H\textsubscript{12}N\textsubscript{6} (276.3): C 65.21, H 4.38, N 30.42. Found: C 65.00, H 4.68, N 30.35.
4.2.11. 5-(1-Benzyl-1\textit{H}-1,2,3-triazol-4-yl)-4-methoxy-7\textit{H}-pyrrolo[2,3-\textit{d}]pyrimidine (8k)

![Chemical structure]

C\textsubscript{16}H\textsubscript{14}N\textsubscript{6}O

306.32

165 mg (0.54 mmol, 54 % yield over two steps) as a colorless solid. Mp 249 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \(\delta\) 4.07 (s, 3 H), 5.70 (s, 2 H), 7.34-7.45 (m, 5 H), 7.84 (s, 1 H), 8.38 (s, 1 H), 8.42 (s, 1 H), 12.3 (br, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \(\delta\) 52.6 (CH\textsubscript{2}), 53.4 (CH\textsubscript{3}), 101.4 (C\textsubscript{quat}), 105.1 (C\textsubscript{quat}), 121.4 (CH), 122.1 (CH), 127.9 (CH), 128.0 (CH), 128.7 (CH), 136.2 (C\textsubscript{quat}), 141.0 (C\textsubscript{quat}), 150.7 (CH), 152.7 (C\textsubscript{quat}), 162.3 (C\textsubscript{quat}). El + MS (m/z (%)): 307 (7), 306 (M\textsuperscript{+}, 32), 278 ((M-N\textsubscript{2})\textsuperscript{+}, 54), 277 (90), 250 (26), 201 (13), 187 (46), 146 (14), 132 (12), 130 (22), 103 (14), 91 (C\textsubscript{7}H\textsubscript{7}\textsuperscript{+}, 100), 65 (C\textsubscript{5}H\textsubscript{5}\textsuperscript{+}, 20), 42 (11). IR (KBr): \(\tilde{\nu}\) 3449 (w) cm\textsuperscript{-1}, 3084 (w), 2969 (w), 2923 (w), 2851 (w), 1581 (s), 1566 (s), 1476 (m), 1455 (m), 1433 (m), 1406 (w), 1376 (w), 1312 (s), 1219 (w), 1143 (w), 1091 (m), 1049 (m), 1031 (w), 962 (w), 936 (w), 880 (m), 851 (w), 798 (w), 771 (w), 720 (w), 691 (w), 671 (w), 633 (w), 575 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{14}N\textsubscript{6}O (306.3): C 62.74, H 4.61, N 27.44. Found: C 62.78, H 4.53, N 27.67.
4.2.12. 4-(2-Methoxyethoxy)-5-(1-benzyl-1H-1,2,3-triazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine (8l)

\[
\begin{align*}
\text{C}_{18}\text{H}_{18}\text{N}_{6}\text{O}_{2} & \\
\text{350.37}
\end{align*}
\]

141 mg (0.40 mmol, 41 % yield over two steps) as a colorless solid. Mp 240 °C. \( ^1 \)H NMR (DMSO-d\(_6\), 500 MHz): \( \delta \) 3.23 (s, 3 H), 3.68-3.71 (m, 2 H), 4.57-4.60 (m, 2 H), 5.65 (s, 2 H), 7.29-7.36 (m, 3 H), 7.37-7.42 (m, 2 H), 7.85 (s, 1 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 12.3 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \( \delta \) 52.9 (CH\(_2\)), 57.9 (CH\(_3\)), 64.7 (CH\(_2\)), 69.8 (CH\(_2\)), 101.3 (C\(_{quat}\)), 105.2 (C\(_{quat}\)), 121.5 (CH), 122.1 (CH), 127.4 (CH), 128.0 (CH), 128.8 (CH), 136.2 (C\(_{quat}\)), 141.3 (C\(_{quat}\)), 150.7 (CH), 152.8 (C\(_{quat}\)), 161.8 (C\(_{quat}\)). EI + MS (m/z (%)): 351 (24), 350 (M\(^+\), 97), 322 (18), 321 (46), 264 (39), 263 (100), 236 (20), 231 (13), 201 (18), 173 (15), 161 (12), 148 (19), 146 (18), 111 (15), 109 (10), 97 (21), 95 (14), 91 (C\(_7\)H\(_7\)+, 97), 85 (17), 83 (20), 81 (12), 71 (24), 69 (22), 65 (C\(_5\)H\(_5\)+, 12), 59 (14), 57 (36), 55 (17), 43 (22). IR (KBr): \( \tilde{\nu} \) 1578 (s) cm\(^{-1}\), 1446 (m), 1321 (m), 1207 (w), 1143 (w), 1091 (m), 1028 (w), 905 (w), 721 (m), 629 (w). Anal. calcd for C\(_{18}\)H\(_{18}\)N\(_6\)O\(_2\) (350.4): C 61.70, H 5.18, N 23.99. Found: C 61.59, H 5.22, N 24.10.
4.2.13. 1-Benzyl-4-(5-(4-methoxyphenyl)-1H-pyrrol-3-yl)-1H-1,2,3-triazole (8m)

![](image)

C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O  
330.38

147 mg (0.44 mmol, 44 % yield over two steps) as a pale yellow solid. Mp 238 °C. ¹H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 3.76 (s, 3 H), 5.60 (s, 2 H), 6.70-6.72 (m, 1 H), 6.93-6.97 (m, 2 H), 7.18-7.20 (m, 1 H), 7.32-7.36 (m, 3 H), 7.37-7.41 (m, 2 H), 7.56-7.60 (m, 2 H), 8.16 (s, 1 H), 11.3 (br, 1 H, NH). ¹³C NMR (DMSO-d<sub>6</sub>, 125 MHz): δ 52.7 (CH₂), 55.0 (CH₃), 102.3 (CH), 114.1 (CH), 115.2 (C<sub>quat</sub>), 115.8 (CH), 119.1 (CH), 124.7 (CH), 125.4 (C<sub>quat</sub>), 127.8 (CH), 128.0 (CH), 128.7 (CH), 131.9 (C<sub>quat</sub>), 136.2 (C<sub>quat</sub>), 143.7 (C<sub>quat</sub>), 157.5 (C<sub>quat</sub>). EI + MS (m/z (%)): 331 (16), 330 (M⁺, 66), 302 (40), 301 (100), 286 (11), 274 (34), 258 (12), 225 (11), 211 (36), 184 (21), 169 (13), 168 (17), 167 (13), 141 (10), 140 (12), 134 (23), 91 (C<sub>7</sub>H₇⁺, 48), 65 (C₆H₅⁺, 10). IR (KBr): ν 3429 (s) cm⁻¹, 1655 (w), 1638 (w), 1560 (w), 1543 (w), 1501 (m), 1458 (w), 1290 (w), 1256 (m), 1051 (m), 1022 (m), 835 (m), 798 (m), 718 (m), 548 (m). Anal. calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O (330.4): C 72.71, H 5.49, N 16.96. Found: C 72.45, H 5.68, N 17.08.
4.2.14. 1-Benzyl-4-(1H-pyrazol-4-yl)-1H-1,2,3-triazole (8n)

86 mg (0.38 mmol, 38 % yield over two steps) as a colorless solid. Mp 218 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 5.60 (s, 2 H), 7.31-7.35 (m, 3 H), 7.36-7.41 (m, 2 H), 7.7-8.2 (br, 2 H), 8.25 (s, 1 H), 13.0 (br, 1 H, NH). \(^13\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 52.8 (CH\(_2\)), 111.8 (C\(_{\text{quat}}\)), 120.2 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 136.0 (C\(_{\text{quat}}\)), 140.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 225 (M\(^+\), 18), 196 ((M-HN\(_2\))\(^+\), 72), 169 (27), 167 (10), 143 (16), 106 (C\(_7\)H\(_8\)N\(^+\), 96), 104 (10), 91 (C\(_7\)H\(_7\)\(^+\), 100), 79 (C\(_8\)H\(_9\)N\(_2\)\(^+\), 15), 65 (C\(_5\)H\(_5\)\(^+\), 24), 51 (C\(_4\)H\(_3\)\(^+\), 10). IR (KBr): \(\tilde{\nu}\) 3122 (s) cm\(^{-1}\), 3064 (m), 2952 (m), 2878 (m), 2878 (m), 1630 (m), 1544 (w), 1496 (w), 1458 (m), 1390 (w), 1360 (m), 1270 (w), 1215 (m), 1142 (w), 1111 (w), 1077 (w), 1049 (m), 1018 (w), 965 (w), 934 (m), 885 (m), 830 (s), 812 (s), 717 (s), 707 (s), 669 (w), 650 (w), 624 (m), 590 (w). Anal. calcd for C\(_{12}\)H\(_{11}\)N\(_5\) (225.3): C 63.99, H 4.92, N 31.09. Found: C 63.75, H 5.05, N 31.10.
4.2.15. 1-Benzyl-4-(1H-imidazol-4-yl)-1H-1,2,3-triazole (8o)

![Chemical Structure](image)

$\text{C}_{12}\text{H}_{11}\text{N}_5$

225.25

46 mg (0.20 mmol, 20% yield over two steps) as a colorless solid. Mp 188 °C. $^1\text{H}$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 5.62 (s, 2 H), 7.29-7.41 (m, 5 H), 7.5 (br, 1 H), 7.70 (s, 1 H), 8.2 (br, 1 H), 12.2 & 12.7 (br, 1 H, NH). EI + MS ($m/z$ (%)): 225 (M$^+$, 30), 197 ((M-N$_2$)$^+$, 18), 196 ((M-HN$_2$)$^+$, 100), 169 (37), 149 (13), 143 (10), 142 (12), 120 (16), 115 (11), 106 (C$_7$H$_8$N$^+$, 86), 105 (11), 93 (11), 92 (18), 91 (C$_7$H$_7^+$, 90), 85 (10), 77 (C$_6$H$_5^+$, 18), 71 (12), 65 (C$_5$H$_5^+$, 25), 57 (13), 55 (10), 52 (C$_4$H$_4^+$, 11), 44 (10), 43 (10), 41 (11). IR (KBr): $\tilde{\nu}$ 3113 (s) cm$^{-1}$, 3032 (m), 2925 (m), 2832 (m), 1655 (w), 1625 (m), 1535 (m), 1498 (w), 1458 (s), 1354 (w), 1215 (s), 1162 (w), 1121 (w), 1097 (w), 1054 (w), 1016 (w), 945 (s), 833 (m), 787 (w), 715 (s), 693 (m), 660 (w), 627 (w), 583 (w).

Anal. calcd for C$_{12}$H$_{11}$N$_5$ (225.3): C 63.99, H 4.92, N 31.09. Found: C 64.08, H 5.08, N 30.85.
4.2.16. 3-(1-(4-Chlorobenzyl)-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8p)

![structure](image)

C\textsubscript{16}H\textsubscript{12}ClN\textsubscript{5}  
309.75

218 mg (0.70 mmol, 45 % yield over two steps) as a colorless solid. Mp 225 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \(\delta\) 5.67 (s, 2 H), 7.18 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.38-7.43 (m, 2 H), 7.45-7.50 (m, 2 H), 7.92 (d, \(J = 2.2\) Hz, 1 H), 8.29 (d, \(J = 4.4\) Hz, 1 H), 8.44 (d, \(J = 7.9\) Hz, 1 H), 8.53 (s, 1 H), 11.9 (br, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \(\delta\) 52.0 (CH\textsubscript{2}), 104.9 (C\textsubscript{quat}), 115.9 (CH), 116.9 (C\textsubscript{quat}), 119.8 (CH), 123.3 (CH), 128.2 (CH), 128.7 (CH), 129.8 (CH), 132.8 (C\textsubscript{quat}), 135.1 (C\textsubscript{quat}), 142.4 (C\textsubscript{quat}), 143.1 (CH), 148.5 (C\textsubscript{quat}). EI + MS (m/z (%)): 311 (M\textsuperscript{37}Cl\textsuperscript{+}, 26), 310 (14), 309 (M\textsuperscript{35}Cl\textsuperscript{+}, 80), 283 (27), 282 (44), 281 (75), 280 (100), 253 (20), 246 (20), 219 (16), 218 (19), 170 (26), 156 (54), 129 (35), 127 (15), 125 (45), 118 (11), 102 (18), 89 (17), 57 (12), 44 (24). IR (KBr): \(\tilde{\nu}\) 3139 (m) cm\textsuperscript{-1}, 2895 (w), 1625 (w), 1584 (s), 1493 (s), 1418 (m), 1326 (w), 1286 (w), 1222 (w), 1130 (w), 1091 (w), 1054 (w), 1016 (w), 941 (w), 897 (w), 801 (m), 771 (s), 653 (w), 619 (w), 586 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{12}ClN\textsubscript{5} (309.8): C 62.04, H 3.90, N 22.61. Found: C 61.92, H 3.90, N 22.54.
4.2.17. 3-(1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8q)

![Chemical structure image](image)

C_{17}H_{15}N_5O

305.33

179 mg (0.58 mmol, 58 % yield over two steps) as a pale yellow solid. After suspension in dichloromethane, sonication in ultrasonic bath, filtration, and drying, a colorless solid was obtained. Mp 185 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 3.74 (s, 3 H), 5.57 (s, 2 H), 6.94-6.97 (m, 2 H), 7.17 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.34-7.38 (m, 2 H), 7.90 (d, $J = 2.5$ Hz, 1 H), 8.28 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 8.44 (dd, $J = 7.9$ Hz, $J = 1.3$ Hz, 1 H), 8.48 (s, 1 H), 11.9 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 52.4 (CH$_2$), 55.0 (CH$_3$), 105.0 (C$_{quat}$), 114.0 (CH), 115.9 (CH), 116.9 (C$_{quat}$), 119.4 (CH), 123.2 (CH), 128.0 (C$_{quat}$), 128.2 (CH), 129.5 (CH), 142.3 (C$_{quat}$), 143.1 (CH), 148.5 (C$_{quat}$), 159.0 (C$_{quat}$). El + MS (m/z (%)): 306 (7), 305 (M$^+$, 36), 277 ((M-N$_2$)$^+$, 43), 276 (72), 249 (19), 170 (18), 156 (40), 129 (36), 122 (11), 121 (C$_8$H$_9$O$^+$, 100), 103 (10), 102 (13), 91 (C$_7$H$_7$$^+$, 13), 78 (C$_6$H$_6$$^+$, 19), 77 (C$_6$H$_5$$^+$, 20). IR (KBr): ν 3447 (m) cm$^{-1}$, 3424 (m), 3136 (w), 2903 (w), 1612 (w), 1584 (m), 1514 (s), 1462 (w), 1419 (m), 1335 (w), 1281 (w), 1249 (s), 1211 (w), 1180 (w), 1127 (w), 1033 (m), 938 (w), 896 (w), 827 (w), 798 (w), 764 (s), 697 (w), 618 (w), 588 (w), 552 (w). Anal. calcd for C$_{17}$H$_{15}$N$_5$O (305.3): C 66.87, H 4.95, N 22.94. Found: C 66.68, H 5.20, N 23.03.
4.2.18. 3-(1-Phenethyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (8r)

\[
\text{C}_{17}\text{H}_{15}\text{N}_{5}
\]

289.33

179 mg (0.62 mmol, 62 % yield over two steps) as a colorless solid. Mp 228 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 3.26 (t, \(J = 7.3\) Hz, 2 H), 4.68 (t, \(J = 7.3\) Hz, 2 H), 7.18 (dd, \(J = 7.9\) Hz, \(J = 4.4\) Hz, 1 H), 7.20-7.32 (m, 5 H), 7.89 (d, \(J = 2.2\) Hz, 1 H), 8.30 (dd, \(J = 4.4\) Hz, \(J = 1.6\) Hz, 1 H), 8.40 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 8.44 (s, 1 H), 11.9 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 35.5 (CH\(_2\)), 50.4 (CH\(_2\)), 105.1 (C\(_{\text{quat}}\)), 115.9 (CH), 116.9 (C\(_{\text{quat}}\)), 119.6 (CH), 126.5 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 137.6 (C\(_{\text{quat}}\)), 141.7 (C\(_{\text{quat}}\)), 143.1 (CH), 148.5 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 289 (M\(^+\), 40), 261 ((M-N\(_2\))\(^+\), 13), 260 (13), 234 (16), 233 (36), 171 (12), 170 (100), 157 (15), 156 (18), 144 (11), 143 (80), 142 (88), 132 (12), 131 (20), 130 (14), 129 (13), 116 (20), 115 (18), 105 (C\(_6\)H\(_5\))\(^+\), 24), 103 (17), 91 (C\(_7\)H\(_7\))\(^+\), 12), 79 (15), 77 (C\(_6\)H\(_5\))\(^+\), 18). IR (KBr): \(\tilde{\nu}\) 3449 (w) cm\(^{-1}\), 3089 (m), 3064 (m), 3028 (w), 2932 (w), 2893 (w), 1624 (w), 1584 (s), 1495 (m), 1455 (m), 1416 (s), 1320 (w), 1283 (m), 1218 (m), 1134 (w), 1112 (w), 1058 (w), 1030 (m), 942 (w), 898 (w), 842 (w), 793 (m), 770 (s), 730 (s), 698 (s), 629 (w), 585 (w). Anal. calcd for C\(_{17}\)H\(_{15}\)N\(_5\) (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.47, H 5.40, N 24.25.
4.2.19. 3-(1-(1-Phenylethyl)-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridin (8s)

\[
\text{C}_{17}\text{H}_{15}\text{N}_5
\]

289.33

160 mg (0.55 mmol, 55 % yield over two steps) as a pale yellow solid. Mp 184 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \(\delta\) 1.96 (d, \(J = 7.3\) Hz, 3 H), 6.00 (q, \(J = 7.3\) Hz, 1 H), 7.18 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.30-7.35 (m, 1 H), 7.37-7.40 (m, 4 H), 7.91 (d, \(J = 2.5\) Hz, 1 H), 8.29 (dd, \(J = 4.4\) Hz, \(J = 1.6\) Hz, 1 H), 8.48 (dd, \(J = 7.9\) Hz, \(J = 1.3\) Hz, 1 H), 8.62 (s, 1 H), 11.9 (br, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \(\delta\) 21.0 (CH\textsubscript{3}), 59.2 (CH), 105.1 (C\textsubscript{quat}), 115.9 (CH), 116.9 (C\textsubscript{quat}), 118.3 (CH), 123.2 (CH), 126.2 (CH), 127.9 (CH), 128.3 (CH), 128.7 (CH), 141.2 (C\textsubscript{quat}), 142.1 (C\textsubscript{quat}), 143.1 (CH), 148.5 (C\textsubscript{quat}). EI + MS (m/z (%)): 290 (6), 289 (M\textsuperscript{+}, 30), 260 (13), 247 (19), 246 (100), 219 (12), 156 (47), 143 (11), 129 (35), 105 (C\textsubscript{8}H\textsubscript{9}\textsuperscript{+}, 34), 103 (17), 102 (12), 79 (13), 77 (C\textsubscript{6}H\textsubscript{5}\textsuperscript{+}, 17). IR (KBr): \(\nu\) 3457 (w) cm\textsuperscript{-1}, 3120 (m), 3080 (m), 2927 (m), 2874 (m), 1623 (w), 1586 (s), 1495 (w), 1458 (m), 1420 (m), 1383 (w), 1333 (m), 1302 (w), 1279 (m), 1234 (w), 1211 (m), 1196 (m), 1136 (m), 1109 (w), 1058 (w), 1040 (w), 1023 (w), 982 (w), 937 (m), 896 (w), 824 (m), 793 (w), 770 (s), 722 (w), 694 (m), 648 (w), 624 (w), 584 (m), 544 (w), 526 (w). Anal. calcd for C\textsubscript{17}H\textsubscript{15}N\textsubscript{5} (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.30, H 5.42, N 24.01.
### 4.2.20. 4-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (9a)

![Chemical Structure](Image)

207 mg (0.75 mmol, 75 % yield over two steps) as a colorless solid. Mp 200 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 5.73 (s, 2 H), 7.00-7.03 (m, 1 H), 7.33-7.44 (m, 5 H), 7.58-7.61 (m, 2 H), 8.29 (dd, $J$ = 5.0 Hz, $J$ = 0.6 Hz, 1 H), 9.03 (d, $J$ = 0.9 Hz, 1 H), 11.8 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 53.0 (CH$_2$), 100.1 (CH), 111.6 (CH), 115.5 (C$_{quat}$), 123.8 (CH), 126.5 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 129.3 (C$_{quat}$), 135.9 (C$_{quat}$), 142.6 (CH), 144.8 (C$_{quat}$), 149.4 (C$_{quat}$). EI + MS (m/z (%)): 276 (10), 275 (M$^+$, 48), 247 (14), 246 (64), 219 (14), 170 (10), 157 (11), 156 (100), 149 (20), 130 (14), 129 (30), 109 (10), 102 (10), 91 (C$_7$H$_7^+$, 98), 85 (11), 71 (13), 65 (C$_5$H$_5^+$, 14), 57 (14). IR (KBr): $\tilde{\nu}$ 3128 (m) cm$^{-1}$, 2869 (m), 1604 (s), 1543 (w), 1498 (m), 1458 (m), 1391 (w), 1333 (s), 1226 (w), 1050 (m), 897 (w), 824 (s), 723 (m), 645 (w), 601 (w). Anal. calcd for C$_{16}$H$_{13}$N$_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.58, H 4.83, N 25.58.
4.2.21. 5-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (9b)

\[
\begin{align*}
\text{Bn} & \quad \text{N} = \text{N} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

C\textsubscript{16}H\textsubscript{13}N\textsubscript{5}

275.31

182 mg (0.66 mmol, 66 % yield over two steps) as a colorless solid. Mp 210 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \textit{\delta} 5.65 (s, 2 H), 6.50 (dd, \textit{J} = 3.5 Hz, \textit{J} = 1.9 Hz, 1 H), 7.32-7.43 (m, 5 H), 7.49-7.51 (m, 1 H), 8.38 (d, \textit{J} = 1.9 Hz, 1 H), 8.64 (s, 1 H), 8.71 (d, \textit{J} = 1.9 Hz, 1 H), 11.7 (br, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \textit{\delta} 53.1 (CH\textsubscript{2}), 100.2 (CH), 118.9 (C\textsubscript{quat}), 119.5 (C\textsubscript{quat}), 120.8 (CH), 124.6 (CH), 127.0 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 136.0 (C\textsubscript{quat}), 140.4 (CH), 145.7 (C\textsubscript{quat}), 148.2 (C\textsubscript{quat}).

EI + MS (m/z (%)): 276 (6), 275 (M\textsuperscript{+}, 28), 247 (23), 246 (100), 219 (25), 170 (22), 156 (68), 129 (39), 91 (C\textsubscript{7}H\textsubscript{7}\textsuperscript{+}, 58), 65 (C\textsubscript{5}H\textsubscript{5}\textsuperscript{+}, 11). IR (KBr): \textit{\nu} 3125 (m) cm\textsuperscript{-1}, 1608 (w), 1585 (w), 1497 (w), 1454 (w), 1435 (w), 1407 (m), 1340 (m), 1314 (w), 1298 (w), 1228 (w), 1214 (w), 1069 (w), 1051 (w), 919 (w), 905 (w), 805 (m), 781 (w), 734 (s), 693 (w), 621 (w), 505 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{13}N\textsubscript{5} (275.3): C 69.80, H 4.76, N 25.44.

Found: C 69.95, H 4.64, N 25.48.
5. Preparation of 3-(4-Benzyl-1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-b]pyridine (10) by the One-Pot Synthesis of 1-Aryl 1,2,3-Triazoles from Aryl Halides and Terminal Alkynes in the Presence of Sodium Azide

Copper(I) iodide (39 mg, 0.20 mmol, 10 mol %) was placed under argon atmosphere in a dry screw-cap vessel with septum. Then, tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f) (688 mg, 2.00 mmol) in 5 mL of dimethylsulfoxide and 1 mL of water was added and the mixture was degassed with argon. Sodium azide (138 mg, 2.10 mmol, 1.05 equiv), sodium ascorbate (40 mg, 0.20 mmol, 10 mol %), benzylacetylene (0.26 mL, 2.00 mmol, 1.00 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 0.30 mmol, 0.15 equiv) were successively added to the mixture which was stirred at room temperature (water bath) for 112 h (monitored by TLC, but the reaction did not go to completion). Then, the mixture was diluted with 10 mL of water, extracted with 10 mL of dichloromethane, the organic phase was washed with water (3 x 10 mL), dried with sodium sulphate, and filtered. The solvents were removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1). After drying in vacuo, 105 mg (0.28 mmol, 14 % yield) of a yellow oil were obtained.
The obtained oil was dissolved in 1.4 mL of methanol, potassium carbonate (98 mg, 0.70 mmol, 2.50 equiv) was added, and the mixture was stirred at room temperature for 1 h. Then, the solvent was removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 (stepwise gradient). After drying in vacuo at 70 °C overnight, 3-(1-benzyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (10) (49 mg, 0.18 mmol, 64 % yield) was obtained as a colorless solid.
3-(4-Benzyl-1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-b]pyridine (10)

![Chemical Structure](image)

C$_{16}$H$_{13}$N$_{5}$

275.31

49 mg (9% yield over two steps) as a colorless solid. Mp 177 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 4.11 (s, 2 H), 7.21-7.26 (m, 2 H), 7.30-7.35 (m, 4 H), 8.11 (d, J = 2.8 Hz, 1 H), 8.30 (dd, J = 7.9 Hz, J = 1.6 Hz, 1 H), 8.37 (dd, J = 4.4 Hz, J = 1.6 Hz, 1 H), 8.46 (s, 1 H), 12.2 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 31.1 (CH$_2$), 112.2 (C$_{quat}$), 113.6 (C$_{quat}$), 116.7 (CH), 117.6 (CH), 121.4 (CH), 126.1 (CH), 127.5 (CH), 128.4 (CH), 128.5 (CH), 139.3 (C$_{quat}$), 144.3 (CH), 146.1 (C$_{quat}$), 146.4 (C$_{quat}$). Ei + MS (m/z (%)): 275 (M$^+$, 1), 247 ((M-N$_2$)$_2^+$, 37), 246 (100), 170 (27), 144 (32), 143 (44), 132 (16), 128 (10), 117 (15), 116 (11), 115 (14), 104 (37), 103 (15), 91 (C$_7$H$_7^+$, 18), 90 (15), 78 (10), 77 (C$_6$H$_5^+$, 14), 65 (C$_5$H$_5^+$, 5). IR (KBr): ν 3447 (s) cm$^{-1}$, 3421 (s), 3144 (w), 3108 (w), 3025 (w), 2920 (w), 2821 (w), 1655 (m), 1613 (s), 1586 (m), 1563 (w), 1515 (w), 1494 (m), 1436 (m), 1409 (s), 1377 (m), 1341 (w), 1288 (s), 1206 (s), 1136 (m), 1103 (m), 1073 (w), 1049 (s), 1021 (w), 947 (m), 895 (m), 830 (w), 790 (m), 766 (s), 721 (s), 691 (m), 665 (w), 616 (w), 586 (m), 531 (w). Anal. calcd for C$_{16}$H$_{13}$N$_{5}$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.63, H 4.96, N 25.20.
6. Preparation of 3-(1-Benzyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (11) by the Masuda Borylation – Suzuki Coupling Sequence\textsuperscript{[5]}

Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1-benzyl-4-bromo-1H-pyrazole (237 mg 1.00 mmol, 1.00 equiv), and cesium carbonate (823 mg, 2.50 mmol, 2.50 equiv) were successively added and the mixture was stirred at 100 °C (preheated oil bath) for 24 h. Then, after cooling to room temperature (water bath) the solvents were removed in vacuo and the residue was absorbed onto Celite\textsuperscript{®} and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH\textsubscript{3} = 100:1:1. After drying in vacuo at 70 °C overnight, 3-(1-benzyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (11) was obtained as a yellow solid. Recrystallization from dichloromethane/n-pentane gave a colorless solid.
3-(1-Benzyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (11)

![Chemical Structure](image)

$\text{C}_{17}\text{H}_{14}\text{N}_{4}$

274.32

41 mg (0.15 mmol, 15 % yield) as a colorless solid (dichloromethane/n-pentane). Mp 198 °C. $^1\text{H}$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 5.37 (s, 2 H), 7.12 (dd, $J = 7.9$ Hz, $J = 4.4$ Hz, 1 H), 7.26-7.32 (m, 3 H), 7.33-7.38 (m, 2 H), 7.71 (d, $J = 2.5$ Hz, 1 H), 7.90 (s, 1 H), 8.21 (dd, $J = 7.9$ Hz, $J = 1.3$ Hz, 1 H), 8.24 (dd, $J = 4.4$ Hz, $J = 1.3$ Hz, 1 H), 8.29 (s, 1 H), 11.7 (br, 1 H, NH). $^{13}\text{C}$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 54.8 (CH$_2$), 106.2 (C$_{\text{quat}}$), 115.4 (CH), 115.6 (C$_{\text{quat}}$), 117.2 (C$_{\text{quat}}$), 121.9 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 127.5 (CH), 128.5 (CH), 136.5 (CH), 137.7 (C$_{\text{quat}}$), 142.7 (CH), 148.6 (C$_{\text{quat}}$). EI + MS ($m/z$ (%)): 275 (26), 274 (M$^+$, 100), 273 ((M-H)$^+$, 10), 183 (C$_{10}\text{H}_7\text{N}_4^+$, 9), 142 (C$_9\text{H}_6\text{N}_2^+$, 7), 91 (C$_7\text{H}_7^+$, 51), 65 (C$_5\text{H}_5^+$, 6). IR (KBr): $\tilde{\nu}$ 3449 (w) cm$^{-1}$, 3103 (m), 3027 (m), 2819 (m), 1655 (w), 1579 (m), 1492 (m), 1459 (w), 1421 (s), 1337 (w), 1288 (m), 1229 (w), 1196 (w), 1149 (w), 1130 (w), 1110 (w), 989 (m), 918 (w), 897 (w), 857 (m), 822 (w), 793 (w), 763 (s), 719 (s), 695 (w), 665 (w), 650 (w), 614 (w), 587 (w), 532 (w). Anal. calcd for C$_{17}\text{H}_{14}\text{N}_4$ (274.3): C 74.43, H 5.14, N 20.42. Found: C 74.41, H 5.22, N 20.27.
7. $^1$H and $^{13}$C NMR Spectra of Compounds 8f, 8g, 8r, 9a, 10, and 11

$^1$H NMR of 8f (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 8f (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 8f (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 8g (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 8g (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 8g (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 8r (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K (δ in ppm).
$^{13}$C NMR of 8r (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 8r (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K (δ in ppm).
$^1$H NMR of 9a (15 mg) in 0.7 mL DMSO-$d_6$ at 295 K (δ in ppm).
$^{13}$C NMR of 9a (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 9a (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 10 (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
\[ ^{13}C \text{ NMR of } 10 \text{ (15 mg) in 0.7 mL DMSO-}d_6 \text{ at 297 K (\( \delta \) in ppm).} \]

\[ ^{13}C \text{ DEPT 135-NMR of } 10 \text{ (15 mg) in 0.7 mL DMSO-}d_6 \text{ at 296 K (\( \delta \) in ppm).} \]
$^1$H NMR of 11 (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 11 (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 11 (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
8. Appendix

8.1. HT-LC-MS Spectra and UV purity of the obtained compounds 8a-s, 9a-b, 10, and 11

HT-LC-MS Spectrum (SOP 2200) of 8a. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8b. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8c. UV purity: 100%
HT-LC-MS Spectrum (SOP 2200) of 8d. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8e. UV purity: 99.9 %
HT-LC-MS Spectrum (SOP 2222) of 8f. UV purity: 100 %

1: MS ES+: $m/z$ 276.12+298.12

2: UV Detector: TIC

Range: $1.314e-3$

$1.0e-3$

1: ELSO

$2.9e+004$

Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found
--- | --- | --- | --- | --- | --- | ---
1 | Found | 1.50 | 7e+005 | 99.76 | 0 | 6e+006 | 275.12
2 | Found | 1.54 | 5e+003 | 100.00 | 0 | 4e+004 | 275.12
3 | Found | 1.91 | 2e+003 | 0.24 | 0 | 1e+004 | 275.12

Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found
--- | --- | --- | --- | --- | --- | ---
1 | Found | 1.46 | 9e+001 | 100.00 | 0 | 1e+003 | 275.12
2 | Found | 1.47 | 3e+003 | 100.00 | 1 | 2e+004 | 275.12
HT-LC-MS Spectrum (SOP 2200) of 8g. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2222) of 8h. UV purity: 100 %

1: MS ES+ : 306.133±328.13

2: UV Detector: TIC

Range: 1.24e-3

103
HT-LC-MS Spectrum (SOP 2200) of 8i. UV purity: 100 %
### Table 1: Mass Spectra Peaks

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### Diagram

- **MS ES- 200.13 Smooth (ES, 2x4)**
- **MS ES- 577.26 Smooth (ES, 2x4)**
- **ES CD Signal Smooth (Ma, 2x3)**

**Range:** 1374.213

**Peak ID Compound | Time | Mass Found**
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HT-LC-MS Spectrum (SOP 2200) of 8k. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8l. UV purity: 100 %
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HT-LC-MS Spectrum (SOP 2200) of 8m. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8n. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8o. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2222) of 8p. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8q. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8r. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 8s. UV purity: 100 %
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**Peak 3 (Time: 2.43) Combine (507:511)**

- Mass (m/z): 216.0, 247.1, 351.3, 394.3, 433.7, 509.5, 574.0, 677.2, 763.5, 785.3, 914.1, 956.8

**Peak 4 (Time: 2.49) Combine (518:522)**

- Mass (m/z): 227.0, 249.0, 395.0, 479.0, 507.9, 644.8, 666.9, 760.8, 803.0, 674.0, 920.8
HT-LC-MS Spectrum (SOP 2200) of 9a. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2222) of 9b. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 10. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2222) of 11. UV purity: 100 %
8.2. HT-LC-MS Methods for the control of identity and purity of compounds
8a-s, 9a-b, 10, and 11

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<tr>
<td></td>
<td>11.00</td>
</tr>
<tr>
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<td>Room temperature</td>
</tr>
<tr>
<td><strong>Injection volume</strong></td>
<td>3 μL</td>
</tr>
<tr>
<td><strong>Sample preparation</strong></td>
<td>Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasonic bath, so that the concentration was 0.5 mM.</td>
</tr>
<tr>
<td></td>
<td>If necessary, the sample was additionally diluted: 100 μL in 500 μL acetonitrile + water 5/95.</td>
</tr>
<tr>
<td><strong>Problem definition</strong></td>
<td>Identity and Purity</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------</td>
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<td><strong>SOP</strong></td>
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<tr>
<td><strong>System</strong></td>
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<td>1 x Waters 2488 Mux-UV Detector</td>
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<td>1 x Waters ZQ-MUX</td>
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<td><strong>Software</strong></td>
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<tr>
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<tr>
<td><strong>Eluent</strong></td>
<td>A: 99.9 % acetonitrile + 0.1 % formic acid</td>
</tr>
<tr>
<td></td>
<td>B: 99.9 % water + 0.1 % formic acid</td>
</tr>
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<td><strong>Gradient</strong></td>
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<td>Room temperature</td>
</tr>
<tr>
<td><strong>Throughput</strong></td>
<td>416 samples: approx. 11 h</td>
</tr>
</tbody>
</table>
8.3. Determination of Cu and Pd contents in compound 8f

| Sample preparation: | 4.8 mg of compound 8f dissolved in 4.8 mL of DMSO |
| Sample introduction: | 50 µL/min Meinhard sprayer, quartz cyclone spray chamber, syringe pump |
| Internal standard: | Rhodium |
| Calibration: | Addition of standard or additions calibration |

<table>
<thead>
<tr>
<th>Additions [µg/g]:</th>
<th>Cu</th>
<th>Pd</th>
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<tbody>
<tr>
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<td>5</td>
<td>5</td>
</tr>
<tr>
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</tr>
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<td>15</td>
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<td>15</td>
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</table>

<table>
<thead>
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<th>Analytical results:</th>
<th>Cu</th>
<th>Pd</th>
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<tbody>
<tr>
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<td>&lt; 2 µg/g</td>
<td>&lt; 1 µg/g</td>
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9. References


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Copper-mediated reactions have been playing an outstanding role in organic chemistry for over a century as manifested in many important transformations and name reactions. Indeed, Ullmann-type reactions can be considered as predecessors of modern cross-couplings. However, copper-mediated transformations have been completely overshadowed by the very dramatic developments in palladium chemistry. Nevertheless, many new remarkable copper-catalyzed processes have appeared in the last decade, thus heralding a renaissance in copper catalysis.[1–5]

In 1963, Stephens and Castro reported a synthesis of diarylacetylenes by a stoichiometric coupling reaction of copper acetylides with aryl iodides, which proceeded in refluxing pyridine under a nitrogen atmosphere.[6] Later, catalytic variants were also developed, some of which allowed milder conditions more tolerant to functional groups.[7] With the advent of the usually more efficient palladium-catalyzed alkynylations[8] and finally the Pd/Cu-catalyzed Sonogashira–Hagihara coupling,[9,10] the Stephens–Castro reaction became far less significant (Scheme 1).

Recently, we reported a new multicomponent approach to alkynes by glyoxylation of electron-rich heterocycles such as indoles and pyrroles with oxalyl chloride under Lewis acid free conditions followed by a novel decarbonylative Sonogashira coupling procedure (Scheme 2).[11]

In optimization studies[14] we found that the best results were obtained with 1.0 equivalent of oxalyl chloride, 5 mol % of CuI, 1.0 equivalent of a terminal alkyne, and 3.0 equivalents of triethylamine. In comparison to the corresponding decarbonylative Sonogashira reaction, the coupling step is slower, but essentially complete within 24 h at room temperature. Increasing the reaction temperature diminishes the yield, and prolonged reaction time (48 h) does not increase the yield. The sequence can be performed conveniently on a 5 mmol scale and is preparatively very straightforward (Table 1). The CuI catalyst was obtained from Aldrich (98%) and used as supplied. An ultrapure batch (Alfa Aesar Puratronic, 99.999% (metals basis)) gave the same yield, thus proving that copper is indeed the catalytically
Table 1: Glyoxylation/Stephens–Castro synthesis of ynediones 3, 4, and 5.[a]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield [%][b] (method[c])</th>
<th>Product</th>
<th>Yield [%][b] (method[c])</th>
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<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>66 (A)</td>
<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td><img src="image3.png" alt="Image" /></td>
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<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td><img src="image5.png" alt="Image" /></td>
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<td><img src="image6.png" alt="Image" /></td>
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<td><img src="image7.png" alt="Image" /></td>
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<tr>
<td><img src="image9.png" alt="Image" /></td>
<td>43 (A)</td>
<td><img src="image10.png" alt="Image" /></td>
<td>77[c] (C)</td>
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<tr>
<td><img src="image11.png" alt="Image" /></td>
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<tr>
<td><img src="image13.png" alt="Image" /></td>
<td>57 (A)</td>
<td><img src="image14.png" alt="Image" /></td>
<td>47 (D)</td>
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<tr>
<td><img src="image15.png" alt="Image" /></td>
<td>35 (A)</td>
<td><img src="image16.png" alt="Image" /></td>
<td>53 (E)</td>
</tr>
<tr>
<td><img src="image17.png" alt="Image" /></td>
<td>2 (A)</td>
<td><img src="image18.png" alt="Image" /></td>
<td>66 (E)</td>
</tr>
<tr>
<td><img src="image19.png" alt="Image" /></td>
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<td><img src="image21.png" alt="Image" /></td>
<td>59 (B)</td>
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<td>33 (A)</td>
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</tbody>
</table>

[a] Reactions were performed in ethereal solvents [c(T) = 0.2 M] using 5.00 mmol of substrate 1. Abbreviations: Ph = phenyl, Me = methyl, TIPS = triisopropylsilyl, Bu = butyl, Bn = benzyl, PMB = p-methoxybenzyl, Bz = benzhydryl. [b] All yields refer to isolated and purified compounds. [c] Method A: THF, 0°C to RT, 4 h; method B: DME, 0°C to 100°C, 2 h; method C: THF, 0°C to 50°C, 4 h; method D: DME, 0°C to 100°C, 24 h; method E: 1,4-dioxane, RT to 100°C, 4 h; method F: 1,4-dioxane, RT to 100°C, 24 h. [d] According to method A, 33% of 4e could be obtained.

active metal. Neither chelating ligands nor phosphines are required.

The structures of the obtained ynediones 3, 4, and 5 were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound 3a (Figure 1).

The sequence proceeds smoothly in ethereal solvents (THF, DME, or 1,4-dioxane), thus making it possible to perform the glyoxylation step in a wide temperature range. The reaction with electron-rich indoles and 7-azaindoles gives derivatives functionalized in the 3-position exclusively (compounds 3a–k). Generally, pyrroles give 2-substituted regioisomers without noticeable amounts of the 3-substituted isomers (compounds 4a–e). Expectedly, when the substrate has a bulky substituent on the nitrogen atom of the pyrrole ring, the 3-position is functionalized (compound 4f). To our great delight, other important heterocycles like pyrazole (compound 5a), thiophene (compounds 5b and 5c), and furan (compound 5d) could be converted to ynediones, although the glyoxylation of these heterocycles to glyoxyl chloride has never been described. Interestingly, there is a method describing a direct carboxylation of 1,3,5-trisubstituted pyrazoles with oxalyl chloride. However, with 1-methyl-1H-pyrazole we observed no decarbonylation but instead formation of compound 5a. A further advantage of the described Lewis acid free method is the possibility of reacting substrates that are not compatible with Lewis-acid-mediated Friedel–Crafts conditions and (compound 5d). Surprisingly, however, the observation that thiophenes turned out to be excellent substrates for the described sequence. The more electron-rich 2-methylfuran gave a lower yield of ynedione 5d along with a by-product resulting from the condensation of two furan molecules with one molecule of oxalyl chloride in 14% yield.

Furthermore, the electron-rich hydrocarbon azulene could be functionalized as well (compound 5e).[15] Aryl acetylenes bearing electron-neutral (compounds 3a, 3g, 3h, 3j, 3k, 4a–f, and 5a–e), electron-donating (compound 3b), or electron-withdrawing (compounds 3c,d) substituents can be carried through the sequence without difficulties. Also heteroaryl (compound 3e) as well as TIPS-substituted acetylenes (compound 3f) can be coupled efficiently. However, an alkyl acetylene gave a very poor yield (compound 3i). In all cases, no decarbonylative products were observed. The products were easily isolated by flash chromatography and were usually obtained in analytically pure form as stable compounds.

The reactivity of the glyoxylation of π nucleophiles can be estimated by considering the nucleophilicity parameters η of the (hetero)aryl substrate as determined by Mayr et al. for some reference nucleophiles.[17] The nucleophilicity parameters of the employed (hetero)arenes range from approximately 1.26 to 6.66, spanning five orders of magnitude (see Table S8 in the Supporting Information).

Azoles, furans, and thiophenes are of paramount importance in the synthesis of products relevant for medicinal chemistry and material science as well as in the synthesis of natural products. Therefore, the described mild and easy-to-perform one-pot functionalization of these prevalent classes of heterocycles opens up remarkable possibilities for their
derivatization. Moreover, the obtained ynediones are densely functionalized, possessing a strongly activated Michael system as well as a dione motif, both important structural units in heterocycle synthesis.

As an illustration of the versatility of alkynediones as building blocks, we extended the sequence to the four-component syntheses of various products (Scheme 4). Simply by adding 1.0 equiv of different mono- and dinucleophiles after the glyoxylation/Stephens–Castro coupling sequence furnishing ynedione 3a, we could achieve the one-pot syntheses of enaminedione 6, quinoxaline 7, indoloyl pyrazole 8a, and indoloyl pyrimidine 9; the final step of this sequence consists of Michael addition, double carbonyl condensation, and Michael addition/cyclocondensation reactions, respectively.

Experimental Section

3f: In an oven-dried screw-cap Schlenk flask with a septum a solution of 1-methyl indole (1a; 669 mg, 5.00 mmol) in 25 mL of anhydrous THF was placed under argon atmosphere. Argon was bubbled through the solution for 5 min which was cooled to 0°C. Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0°C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), tris(isopropyl)silyl (2f; 1.13 mL, 5.00 mmol), and anhydrous triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture, and the reaction mixture was stirred at room temperature for 24 h. After complete conversion, distilled water (25 mL) was added, the phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, the residue was adsorbed onto Celite and purified by chromatography on silica gel (petroleum ether/ethyl acetate 7:1) to give the analytically pure 3f (1.35 g; 74%) as a yellow solid, Rf = 0.25. M.p. 127°C.

1H NMR (500 MHz, CDCl3): δ = 1.13–1.17 (m, 21H), 3.86 (s, 3H), 7.33–7.38 (m, 3H), 8.25 (s, 1H), 8.42–8.46 ppm (m, 1H).

13C NMR (125 MHz, CDCl3): δ = 11.1 (CH), 18.5 (CH3), 33.8 (CH3), 103.4 (Cquat.), 103.9 (Cquat.), 109.9 (CH), 110.9 (Cquat.), 122.8 (CH), 123.5 (CH), 123.5 (CH).

It is worth mentioning that tert-butoxycarbonyl(Boc)-protected hydrazine can be used for the selective synthesis of the 2-acyl pyrazole 8a without formation of the corresponding pyridazinone, thus giving direct and very efficient access to 2-acyl pyrazoles. So far, there has been no preparatively useful approach to this class of compounds. This unprecedented strategy is currently under investigation.

In conclusion, we have developed a new three-component approach to heterocyclic ynediones, which are very likely to become important intermediates in the synthesis of diverse, pharmaceutically interesting heterocycles. The use of catalytic Stephens–Castro conditions is crucial for the success of the reaction. The design of new diverse four-component syntheses of heterocycles with the intermediacy of ynediones has been highlighted successfully. It should be emphasized that all reagents in these three- and four-component reactions are required in equimolar ratios, rendering these sequences highly atom economical. Further generalizations of this strategy as well as diverse synthetic applications of ynediones are currently under investigation and will be reported in due course.
Received: November 16, 2010
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Keywords: carbonylation · C–C coupling · copper · heterocycles · multicomponent reactions


[14] For the optimization of the reaction for 3a, see the Supporting Information.


[18] CCDC 796698 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Supporting Information

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69451 Weinheim, Germany

Three-Component Synthesis of Ynediones by a Glyoxylation/
Stephens–Castro Coupling Sequence**

Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, and Thomas J. J. Müller*

ange_201007194_sm_miscellaneous_information.pdf
Supporting Information

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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. Tetrahydrofuran was dried using MBraun system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased by Sigma-Aldrich Chemie GmbH.

Compounds 1b-f were prepared according to the literature procedure.[1] Compound 1i was prepared according to the literature procedure.[2] Commercial grade reagents were used as supplied without further purification and were purchased from Acros Organics, Sigma-Aldrich Chemie GmbH, Fluka AG, ABCR GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, Riedel-de Haën, Maybridge, and Merck Serono KGaA. Oxalyl chloride was obtained from Merck Serono KGaA and used neat without further purification.

The content of Pd (4 μg/g) in copper(I) iodide was determined in the laboratory Elementaranalytik of Merck Serono KGaA.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA Darmstadt using flash technique and under pressure of 2 bar. The purification of alkynediones was performed on Biotage SP-1 system using cartridges filled with ca. 340 g silica gel. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from Merck Serono KGaA Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

\(^1\)H, \(^13\)C, and 135-DEPT NMR spectra were recorded on Bruker Advanced DRX 500 spectrometer. CDCl\(_3\) and DMSO-d\(_6\) were used as deuterated solvents. TMS was used as reference (\(\delta = 0.0\)) or the resonances of the solvents were locked as internal standards (CDCl\(_3\): \(^1\)H \(\delta\) 7.26, \(^13\)C \(\delta\) 77.0; DMSO-d\(_6\): \(^1\)H \(\delta\) 2.50, \(^13\)C \(\delta\) 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets; ddd: doublet of doublets of doublets; dt: doublet of triplets; td: triplet of doublets; tt: triplet of triplets; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer.
IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak).

The melting points (uncorrected) were measured on Büchi Melting Point B-540. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

The X-ray structure analysis was performed on Bruker APEX at Ruprecht-Karls-Universität Heidelberg.
2. Preparation of Ynediones 3a-k, 4a-f and 5a-e via Glyoxylation – Stephens–Castro Coupling Sequence

2.1. Optimization of the Synthetic Procedure with 1-Methyl-1H-indole (1a)

The optimization of the procedure is depicted in Table 1.

**Table 1.** Optimization of the synthesis of indolyl alkynedione 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylation step[a]</th>
<th>Stephens-Castro coupling step[b]</th>
<th>Isolated yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(COX)₂ (1.00 equiv)</td>
<td>Catalyst</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>Phenylacetylene 2a Base</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reaction temperature</td>
<td>Reaction temperature and time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and time</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(COCl)₂ THF</td>
<td>5 mol % CuI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 °C [^c] → RT [^d]</td>
<td>1.00 equiv (2a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>5 mL NEt₃[^e]</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RT 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63 %</td>
</tr>
<tr>
<td>2</td>
<td>(COCl)₂ THF</td>
<td>1 mol % CuI</td>
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</tr>
<tr>
<td></td>
<td>0 °C → RT</td>
<td>1.00 equiv (2a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 %</td>
</tr>
<tr>
<td>3</td>
<td>(COCl)₂ THF</td>
<td>5 mol % CuI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 °C → RT</td>
<td>1.00 equiv (2a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 %</td>
</tr>
</tbody>
</table>

[a] The optimization reactions were performed on a 5.00 mmol scale (c (1a) = 0.2 M).
[b] The order in which the reagents appear in the table corresponds to the order in which they were added to the reaction mixture.
[c] The reaction vessel was cooled for 15 min in a water/ice bath.
[d] The reaction vessel was placed in a water bath.
[e] Reaction parameters or reagents different from the optimal conditions (entry 3, in bold) are underlined.
Table 1 (continuation). Optimization of the synthesis of indolyl alkynedione 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylation step</th>
<th>Stephens-Castro coupling step</th>
<th>Isolated yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(COX)$_2$ (1.00 equiv) Solvent</td>
<td>Catalyst Phenylacetylene 2a Base</td>
<td>Reaction temperature and time</td>
</tr>
<tr>
<td></td>
<td>Glyoxylation step</td>
<td>Reaction temperature and time</td>
<td>Stephens-Castro coupling step</td>
</tr>
<tr>
<td></td>
<td>(COCl)$_2$ 0 °C → RT 4 h</td>
<td>5 mol % CuI 1.10 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>RT 24 h</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(COCl)$_2$ 0 °C → RT 4 h</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(COCl)$_2$ 0 °C → RT 4 h</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 eq. NEt$_3$</td>
<td>60 °C 2 h</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>5 mol % CuI 2.00 equiv (2a) 4.00 equiv NEt$_3$</td>
<td>RT 24 h</td>
</tr>
<tr>
<td>8</td>
<td>(COCl)$_2$ 0 °C → 60 °C 1 h</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>RT 24 h</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>60 °C 4 h</td>
</tr>
<tr>
<td>10</td>
<td>(COCl)$_2$ 0 °C → 60 °C 1 h</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>60 °C 4 h</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>RT 21 h</td>
</tr>
<tr>
<td>12</td>
<td>(COCl)$_2$ 0 °C → 60 °C 1 h</td>
<td>5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt$_3$</td>
<td>RT 48 h</td>
</tr>
<tr>
<td>13</td>
<td>THF</td>
<td>5 mol % CuI 1.00 equiv (2a) 2.00 equiv NEt$_3$</td>
<td>RT 24 h</td>
</tr>
</tbody>
</table>

[f] 5 mol % CuI were already added in the glyoxylation step.
Table 1 (continuation). Optimization of the synthesis of indolyl alkynedione 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylation step</th>
<th>Stephens-Castro coupling step</th>
<th>Isolated yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(COX)_2 (1.00 equiv)</td>
<td>Catalyst Phenylacetylene 2a Base</td>
<td>Reaction temperature and time</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>Catalyst</td>
<td>Phenylacetylene 2a</td>
</tr>
<tr>
<td></td>
<td>Reaction temperature and time</td>
<td>Reaction temperature and time</td>
<td>Isolated yield of 3a (%)</td>
</tr>
<tr>
<td>14</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>48 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv NEt_3</td>
<td>24 h</td>
</tr>
<tr>
<td>15</td>
<td>(COCl)_2</td>
<td>5 mol % Au 1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv NEt_3</td>
<td>24 h</td>
</tr>
<tr>
<td>16</td>
<td>(COBr)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv NEt_3</td>
<td>24 h</td>
</tr>
<tr>
<td>17</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>40 °C</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv NEt_3</td>
<td>24 h</td>
</tr>
<tr>
<td>18</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 5 mol % 1,10-phenanthroline</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.00 equiv NEt_3</td>
<td>24 h</td>
</tr>
<tr>
<td>19</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv NEtPr_2^a</td>
<td>24 h</td>
</tr>
<tr>
<td>20</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv TMEDA^h</td>
<td>24 h</td>
</tr>
<tr>
<td>21</td>
<td>(COCl)_2</td>
<td>5 mol % Cu 1.00 equiv (2a)</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>THF</td>
<td>3.00 equiv DMAP^i</td>
<td>24 h</td>
</tr>
</tbody>
</table>

[g] DIPEA, Hüning’s base.
[h] N,N,N’,N’-Tetramethylethylenediamine.
[i] 4-Dimethylaminopyridine.
**Table 1 (continuation).** Optimization of the synthesis of indolyl alkynedione 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glyoxylation step</th>
<th>Stephens-Castro coupling step</th>
<th>Isolated yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(COX)₂ (1.00 equiv)</td>
<td>Catalyst</td>
<td>Reaction temperature and time</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>Phenylacetylene 2a</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>(COCl)₂ 1,4-dioxane</td>
<td>5 mol % CuI</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>4 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>(COCl)₂ 1,4-dioxane</td>
<td>5 mol % CuI</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT → 100 °C 1 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>(COCl)₂ 1,4-dioxane</td>
<td>5 mol % CuI</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT 4 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>(COCl)₂ 1,4-dioxane</td>
<td>5 mol % CuI</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT 1 h</td>
<td>3.00 equiv NEt₃</td>
<td></td>
</tr>
</tbody>
</table>

[j] The reaction vessel was placed in a preheated oil bath.

The conditions shown in *entry 3* were considered as optimized and were used in the general procedure for the preparation of compounds 3a-i, 4a-d and 5e (procedure A).
2.2. General Procedure for the Preparation of Compounds 3a-i, 4a-d, 5e and 4e-f (Procedures A and C)
5.00 mmol of N-substituted indole 1a-d or pyrrole 1g-l (or azulene 1q) in dry THF (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) or 50 °C (for 1k-l, preheated oil bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), 5.00 mmol of terminal alkyne 2 and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the alkynediones 3a-i, 4a-d and 5e.

The experimental details are given in Table 2.
2.3. General Procedure for the Preparation of Compounds 3j-k and 5a ( Procedures B and D)

5.00 mmol of N-substituted 7-azaindole 1e-f or pyrazole 1m in dry DME (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath), stirred for 15 min. and then stirred at 100 °C (preheated oil bath) for 2 h in case of 7-azaindoles 1e-f and for 24 h in case of pyrazole 1m. Then, after cooling to room temperature (water bath, for 15 min), CuI (49 mg, 0.25 mmol), phenylacetylene 2a (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the analytically pure alkynediones 3j-k or 5a.

The experimental details are given in Table 2.
2.4. General Procedure for the Preparation of Compounds 5b-c and 5d (Procedures E and F)

5.00 mmol of thiophene 1n-o or furan 1p in dry 1,4-dioxane (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at room temperature. The mixture was then stirred at 100 °C (preheated oil bath) for 4 h (for 24 h in case of furan 1p). Then, after cooling to room temperature (water bath, for 15 min), CuI (49 mg, 0.25 mmol), phenylacetylene 2a (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the analytically pure alkyndiones 5b-e.

The experimental details are given in Table 2.
Table 2. Experimental details of the three-component glyoxylation-Stephens-Castro coupling sequence for the synthesis of indolyl ynediones 3a-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted indole 1 (5.00 mmol)</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 3 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R_f (eluent)</td>
</tr>
<tr>
<td>1</td>
<td>1-Methyl-1H-indole (Merck) 669 mg 1a</td>
<td>Phenylacetylene (Merck) 0.57 mL 2a</td>
<td>948 mg (3.30 mmol, 66 %) 3a</td>
<td>PE-EA = 3:1 R_f (PE-EA = 3:1): 0.39</td>
</tr>
<tr>
<td>2</td>
<td>669 mg 1a</td>
<td>4-Ethynylanisole (Maybridge) 661 mg 2b</td>
<td>1.08 g (3.40 mmol, 68 %) 3b</td>
<td>PE-EA = 4:1 R_f (PE-EA = 4:1): 0.10</td>
</tr>
<tr>
<td>3</td>
<td>669 mg 1a</td>
<td>4-Fluorophenylacetylene (Alfa Aesar) 0.58 mL 2c</td>
<td>1.12 g (3.66 mmol, 73 %) 3c</td>
<td>PE-EA = 3:1 R_f (PE-EA = 3:1): 0.20</td>
</tr>
<tr>
<td>4</td>
<td>669 mg 1a</td>
<td>2-Chlorophenylacetylene (ABCR) 697 mg 2d</td>
<td>970 mg (3.01 mmol, 60 %) 3d</td>
<td>PE-EA = 4:1 R_f (PE-EA = 4:1): 0.20</td>
</tr>
<tr>
<td>5</td>
<td>669 mg 1a</td>
<td>3-Ethynylpyridine (Aldrich) 526 mg 2e</td>
<td>613 mg (2.13 mmol, 43 %) 3e</td>
<td>PE-EA = 1:1 R_f (PE-EA = 1:1): 0.22</td>
</tr>
</tbody>
</table>
Table 2 (continuation). Experimental details of the three-component glyoxyl ation-
Stephens-Castro coupling sequence for the synthesis of indolyl alkynediones 3f-i.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted indole 1 (5.00 mmol)</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 3 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>669 mg 1a</td>
<td>Triisopropylsilyl-acetylene (Fluka) 1.13 mL 2f</td>
<td>1.35 g (3.68 mmol, 74 %)</td>
<td>PE-EA = 7:1 R_f (PE-EA = 7:1): 0.25</td>
</tr>
<tr>
<td>7</td>
<td>1-Benzyl-5-methoxy-1H-indole^[1] 1.19 g 1b</td>
<td>0.57 mL 2a</td>
<td>1.13 g (2.87 mmol, 57 %)</td>
<td>PE-EA = 5:1 R_f (PE-EA = 5:1): 0.38</td>
</tr>
<tr>
<td>8</td>
<td>1-Benzyl-5-iodo-1H-indole^[1] 1.67 g 1c</td>
<td>0.57 mL 2a</td>
<td>864 mg (1.77 mmol, 35 %)</td>
<td>PE-EA = 7:1 R_f (PE-EA = 7:1): 0.23</td>
</tr>
<tr>
<td>9</td>
<td>1-Benzyl-1H-indole^[1] 1.04 g 1d</td>
<td>1-Hexyne (Acros) 0.59 mL 2h</td>
<td>36 mg (0.10 mmol, 2 %)</td>
<td>PE-EA = 10:1 R_f (PE-EA = 10:1): 0.25</td>
</tr>
</tbody>
</table>
**Table 2 (continuation).** Experimental details of the three-component glyoxylation-
Stephens-Castro coupling sequence for the synthesis of 7-azaindolyl alkynediones 3j-k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted 7-azaindole 1 (5.00 mmol)</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 3 (isolated yield %)</th>
<th>Chromatographic purification (eluent) Rf (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1-Benzyl-1H-pyrrolo[2,3-b]-pyridine[1]</td>
<td>0.57 mL</td>
<td>1.13 g (3.10 mmol, 62 %)</td>
<td>PE-EA = 4:1 Rf (PE-EA = 4:1): 0.29</td>
</tr>
<tr>
<td></td>
<td>1e</td>
<td>1.04 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1-(4-Methoxy-benzyl)-1H-pyrrolo[2,3-b]-pyridine[1]</td>
<td>0.57 mL</td>
<td>1.16 g (2.95 mmol, 59 %)</td>
<td>PE-EA = 3:1 Rf (PE-EA = 3:1): 0.30</td>
</tr>
<tr>
<td></td>
<td>1f</td>
<td>1.19 g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 (continuation). Experimental details of the three-component glyoxylation-Stephens-Castro coupling sequence for the synthesis of pyrrolyl alkynediones 4a-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted pyrrole 1 (5.00 mmol)</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1-Methyl-1H-pyrrole (Merck) 420 mg</td>
<td>Phenylacetylene (Merck) 0.57 mL</td>
<td>754 mg (3.18 mmol, 64 %)</td>
<td>PE-EA = 7:1 R&lt;sub&gt;f&lt;/sub&gt; (PE-EA = 7:1): 0.34</td>
</tr>
<tr>
<td></td>
<td>1g</td>
<td>2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1-Benzyl-1H-pyrrole (Aldrich) 810 mg</td>
<td>0.57 mL 1.16 g (3.70 mmol, 74 %)</td>
<td>PE-EA = 9:1 R&lt;sub&gt;f&lt;/sub&gt; (PE-EA = 9:1): 0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1h</td>
<td>2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1-Benzhydryl-1H-pyrrole&lt;sup&gt;2&lt;/sup&gt; 1.17 g</td>
<td>0.57 mL 1.31 g (3.36 mmol, 67 %)</td>
<td>PE-EA = 9:1 R&lt;sub&gt;f&lt;/sub&gt; (PE-EA = 9:1): 0.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1i</td>
<td>2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1-(2-Cyanoethyl)-1H-pyrrole (Aldrich) 607 mg</td>
<td>0.57 mL 830 mg (3.00 mmol, 60 %)</td>
<td>PE-EA = 2:1 R&lt;sub&gt;f&lt;/sub&gt; (PE-EA = 2:1): 0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1j</td>
<td>2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1-Phenyl-1H-pyrrole (ABCR) 723 mg</td>
<td>0.57 mL 1.15 g (3.84 mmol, 77 %)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PE-EA = 9:1 R&lt;sub&gt;f&lt;/sub&gt; (PE-EA = 9:1): 0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1k</td>
<td>2a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> According to procedure A, 491 mg (1.64 mmol, 33 %) of 4e were obtained.
Table 2 (continuation). Experimental details of the three-component glyoxylatation-Stephens-Castro coupling sequence for the synthesis of pyrrolyl alkynedione 4f-e and pyrazolyl alkynedione 5a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted pyrrole or pyrazole</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 4 or 5 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>1-(Triisopropylsilyl)-1H-pyrrole (Alfa Aesar) 1.18 g 1l</td>
<td>0.57 mL 2a</td>
<td>836 mg (2.20 mmol, 44 %)</td>
<td>PE-EA = 20:1 R_f (PE-EA = 20:1): 0.24</td>
</tr>
<tr>
<td>18</td>
<td>1-Methyl-1H-pyrazole (Aldrich) 415 mg 1m</td>
<td>0.57 mL 2a</td>
<td>564 mg (2.37 mmol, 47 %)</td>
<td>PE-EA = 3:1 R_f (PE-EA = 3:1): 0.13</td>
</tr>
</tbody>
</table>
Table 2 (continuation). Experimental details of the three-component glyoxylation-
Stephens-Castro coupling sequence for the synthesis of thienyl, furyl and azulenyl
alkynediones 5b-c, 5d and 5e, respectively.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan, thiophene or azulene 1 (5.00 mmol)</th>
<th>Alkyne 2 (5.00 mmol)</th>
<th>Ynedione 5 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Methoxythiophene (Alfa Aesar) 577 mg 1n</td>
<td>Phenylacetylene (Merck) 2a 0.57 mL</td>
<td>712 mg (2.63 mmol, 53 %)</td>
<td>PE-EA = 10:1 Rf (PE-EA = 10:1): 0.20</td>
</tr>
<tr>
<td>20</td>
<td>2,3-Dihydrothieno-[3,4-b][1,4]dioxine (Aldrich) 711 mg 1o</td>
<td>2a 0.57 mL</td>
<td>978 mg (3.28 mmol, 66 %)</td>
<td>PE-EA = 20:1 Rf (PE-EA = 20:1): 0.30</td>
</tr>
<tr>
<td>21</td>
<td>2-Methylfuran (Merck) 415 mg 1p</td>
<td>2a 0.57 mL</td>
<td>457 mg (1.92 mmol, 38 %)</td>
<td>PE-EA = 10:1 Rf (PE-EA = 10:1): 0.15</td>
</tr>
<tr>
<td>22</td>
<td>(4Z,6Z,8Z)-Azulene (Azulene) (Alfa Aesar) 647 mg 1q</td>
<td>2a 0.57 mL</td>
<td>462 mg (1.63 mmol, 33 %)</td>
<td>PE-EA = 8:1 Rf (PE-EA = 8:1): 0.29</td>
</tr>
</tbody>
</table>
2.5. Spectroscopic Data of Compounds 3a-k

2.5.1. 1-(1-Methyl-1H-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3a)

\[
\text{C}_{19}\text{H}_{13}\text{NO}_2 \\
287.31
\]

948 mg (3.30 mmol, 66 % yield) as a yellow solid. Mp 129-130 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.87 (s, 3 H), 7.35-7.43 (m, 5 H), 7.46-7.51 (m, 1 H), 7.69-7.72 (m, 2 H), 8.33 (s, 1 H), 8.45-8.49 (m, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 33.8 (CH\(_3\)), 87.7 (C\(_{quat}\)), 97.6 (C\(_{quat}\)), 110.0 (CH), 110.9 (C\(_{quat}\)), 119.8 (C\(_{quat}\)), 122.8 (CH), 123.6 (CH), 124.2 (CH), 127.2 (C\(_{quat}\)), 128.6 (CH), 131.3 (CH), 133.7 (CH), 137.3 (C\(_{quat}\)), 140.3 (CH), 178.7 (C\(_{quat}\)), 180.2 (C\(_{quat}\)). EI + MS (m/z (%)): 287 (M\(^+\), 11), 158 ((M-C\(_9\)H\(_5\)O\(^+\), 100), 130 (C\(_8\)H\(_9\)N\(^+\), 6), 103 (7), 77 (C\(_6\)H\(_5\)\(^+\), 6). IR (KBr): \(\tilde{\nu}\) 2203 (m) cm\(^{-1}\), 1646 (s), 1627 (s), 1528 (m), 1466 (m), 1379 (w), 1283 (w), 1131 (w), 1075 (m), 1033 (m), 881 (w), 772 (w), 758 (w), 741 (m), 689 (w). Anal. calcd for C\(_{19}\)H\(_{13}\)NO\(_2\) (287.3): C 79.43, H 4.56, N 4.88. Found: C 79.25, H 4.46, N 4.86.
2.5.2. 4-(4-Methoxyphenyl)-1-(1-methyl-1H-indol-3-yl)but-3-yne-1,2-dione (3b)

\[
\text{C}_{20}\text{H}_{15}\text{NO}_3
\]

317.34

1.08 g (3.40 mmol, 68 % yield) as a yellow solid. Mp 141-142 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.85 (s, 3 H), 3.88 (s, 3 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.34-7.40 (m, 3 H), 7.67 (d, J = 8.8 Hz, 2 H), 8.34 (s, 1 H), 8.45-8.50 (m, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 34.0 (CH\(_3\)), 55.7 (CH\(_3\)), 88.3 (C\(_{\text{quat}}\)), 99.4 (C\(_{\text{quat}}\)), 110.2 (CH), 111.2 (C\(_{\text{quat}}\)), 111.8 (C\(_{\text{quat}}\)), 114.6 (CH), 123.0 (CH), 123.8 (CH), 124.4 (CH), 127.5 (C\(_{\text{quat}}\)), 136.2 (CH), 137.5 (C\(_{\text{quat}}\)), 140.5 (CH), 162.4 (C\(_{\text{quat}}\)), 178.8 (C\(_{\text{quat}}\)), 180.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 317 (M\(^+\), 8), 158 ((M-C\(_{10}\)H\(_7\)O\(_2\))^+\), 100), 130 (C\(_9\)H\(_8\)N\(^+\), 5), 103 (4), 77 (C\(_6\)H\(_5\)^+, 3). IR (KBr): \(\tilde{\nu}\) 2162 (m) cm\(^{-1}\), 1625 (s), 1597 (s), 1524 (m), 1508 (s), 1466 (m), 1442 (w), 1377 (m), 1289 (w), 1256 (s), 1168 (w), 1112 (w), 1073 (m), 1032 (s), 883 (w), 836 (w), 808 (w), 790 (w), 715 (m), 575 (w), 542 (w). Anal. calcd for C\(_{20}\)H\(_{15}\)NO\(_3\) (317.3): C 75.70, H 4.76, N 4.41. Found: C 75.42, H 4.78, N 4.48.
2.5.3. 4-(4-Fluorophenyl)-1-(1-methyl-1H-indol-3-yl)but-3-yne-1,2-dione (3c)

![Chemical Structure]

C\textsubscript{19}H\textsubscript{12}FNO\textsubscript{2}

305.30

1.12 g (3.66 mmol, 73 % yield) as a yellow solid. Mp 156 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 3.87 (s, 3 H), 7.08-7.13 (m, 2 H), 7.35-7.40 (m, 3 H), 7.68-7.73 (m, 2 H), 8.33 (s, 1 H), 8.44-8.48 (m, 1 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): δ 33.9 (CH\textsubscript{3}), 87.7 (d, J = 1.8 Hz, C\textsubscript{quat}), 96.5 (C\textsubscript{quat}), 110.0 (CH), 110.9 (C\textsubscript{quat}), 115.9 (d, J = 3.7 Hz, C\textsubscript{quat}), 116.3 (d, J = 22.9 Hz, CH), 122.8 (CH), 123.7 (CH), 124.3 (CH), 127.3 (C\textsubscript{quat}), 136.1 (d, J = 9.2 Hz, CH), 137.3 (C\textsubscript{quat}), 140.3 (CH), 164.3 (d, J = 254.8 Hz, C\textsubscript{quat}), 178.5 (C\textsubscript{quat}), 180.0 (C\textsubscript{quat}).

EI + MS (m/z (%)): 305 (M\textsuperscript{+}, 6), 158 ((M-C\textsubscript{9}H\textsubscript{4}FO\textsuperscript{+}, 100), 130 (C\textsubscript{9}H\textsubscript{8}N\textsuperscript{+}, 6), 103 (7), 77 (C\textsubscript{6}H\textsubscript{5}\textsuperscript{+}, 5). IR (KBr): ν 2204 (m) cm\textsuperscript{-1}, 1655 (s), 1619 (s), 1544 (w), 1509 (m), 1459 (m), 1366 (m), 1216 (m), 1126 (m), 1070 (m), 1028 (m), 881 (w), 842 (m), 811 (m), 743 (m), 719 (m), 575 (w), 537 (m). Anal. calcd for C\textsubscript{19}H\textsubscript{12}FNO\textsubscript{2} (305.3): C 74.75, H 3.96, N 4.59. Found: C 74.79, H 3.95, N 4.47.
2.5.4. 4-(2-Chlorophenyl)-1-(1-methyl-1H-indol-3-yl)but-3-yne-1,2-dione (3d)

\[
\text{C}_{19}\text{H}_{12}\text{ClNO}_2
\]

321.76

970 mg (3.01 mmol, 60 % yield) as a yellow solid. Mp 148-150 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.87 (s, 3 H), 7.30 (td, \(J = 7.6\) Hz, \(J = 0.9\) Hz, 1 H), 7.35-7.38 (m, 3 H), 7.41 (td, \(J = 7.6\) Hz, \(J = 1.6\) Hz, 1 H), 7.47 (dd, \(J = 8.2\) Hz, \(J = 0.9\) Hz, 1 H), 7.71 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 8.33 (s, 1 H), 8.45-8.49 (m, 1 H). \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 33.9 (CH\(_3\)), 91.6 (C\(_{\text{quat}}\)), 93.2 (C\(_{\text{quat}}\)), 110.0 (CH), 110.9 (C\(_{\text{quat}}\)), 120.1 (C\(_{\text{quat}}\)), 122.8 (CH), 123.6 (CH), 124.3 (CH), 126.8 (CH), 127.2 (C\(_{\text{quat}}\)), 129.7 (CH), 132.1 (CH), 135.3 (CH), 137.3 (C\(_{\text{quat}}\)), 137.9 (C\(_{\text{quat}}\)), 140.3 (CH), 178.4 (C\(_{\text{quat}}\)), 179.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 323 (M\(^{37}\)Cl\(^+\), 2), 321 (M\(^{35}\)Cl\(^+\), 5), 158 ((M-C\(_9\)H\(_4\)ClO\(^+\), 100), 130 (C\(_9\)H\(_8\)N\(^+\), 6), 103 (5), 77 (C\(_6\)H\(_5\)\(^+\), 5). IR (KBr): \(\nu\) 3115 (w) cm\(^{-1}\), 2207 (m), 1667 (m), 1626 (s), 1524 (m), 1460 (m), 1375 (m), 1290 (m), 1226 (m), 1128 (m), 1073 (m), 1028 (m), 879 (m), 774 (m), 750 (s), 693 (w), 622 (w), 527 (w). Anal. calcd for C\(_{19}\)H\(_{12}\)ClNO\(_2\) (321.8): C 70.92, H 3.76, N 4.35. Found: C 70.87, H 3.85, N 4.13.
2.5.5. 1-(1-Methyl-1\textit{H}-indol-3-yl)-4-(pyridin-3-yl)but-3-yn-1,2-dione (3e)

![Chemical structure of 1-(1-Methyl-1\textit{H}-indol-3-yl)-4-(pyridin-3-yl)but-3-yn-1,2-dione (3e)](C_{18}H_{12}N_{2}O_{2})

613 mg (2.13 mmol, 43 % yield) as a yellow-orange solid. Mp 144-146 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.88 (s, 3 H), 7.33-7.40 (m, 4 H), 7.98 (dt, $J$ = 7.9 Hz, $J$ = 1.9 Hz, 1 H), 8.34 (s, 1 H), 8.43-8.47 (m, 1 H), 8.69 (dd, $J$ = 5.0 Hz, $J$ = 1.6 Hz, 1 H), 8.91 (d, $J$ = 1.6 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 33.9 (CH$_3$), 90.1 (C$_{quat}$), 93.2 (C$_{quat}$), 110.1 (CH), 110.8 (C$_{quat}$), 117.2 (C$_{quat}$), 122.7 (CH), 123.3 (CH), 123.8 (CH), 124.4 (CH), 127.2 (C$_{quat}$), 137.3 (C$_{quat}$), 140.3 (CH), 140.4 (CH), 151.1 (CH), 153.8 (CH), 178.1 (C$_{quat}$), 179.5 (C$_{quat}$). EI + MS (m/z (%)): 288 (M$^+$, 7), 158 ((M-C$_8$H$_4$NO)$^+$, 100), 130 (C$_9$H$_8$N$^+$, 6), 103 (6), 77 (C$_6$H$_5^+$, 6). IR (KBr): $\tilde{\nu}$ 2207 (m) cm$^{-1}$, 1661 (m), 1620 (s), 1578 (w), 1525 (m), 1466 (m), 1412 (m), 1377 (m), 1336 (w), 1279 (m), 1225 (w), 1191 (w), 1125 (w), 1075 (m), 1024 (m), 880 (m), 811 (w), 773 (m), 744 (m), 705 (m), 638 (m), 573 (w), 519 (w). Anal. calcd for C$_{18}$H$_{12}$N$_2$O$_2$ (288.3): C 74.99, H 4.20, N 9.12. Found: C 74.99, H 4.14, N 9.40.
2.5.6. 4-(Triisopropylsilyl)-1-(1-methyl-1H-indol-3-yl)but-3-yn-1,2-dione (3f)

![Chemical structure of 4-(Triisopropylsilyl)-1-(1-methyl-1H-indol-3-yl)but-3-yn-1,2-dione (3f)]

C\textsubscript{22}H\textsubscript{29}NO\textsubscript{2}Si

367.56

1.35 g (3.68 mmol, 74 % yield) as a yellow solid. Mp 127 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 1.13-1.17 (m, 21 H), 3.86 (s, 3 H), 7.33-7.38 (m, 3 H), 8.25 (s, 1 H), 8.42-8.46 (m, 1 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 11.1 (CH), 18.5 (CH\textsubscript{3}), 33.8 (CH\textsubscript{3}), 103.4 (C\textsubscript{quat}), 103.9 (C\textsubscript{quat}), 109.9 (CH), 110.9 (C\textsubscript{quat}), 122.8 (CH), 123.5 (CH), 124.2 (CH), 127.2 (C\textsubscript{quat}), 137.3 (C\textsubscript{quat}), 140.0 (CH), 178.2 (C\textsubscript{quat}), 180.1 (C\textsubscript{quat}). El + MS (m/z (%)): 367 (M\textsuperscript{+}, 3), 158 ((M-C\textsubscript{12}H\textsubscript{21}OSi\textsuperscript{+}, 100), 130 (C\textsubscript{9}H\textsubscript{8}N\textsuperscript{+}, 2). IR (KBr): \(\tilde{\nu}\) 2941 (m) cm\textsuperscript{-1}, 2864 (m), 2146 (w), 1664 (s), 1633 (s), 1522 (m), 1466 (m), 1374 (m), 1258 (m), 1176 (m), 1124 (m), 1073 (s), 1033 (m), 994 (m), 868 (s), 801 (w), 748 (s), 718 (w), 681 (m), 583 (w). Anal. calcd for C\textsubscript{22}H\textsubscript{29}NO\textsubscript{2}Si (367.6): C 71.89, H 7.95, N 3.81. Found: C 72.06, H 7.94, N 3.70.
2.5.7. 1-(1-Benzyl-5-methoxy-1H-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3g)

![Chemical Structure](image)

\[ C_{26}H_{19}NO_3 \]

393.43

1.13 g (2.87 mmol, 57 % yield) as an orange solid. Mp 112 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.90 (s, 3 H), 5.33 (s, 2 H), 6.91 (dd, \(J = 8.8\) Hz, \(J = 2.5\) Hz, 1 H), 7.15-7.19 (m, 3 H), 7.29-7.35 (m, 3 H), 7.38-7.42 (m, 2 H), 7.46-7.51 (m, 1 H), 7.68-7.72 (m, 2 H), 8.00 (d, \(J = 2.5\) Hz, 1 H), 8.38 (s, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 51.4 (CH\(_2\)), 55.7 (CH\(_3\)), 87.7 (C\(_\text{quat}\)), 97.5 (C\(_\text{quat}\)), 104.1 (CH), 111.0 (C\(_\text{quat}\)), 111.5 (CH), 114.6 (CH), 119.7 (C\(_\text{quat}\)), 126.9 (CH), 128.3 (CH), 128.5 (C\(_\text{quat}\)), 128.6 (CH), 129.1 (CH), 131.2 (CH), 131.5 (C\(_\text{quat}\)), 133.6 (CH), 135.1 (C\(_\text{quat}\)), 139.5 (CH), 157.2 (C\(_\text{quat}\)), 178.5 (C\(_\text{quat}\)), 180.2 (C\(_\text{quat}\)). EI + MS (m/z (%)): 393 (M\(^+\), 1), 265 (C\(_{17}\)H\(_{15}\)NO\(_2\)^+, 15), 264 (C\(_{17}\)H\(_{14}\)NO\(_2\)^+, 86), 129 (C\(_6\)H\(_5\)O\(^+\), 5), 91 (C\(_7\)H\(_7\)^+, 100), 65 (C\(_6\)H\(_5\)^+, 4). IR (KBr): \(\tilde{\nu}\) 2194 (m) cm\(^{-1}\), 1655 (s), 1624 (s), 1510 (m), 1479 (m), 1453 (m), 1398 (m), 1262 (m), 1208 (m), 1178 (m), 1142 (m), 1121 (m), 1102 (w), 1040 (m), 1013 (m), 907 (w), 854 (m), 781 (w), 758 (m), 740 (m), 702 (m), 644 (w), 538 (w). Anal. calcd for C\(_{26}\)H\(_{19}\)NO\(_3\) (393.4): C 79.37, H 4.87, N 3.56. Found: C 79.21, H 5.03, N 3.51.
2.5.8. 1-(1-Benzyl-5-iodo-1\textit{H}-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3h)

\[\text{C}_{25}\text{H}_{16}\text{INO}_2\]

489.30

864 mg (1.77 mmol, 35 % yield) as a yellow solid. Mp 153-163 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.35 (s, 2 H), 7.06 (d, $J = 8.5$ Hz, 1 H), 7.13-7.17 (m, 2 H), 7.28-7.36 (m, 3 H), 7.39-7.44 (m, 2 H), 7.47-7.53 (m, 1 H), 7.54 (dd, $J = 8.5$ Hz, $J = 1.6$ Hz, 1 H), 7.68-7.72 (m, 2 H), 8.38 (s, 1 H), 8.87 (d, $J = 1.6$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 51.4 (CH$_2$), 87.5 (C$_{\text{quat}}$), 88.1 (C$_{\text{quat}}$), 98.1 (C$_{\text{quat}}$), 110.5 (C$_{\text{quat}}$), 112.5 (CH), 119.6 (C$_{\text{quat}}$), 126.9 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.6 (C$_{\text{quat}}$), 131.4 (CH), 131.6 (CH), 132.8 (CH), 133.7 (CH), 134.7 (C$_{\text{quat}}$), 135.9 (C$_{\text{quat}}$), 139.8 (CH), 178.0 (C$_{\text{quat}}$), 180.0 (C$_{\text{quat}}$). El + MS (m/z (%)): 489 (M$^+$, 0.6), 433 ((M-C$_2$O$_2$)$^+$, 1), 360 (C$_{16}$H$_{11}$INO$_2^+$, 39), 129 (C$_9$H$_5$O$^+$, 6), 91 (C$_7$H$_7^+$, 100), 65 (C$_6$H$_5^+$, 5). IR (KBr): $\tilde{\nu}$ 2205 (m) cm$^{-1}$, 1655 (s), 1629 (s), 1560 (w), 1510 (m), 1459 (m), 1389 (m), 1305 (w), 1162 (m), 1104 (m), 1079 (w), 1022 (m), 882 (m), 808 (w), 787 (w), 775 (w), 759 (m), 731 (m), 700 (m), 686 (w), 648 (w), 579 (w), 538 (w). Anal. calcd for C$_{25}$H$_{16}$INO$_2$ (489.3): C 61.37, H 3.30, N 2.86. Found: C 61.21, H 3.52, N 2.92.
2.5.9. 1-(1-Benzyl-1H-indol-3-yl)oct-3-yne-1,2-dione (3i)

36 mg (0.10 mmol, 2 % yield) as a brown solid.Mp 84-86 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.94 (t, $J$ = 7.6 Hz, 3 H), 1.48 (sext, $J$ = 7.6 Hz, 2 H), 1.64 (quint, $J$ = 7.3 Hz, 2 H), 2.50 (t, $J$ = 7.3 Hz, 2 H), 5.36 (s, 2 H), 7.15-7.19 (m, 2 H), 7.26-7.36 (m, 6 H), 8.37 (s, 1 H), 8.46 (d, $J$ = 7.9 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 13.5 (CH$_3$), 19.3 (CH$_2$), 22.0 (CH$_2$), 29.6 (CH$_2$), 51.2 (CH$_2$), 80.2 (C$_{quat}$), 102.1 (C$_{quat}$), 110.6 (CH), 111.3 (C$_{quat}$), 122.9 (CH), 123.6 (CH), 124.3 (CH), 127.0 (CH), 127.5 (C$_{quat}$), 128.4 (CH), 129.1 (CH), 135.2 (C$_{quat}$), 136.8 (C$_{quat}$), 139.6 (CH), 178.6 (C$_{quat}$), 180.6 (C$_{quat}$). EI + MS (m/z (%)): 343 (M$^+$, 5), 234 ((M-C$_7$H$_9$O)$^+$, 100), 91 (C$_7$H$_7^+$, 92), 65 (C$_5$H$_5^+$, 7), 43 (C$_3$H$_7^+$, 5). IR (KBr): $\tilde{v}$ 3108 (w) cm$^{-1}$, 3031 (w), 2959 (w), 2931 (w), 2870 (w), 2211 (m), 1653 (s), 1633 (s), 1527 (m), 1493 (w), 1467 (w), 1449 (w), 1391 (m), 1198 (m), 1159 (m), 1140 (w), 1055 (w), 979 (w), 816 (w), 780 (m), 748 (m), 732 (m). Anal. calcd for C$_{23}$H$_{21}$NO$_2$ (343.4): C 80.44, H 6.16, N 4.08. Found: C 80.22, H 6.16, N 4.03.
2.5.10. 1-(1-Benzyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-4-phenylbut-3-yne-1,2-dione (3j)

\[
\text{C}_{24}\text{H}_{16}\text{N}_{2}\text{O}_{2}
\]

364.40

1.13 g (3.10 mmol, 62 % yield) as a yellow solid. Mp 121 °C. \( ^1\text{H} \) NMR (CDCl\(_3\), 500 MHz): \( \delta \) 5.55 (s, 2 H), 7.27-7.37 (m, 6 H), 7.38-7.43 (m, 2 H), 7.47-7.51 (m, 1 H), 7.67-7.71 (m, 2 H), 8.46 (dd, \( J = 4.7 \) Hz, \( J = 1.6 \) Hz, 1 H), 8.49 (s, 1 H), 8.71 (ddd, \( J = 7.9 \) Hz, \( J = 1.6 \) Hz, \( J = 0.6 \) Hz, 1 H). \( ^{13}\text{C} \) NMR (CDCl\(_3\), 125 MHz): \( \delta \) 48.8 (CH\(_2\)), 87.4 (C\(_{\text{quat}}\)), 98.1 (C\(_{\text{quat}}\)), 109.9 (C\(_{\text{quat}}\)), 119.5 (CH), 119.5 (C\(_{\text{quat}}\)), 119.6 (C\(_{\text{quat}}\)), 127.8 (CH), 128.3 (CH), 128.6 (CH), 129.0 (CH), 131.1 (CH), 131.4 (CH), 133.7 (CH), 135.8 (C\(_{\text{quat}}\)), 139.0 (CH), 145.3 (CH), 148.2 (C\(_{\text{quat}}\)), 177.8 (C\(_{\text{quat}}\)), 180.2 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 364 (M\(^+\), 1), 308 ((M-C\(_2\)O\(_2\))^+, 3), 235 (C\(_{15}\)H\(_{11}\)N\(_2\)O\(^+\), 99), 129 (8), 91 (C\(_7\)H\(_7^+\), 100). IR (KBr): \( \tilde{\nu} \) 3142 (w) cm\(^{-1}\), 2202 (s), 1644 (s), 1597 (w), 1575 (w), 1519 (m), 1445 (m), 1425 (w), 1391 (m), 1356 (w), 1297 (w), 1236 (w), 1171 (m), 1123 (w), 1076 (w), 1029 (m), 881 (m), 793 (w), 774 (w), 759 (m), 730 (w), 699 (w), 681 (w), 642 (w), 622 (w), 555 (w), 536 (w), 505 (w). Anal. calcd for C\(_{24}\)H\(_{16}\)N\(_2\)O\(_2\) (364.4): C 79.11, H 4.43, N 7.69. Found: C 79.20, H 4.14, N 7.43.
2.5.11. 1-(1-(4-Methoxybenzyl)-1\textit{H}-pyrrolo[2,3-\textit{b}]pyridin-3-yl)-4-phenylbut-3-yne-1,2-dione (3k)

\[
\text{C}_{25}\text{H}_{18}\text{N}_{2}\text{O}_{3} \\
394.42
\]

1.16 g (2.95 mmol, 59 \% yield) as a yellow solid. Mp 117 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 3.78 (s, 3 H), 5.47 (s, 2 H), 6.85-6.89 (m, 2 H), 7.27-7.30 (m, 2 H), 7.32 (dd, \(J = 7.9 \text{ Hz, } J = 4.7 \text{ Hz, } 1 \text{ H}\), 7.38-7.43 (m, 2 H), 7.49 (tt, \(J = 7.6 \text{ Hz, } J = 1.3 \text{ Hz, } 1 \text{ H}\), 7.67-7.70 (m, 2 H), 8.45 (s, 1 H), 8.47 (dd, \(J = 4.7 \text{ Hz, } J = 1.6 \text{ Hz, } 1 \text{ H}\), 8.70 (dd, \(J = 7.9 \text{ Hz, } J = 1.6 \text{ Hz, } 1 \text{ H}\)). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 48.3 (CH\textsubscript{2}), 55.3 (CH\textsubscript{3}), 87.5 (C\textsubscript{quat}), 98.0 (C\textsubscript{quat}), 109.8 (C\textsubscript{quat}), 114.4 (CH), 119.5 (CH), 119.6 (C\textsubscript{quat}), 119.7 (C\textsubscript{quat}), 127.8 (C\textsubscript{quat}), 128.7 (CH), 129.5 (CH), 131.1 (CH), 131.4 (CH), 133.7 (CH), 138.9 (CH), 145.3 (CH), 148.2 (C\textsubscript{quat}), 159.6 (C\textsubscript{quat}), 177.9 (C\textsubscript{quat}), 180.2 (C\textsubscript{quat}). EI + MS (\textit{m/z} %): 394 (M\textsuperscript{+}, 1), 265 ((M-C\textsubscript{9}H\textsubscript{5}O\textsuperscript{+}), 24), 121 (C\textsubscript{8}H\textsubscript{5}O\textsuperscript{+}, 100), 71 (11), 57 (11). IR (KBr): \(\tilde{\nu}\) 3132 (w) cm\textsuperscript{-1}, 2958 (w), 2929 (w), 2834 (w), 2203 (s), 1661 (s), 1648 (s), 1614 (w), 1576 (w), 1521 (s), 1510 (s), 1490 (w), 1445 (m), 1422 (m), 1393 (s), 1296 (w), 1242 (s), 1189 (w), 1177 (s), 1166 (m), 1121 (m), 1073 (w), 1030 (s), 924 (w), 881 (s), 814 (m), 793 (w), 776 (w), 762 (m), 750 (s), 690 (m), 648 (w), 619 (w), 584 (w), 533 (w), 510 (w). Anal. calcd for C\textsubscript{25}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3} (394.4): C 76.13, H 4.60, N 7.10. Found: C 75.94, H 4.89, N 6.89.
2.6. Spectroscopic Data of Compounds 4a-f

2.6.1. 1-(1-Methyl-1H-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4a)

754 mg (3.18 mmol, 64 % yield) as a yellow-brown oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.02 (s, 3 H), 6.23 (dd, $J = 4.1$ Hz, $J = 2.2$ Hz, 1 H), 7.01-7.04 (m, 1 H), 7.33 (dd, $J = 4.1$ Hz, $J = 1.6$ Hz, 1 H), 7.37-7.42 (m, 2 H), 7.48 (tt, $J = 7.6$ Hz, $J = 1.3$ Hz, 1 H), 7.63-7.67 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 37.8 (CH$_3$), 87.6 (C$_{quat}$), 97.5 (C$_{quat}$), 110.2 (CH), 119.7 (C$_{quat}$), 125.4 (CH), 126.5 (C$_{quat}$), 128.8 (CH), 131.5 (CH), 133.7 (CH), 134.7 (CH), 177.1 (C$_{quat}$), 178.2 (C$_{quat}$). EI + MS (m/z (%)): 237 (M$^+$, 4), 209 (6), 181 (11), 129 ((M-C$_6$H$_6$NO)$^+$, 10), 108 ((M-C$_9$H$_5$O)$^+$, 100), 80 (C$_5$H$_6$N$^+$, 5), 53 ((C$_3$O+H)$^+$, 8). IR (film): $\tilde{\nu}$ 3112 (w) cm$^{-1}$, 3059 (w), 2953 (w), 2182 (s), 1634 (s), 1525 (m), 1489 (m), 1463 (m), 1444 (m), 1404 (s), 1335 (m), 1281 (m), 1239 (w), 1125 (m), 1092 (m), 1061 (m), 1027 (m), 913 (m), 877 (m), 799 (w), 754 (s), 689 (m), 635 (w), 602 (w), 538 (m), 515 (w). Anal. calcd for C$_{15}$H$_{11}$NO$_2$ (237.3): C 75.94, H 4.67, N 5.90. Found: C: 75.90, H 4.87, N 5.74.
2.6.2. 1-(1-Benzyl-1H-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4b)

![Chemical Structure]

\[ \text{C}_{21}\text{H}_{15}\text{NO}_2 \]

313.35

1.16 g (3.70 mmol, 74 % yield) as a yellow-red oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 5.63 (s, 2 H), 6.30 (dd, \(J = 4.4\) Hz, \(J = 2.5\) Hz, 1 H), 7.11 (dd, \(J = 2.5\) Hz, \(J = 1.6\) Hz, 1 H), 7.15-7.18 (m, 2 H), 7.25-7.30 (m, 1 H), 7.30-7.35 (m, 2 H), 7.36-7.41 (m, 3 H), 7.47 (tt, \(J = 7.6\) Hz, \(J = 1.3\) Hz, 1 H), 7.61-7.65 (m, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 52.8 (CH\(_2\)), 87.4 (C\(_{\text{quat}}\)), 97.4 (C\(_{\text{quat}}\)), 110.6 (CH), 119.6 (C\(_{\text{quat}}\)), 125.9 (CH), 127.3 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 131.3 (CH), 133.5 (CH), 133.9 (CH), 137.2 (C\(_{\text{quat}}\)), 176.8 (C\(_{\text{quat}}\)), 177.9 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 313 (M\(^+\), 4), 184 ((M-C\(_9\)H\(_5\)O\(^-\)), 100), 149 (9), 129 (C\(_9\)H\(_5\)O\(^-\), 6), 91 (C\(_7\)H\(_7\)\(^+\), 32). IR (film): \(\tilde{\nu}\) 3110 (w) cm\(^{-1}\), 3064 (w), 3033 (w), 2931 (w), 2205 (s), 1634 (s), 1523 (w), 1490 (w), 1488 (w), 1455 (w), 1444 (w), 1411 (s), 1341 (w), 1279 (m), 1234 (w), 1174 (w), 1121 (m), 1086 (s), 1033 (s), 999 (w), 914 (m), 876 (m), 799 (w), 751 (s), 689 (s), 609 (m), 538 (w). Anal. calcd for C\(_{21}\)H\(_{15}\)NO\(_2\) (313.4): C 80.49, H 4.82, N 4.47. Found: C 80.34, H 5.04, N 4.48.
2.6.3. 1-(1-Benzhydryl-1H-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4c)

\[
\begin{align*}
\text{C}_{27}\text{H}_{19}\text{NO}_2 \\
389.45
\end{align*}
\]

1.31 g (3.36 mmol, 67 % yield) as an orange oil. \(^1\text{H}\) NMR (CDCl\(_3\), 500 MHz): \(\delta\) 6.27 (dd, \(J = 4.1\) Hz, \(J = 2.5\) Hz, 1 H), 6.90-6.93 (m, 1 H), 7.05-7.10 (m, 4 H), 7.28-7.40 (m, 8 H), 7.44-7.50 (m, 2 H), 7.59-7.62 (m, 2 H), 7.84 (s, 1 H). \(^{13}\text{C}\) NMR (CDCl\(_3\), 125 MHz): \(\delta\) 65.2 (CH), 87.4 (C\text{quat}), 97.3 (C\text{quat}), 110.3 (CH), 119.6 (C\text{quat}), 126.4 (C\text{quat}), 126.5 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 131.3 (CH), 133.0 (CH), 133.6 (CH), 139.7 (C\text{quat}), 176.8 (C\text{quat}), 177.8 (C\text{quat}). EI + MS (m/z (%)): 389 (M\(^+\), 3), 260 ((M-C\(_9\)H\(_5\)O\(^+\), 28), 167 (C\(_{13}\)H\(_{11}\)\(^+\), 100), 165 ((C\(_{13}\)H\(_{11}\)-2H\(^+\), 54), 152 (26), 129 (C\(_9\)H\(_5\)O\(^+\), 23), 115 (6), 75 (7). IR (film): \(\tilde{\nu}\) 3063 (w) cm\(^{-1}\), 3031 (w), 2926 (w), 2186 (s), 1714 (w), 1634 (s), 1519 (w), 1495 (m), 1454 (m), 1412 (s), 1359 (w), 1276 (m), 1224 (m), 1185 (w), 1118 (w), 1083 (m), 1031 (s), 1000 (w), 932 (m), 914 (m), 877 (m), 796 (w), 750 (s), 698 (s), 643 (m), 613 (m), 538 (w), 518 (w). Anal. calcd for C\(_{27}\)H\(_{19}\)NO\(_2\) (389.5): C 83.27, H 4.92, N 3.60. Found: C 83.16, H 4.75, N 3.50.
2.6.4. 3-(2-(2-Oxo-4-phenylbut-3-ynoyl)-1H-pyrrol-1-yl)propanenitrile (4d)

![Chemical Structure](image)

C₁₇H₁₂N₂O₂

276.29

830 mg (3.00 mmol, 60 % yield) as yellow-brown oil. \(^1\)H NMR (CDCl₃, 500 MHz): \(\delta\) 2.95 (t, \(J = 6.3\) Hz, 2 H), 4.61 (t, \(J = 6.3\) Hz, 2 H), 6.34 (dd, \(J = 4.1\) Hz, \(J = 2.5\) Hz, 1 H), 7.22 (dd, \(J = 2.2\) Hz, \(J = 1.6\) Hz, 1 H), 7.39-7.43 (m, 2 H), 7.47-7.52 (m, 2 H), 7.65-7.68 (m, 2 H). \(^1\)C NMR (CDCl₃, 125 MHz): \(\delta\) 20.0 (CH₂), 45.8 (CH₂), 87.2 (C quat), 97.9 (C quat), 111.2 (CH), 117.1 (C quat), 119.3 (C quat), 125.5 (C quat), 126.9 (CH), 128.7 (CH), 131.5 (CH), 133.6 (CH), 134.6 (CH), 176.7 (C quat), 177.2 (C quat). EI + MS (m/z (%)): 276 (M⁺, 6), 248 (7), 220 (14), 147 ((M-C₇H₅O⁺, 100), 129 (C₇H₅O⁺, 31), 107 (5), 79 (C₅H₅N⁺, 6). IR (film): \(\tilde{\nu}\) 3114 (w) cm⁻¹, 2967 (w), 2195 (s), 1633 (s), 1525 (w), 1489 (w), 1469 (w), 1444 (w), 1412 (m), 1347 (w), 1281 (m), 1239 (w), 1169 (w), 1123 (m), 1088 (m), 1041 (m), 898 (m), 876 (w), 754 (s), 689 (m), 606 (w), 538 (w). Anal. calcd for C₁₇H₁₂N₂O₂ (276.3): C 73.90, H 4.38, N 10.14. Found: C 73.64, H 4.16, N 9.94.
2.6.5. 4-Phenyl-1-(1-phenyl-1H-pyrrol-2-yl)but-3-yn-1,2-dione (4e)

![Chemical Structure](image)

C$_{20}$H$_{13}$NO$_2$

299.32

1.15 g (3.84 mmol, 77 % yield) as a yellow solid. Mp 74-75 °C. $^1$H NMR (CDCl$_3$, 500 MHz): δ 6.42 (dd, $J = 4.1$ Hz, $J = 2.5$ Hz, 1 H), 7.17 (dd, $J = 2.5$ Hz, $J = 1.6$ Hz, 1 H), 7.30-7.39 (m, 4 H), 7.40-7.48 (m, 4 H), 7.49 (dd, $J = 4.1$ Hz, $J = 1.6$ Hz, 1 H), 7.59-7.62 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 87.3 (C$_{\text{quat}}$), 97.5 (C$_{\text{quat}}$), 111.2 (CH), 119.5 (C$_{\text{quat}}$), 126.0 (CH), 126.1 (CH), 126.8 (C$_{\text{quat}}$), 128.2 (CH), 128.6 (CH), 128.9 (CH), 131.3 (CH), 133.6 (CH), 134.4 (CH), 139.9 (C$_{\text{quat}}$), 175.7 (C$_{\text{quat}}$), 177.7 (C$_{\text{quat}}$). EI + MS (m/z (%)): 299 (M$^+$, 3), 271 (5), 243 (3), 170 ((M-C$_9$H$_5$O)$^+$, 100), 115 (19). IR (KBr): ν 2201 (m) cm$^{-1}$, 1671 (m), 1638 (s), 1560 (w), 1543 (w), 1509 (w), 1491 (m), 1442 (w), 1412 (m), 1363 (w), 1281 (m), 1203 (w), 1130 (w), 1090 (m), 1043 (m), 985 (m), 895 (m), 872 (w), 769 (s), 748 (s), 690 (m), 595 (w), 536 (w). Anal. calcd for C$_{20}$H$_{13}$NO$_2$ (299.3): C 80.25, H 4.38, N 4.68. Found: C 80.11, H 4.51, N 4.63.
2.6.6. 1-(1-(Triisopropylsilyl)-1H-pyrrol-3-yl)-4-phenylbut-3-yne-1,2-dione (4f)

\[
\text{C}_23\text{H}_29\text{NO}_2\text{Si} \quad 379.57
\]

836 mg (2.20 mmol, 44 % yield) as an orange oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.12 (d, \(J = 7.6\) Hz, 18 H), 1.49 (sept, \(J = 7.6\) Hz, 3 H), 6.79 (dd, \(J = 2.8\) Hz, \(J = 2.2\) Hz, 1 H), 6.93 (dd, \(J = 2.8\) Hz, \(J = 1.3\) Hz, 1 H), 7.38-7.42 (m, 2 H), 7.46-7.50 (m, 1 H), 7.66-7.69 (m, 2 H), 7.81-7.83 (m, 1 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 11.4 (CH\(_3\)), 17.6 (CH), 87.5 (C\(_{\text{quat}}\)), 97.2 (C\(_{\text{quat}}\)), 111.9 (CH), 119.7 (C\(_{\text{quat}}\)), 122.1 (C\(_{\text{quat}}\)), 126.2 (CH), 128.6 (CH), 131.2 (CH), 133.6 (CH), 134.7 (CH), 178.6 (C\(_{\text{quat}}\)), 181.5 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 380 (M\(^+\), 1), 156 (12), 155 (C\(_{11}\)H\(_7\)O\(^+\), 100), 149 (21), 127 (C\(_{10}\)H\(_7\)\(^+\), 27), 101 (C\(_8\)H\(_5\)\(^+\), 4), 94 (24), 77 (C\(_6\)H\(_5\)\(^+\), 6). IR (film): \(\tilde{\nu}\) 2949 (m) cm\(^{-1}\), 2869 (m), 2200 (s), 1651 (s), 1520 (s), 1489 (m), 1464 (m), 1392 (w), 1261 (m), 1223 (m), 1150 (w), 1093 (s), 1067 (s), 1018 (w), 993 (w), 956 (w), 923 (w), 883 (m), 836 (w), 796 (w), 755 (s), 690 (m), 660 (m), 634 (w), 577 (w), 527 (w). Anal. calcd for C\(_{23}\)H\(_{29}\)NO\(_2\)Si (379.6): C 72.78, H 7.70, N 3.69. Found: C 72.58, H 7.91, N 3.50.
2.7. Spectroscopic Data of Compounds 5a-e

2.7.1. 1-(1-Methyl-1H-pyrazol-4-yl)-4-phenylbut-3-yne-1,2-dione (5a)

\[
\text{C}_{14}\text{H}_{10}\text{N}_{2}\text{O}_{2}
\]

564 mg (2.37 mmol, 47 % yield) as a yellow solid. Mp 112 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.98 (s, 3 H), 7.40-7.44 (m, 2 H), 7.49-7.53 (m, 1 H), 7.68-7.71 (m, 2 H), 8.20 (s, 1 H), 8.32 (s, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 39.4 (CH\(_3\)), 86.9 (C\(_{\text{quat}}\)), 98.9 (C\(_{\text{quat}}\)), 117.9 (C\(_{\text{quat}}\)), 119.4 (C\(_{\text{quat}}\)), 128.7 (CH), 131.6 (CH), 133.8 (CH), 135.7 (CH), 142.7 (CH), 177.0 (C\(_{\text{quat}}\)), 179.3 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 238 (M\(^+\), 0.4), 237 ((M-H)\(^+\), 0.8), 210 ((M-CO)\(^+\), 4), 182 ((M-C\(_2\)O\(_2\))\(^+\), 10), 129 (C\(_9\)H\(_5\)O\(^+\), 17), 110 (7), 109 (C\(_9\)H\(_5\)N\(_2\)O\(^+\), 100). IR (KBr): \(\tilde{\nu}\) 3129 (w) cm\(^{-1}\), 2203 (m), 1657 (s), 1536 (m), 1489 (w), 1444 (w), 1276 (w), 1214 (w), 1115 (m), 968 (w), 895 (m), 769 (m), 754 (m), 680 (w), 655 (w), 621 (w), 592 (w), 539 (w). Anal. calcd for C\(_{14}\)H\(_{10}\)N\(_2\)O\(_2\) (238.2): C 70.58, H 4.23, N 11.76. Found: C 70.73, H 4.45, N 11.80.
2.7.2. 1-(5-Methoxythiophen-2-yl)-4-phenylbut-3-yne-1,2-dione (5b)

\[
\text{C}_{15}\text{H}_{10}\text{O}_{3}\text{S}
\]

712 mg (2.63 mmol, 53 % yield) as a yellow solid. Mp 83 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 4.03 (s, 3 H), 6.37 (d, \(J = 4.4\) Hz, 1 H), 7.39-7.43 (m, 2 H), 7.48-7.52 (m, 1 H), 7.66-7.70 (m, 2 H), 7.99 (d, \(J = 4.4\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 60.9 (CH\(_3\)), 87.2 (C\(_{\text{quat}}\)), 98.4 (C\(_{\text{quat}}\)), 108.0 (CH), 119.5 (C\(_{\text{quat}}\)), 128.7 (CH), 131.5 (CH), 133.7 (CH), 139.3 (CH), 176.7 (C\(_{\text{quat}}\)), 177.2 (C\(_{\text{quat}}\)), 177.2 (C\(_{\text{quat}}\)), 178.5 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 270 (M\(^+\), 1), 242 ((M-CO)\(^+\), 1), 214 ((M-C\(_2\)O\(_2\))\(^+\), 7), 141 (C\(_9\)H\(_5\)O\(_2\)S\(^+\), 100), 129 (C\(_9\)H\(_5\)O\(^+\), 13), 98 (14), 85 (12), 71 (13), 57 (11). IR (KBr): \(\tilde{\nu}\) 3106 (w) cm\(^{-1}\), 3092 (w), 2208 (s), 2187 (s), 1637 (s), 1595 (m), 1535 (m), 1471 (s), 1421 (s), 1354 (m), 1325 (m), 1269 (w), 1233 (m), 1221 (m), 1113 (m), 1056 (s), 999 (w), 981 (m), 925 (w), 876 (m), 799 (w), 782 (w), 754 (s), 733 (w), 683 (m), 618 (m), 583 (w), 536 (w), 514 (w). Anal. calcd for C\(_{15}\)H\(_{10}\)O\(_3\)S (270.3): C 66.65, H 3.73. Found: C 66.42, H 4.02.
2.7.3. 1-(2,3-Dihydrothieno[3,4-b][1,4]dioxin-7-yl)-4-phenylbut-3-yn-1,2-dione (5c)

![Chemical Structure](attachment:image.png)

C\textsubscript{16}H\textsubscript{10}O\textsubscript{4}S

298.31

978 mg (3.28 mmol, 66 % yield) as an orange solid. Mp 117 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 4.25-4.28 (m, 2 H), 4.40-4.43 (m, 2 H), 6.89 (s, 1 H), 7.39-7.43 (m, 2 H), 7.50 (tt, \(J = 7.6\) Hz, \(J = 1.3\) Hz, 1 H), 7.65-7.69 (m, 2 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 63.9 (CH\textsubscript{2}), 65.5 (CH\textsubscript{2}), 86.5 (C\textsubscript{quat}), 99.1 (C\textsubscript{quat}), 111.3 (C\textsubscript{quat}), 113.9 (CH), 119.4 (C\textsubscript{quat}), 128.7 (CH), 131.5 (CH), 133.7 (CH), 141.8 (C\textsubscript{quat}), 149.5 (C\textsubscript{quat}), 177.4 (C\textsubscript{quat}), 177.5 (C\textsubscript{quat}). EI + MS (m/z (%)): 298 (M\textsuperscript{+}, 0.5), 270 ((M-CO)\textsuperscript{+}, 3), 242 ((M-C\textsubscript{2}O\textsubscript{2})\textsuperscript{+}, 12), 169 (C\textsubscript{7}H\textsubscript{5}O\textsubscript{3}S\textsuperscript{+}, 100), 143 (9), 141 (C\textsubscript{6}H\textsubscript{5}O\textsubscript{2}S\textsuperscript{+}, 3), 129 (C\textsubscript{9}H\textsubscript{5}O\textsuperscript{+}, 17), 113 (C\textsubscript{4}HO\textsubscript{2}S\textsuperscript{+}, 7), 97 (C\textsubscript{4}HOS\textsuperscript{+}, 3). IR (KBr): \(\tilde{\nu}\) 3095 (w) cm\textsuperscript{-1}, 2944 (w), 2189 (s), 1651 (s), 1637 (s), 1595 (w), 1479 (s), 1432 (s), 1365 (s), 1318 (w), 1265 (m), 1184 (w), 1161 (m), 1086 (s), 1009 (m), 995 (w), 918 (m), 885 (s), 851 (w), 760 (m), 735 (s), 688 (m), 560 (w), 542 (w), 510 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{10}O\textsubscript{4}S (298.3): C 64.42, H 3.38. Found: C 64.59, H 3.55.
2.7.4. 1-(5-Methylfuran-2-yl)-4-phenylbut-3-yn-1,2-dione (5d)

\[ \text{C}_{15}\text{H}_{10}\text{O}_3 \]

457 mg (1.92 mmol, 38 % yield) as an orange solid. Mp 81 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 2.47 (s, 3 H), 6.29 (d, \(J = 3.8\) Hz, 1 H), 7.39-7.44 (m, 2 H), 7.49-7.53 (m, 1 H), 7.66-7.70 (m, 3 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 14.3 (CH\(_3\)), 87.0 (C\(_\text{quat}\)), 98.7 (C\(_\text{quat}\)), 110.4 (CH), 119.4 (C\(_\text{quat}\)), 127.5 (CH), 128.7 (CH), 131.6 (CH), 133.8 (CH), 147.6 (C\(_\text{quat}\)), 161.9 (C\(_\text{quat}\)), 172.8 (C\(_\text{quat}\)), 176.2 (C\(_\text{quat}\)). El + MS (m/z (%)): 238 (M\(^+\), 0.7), 210 ((M-CO\(^+\)), 21), 182 ((M-C\(_2\)O\(_2\))^+), 35), 130 (10), 129 (C\(_9\)H\(_5\)O\(^+\), 100), 109 ((M-C\(_9\)H\(_5\)O)^+), 99), 75 (11). IR (KBr): \(\tilde{\nu}\) 2925 (w) cm\(^{-1}\), 2198 (s), 1653 (s), 1573 (w), 1504 (s), 1444 (m), 1370 (w), 1329 (w), 1274 (m), 1210 (w), 1142 (m), 1032 (m), 1011 (m), 999 (m), 873 (w), 953 (m), 883 (m), 812 (w), 759 (s), 689 (m), 659 (w), 592 (w), 541 (w), 514 (w).

Anal. calcd for C\(_{15}\)H\(_{10}\)O\(_3\) (238.2): C 75.62, H 4.23. Found: C 75.87, H 4.44.
2.7.5. 1-((4Z,6Z,8Z)-Azulen-1-yl)-4-phenylbut-3-yne-1,2-dione (5e)

\[
\begin{align*}
\text{C}_{20}\text{H}_{12}\text{O}_{2} & \quad 284.31 \\
\end{align*}
\]

462 mg (1.63 mmol, 33 % yield) as a brown solid. Mp 103 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.32 (d, \(J = 4.4\) Hz, 1 H), 7.37-7.42 (m, 2 H), 7.45-7.50 (m, 1 H), 7.63 (t, \(J = 9.8\) Hz, 1 H), 7.66-7.69 (m, 2 H), 7.75 (t, \(J = 9.8\) Hz, 1 H), 7.89-7.95 (m, 1 H), 8.51-8.54 (m, 2 H), 9.92 (d, \(J = 9.8\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 87.8 (C\(_{\text{quat}}\)), 97.2 (C\(_{\text{quat}}\)), 119.2 (C\(_{\text{quat}}\)), 119.7 (CH), 119.7 (C\(_{\text{quat}}\)), 128.6 (CH), 129.6 (CH), 131.1 (CH), 131.2 (CH), 133.5 (CH), 138.8 (CH), 139.7 (CH), 140.2 (CH), 142.9 (CH), 143.5 (C\(_{\text{quat}}\)), 147.3 (C\(_{\text{quat}}\)), 179.7 (C\(_{\text{quat}}\)), 183.6 (C\(_{\text{quat}}\)). EI + MS (\(m/z\) (%)): 284 (M\(^+\), 1), 256 ((M-CO\(^+\)), 0.3), 228 ((M-C\(_2\)O\(_2\))^+\)), 1), 156 (12), 155 (C\(_{11}\)H\(_7\)O\(^+\), 100), 149 (21), 129 (C\(_8\)H\(_5\)O\(^+\), 4) 127 (C\(_{10}\)H\(_7\)^+\), 27), 101 (C\(_8\)H\(_5\)^+, 4), 94 (24), 77 (C\(_6\)H\(_5\)^+, 6). IR (KBr): \(\tilde{\nu}\) 2203 (m) cm\(^{-1}\), 1641 (s), 1625 (s), 1599 (w), 1589 (w), 1576 (w), 1539 (w), 1491 (m), 1458 (w), 1447 (w), 1414 (m), 1394 (s), 1323 (w), 1275 (m), 1227 (w), 1182 (w), 1147 (m), 1053 (m), 1032 (m), 1020 (s), 997 (w), 966 (w), 922 (w), 893 (m), 856 (m), 802 (w), 773 (s), 745 (s), 712 (s), 677 (m), 610 (m). Anal. calcd for C\(_{20}\)H\(_{12}\)O\(_2\) (284.3): C 84.49, H 4.25. Found: C 84.27, H 4.36.
3. One-Pot Reactions with Ynediones as Intermediates

3.1. One-Pot Four Component Glyoxylation - Stephens-Castro - Michael-Addition Sequence

\[
\begin{align*}
\text{N-Methyl-1H-indole } & \text{1a (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene 2a (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL) and benzylamine (0.55 mL, 5.00 mmol) were added, and the mixture was stirred for 1 h at 50 °C (preheated oil bath). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 ºC)/ethyl acetate PE-EA = 3:1, 1 Vol % triethylamine.}
\end{align*}
\]
(Z)-4-(Benzylamino)-1-(1-methyl-1H-indol-3-yl)-4-phenylbut-3-ene-1,2-dione (6)

![Chemical Structure](image)

C<sub>26</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> 394.47

1.18 g (2.99 mmol, 60 % yield) as a yellow solid. Mp 143-146 °C. R<sub>f</sub> (PE-EA = 3:1, 1 Vol % NEt<sub>3</sub>) = 0.37. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 3.83 (s, 3 H), 4.50 (d, J = 6.3 Hz, 2 H), 6.06 (s, 1 H), 7.23-7.38 (m, 8 H), 7.40-7.47 (m, 6 H), 8.46-8.51 (m, 1 H), 8.56 (s, 1 H), 11.64 (t, J = 5.4 Hz, 1 H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 33.5 (CH<sub>3</sub>), 48.8 (CH<sub>2</sub>), 93.8 (CH), 109.6 (CH), 112.5 (C<sub>quat</sub>), 122.8 (CH), 122.8 (CH), 123.4 (CH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.7 (C<sub>quat</sub>), 128.6 (CH), 128.9 (CH), 130.0 (CH), 134.6 (C<sub>quat</sub>), 137.0 (C<sub>quat</sub>), 137.9 (C<sub>quat</sub>), 140.1 (CH), 168.9 (C<sub>quat</sub>), 186.9 (C<sub>quat</sub>), 187.0 (C<sub>quat</sub>). EI + MS (m/z (%)): 394 (M<sup>+</sup>, 7), 236 (C<sub>16</sub>H<sub>14</sub>NO<sup>+</sup>, 100), 158 (C<sub>10</sub>H<sub>8</sub>NO<sup>+</sup>, 11), 130 (C<sub>9</sub>H<sub>8</sub>N<sup>+</sup>, 3), 91 (C<sub>7</sub>H<sub>7</sub>N<sup>+</sup>, 50), 65 (C<sub>5</sub>H<sub>5</sub>N<sup>+</sup>, 2). IR (KBr): ν 3126 (w) cm<sup>-1</sup>, 3054 (w), 1626 (m), 1561 (s), 1511 (m), 1482 (m), 1465 (m), 1420 (w), 1368 (m), 1329 (s), 1267 (m), 1213 (m), 1152 (w), 1124 (w), 1070 (m), 1038 (w), 907 (w), 847 (w), 820 (w), 750 (s), 722 (m), 697 (m), 618 (w), 598 (w), 570 (w), 541 (w). Anal. calcd for C<sub>26</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> (394.5): C 79.16, H 5.62, N 7.10. Found: C 79.07, H 5.83, N 6.84.
3.2. One-Pot Four-Component Synthesis of 2-(1-Methyl-1H-indol-3-yl)-3-(phenylethynyl)quinoxaline (7)

\[ \text{N-Methyl-1H-indole 1a (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice bath, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, Cul (49 mg, 0.25 mmol), phenylacetylene 2a (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL), glacial acetic acid (5 mL) and 1,2-phenylenediamine (541 mg, 5.00 mmol) were added, and the mixture was stirred for 3 h at 50 °C (preheated oil bath). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane.} \]
2-(1-Methyl-1H-indol-3-yl)-3-(phenylethynyl)quinoxaline (7)

1.29 g (3.59 mmol, 72 % yield) as a yellow solid. Mp 157-158 °C. Rf (dichloromethane) = 0.67. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.89 (s, 3 H), 7.30-7.43 (m, 6 H), 7.59-7.62 (m, 2 H), 7.64-7.68 (m, 1 H), 7.70-7.75 (m, 1 H), 8.06 (dd, $J = 8.5$ Hz, $J = 1.6$ Hz, 1 H), 8.13 (dd, $J = 8.2$ Hz, $J = 1.3$ Hz, 1 H), 8.44 (s, 1 H), 8.74-8.77 (m, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 33.4 (CH$_3$), 89.7 (C$_{quat}$), 94.0 (C$_{quat}$), 109.5 (CH), 112.4 (C$_{quat}$), 121.4 (CH), 122.0 (C$_{quat}$), 122.9 (CH), 122.9 (CH), 127.5 (C$_{quat}$), 128.6 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.6 (CH), 130.4 (CH), 132.0 (CH), 132.6 (CH), 137.0 (C$_{quat}$), 137.3 (C$_{quat}$), 139.4 (C$_{quat}$), 141.1 (C$_{quat}$), 150.6 (C$_{quat}$). EI + MS ($m/z$ (%)): 359 (M$^+$, 97), 358 ((M-H)$^+$, 100), 344 ((M-CH$_3$)$^+$, 10), 282 ((M-C$_6$H$_5$)$^+$, 3), 231 (11), 203 (C$_{15}$H$_9$N$^+$, 3), 180 (12), 156 (C$_{10}$H$_8$N$_2^+$, 10). IR (KBr): $\tilde{\nu}$ 2211 (m) cm$^{-1}$, 1655 (w), 1638 (w), 1536 (s), 1491 (m), 1477 (m), 1456 (m), 1425 (w), 1406 (w), 1373 (m), 1339 (w), 1237 (w), 1215 (m), 1129 (m), 1113 (m), 1084 (m), 1012 (w), 938 (w), 748 (s), 683 (w), 613 (w), 528 (w). Anal. calcd for C$_{25}$H$_{17}$N$_3$ (359.4): C 83.54, H 4.77, N 11.69. Found: C 83.40, H 4.62, N 11.62.

\[ \text{N-Methyl-1H-indole 1a (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, Cul (49 mg, 0.25 mmol), phenylacetylene 2a (0.57 mL, 5.00 mmol), and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL) and tert-butyl carbazate (667 mg, 5.00 mmol) were added, and the mixture was stirred for 24 h at 50 °C (preheated oil bath, product monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate PE-EA = 3:1 → 2:1, 1 Vol % triethylamine. After drying in vacuo, compound 8a (1.55 g, 3.86 mmol, 77 % yield) was obtained as a pale brown solid. } \]

\[ \text{R}_f (\text{PE-EA} = 3:1) = 0.15. \text{ Mp 179-184 °C. It was used without further purification.} \]
The obtained compound was suspended in methanol (19 mL) and treated with potassium carbonate (1.35 g, 9.64 mmol). After stirring for 1 h at room temperature (water bath), the mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia as eluent (DCM-NH₃ = 100:1 → DCM-MeOH-NH₃ = 100:1:1 → DCM-MeOH-NH₃ = 100:2:1, stepwise gradient). After drying in vacuo, compound 8b (923 mg, 3.06 mmol, 79 % yield) was obtained as a pale yellow solid.

(1-Methyl-1H-indol-3-yl)(3-phenyl-1H-pyrazol-5-yl)methanone (8b)

[Chemical structure image]

C₁₉H₁₅N₃O
301.34

923 mg (3.06 mmol, 61 % total yield over two steps) as a pale yellow solid. Colorless solid was obtained after further purification by suspending in dichloromethane, sonication in ultrasound bath, filtration and drying in vacuo overnight. Mp 224-225 °C. ¹H NMR (DMSO-d₆, 500 MHz, 100 °C): δ 3.94 (s, 3 H), 7.25-7.41 (m, 4 H), 7.45-7.51 (m, 2 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.9 (br, 2 H), 8.4 (br, 1 H), 8.7 (br, 1 H), 13.5 (br, 1 H, NH). EI + MS (m/z (%)): 301 (M⁺, 9), 158 ((M-C₉H₇N₂)⁺, 71), 131 ((C₉H₈N+H)⁺, 100), 130 (C₉H₈N⁺, 41), 114 (13), 103 (C₇H₅N⁺, 24), 89 (17), 77 (C₆H₅⁺, 90), 63 (11), 51 (C₄H₃⁺, 18). IR (KBr): ν 3240 (w) cm⁻¹, 3136 (w), 2923 (w), 2854 (w), 1593 (s), 1574 (m), 1516 (s), 1491 (w), 1472 (m), 1461 (m), 1418 (w), 1399 (w), 1380 (w), 1364 (m), 1259 (w), 1222 (m), 1178 (w), 1128 (w), 1081 (m), 1013 (w), 990 (w), 960 (w), 913 (w), 823 (w), 784 (w), 772 (m), 754 (m), 692 (w), 672 (w), 613 (w), 578 (w), 507 (w). Anal. calcd for C₁₉H₁₅N₃O (301.3): C 75.73, H 5.02, N 13.94. Found: C 75.66, H 5.07, N 13.92.
3.4. One-Pot Four-Component Synthesis of (1-Methyl-1H-indol-3-yl)(2,6-diphenylpyrimidin-4-yl)methanone (9)

\[ \begin{align*}
1a & \xrightarrow{\text{OCCl}} 2a \\
\text{OCl} & \xrightarrow{\text{H}_2\text{N} \cdot \text{HCl}} 9
\end{align*} \]

\( N \)-Methyl-1H-indole \( 1a \) (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice bath, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene \( 2a \) (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL), benzamidine hydrochloride (791 mg, 5.00 mmol) and potassium carbonate (1.75 g, 12.5 mmol) were added, and the mixture was stirred for 21 h at 50 °C (preheated oil bath, product monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate PE-EA = 10:1, 1 Vol % triethylamine. After drying in vacuo, compound \( 9 \) (800 mg, 2.05 mmol, 41 % yield) was obtained as a yellow solid. Further purification was performed by recrystallization from dichloromethane/n-pentane to give the analytically pure \( 9 \) as yellow crystals.
(1-Methyl-1\textit{H}-indol-3-yl)(2,6-diphenylpyrimidin-4-yl)methanone (9)

\[
\begin{align*}
\text{C}_{26}\text{H}_{19}\text{N}_3\text{O} & \quad 389.45 \\
\end{align*}
\]

800 mg (2.05 mmol, 41 % yield) as a yellow solid. R\text{f} (PE-EA = 10:1): 0.31. Mp 196 °C. 
\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 3.88 (s, 3 H), 7.34-7.41 (m, 3 H), 7.52-7.59 (m, 6 H), 8.30-8.34 (m, 2 H), 8.35 (s, 1 H), 8.60-8.65 (m, 3 H), 8.85 (s, 1 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 33.8 (CH\textsubscript{3}), 109.7 (CH), 112.7 (CH), 113.7 (C\textsubscript{quat}), 123.0 (CH), 123.3 (CH), 123.8 (CH), 127.4 (CH), 128.0 (C\textsubscript{quat}), 128.4 (CH), 128.7 (CH), 129.0 (CH), 130.9 (CH), 131.2 (CH), 136.8 (C\textsubscript{quat}), 137.1 (C\textsubscript{quat}), 137.9 (C\textsubscript{quat}), 140.8 (CH), 163.8 (C\textsubscript{quat}), 163.9 (C\textsubscript{quat}), 165.7 (C\textsubscript{quat}), 185.2 (C\textsubscript{quat}). EI + MS (\textit{m/z} (%)): 389 (M\textsuperscript{+}, 11), 191 (10), 189 (15), 159 (12), 158 (C\textsubscript{10}H\textsubscript{8}NO\textsuperscript{+}, 100), 130 (C\textsubscript{6}H\textsubscript{5}N\textsuperscript{+}, 9), 77 (C\textsubscript{6}H\textsubscript{5}, 10), 57 (19), 43 (56), 42 (23), 41 (18). IR (KBr): \(\tilde{\nu}\) 3132 (w) cm\textsuperscript{-1}, 1620 (s), 1566 (m), 1522 (s), 1460 (m), 1420 (w), 1403 (w), 1373 (s), 1232 (w), 1197 (w), 1125 (w), 1086 (w), 932 (w), 916 (w), 893 (w), 779 (w), 718 (s), 736 (s), 691 (m), 657 (w), 644 (w), 632 (w), 579 (w), 544 (w). Anal. calcd for C\textsubscript{26}H\textsubscript{19}N\textsubscript{3}O (389.5): C 80.18, H 4.92, N 10.79. Found: C 79.97, H 5.07, N 10.82.
4. $^1$H and $^{13}$C NMR Spectra of Compounds 3a-k

$^1$H NMR of 3a in CDCl$_3$ at 296 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3a in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3a in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1\text{H}$ NMR of 3b in CDCl$_3$ at 299 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of $3b$ in CDCl$_3$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of $3b$ in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 3c in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3c in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3c in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 3d in CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3d in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 3d in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 3e in CDCl$_3$ at 299 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3e in CDCl$_3$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3e in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 3f in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^{13}$C NMR of 3f in CDCl$_3$ at 298 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 3f in CDCl$_3$ at 298 K (δ in ppm).
$^1$H NMR of 3g in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3g in CDCl$_3$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3g in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 3h in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3h in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 3h in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 3i in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of 3i in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3i in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3j in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3j in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 3j in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 3k in CDCl$_3$ at 295 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3k in CDCl$_3$ at 295 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3k in CDCl$_3$ at 295 K ($\delta$ in ppm).
5. $^1$H and $^{13}$C NMR Spectra of Compounds 4a-f

$^1$H NMR of 4a in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^{13}$C NMR of 4a in CDCl$_3$ at 299 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4a in CDCl$_3$ at 299 K (δ in ppm).
$^1$H NMR of 4b in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4b in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4b in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4c in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4c in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 4c in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4d in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4d in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 4d in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4e in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4e in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4e in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4f in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4f in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 4f in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
6. $^1$H and $^{13}$C NMR Spectra of Compounds 5a-e

$^1$H NMR of 5a in CDCl$_3$ at 295 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 5a in CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 5a in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
$^1$H NMR of 5b in CDCl$_3$ at 296 K (δ in ppm).
$^{13}$C NMR of 5b in CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 5b in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 5c in CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 5c in CDCl$_3$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 5c in CDCl$_3$ at 296 K (δ in ppm).
$^1$H NMR of 5d in CDCl$_3$ at 295 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 5d in CDCl$_3$ at 296 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 5d in CDCl$_3$ at 295 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 5e in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of $\text{5e}$ in CDCl$_3$ at 298 K (δ in ppm).

$^{13}$C DEPT 135-NMR of $\text{5e}$ in CDCl$_3$ at 298 K (δ in ppm).
7. $^1$H and $^{13}$C NMR Spectra of Compounds 6, 7 and 9

$^1$H NMR of 6 in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 6 in CDCl$_3$ at 299 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 6 in CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^1$H NMR of 7 in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 7 in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 7 in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 9 in CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 9 in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 9 in CDCl$_3$ at 298 K (δ in ppm). *Impurities from residual solvents.
8. Crystallographic Data of Compound 3a

*Table 3.* Crystal data and structure refinement for 1-(1-methyl-1H-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3a).

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<td>Space group</td>
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</tr>
<tr>
<td>Volume</td>
<td>725.3(3) Å</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.32 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.09 mm⁻¹</td>
</tr>
<tr>
<td>Crystal shape</td>
<td>polyhedron</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.31 x 0.20 x 0.11 mm³</td>
</tr>
<tr>
<td>Crystal color</td>
<td>orange</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.8 to 28.4 deg.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9≤h≤9, -12≤k≤12, -15≤l≤14</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>7335</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3564 (R(int) = 0.1129)</td>
</tr>
<tr>
<td>Observed reflections</td>
<td>2655 (I &gt;2σ(I))</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.99 and 0.97</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>3564 / 0 / 200</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.11</td>
</tr>
<tr>
<td>Final R indices (I&gt;2σ(I))</td>
<td>R1 = 0.075, wR2 = 0.159</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.29 and -0.32 eÅ⁻³</td>
</tr>
</tbody>
</table>
Table 4. Atomic coordinates and equivalent isotropic displacement parameters (Å\(^2\)) for 3a. \(U_{\text{eq}}\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(U_{\text{eq}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.1907(4)</td>
<td>0.1256(3)</td>
<td>1.2186(2)</td>
<td>0.0354(5)</td>
</tr>
<tr>
<td>N1</td>
<td>0.2007(3)</td>
<td>0.1024(2)</td>
<td>1.0941(1)</td>
<td>0.0257(4)</td>
</tr>
<tr>
<td>C2</td>
<td>0.1302(3)</td>
<td>0.2081(2)</td>
<td>1.0104(2)</td>
<td>0.0265(5)</td>
</tr>
<tr>
<td>C3</td>
<td>0.1508(3)</td>
<td>0.1450(2)</td>
<td>0.9042(2)</td>
<td>0.0242(4)</td>
</tr>
<tr>
<td>C4</td>
<td>0.0828(3)</td>
<td>0.2198(2)</td>
<td>0.7969(2)</td>
<td>0.0242(4)</td>
</tr>
<tr>
<td>O4</td>
<td>0.0775(2)</td>
<td>0.1593(2)</td>
<td>0.7100(1)</td>
<td>0.0349(4)</td>
</tr>
<tr>
<td>C5</td>
<td>0.0182(3)</td>
<td>0.3906(2)</td>
<td>0.7885(2)</td>
<td>0.0295(5)</td>
</tr>
<tr>
<td>O5</td>
<td>0.0936(3)</td>
<td>0.4614(2)</td>
<td>0.8359(2)</td>
<td>0.0463(5)</td>
</tr>
<tr>
<td>C6</td>
<td>-0.1318(4)</td>
<td>0.4645(2)</td>
<td>0.7139(2)</td>
<td>0.0332(5)</td>
</tr>
<tr>
<td>C7</td>
<td>-0.2597(3)</td>
<td>0.5392(2)</td>
<td>0.6600(2)</td>
<td>0.0300(5)</td>
</tr>
<tr>
<td>C11</td>
<td>-0.4164(3)</td>
<td>0.6285(2)</td>
<td>0.5976(2)</td>
<td>0.0287(5)</td>
</tr>
<tr>
<td>C12</td>
<td>-0.3840(4)</td>
<td>0.7435(3)</td>
<td>0.5150(2)</td>
<td>0.0410(6)</td>
</tr>
<tr>
<td>C13</td>
<td>-0.5369(5)</td>
<td>0.8278(3)</td>
<td>0.4553(3)</td>
<td>0.0530(8)</td>
</tr>
<tr>
<td>C14</td>
<td>-0.7185(4)</td>
<td>0.7993(3)</td>
<td>0.4763(3)</td>
<td>0.0506(7)</td>
</tr>
<tr>
<td>C15</td>
<td>-0.7511(4)</td>
<td>0.6864(3)</td>
<td>0.5583(2)</td>
<td>0.0427(6)</td>
</tr>
<tr>
<td>C16</td>
<td>-0.5999(4)</td>
<td>0.6006(3)</td>
<td>0.6188(2)</td>
<td>0.0347(5)</td>
</tr>
<tr>
<td>C21</td>
<td>0.2726(3)</td>
<td>-0.0348(2)</td>
<td>1.0451(2)</td>
<td>0.0234(4)</td>
</tr>
<tr>
<td>C22</td>
<td>0.3613(3)</td>
<td>-0.1742(2)</td>
<td>1.0974(2)</td>
<td>0.0292(5)</td>
</tr>
<tr>
<td>C23</td>
<td>0.4170(4)</td>
<td>-0.2922(2)</td>
<td>1.0273(2)</td>
<td>0.0359(6)</td>
</tr>
<tr>
<td>C24</td>
<td>0.3851(4)</td>
<td>-0.2743(2)</td>
<td>0.9092(2)</td>
<td>0.0364(6)</td>
</tr>
<tr>
<td>C25</td>
<td>0.2980(3)</td>
<td>-0.1349(2)</td>
<td>0.8569(2)</td>
<td>0.0283(5)</td>
</tr>
<tr>
<td>C26</td>
<td>0.2418(3)</td>
<td>-0.0134(2)</td>
<td>0.9251(2)</td>
<td>0.0232(4)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates and isotropic displacement parameters (Å$^2$) for 3a.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1A</td>
<td>0.1334</td>
<td>0.2315</td>
<td>1.2313</td>
<td>0.053</td>
</tr>
<tr>
<td>H1B</td>
<td>0.3253</td>
<td>0.0906</td>
<td>1.2387</td>
<td>0.053</td>
</tr>
<tr>
<td>H1C</td>
<td>0.1067</td>
<td>0.0701</td>
<td>1.2694</td>
<td>0.053</td>
</tr>
<tr>
<td>H2</td>
<td>0.0745</td>
<td>0.3109</td>
<td>1.0224</td>
<td>0.032</td>
</tr>
<tr>
<td>H12</td>
<td>-0.2589</td>
<td>0.7636</td>
<td>0.5000</td>
<td>0.049</td>
</tr>
<tr>
<td>H13</td>
<td>-0.5161</td>
<td>0.9061</td>
<td>0.3992</td>
<td>0.064</td>
</tr>
<tr>
<td>H14</td>
<td>-0.8216</td>
<td>0.8574</td>
<td>0.4343</td>
<td>0.061</td>
</tr>
<tr>
<td>H15</td>
<td>-0.8769</td>
<td>0.6674</td>
<td>0.5732</td>
<td>0.051</td>
</tr>
<tr>
<td>H16</td>
<td>-0.6221</td>
<td>0.5227</td>
<td>0.6749</td>
<td>0.042</td>
</tr>
<tr>
<td>H22</td>
<td>0.3821</td>
<td>-0.1868</td>
<td>1.1777</td>
<td>0.035</td>
</tr>
<tr>
<td>H23</td>
<td>0.4790</td>
<td>-0.3886</td>
<td>1.0598</td>
<td>0.043</td>
</tr>
<tr>
<td>H24</td>
<td>0.4236</td>
<td>-0.3588</td>
<td>0.8639</td>
<td>0.044</td>
</tr>
<tr>
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<td>0.2775</td>
<td>-0.1235</td>
<td>0.7766</td>
<td>0.034</td>
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Table 6. Anisotropic displacement parameters ($\text{Å}^2$) for 3a. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 (h^2 a^* U_{11} + ... + 2 h k b^* U_{12})$.

<table>
<thead>
<tr>
<th>Atom</th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{23}$</th>
<th>$U_{13}$</th>
<th>$U_{12}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.0497(14)</td>
<td>0.0323(12)</td>
<td>0.0234(11)</td>
<td>-0.0032(9)</td>
<td>-0.0093(10)</td>
<td>-0.0083(10)</td>
</tr>
<tr>
<td>N1</td>
<td>0.0310(9)</td>
<td>0.0231(8)</td>
<td>0.0220(9)</td>
<td>0.0020(7)</td>
<td>-0.0067(7)</td>
<td>-0.0065(7)</td>
</tr>
<tr>
<td>C2</td>
<td>0.0317(11)</td>
<td>0.0200(9)</td>
<td>0.0268(11)</td>
<td>0.0032(8)</td>
<td>-0.0073(9)</td>
<td>-0.0067(8)</td>
</tr>
<tr>
<td>C3</td>
<td>0.0263(10)</td>
<td>0.0196(9)</td>
<td>0.0258(10)</td>
<td>0.0027(8)</td>
<td>-0.0065(8)</td>
<td>-0.0058(8)</td>
</tr>
<tr>
<td>C4</td>
<td>0.0247(10)</td>
<td>0.0229(9)</td>
<td>0.0236(10)</td>
<td>0.0034(8)</td>
<td>-0.0057(8)</td>
<td>-0.0060(8)</td>
</tr>
<tr>
<td>O4</td>
<td>0.0467(10)</td>
<td>0.0301(8)</td>
<td>0.0260(8)</td>
<td>0.0033(6)</td>
<td>-0.0123(7)</td>
<td>-0.0068(7)</td>
</tr>
<tr>
<td>C5</td>
<td>0.0396(12)</td>
<td>0.0246(10)</td>
<td>0.0252(11)</td>
<td>0.0075(8)</td>
<td>-0.0113(9)</td>
<td>-0.0106(9)</td>
</tr>
<tr>
<td>O5</td>
<td>0.0693(13)</td>
<td>0.0294(8)</td>
<td>0.0496(11)</td>
<td>0.0121(8)</td>
<td>-0.0308(10)</td>
<td>-0.0209(8)</td>
</tr>
<tr>
<td>C6</td>
<td>0.0442(13)</td>
<td>0.0241(10)</td>
<td>0.0291(11)</td>
<td>0.0070(9)</td>
<td>-0.0111(10)</td>
<td>-0.0076(10)</td>
</tr>
<tr>
<td>C7</td>
<td>0.0407(13)</td>
<td>0.0254(10)</td>
<td>0.0226(10)</td>
<td>0.0017(8)</td>
<td>-0.0071(9)</td>
<td>-0.0082(9)</td>
</tr>
<tr>
<td>C11</td>
<td>0.0378(12)</td>
<td>0.0238(10)</td>
<td>0.0212(10)</td>
<td>0.0004(8)</td>
<td>-0.0085(9)</td>
<td>-0.0029(9)</td>
</tr>
<tr>
<td>C12</td>
<td>0.0456(14)</td>
<td>0.0406(13)</td>
<td>0.0375(13)</td>
<td>0.0126(11)</td>
<td>-0.0171(11)</td>
<td>-0.0132(11)</td>
</tr>
<tr>
<td>C13</td>
<td>0.0676(19)</td>
<td>0.0456(15)</td>
<td>0.0454(15)</td>
<td>0.0220(12)</td>
<td>-0.0290(14)</td>
<td>-0.0137(14)</td>
</tr>
<tr>
<td>C14</td>
<td>0.0500(16)</td>
<td>0.0486(15)</td>
<td>0.0471(15)</td>
<td>0.0028(12)</td>
<td>-0.0260(13)</td>
<td>0.0027(13)</td>
</tr>
<tr>
<td>C15</td>
<td>0.0344(13)</td>
<td>0.0532(15)</td>
<td>0.0384(14)</td>
<td>-0.0117(12)</td>
<td>-0.0086(11)</td>
<td>-0.0049(11)</td>
</tr>
<tr>
<td>C16</td>
<td>0.0432(14)</td>
<td>0.0323(12)</td>
<td>0.0269(11)</td>
<td>-0.0021(9)</td>
<td>-0.0048(10)</td>
<td>-0.0093(10)</td>
</tr>
<tr>
<td>C21</td>
<td>0.0235(10)</td>
<td>0.0234(10)</td>
<td>0.0226(10)</td>
<td>0.0012(8)</td>
<td>-0.0043(8)</td>
<td>-0.0068(8)</td>
</tr>
<tr>
<td>C22</td>
<td>0.0326(11)</td>
<td>0.0274(11)</td>
<td>0.0243(10)</td>
<td>0.0064(8)</td>
<td>-0.0107(9)</td>
<td>-0.0036(9)</td>
</tr>
<tr>
<td>C23</td>
<td>0.0415(13)</td>
<td>0.0232(11)</td>
<td>0.0348(12)</td>
<td>0.0069(9)</td>
<td>-0.0111(10)</td>
<td>0.0014(10)</td>
</tr>
<tr>
<td>C24</td>
<td>0.0459(14)</td>
<td>0.0221(10)</td>
<td>0.0340(12)</td>
<td>-0.0040(9)</td>
<td>-0.0059(11)</td>
<td>0.0006(10)</td>
</tr>
<tr>
<td>C25</td>
<td>0.0337(12)</td>
<td>0.0256(10)</td>
<td>0.0217(10)</td>
<td>0.0015(8)</td>
<td>-0.0042(9)</td>
<td>-0.0046(9)</td>
</tr>
<tr>
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<td>0.0244(10)</td>
<td>0.0212(9)</td>
<td>0.0236(10)</td>
<td>0.0048(8)</td>
<td>-0.0076(8)</td>
<td>-0.0065(8)</td>
</tr>
</tbody>
</table>
Table 7. Bond lengths (Å) and angles (deg) for 3a.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length/Angle</th>
</tr>
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<tbody>
<tr>
<td>C1-N1</td>
<td>1.457(3)</td>
</tr>
<tr>
<td>C1-H1A</td>
<td>0.9800</td>
</tr>
<tr>
<td>C1-H1B</td>
<td>0.9800</td>
</tr>
<tr>
<td>C1-H1C</td>
<td>0.9800</td>
</tr>
<tr>
<td>N1-C2</td>
<td>1.350(2)</td>
</tr>
<tr>
<td>N1-C21</td>
<td>1.391(3)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.386(3)</td>
</tr>
<tr>
<td>C2-H2</td>
<td>0.9500</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.436(3)</td>
</tr>
<tr>
<td>C3-C26</td>
<td>1.452(3)</td>
</tr>
<tr>
<td>C4-O4</td>
<td>1.225(3)</td>
</tr>
<tr>
<td>C4-C5</td>
<td>1.539(3)</td>
</tr>
<tr>
<td>C5-O5</td>
<td>1.213(3)</td>
</tr>
<tr>
<td>C5-C6</td>
<td>1.456(3)</td>
</tr>
<tr>
<td>C6-C7</td>
<td>1.198(3)</td>
</tr>
<tr>
<td>C7-C11</td>
<td>1.437(3)</td>
</tr>
<tr>
<td>C11-C16</td>
<td>1.387(3)</td>
</tr>
<tr>
<td>C11-C12</td>
<td>1.399(3)</td>
</tr>
<tr>
<td>C12-C13</td>
<td>1.387(3)</td>
</tr>
<tr>
<td>C12-H12</td>
<td>0.9500</td>
</tr>
<tr>
<td>C13-C14</td>
<td>1.377(4)</td>
</tr>
<tr>
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</tr>
<tr>
<td>C14-C15</td>
<td>1.381(4)</td>
</tr>
<tr>
<td>C14-H14</td>
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</tr>
<tr>
<td>C15-C16</td>
<td>1.388(3)</td>
</tr>
<tr>
<td>C15-H15</td>
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</tr>
<tr>
<td>C16-H16</td>
<td>0.9500</td>
</tr>
<tr>
<td>C21-C22</td>
<td>1.396(3)</td>
</tr>
<tr>
<td>C21-C26</td>
<td>1.417(3)</td>
</tr>
<tr>
<td>C22-C23</td>
<td>1.373(3)</td>
</tr>
<tr>
<td>C22-H22</td>
<td>0.9500</td>
</tr>
<tr>
<td>C23-C24</td>
<td>1.399(3)</td>
</tr>
<tr>
<td>C23-H23</td>
<td>0.9500</td>
</tr>
<tr>
<td>C24-C25</td>
<td>1.393(3)</td>
</tr>
<tr>
<td>C24-H24</td>
<td>0.9500</td>
</tr>
<tr>
<td>C25-C26</td>
<td>1.386(3)</td>
</tr>
<tr>
<td>C25-H25</td>
<td>0.9500</td>
</tr>
<tr>
<td>N1-C1-H1A</td>
<td>109.5</td>
</tr>
<tr>
<td>N1-C1-H1B</td>
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<tr>
<td>H1A-C1-H1B</td>
<td>109.5</td>
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<tr>
<td>N1-C1-H1C</td>
<td>109.5</td>
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<tr>
<td>H1A-C1-H1C</td>
<td>109.5</td>
</tr>
<tr>
<td>C2-N1-C21</td>
<td>109.22(16)</td>
</tr>
<tr>
<td>C2-N1-C1</td>
<td>125.76(18)</td>
</tr>
<tr>
<td>C21-N1-C1</td>
<td>124.88(16)</td>
</tr>
<tr>
<td>N1-C2-C3</td>
<td>110.25(18)</td>
</tr>
<tr>
<td>N1-C2-H2</td>
<td>124.9</td>
</tr>
<tr>
<td>C3-C2-H2</td>
<td>124.9</td>
</tr>
<tr>
<td>C2-C3-C4</td>
<td>126.74(18)</td>
</tr>
<tr>
<td>C2-C3-C26</td>
<td>106.68(16)</td>
</tr>
<tr>
<td>C4-C3-C26</td>
<td>126.45(19)</td>
</tr>
<tr>
<td>O4-C4-C3</td>
<td>125.52(19)</td>
</tr>
<tr>
<td>O4-C4-C5</td>
<td>117.10(17)</td>
</tr>
<tr>
<td>C3-C4-C5</td>
<td>117.34(18)</td>
</tr>
<tr>
<td>O5-C5-C6</td>
<td>120.96(19)</td>
</tr>
<tr>
<td>O5-C5-C4</td>
<td>122.60(18)</td>
</tr>
<tr>
<td>C6-C5-C4</td>
<td>116.35(19)</td>
</tr>
<tr>
<td>C7-C6-C5</td>
<td>172.5(2)</td>
</tr>
<tr>
<td>C6-C7-C11</td>
<td>178.7(2)</td>
</tr>
<tr>
<td>C16-C11-C12</td>
<td>119.8(2)</td>
</tr>
<tr>
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<td>Angle (°)</td>
</tr>
<tr>
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<tr>
<td>C16-C11-C7</td>
<td>120.12(19)</td>
</tr>
<tr>
<td>C12-C11-C7</td>
<td>120.1(2)</td>
</tr>
<tr>
<td>C13-C12-C11</td>
<td>119.1(3)</td>
</tr>
<tr>
<td>C13-C12-H12</td>
<td>120.4</td>
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<tr>
<td>C11-C12-H12</td>
<td>120.4</td>
</tr>
<tr>
<td>C14-C13-C12</td>
<td>120.8(2)</td>
</tr>
<tr>
<td>C14-C13-H13</td>
<td>119.6</td>
</tr>
<tr>
<td>C12-C13-H13</td>
<td>119.6</td>
</tr>
<tr>
<td>C13-C14-C15</td>
<td>120.2(2)</td>
</tr>
<tr>
<td>C13-C14-H14</td>
<td>119.9</td>
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<tr>
<td>C15-C14-H14</td>
<td>119.9</td>
</tr>
<tr>
<td>C14-C15-C16</td>
<td>119.9(3)</td>
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<tr>
<td>C14-C15-H15</td>
<td>120.1</td>
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<tr>
<td>C16-C15-H15</td>
<td>120.1</td>
</tr>
<tr>
<td>C11-C16-C15</td>
<td>120.2(2)</td>
</tr>
<tr>
<td>C11-C16-H16</td>
<td>119.9</td>
</tr>
<tr>
<td>C15-C16-H16</td>
<td>119.9</td>
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<tr>
<td>N1-C21-C22</td>
<td>129.43(19)</td>
</tr>
<tr>
<td>N1-C21-C26</td>
<td>108.10(16)</td>
</tr>
<tr>
<td>C22-C21-C26</td>
<td>122.5(2)</td>
</tr>
<tr>
<td>C23-C22-C21</td>
<td>116.87(19)</td>
</tr>
<tr>
<td>C23-C22-H22</td>
<td>121.6</td>
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<td>C21-C22-H22</td>
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<td>C22-C23-C24</td>
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<tr>
<td>C22-C23-H23</td>
<td>119.1</td>
</tr>
<tr>
<td>C24-C23-H23</td>
<td>119.1</td>
</tr>
<tr>
<td>C25-C24-C23</td>
<td>121.3(2)</td>
</tr>
<tr>
<td>C25-C24-H24</td>
<td>119.4</td>
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<tr>
<td>C23-C24-H24</td>
<td>119.4</td>
</tr>
<tr>
<td>C26-C25-C24</td>
<td>118.33(19)</td>
</tr>
<tr>
<td>C26-C25-H25</td>
<td>120.8</td>
</tr>
<tr>
<td>C24-C25-H25</td>
<td>120.8</td>
</tr>
<tr>
<td>C25-C26-C21</td>
<td>119.29(17)</td>
</tr>
<tr>
<td>C25-C26-C3</td>
<td>134.97(18)</td>
</tr>
<tr>
<td>C21-C26-C3</td>
<td>105.74(18)</td>
</tr>
</tbody>
</table>
Figure 1. X-ray analysis of compound 3a.
Short experimental part: orange crystal (polyhedron), dimensions 0.31 x 0.20 x 0.11 mm$^3$, crystal system triclinic, space group P $\overline{1}$, Z = 2, a = 7.1512(15) Å, b = 9.500(2) Å, c = 11.479(3) Å, alpha = 82.834(4) deg, beta = 78.622(4) deg, gamma = 71.956(4) deg, V = 725.3(3) Å$^3$, rho = 1.316 g/cm$^3$, T = 200(2) K, Theta$^\text{max}$ = 28.38 deg, radiation Mo Kalpha, lambda = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 7335 reflections measured, 3564 unique (R(int) = 0.1129), 2655 observed (I > 2\sigma(I)), intensities were corrected for Lorentz and polarization effects, no empirical absorption correction was applied, due to the low absorption of the crystal and the low redundancy of the data, mu = 0.09 mm$^{-1}$, T$^\text{min}$ = 0.97, T$^\text{max}$ = 0.99, structure solved by direct methods and refined against F$^2$ with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (6.10) software package$^2$, 200 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.11 for observed reflections, final residual values R1(F) = 0.075, wR(F$^2$) = 0.159 for observed reflections, residual electron density -0.32 to 0.29 eÅ$^{-3}$. CCDC 796698 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Lit. 1: (program SADABS 2008/1 for absorption correction)
G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2008

Lit. 2: (software package SHELXTL 2008/1 for structure solution and refinement)
9. Nucleophilicity Parameters of Substrates

*Table 8.* Estimation of nucleophilicity parameters $N$ of substrates successfully converted to ynediones.

<table>
<thead>
<tr>
<th>Reference nucleophile with known parameter $N$</th>
<th>Parameter $N^{[a]}$</th>
<th>Substrates similar to or identical with the reference nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="benzimidazole" /></td>
<td>5.75</td>
<td><img src="image" alt="benzimidazole" /> $R = \text{Me, Bn}$</td>
</tr>
<tr>
<td><img src="image" alt="quinoxaline" /></td>
<td>3.87</td>
<td><img src="image" alt="quinoxaline" /> $R = \text{Bn, PMB}$</td>
</tr>
<tr>
<td><img src="image" alt="pyridine" /></td>
<td>5.85</td>
<td><img src="image" alt="pyridine" /> $R = \text{Me, Bn}$</td>
</tr>
<tr>
<td><img src="image" alt="pyrrole" /></td>
<td>3.12</td>
<td><img src="image" alt="pyrrole" /> TIPS</td>
</tr>
<tr>
<td><img src="image" alt="pyrazole" /></td>
<td>3.61</td>
<td><img src="image" alt="pyrazole" /></td>
</tr>
<tr>
<td><img src="image" alt="thiophene" /></td>
<td>1.26</td>
<td><img src="image" alt="thiophene" /> $R = \text{OMe, O(CH_2)_2O}$</td>
</tr>
<tr>
<td><img src="image" alt="fluorene" /></td>
<td>6.66</td>
<td><img src="image" alt="fluorene" /></td>
</tr>
</tbody>
</table>

[a] The parameters refer to reactions in CH$_2$Cl$_2$ at 20 °C.
10. References


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Consecutive Three-Component Synthesis of Yrones by Decarbonylative Sonogashira Coupling

Eugen Merkul,[a] Thomas Oeser,[b] and Thomas J. J. Müller*[a]

Dedicated to Armin de Meijere on the occasion of his 70th birthday

Alkynones are important intermediates in organic syntheses,[1] and due to their bifunctional electrophilicity they have found broad application as three-carbon building blocks in heterocyclic synthesis. Therefore, efficient, mild, and catalytic methodologies for their preparation are highly desirable. Besides catalytic acylations of terminal alkynes following the Sonogashira protocol represents an elegant three-component synthesis of alkynones, which were as well elaborated into one-pot syntheses of pharmaceutically relevant heterocycles such as pyrazoles[2] and pyrimidines.[3]

Carbonylations of aryl halides usually require carbon monoxide or molybdenum hexacarbonyl as suitable CO sources. However, the effective concentration of CO in the reaction medium plays a crucial role for the outcome of carbonylative alkynylation. An alternative mode, which also dispenses the use of aryl halides, could be a decarbonylation of an α-dicarbonyl compound. Rhodium-mediated decarbonylations of aldehydes (Tsuji–Wilkinson reaction) are well preceded,[4] however, the process becomes catalytic only at temperatures over 200°C and most applications in total syntheses have remained stoichiometric.[5] Decarbonylations of acid chlorides are less common.[6] In 2002, iridium-catalyzed decarbonylative homologizations of aryl chlorides in boiling xylene were reported.[7] Palladium complexes are not commonly used for decarbonylations. Besides decarbonylative carbostannylations,[10] Gooßen has reported decarbonylative Heck reactions with reaction times of 16 h at 160°C in NMP as a solvent.[11] Just recently, the same group has introduced Pd/Cu-catalyzed decarboxylative cross-couplings of α-oxocarboxylates with aromatic bromides[12] and chlorides[13] at high temperatures and long reaction times. Interestingly, although oxalyl chloride has been applied in the presence of aluminium chloride as a phosgene surrogate for Friedel–Crafts acylations[14] or as a source of carbon monoxide in stoichiometric copper-mediated synthesis of cyclopentadienones from organolithium and organozirconium compounds,[15] there is no report of its use in any catalytic application.

In continuation of our program to develop transition metal catalyzed multicomponent syntheses of heterocycles[16] and functional organic materials,[17] we report our first findings on consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling starting from electron-rich heterocycles and oxalyl chloride as a source of the CO building block via intermediary glyoxyxyl chlorides. Conceptually, this methodology complements the carbonylative alkynylation of halides of heterocycles with diminished electron density.[5]

It has been known for quite some time that many indole derivatives directly and without Lewis acid activation react with oxalyl chloride in a Friedel–Crafts acylation to furnish indole-3-glyoxylyl chlorides 1 in high yields.[18] Due to the generality and smoothness of this glyoxylation the idea was now to use the notoriously unstable and reactive indole-3-glyoxylyl chlorides 1 as synthetic equivalents of acid chlorides in transition metal catalyzed cross-coupling reactions. Therefore, for establishing a decarbonylative alkynylation we first tested indole-3-glyoxylyl chlorides 1 without substitution (1a) and with a benzyl substituent (1b) on the indole nitrogen atom in a model reaction with 1-hexyne (2a) under modified Sonogashira conditions[19] (Scheme 1, Table 1). Immediately, it was apparent that only the benzyl derivative 1b can be transformed into the corresponding alkynone 3b (entries 3–9).
Although the desired alkynone 3b could be immediately detected by TLC monitoring of the reaction it was only isolable if the formation of the non-decarbonylated byproduct could be suppressed. Therefore, the influence of the ratios of the substrates, the catalysts and the solvent were studied qualitatively. Besides spectroscopic and combustion analytical characterization the structure of compound 3b was unambiguously corroborated by an X-ray structure analysis (Figure 1).[20]

The most crucial point for the successful transformation and high conversion is the well-balanced equimolar ratio of [PdCl₂(PPh₃)₂] and CuI (entries 5, 8, and 9). Dimethoxyethane (DME) and THF are both good solvents. Performing the reaction under a CO atmosphere to block the decarbonylation resulted in the formation of the ynone (entry 6), whereas the addition of 2 mol% of PPh₃ completely stopped the conversion (entry 10). Switching the palladium catalyst precursor to [PdCl₂(dppf)] did not result in ynone formation (entry 12). Therefore, the most favorable conditions for the development of a sequence with the decarbonylative Sonogashira coupling suggest the use of an equimolar ratio of glyoxylyl chloride 1b and alkyne 2a giving a clean reaction and 70% isolated yield of alkynone 3b (entry 9). Hence, the mechanistic rationale of this new decarbonylative Sonogashira coupling can be rationalized as follows (Scheme 2).

After the oxidative addition of indole-3-glyoxylyl chloride (1), adduct 4 undergoes a migratory de-insertion and elimination of carbon monoxide furnishing the acyl-Pd species 5. The driving force of this reaction is the apparent relative instability of the dicarbonyl species 4 compared with the acyl species 5. Then, transmetallation of the in situ generated copper acetylide to 5 gives rise to the formation of the acylalkynyl-Pd complex 6, which undergoes reductive elimination to give the alkynone 3 and the catalytically active Pd species to start a new catalytic cycle.

Encouraged by these initial successful experiments we decided to combine the formation of relatively labile glyoxylyl chloride 1 and the subsequent decarbonylative alkynylation to a consecutive three-component reaction in a one-pot transformation. Indeed, N-substituted indoles (X = CH) and 7-aza-indoles (X = N) 7 or pyrroles 8 were glyoxylated with oxalyl chloride in THF or DME on a 5 mmol scale and the transient glyoxylyl chlorides 1 were reacted with equimolar amounts of the alkynes 2 for 1 h at room temperature.
for 1–48 h in the presence of two equivalents of triethylamine and catalytic amounts of [PdCl₂(PPh₃)₂] and CuI to give the corresponding alkynones 3 and 9 in moderate to good yields (Scheme 3, Table 2). The presence of two stoichiometrically necessary equivalents of triethylamine assures that the hydrogen chloride formed upon glyoxylation is bound and that the decarbonylative Sonogashira coupling occurs by scavenging the hydrochloric acid from the catalytic cycles. Expectedly, as a consequence of the regioselective glyoxylation of pyrroles in the 2-position the ynones 9 were obtained by the same protocol, simultaneously illustrating the methodological potential for the application to electron-rich π systems.

Scheme 3. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones 3 and 9;

With this versatile alkynone synthesis in hand, we tested the application of the products in pyrimidine synthesis. As previously shown, 4-(indol-3-yl)- and 4-(7-aza-indol-3-yl)-2-amino pyrimidines, which are structurally related to the marine natural products class of meridianins, have displayed a considerable potential as kinase inhibitors. Therefore,

Table 2. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones 3 and 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Substituted indole or 7-aza-indole 7</th>
<th>Alkyne 2</th>
<th>Ynone 3 (isolated yield/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X=CH, R¹=Si(iPr)₃</td>
<td>2a:</td>
<td>3a: (43)⁹</td>
</tr>
<tr>
<td>2</td>
<td>X=CH, R¹=Bn</td>
<td>2a:</td>
<td>3b: (74)⁹</td>
</tr>
<tr>
<td>3</td>
<td>X=CH, R²=CH₂OMe</td>
<td>2b:</td>
<td>3c: (66)⁹</td>
</tr>
<tr>
<td>4</td>
<td>X=CH, R¹=Bn</td>
<td>2c:</td>
<td>3d: (85)⁹</td>
</tr>
<tr>
<td>5</td>
<td>X=CH, R²=SiMe₃</td>
<td>2d:</td>
<td>3e: (76)⁹</td>
</tr>
<tr>
<td>6</td>
<td>X=CH, R¹=Me</td>
<td>2d:</td>
<td>3f: (64)⁹</td>
</tr>
<tr>
<td>7</td>
<td>X=CH, R¹=Me</td>
<td>2a:</td>
<td>3g: (45)⁹</td>
</tr>
<tr>
<td>8</td>
<td>X=N, R¹=Me</td>
<td>2a:</td>
<td>3b: (63)⁹</td>
</tr>
<tr>
<td>9</td>
<td>X=N, R¹=Bn</td>
<td>2c:</td>
<td>3i: (61)⁹</td>
</tr>
<tr>
<td>10</td>
<td>R¹=Me</td>
<td>2a:</td>
<td>9a: (61)⁹</td>
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</tbody>
</table>
upon reacting indolyl (X = CH) and 7-aza-indolyl (X = N) substituted alkynes 3 or the pyrrolyl ynones 9 with an excess of guanidinium hydrochloride (10) and potassium carbonate in 2-methoxyethanol at 120 °C for 12–24 h the 2-amino pyrimidines 11 were obtained in good to excellent yields (Scheme 4, Table 3). Compounds 11e and 11f can be considered as N-alkyl derivatives of the naturally occurring meridianin G.21 The structures of the 2-amino pyrimidines 11 were unambiguously supported by NMR spectroscopy and mass spectrometry, and later by an X-ray structure analysis of compound 11b (Figure 2).20

In conclusion, we have disclosed a new consecutive three-component synthesis of alkynes by glyoxylation of very easily accessible indole, 7-aza-indole, and pyrrole derivatives with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation of the heteroaryl glyoxyl chloride with terminal alkynes. This new Sonogashira protocol proceeds considerably faster than carbonylative alkynyations of (hetero)aryl iodides with carbon monoxide5 and a lower catalyst loading is needed. The mild conditions for decarbonylations are unprecedented, and the reagents are only applied in equimolar quantities with a high tolerance for various substituents. The application of the alkynes in a subsequent transformation to pyrimidines also illustrates the
vast potential to diversity-oriented syntheses of heterocycles. Studies expanding the scope of this novel access to alkyrones and their elaboration towards multi-component syntheses of heterocycles are currently underway. In addition, the stage has been set for the methodological expansion to further decarboxylative cross-couplings that are currently under investigation.

**Experimental Section**

**General methods** and further reactions are given in the Supporting Information.

**Three-component synthesis of alkynone 3b:** N-Benzyl-1H-indole (7a) (1.04 g, 5.00 mmol) in dry THF (25 mL) was placed under argon in a screw-cap vessel with septum, degassed with argon and cooled to 0°C (waterice). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0°C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, [PdCl2(PPh3)2] (35 mg, 0.05 mmol), Cul (10 mg, 0.05 mmol), 1-hexyne (2a) (0.59 mL, 5.00 mmol), and dry triethylamine (1.39 mL, 10.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. The evolution of CO can be observed. After complete conversion (monitored by TLC) saturated brine (25 mL) was added, and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with hexanes/ethyl acetate to give the alky none 3b (1.17 g, 74%) as a yellow solid. M.p. 84–85°C; 1H NMR (300 MHz, CDCl3, 25°C, TMS): 6 = 8.40–8.33 (m, 1H), 7.84 (s, 1H), 7.35–7.18 (m, 6H), 7.18–7.11 (m, 6H); 13C NMR (75 MHz, CDCl3, 25°C, TMS): 127.9 (CH), 126.9 (CH), 126.3 (C), 121.7 (CH), 119.0 (C), 110.3 (CH), 91.0 (C), 80.6 (C), 50.9 (CH), 30.0 (CH), 22.1 (CH), 18.7 (CH), 13.6 ppm (CH); El-MS: m/z (%): 315 (100) [M+], 91 (40) [CH3]+; IR (KB): v = 730, 752, 781, 827, 1124, 1360, 1400, 1453, 1465, 1486, 1495, 1522, 1576, 1607, 2226, 2870, 2932, 2955 3191 cm−1; elemental analysis calcd (%) for C7H5NO: C 83.78, H 6.71, N 4.44; found: C 83.64, H 6.71, N 4.43.

**2-Aminopyrimidines 11b:** In a screw-cap vessel under argon the alky none 3b (315 mg, 1.00 mmol) was dissolved in 2-methoxyethanol (5 mL). Then, potassium carbonate (346 mg, 2.50 mmol), and guanidinium hydrochloride (10) (239 mg, 2.50 mmol) were added and the mixture was stirred at 120°C over night. Then, after cooling to room temperature saturated brine (20 mL) was added, and the mixture was extracted with dichloromethane (5 x 20 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with di chloromethane and...dichloromethane/methanol/aqueous ammonia (100:1:1) to give the 2-aminopyrimidine 11b (305 mg, 86%) as a pale yellow solid. M.p. 174–175°C; 1H NMR (300 MHz, CDCl3, 27°C, TMS): 6 = 8.40–8.33 (m, 1H), 7.84 (s, 1H), 7.35–7.18 (m, 6H), 7.18–7.11 (m, 2H), 6.89 (s, 1H), 5.35 (s, 2H), 5.05 (s, 2H, NH2), 2.60 (s, t, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.42 (s, t, J = 7.5 Hz, 2H), 0.95 ppm (t, J = 7.5 Hz, 3H); 13C NMR (75 MHz, CDCl3, 27°C, TMS): 315 (C), 163.1 (C), 162.5 (C), 137.4 (C), 136.5 (C), 130.3 (CH), 127.9 (CH), 126.9 (CH), 126.3 (C), 127.1 (CH), 121.2 (CH), 114.8 (C), 110.3 (CH), 106.4 (CH), 50.5 (CH), 37.8 (CH), 31.2 (CH), 22.6 (CH), 14.0 ppm (CH); El-MS: m/z (%): 356 (27) [M•]+, 341 (3) [M•–CH3], 288 (7) [M•–CH2•], 314 (100) [M•–CH2•], 223 (5) [M•–C2H5], 91 (14) [CH3]+; IR (KB): v = 743, 715, 1385, 1456, 1469, 1521, 1577, 1628, 1645, 2800, 2927, 2956, 3442, 3463 cm−1; elemental analysis calcd (%) for C7H5NO•C77.50, H 6.79, N 4.44; found: C 77.50, H 6.75, N 15.77.

**Acknowledgements**

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**Keywords:** acylation · alkyrones · C–C coupling · multicomponent reactions · pyrimidines

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Decarbonylative Sonogashira Coupling

[20] CCDC 710258 (3b) and CCDC 710259 (11b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Consecutive Three-Component Synthesis of Ynones by Decarbonylative Sonogashira Coupling

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3.10. 4-(1-Benzyl-1H-pyrrolo-2-yl)-6-phenylpyrimid-2-yl-amine (11j) 29

4. \(^1\)H and \(^{13}\)C MNR Spectra of Compounds 3a-l, 9a-b, and 11a-j 30

5. Crystallographic Data of Compounds 3b and 11b 76
1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using MBraun system MB-SPS-800, dry DME was purchased from Aldrich and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

The starting materials were prepared according to literature procedures: 1-Benzyl-1H-indole (7b),[1] 1-Benzyl-1H-pyrrolo[2,3-b]pyridine (7d),[1] 1-Methyl-1H-pyrrolo[2,3-b]pyridine (7e),[1] 1-(Triisopropylsilyl)-1H-indole (7a),[2][3] (1-Benzyl-1H-indol-3-yl)-oxoacetylchloride (1b).[4] 1-Methyl-1H-indole (7c) is commercially available by Merck Serono KGaA. Commercial grade reagents were used as supplied without further purification and were purchased from Acros Organics N. V., Aldrich Chemie GmbH, Fluka AG, ACR GmBH & Co. KG, Riedel-de Haën, BRL and Merck Serono KGaA.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from Merck Serono KGaA Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F254 5 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

1H, 13C, and 135-DEPT NMR spectra were recorded on Bruker DRX 300 and DRX 500 spectrometers. CDCl3, acetone-d6 and DMSO-d6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standard (CDCl3: 1H δ 7.24, 13C δ 77.2; acetone-d6: 1H δ 2.05, 13C δ 29.9/206.7; DMSO-d6: 1H δ 2.50, 13C δ 39.5). The multiplicities of signals were abbreviated as follows: s: singulett; d: dublett; t: triplett; q: quartett; quint: quintett; sext: sextett, dd: dublett of dubletts, dt: dublett of tripletts, td: triplett of dubletts, m: multiplett and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Varian MAT 311 A and Finnigan MAT 8200. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out in the
microanalytical laboratory of the Organisch-Chemisches Institut der Universität Heidelberg and in the microanalytical laboratory of Institut für Pharmazeutische Chemie in Düsseldorf.

X-ray structures were measured on Bruker Smart APEX and Bruker Smart CCD.

**Crystal data:** Compound 3b: Colorless crystal (irregular), dimensions 0.27 x 0.07 x 0.05 mm³, crystal system monoclinic, space group P2₁/n, Z = 4, a = 12.616(1) Å, b = 7.4046(9) Å, c = 19.386(2) Å, α = 90.0 deg, β = 104.449(3) deg, γ = 90.0 deg, V = 1753.8(4) Å³, D = 1.195 g/cm³, T = 200(2) K, θ_max = 22.46 deg, radiation Mo K, D = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 10845 reflections measured, 2278 unique (R(int) = 0.046), 1771 observed (I > 2σ(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS (program SADABS V2.03 for absorption correction, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001) based on the Laue symmetry of the reciprocal space, μ = 0.07 mm⁻¹, T_min = 0.98, T_max = 1.00, structure solved by direct methods and refined against F² with a Full-matrix least-squares algorithm using the SHELXTL (6.12) software package (software package SHELXTL V6.12 for structure solution and refinement, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001), 301 parameters refined, hydrogen atoms were refined isotropically, goodness of fit 1.06 for observed reflections, final residual values R1(F) = 0.039, wR(F²) = 0.083 for observed reflections, residual electron density -0.14 to 0.12 eÅ⁻³. Compound 11b: colorless crystal (polyhedron), dimensions 0.50 x 0.14 x 0.10 mm³, crystal system triclinic, space group P T, Z = 2, a = 6.4203(3) Å, b = 10.0329(4) Å, c = 15.2326(7) Å, α = 98.2440(10) deg, β = 91.0590(10) deg, γ = 90.5330(10) deg, V = 970.82(7) Å³, D = 1.219 g/cm³, T = 200(2) K, θ_max = 27.48 deg, radiation Mo K, D = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 9852 reflections measured, 4397 unique (R(int) = 0.034), 2913 observed (I > 2σ(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS (program SADABS V2.03 for absorption correction, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001) based on the Laue symmetry of the reciprocal space, μ = 0.07 mm⁻¹, T_min = 0.98, T_max = 0.99, structure solved by direct methods and refined against F² with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (5.10) software package (software package SHELXTL V5.10 for structure solution and refinement, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 1997), 254 parameters refined, hydrogen atoms were treated using appropriate riding models, except of the hydrogen atoms of N23, which were refined isotropically, goodness of fit 1.02 for observed reflections, final residual values R1(F) = 0.048, wR(F²) = 0.101 for observed reflections, residual electron density -0.17 to 0.24 eÅ⁻³.
2. Three-Component Glyoxylation-Decarbonylative Alkynylation Synthesis of Alkynones 3 and 9

5.00 mmol of \(N\)-substituted \(1H\)-(7-aza)indole 7 or pyrrole 8 in dry THF (25 mL) were placed under argon in a screw-cap vessel with septum, degassed with argon and cooled to 0 °C (water/ice). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, \(\text{PdCl}_2(\text{PPh}_3)_2\) (35 mg, 0.05 mmol), \(\text{CuI}\) (10 mg, 0.05 mmol), 5.00 mmol of terminal alkyne 2 and dry triethylamine (1.39 mL, 10.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. The evolution of CO can be observed. After complete conversion (the evolution of CO ceased, the product formation was monitored by TLC) saturated brine (25 mL) was added, and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with hexanes/ethylacetate or petrolether (boiling range 40-60 °C)/ethyl acetate to give the alkynones 3 or 9 (For experimental details see Table 1).
Table 1. Experimental details of the three-component glyoxylatation-decarbonylative alkynylation synthesis of ynones 3 and 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-substituted (7-aza)indole 7 or pyrrole 8</th>
<th>Alkyne 2</th>
<th>Ynone 3 or 9 (isolated yield %)</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R_f (eluent)</td>
</tr>
<tr>
<td>1</td>
<td>1.37 g (5.00 mmol) of 7a</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>479 mg (43 %)^[a] of 3a</td>
<td>DCM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R_f (DCM) : 0.26</td>
</tr>
<tr>
<td>2</td>
<td>1.04 g (5.00 mmol) of 7b</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>1.17 g (74 %) of 3b</td>
<td>HE-EE = 10:1 → 6:1</td>
</tr>
<tr>
<td>3</td>
<td>1.04 g (5.00 mmol) of 7b</td>
<td>0.44 mL (5.00 mmol) of 2b</td>
<td>1.00 g (66 %) of 3c</td>
<td>PE-EE = 7:1 → 5:1 → 3:1</td>
</tr>
<tr>
<td>4</td>
<td>1.04 g (5.00 mmol) of 7b</td>
<td>0.56 mL (5.00 mmol) of 2c</td>
<td>1.42 g (85 %) of 3d</td>
<td>R_f (PE-EE = 3:1) : 0.19</td>
</tr>
<tr>
<td>5</td>
<td>1.04 g (5.00 mmol) of 7b</td>
<td>0.73 mL (5.00 mmol) of 2d</td>
<td>1.27 g (76 %) of 3e</td>
<td>PE-EE = 10:1 → 7:1 → 5:1</td>
</tr>
<tr>
<td>6</td>
<td>676 mg (5.00 mmol) of 7c</td>
<td>0.73 mL (5.00 mmol) of 2d</td>
<td>819 mg (64 %) of 3f</td>
<td>R_f (PE-EE = 8:1) : 0.31</td>
</tr>
<tr>
<td>7</td>
<td>1.37 g (5.00 mmol) of 7a</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>855 mg (45 %) of 3g</td>
<td>R_f (PE-EE = 6:1) : 0.23</td>
</tr>
<tr>
<td>8</td>
<td>1.04 g (5.00 mmol) of 7d</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>990 mg (63 %) of 3h</td>
<td>PE-EE = 100:1 → 50:1 → 20:1</td>
</tr>
<tr>
<td>9</td>
<td>661 mg (5.00 mmol) of 7e</td>
<td>0.56 mL (5.00 mmol) of 2c</td>
<td>793 mg (61 %) of 3i</td>
<td>R_f (PE-EE = 2:1) : 0.23</td>
</tr>
<tr>
<td>10</td>
<td>410 mg (5.00 mmol) of 8a</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>577 mg (61 %)^[d] of 9a</td>
<td>PE-EE = 20:1</td>
</tr>
<tr>
<td>11</td>
<td>0.79 mL (5.00 mmol) of 8b</td>
<td>0.59 mL (5.00 mmol) of 2a</td>
<td>574 mg (43 %)^[e] of 9b</td>
<td>R_f (PE-EE = 20:1) : 0.26</td>
</tr>
</tbody>
</table>

[a] After addition of 1.1 equiv of TBAF (1 M in THF) to the reaction mixture and stirring at room temperature for 5 min. the product 3a was obtained.

[b] The chromatographic purification was performed on the SP1 purification system of Biotage using a SNAP-cartridge (silica gel, 50 g). The TLC-method was applied using PE-EE gradient.

[c] The chromatographic purification was performed on the SP1 purification system of Biotage using a SNAP-cartridge (silica gel, 100 g). The TLC-method was applied using PE-EE gradient.

[d] The decarbonylative alkynylation step was carried out for 2 d.

[e] The decarbonylative alkynylation step was carried out overnight.
2.1. 1-(1H-Indol-3-yl)hept-2-yn-1-one (3a)

\[
\text{O} \quad \equiv \quad \begin{array}{c}
\text{C} \\
\text{H} \\
\text{C} \end{array}
\]

\text{C}_{15}\text{H}_{15}\text{NO}

225.29

479 m (43 \% yield) as a yellow solid. Mp. 108-109 °C. \(^1\)H NMR (DMSO-d\textsubscript{6}, 500 MHz): \(\delta\) 0.93 (t, \(J = 7.3\) Hz, 3 H), 1.45 (sext, \(J = 7.3\) Hz, 2 H), 1.59 (quint, \(J = 7.3\) Hz, 2 H), 2.50 (t, \(J = 7.3\) Hz, 2 H), 7.19-7.27 (m, 2 H), 7.51 (d, \(J = 8.2\) Hz, 1 H), 8.13 (dd, \(J = 7.6\) Hz, \(J = 0.6\) Hz, 1 H), 8.22 (d, \(J = 3.2\) Hz, 1 H), 12.2 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\textsubscript{6}, 125 MHz): \(\delta\) 13.4 (CH\textsubscript{3}), 17.8 (CH\textsubscript{2}), 21.5 (CH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 80.3 (C\textsubscript{quat}), 90.6 (C\textsubscript{quat}), 112.5 (CH), 118.2 (C\textsubscript{quat}), 121.0 (CH), 122.2 (CH), 123.3 (CH), 124.7 (C\textsubscript{quat}), 136.9 (CH), 136.9 (C\textsubscript{quat}), 171.0 (C\textsubscript{quat}). EI + MS (m/z (%)): 225 (M\textsuperscript{+}, 100), 196 ((M-C\textsubscript{5}H\textsubscript{5})\textsuperscript{+}, 29), 183 ((M-C\textsubscript{3}H\textsubscript{7}+H\textsuperscript{+}, 48), 168 ((M-C\textsubscript{4}H\textsubscript{9})\textsuperscript{+}, 20), 154 (57), 144 (C\textsubscript{9}H\textsubscript{5}NO\textsuperscript{+}, 32), 127 (14), 117 (C\textsubscript{9}H\textsubscript{7}N\textsuperscript{+}, 20), 89 (10). IR (KBr): \(\tilde{\nu}\) 3214 (s) cm\textsuperscript{-1}, 2953 (m), 2215 (m), 1592 (m), 1568 (s), 1519 (m), 1491 (w), 1456 (m), 1422 (s), 1382 (m), 1315 (m), 1229 (m), 1188 (w), 1123 (w), 1090 (w), 1050 (w), 1011 (w), 992 (w), 902 (w), 886 (w), 861 (w), 768 (w), 756 (m), 732 (w), 675 (w), 623 (w), 577 (w), 517 (w). Anal. calcd. for C\textsubscript{15}H\textsubscript{15}NO (225.3): C 79.97, H 6.71, N 6.22. Found: C 79.82, H 6.79, N 6.19.
2.2. 1-(1-Benzyl-1H-indol-3-yl)hept-2-yn-1-one (3b)

\[
\text{C}_{22}\text{H}_{21}\text{NO}
\]

\[
\text{315.41}
\]

1.17 g (74 % yield) as a yellow solid. Mp. 84-85 °C. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 0.94 (t, \(J = 7.5 \text{ Hz}, 3 \text{ H})\), 1.47 (sext, \(J = 8.3 \text{ Hz}, 2 \text{ H})\), 1.62 (quint, \(J = 8.3 \text{ Hz}, 2 \text{ H})\), 2.44 (t, \(J = 7.5 \text{ Hz}, 2 \text{ H})\), 5.35 (s, 2 H), 7.13-7.39 (m, 8 H), 7.90 (s, 1 H), 8.38-8.44 (m, 1 H). \(^1^3\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 13.6 (CH\(_3\)), 18.7 (CH\(_2\)), 22.1 (CH\(_2\)), 30.0 (CH\(_2\)), 50.9 (CH\(_2\)), 80.6 (C\(_\text{quat}\)), 91.0 (C\(_\text{quat}\)), 110.3 (CH), 118.9 (C\(_\text{quat}\)), 122.6 (CH), 123.0 (CH), 123.1 (C\(_\text{quat}\)), 126.1 (C\(_\text{quat}\)), 127.1 (CH), 128.1 (CH), 129.1 (CH), 135.5 (C\(_\text{quat}\)), 137.3 (C\(_\text{quat}\)), 138.1 (CH), 171.8 (C\(_\text{quat}\)). EI + MS (m/z (%)): 315 (M\(^+\), 100), 91 (C\(_7\)H\(_7^+\), 40). IR (KBr): \(\tilde{\nu}\) 3119 (w) cm\(^{-1}\), 2955 (w), 2932 (w), 2870 (w), 2226 (w), 1607 (s), 1576 (w), 1522 (s), 1495 (s), 1486 (s), 1465 (w), 1453 (m), 1440 (w), 1386 (s), 1360 (w), 1237 (w), 1184 (s), 1027 (w), 827 (w), 771 (w), 752 (m), 730 (w). UV/Vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (\(\varepsilon\)): 258 nm (12900), 272 (8700), 326 (16900). Anal. calcd. for C\(_{22}\)H\(_{21}\)NO (315.4) : C 83.78, H 6.71, N 4.44. Found: C 83.64, H 6.71, N 4.43.
2.3. 1-(1-Benzyl-1H-indol-3-yl)-4-methoxybut-2-yn-1-one (3c)

\[
\text{C}_{20}\text{H}_{17}\text{NO}_2
\]

1.00 g (66 % yield) as a brown solid (crystallization from dichloromethane/pentane gave upon cooling brown crystals). Mp. 109-111 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 3.43 (s, 3 H), 4.33 (s, 2 H), 5.35 (s, 2 H), 7.17 (d, \(J = 7.3\) Hz, 2 H), 7.25-7.37 (m, 6 H), 7.94 (s, 1 H), 8.40 (d, \(J = 7.6\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 51.0 (CH\(_2\)), 58.1 (CH\(_3\)), 59.9 (CH\(_2\)), 84.3 (C\(_\text{quat}\)), 85.1 (C\(_\text{quat}\)), 110.5 (CH), 118.5 (C\(_\text{quat}\)), 122.6 (CH), 123.3 (CH), 124.1 (CH), 125.9 (C\(_\text{quat}\)), 127.0 (CH), 128.3 (CH), 129.1 (CH), 135.3 (C\(_\text{quat}\)), 137.3 (C\(_\text{quat}\)), 138.6 (CH), 170.6 (C\(_\text{quat}\)). EI + MS (m/z (%)): 303 (M\(^+\), 32), 91 (C\(_7\)H\(_7\)^+, 100), 65 (C\(_5\)H\(_5\)^+, 12). IR (KBr): \(\tilde{\nu}\) 3450 (m) cm\(^{-1}\), 3119 (m), 3057 (m), 2989 (m), 2938 (m), 2822 (m), 2234 (m), 1609 (s), 1528 (s), 1487 (m), 1467 (m), 1453 (m), 1443 (m), 1392 (s), 1374 (m), 1241 (w), 1190 (s), 1166 (m), 1109 (m), 1029 (w), 952 (w), 871 (m), 750 (m), 740 (m). UV/Vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (\(\epsilon\)): 268 nm (20800), 282 (17900), 338 (19100). Anal. calcd. for \(\text{C}_{20}\text{H}_{17}\text{NO}_2\) (303.4) : C 79.19, H 5.65, N 4.62. Found: C 78.90, H 5.48, N 4.72.
2.4. 1-(1-Benzyl-1H-indol-3-yl)-3-phenylprop-2-yn-l-one (3d)

\[
\text{O} \quad \equiv \quad \text{C} \\
\begin{array}{c}
\text{N} \\
\text{C}_{24}H_{17}NO \\
335.40
\end{array}
\]

1.42 g (85 % yield) as a brown solid (recrystallization from hot ethylacetate gave upon cooling red crystals). Mp. 160-162 ºC. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 5.38 (s, 2 H), 7.16-7.20 (m, 2 H), 7.25-7.46 (m, 9 H), 7.59-7.63 (m, 2 H), 8.02 (s, 1 H), 8.46 (dt, \(J = 7.6\) Hz, \(J = 0.9\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 51.0 (CH\(_2\)), 87.9 (C\(_{\text{quat}}\)), 87.9 (C\(_{\text{quat}}\)), 110.5 (CH), 118.9 (C\(_{\text{quat}}\)), 120.7 (C\(_{\text{quat}}\)), 122.6 (CH), 123.2 (CH), 124.0 (CH), 126.1 (C\(_{\text{quat}}\)), 127.1 (CH), 128.3 (CH), 128.6 (CH), 129.1 (CH), 130.1 (CH), 132.7 (CH), 135.4 (C\(_{\text{quat}}\)), 137.3 (C\(_{\text{quat}}\)), 138.2 (CH), 171.3 (C\(_{\text{quat}}\)). EL + MS (m/z (%)): 335 (M\(^+\), 6), 307 ((M-CO\(^+\), 1), 216 ((M-CO-C\(_7\)H\(_7\))\(^+\), 3), 129 (C\(_9\)H\(_5\)O\(^+\), 6), 91 (C\(_7\)H\(_7\)), 65 (C\(_8\)H\(_5\)), 100). IR (KBr): \(\tilde{\nu}\) 3431 (m) cm\(^{-1}\), 3109 (w), 3060 (w), 3032 (w), 2226 (m), 2195 (m), 1600 (s), 1521 (s), 1490 (m), 1461 (m), 1446 (m), 1389 (s), 1338 (w), 1275 (w), 1254 (w), 1174 (s), 1064 (m), 949 (m), 795 (w), 752 (s), 732 (m), 693 (m). UV/Vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (\(\varepsilon\)): 268 nm (20800), 282 (17900), 338 (19100). Anal. calcd. for C\(_{24}\)H\(_{17}\)NO (335.4): C 85.95, H 5.11, N 4.18. Found: C 85.78, H 5.11, N 4.04.
2.5. 1-(1-Benzyl-1H-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one (3e)

\[
\begin{align*}
\text{O} & \quad \equiv \quad \text{Si} \\
\text{C}_{21}\text{H}_{21}\text{NOSi} & \\
& \\
& \text{331.48}
\end{align*}
\]

1.27 g (76 % yield) as a brown oil (crystallization from dichloromethane/pentane gave upon cooling pale yellow crystals). Mp. 128-129 °C. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta \) 0.27 (s, 9 H), 5.36 (s, 2 H), 7.15-7.40 (m, 8 H), 7.89 (s, 1 H), 8.37-8.43 (m, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta \) -0.6 (CH\(_3\)), 51.0 (CH\(_2\)), 94.4 (C\(_{\text{quat}}\)), 102.4 (C\(_{\text{quat}}\)), 110.4 (CH), 118.6 (C\(_{\text{quat}}\)), 122.6 (CH), 123.1 (CH), 124.0 (CH), 126.0 (C\(_{\text{quat}}\)), 127.2 (CH), 128.4 (CH), 129.1 (CH), 135.2 (C\(_{\text{quat}}\)), 137.4 (C\(_{\text{quat}}\)), 138.4 (CH), 170.9 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 331 (M\(^+\), 100), 316 ((M-CH\(_3\))\(^+\), 6), 288 ((M-CH\(_3\)-CO\(^+\)), 9), 91 (C\(_7\)H\(_7\)^+, 40). IR (KBr): \(\tilde{\nu} \) 3109 (w) cm\(^{-1}\), 3032 (w), 2961 (w), 2903 (w), 2161 (w), 1606 (s), 1576 (m), 1522 (s), 1485 (m), 1464 (m), 1455 (m), 1441 (m), 1385 (s), 1358 (m), 1252 (m), 1177 (s), 1150 (m), 1068 (m), 956 (s), 856 (s), 848 (s), 771 (m), 762 (s), 753 (s), 740 (m). UV/Vis (CH\(_2\)Cl\(_2\)) \(\lambda_{\text{max}}\) (\(\varepsilon\)): 260 nm (13500), 274 (9500), 334 (17800), 340 (16000). Anal. calcd. for C\(_{21}\)H\(_{21}\)NOSi (331.5): C 76.09, H 6.39, N 4.23. Found: C 76.15, H 6.46, N 4.24.
2.6. 1-(1-Methyl-1H-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one (3f)

819 mg (64 % yield) as a pale yellow solid (crystallization from dichloromethane/pentane gave upon cooling pale yellow needles). Mp. 103-104 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta 0.31\) (s, 9 H), 3.86 (s, 3 H), 7.28-7.35 (m, 3 H), 7.85 (s, 1 H), 8.35-8.40 (m, 1 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz):\(\delta\) -0.5 (CH\(_3\)), 33.7 (CH\(_3\)), 94.1 (C\(_{\text{quat}}\)), 102.4 (C\(_{\text{quat}}\)), 109.8 (CH), 118.1 (C\(_{\text{quat}}\)), 122.5 (CH), 123.0 (CH), 123.9 (CH), 125.7 (C\(_{\text{quat}}\)), 137.8 (C\(_{\text{quat}}\)), 139.1 (CH), 170.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 255 (M\(^+\), 100), 240 ((M-CH\(_3\))^+), 212 ((M-CH\(_3\)CO)^+), 158 ((M-C\(_5\)H\(_5\)Si)^+), 139 (12), 130 (C\(_9\)H\(_8\)N^+), 120 (17), 103 (20), 77 (16). IR (KBr): \(\tilde{\nu}\) 3443 (m) cm\(^{-1}\), 3115 (m), 3055 (m), 2963 (m), 2900 (m), 2151 (w), 1678 (w), 1606 (s), 1576 (m), 1527 (s), 1485 (m), 1465 (s), 1423 (w), 1392 (m), 1375 (s), 1336 (m), 1252 (s), 1212 (s), 1167 (w), 1149 (m), 1127 (m), 1089 (s), 1050 (m), 1011 (w), 952 (s), 859 (s), 768 (s), 741 (s), 709 (w), 633 (w), 617 (w), 571 (w). Anal. calcd. for C\(_{15}\)H\(_{17}\)NOSi (255.4) : C 70.54, H 6.71, N 5.48. Found: C 70.38, H 6.73, N 5.25.
2.7. 1-(1-(Triisopropylsilyl)-1H-indol-3-yl)hept-2-yn-1-one (3g)

855 mg (45 % yield) as an orange oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.98 (t, $J$ = 7.6 Hz, 3 H), 1.18 (d, $J$ = 7.6 Hz, 18 H), 1.54 (sext, $J$ = 7.6 Hz, 2 H), 1.66 (quint, $J$ = 7.6 Hz, 2 H), 1.73 (sept, $J$ = 7.6 Hz, 3 H), 2.49 (t, $J$ = 6.9 Hz, 2 H), 7.23-7.26 (m, 1 H), 7.28 (td, $J$ = 7.3 Hz, $J$ = 1.3 Hz, 1 H), 7.50 (d, $J$ = 8.2 Hz, 1 H), 8.08 (s, 1 H), 8.38-8.42 (m, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 12.7 (CH$_3$), 17.7 (CH), 18.0 (CH$_3$), 18.7 (CH$_2$), 22.1 (CH$_2$), 30.1 (CH$_2$), 80.8 (C$_{quat}$), 90.8 (C$_{quat}$), 114.1 (CH), 121.8 (C$_{quat}$), 122.3 (CH), 122.7 (CH), 123.4 (CH), 128.0 (C$_{quat}$), 141.7 (C$_{quat}$), 142.7 (CH), 172.2 (C$_{quat}$). EI + MS (m/z (%)): 382 (M$^+$, 1), 225 ((M-C$_9$H$_{21}$Si+H)$^+$, 38), 196 (16), 183 (31), 167 (24), 154 (100), 139 (12), 131 (22), 127 (39), 116 (36), 103 (21), 89 (52), 75 (59), 61 (30), 41 (69). IR (KBr): $\tilde{\nu}$ 3160 (m) cm$^{-1}$, 2953 (m), 2931 (m), 2869 (m), 2215 (m), 1592 (s), 1569 (s), 1519 (s), 1492 (m), 1456 (m), 1422 (s), 1382 (m), 1314 (m), 1229 (s), 1189 (m), 1123 (m), 1011 (w), 992 (w), 902 (w), 889 (w), 861 (m), 769 (m), 755 (s), 732 (m), 675 (w), 623 (w), 577 (w), 516 (w). Anal. calcd. for C$_{24}$H$_{35}$NOSi (381.6) : C 75.53, H 9.24, N 3.67. Found: C 75.41, H 9.46, N 3.44.
2.8. 1-(1-Benzyl-1H-pyrrolo[2,3-b]pyridin-3-yl)hept-2-yn-1-one (3h)

\[
\text{O} \quad \begin{array}{c}
\text{C}_{21}\text{H}_{20}\text{N}_{2}\text{O} \\
316.40
\end{array}
\]

990 mg (63 % yield) as an orange oil. $^1$H NMR (CDCl$_3$, 500 MHz): \( \delta 0.93 \) (t, \( J = 7.3 \) Hz, 3 H), 1.45 (sext, \( J = 7.6 \) Hz, 2 H), 1.60 (quint, \( J = 7.3 \) Hz, 2 H), 2.43 (t, \( J = 7.3 \) Hz, 2 H), 5.53 (s, 2 H), 7.25-7.38 (m, 6 H), 7.96 (s, 1 H), 8.42 (d, \( J = 4.7 \) Hz, 1 H), 8.63 (d, \( J = 7.9 \) Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): \( \delta 13.5 \) (CH$_3$), 18.7 (CH$_2$), 22.0 (CH$_2$), 29.9 (CH$_2$), 48.5 (CH$_2$), 80.1 (C$_{quat}$), 92.0 (C$_{quat}$), 117.1 (C$_{quat}$), 118.3 (C$_{quat}$), 119.0 (CH), 127.8 (CH), 128.2 (CH), 129.0 (CH), 130.8 (CH), 136.1 (C$_{quat}$), 137.0 (CH), 144.9 (CH), 148.4 (C$_{quat}$), 171.7 (C$_{quat}$). EI + MS (m/z (%)): 317 (M+H)$^+$, 28, 288 (M-CO)$^+$, 3, 207 (C$_{14}$H$_{11}$N$_2$$^+$, 20), 91 (C$_7$H$_7$$^+$, 100), 65 (C$_5$H$_5$$^+$, 17). IR (KBr): \( \tilde{\nu} \) 3103 (w), 3057 (w), 3032 (w), 2959 (m), 2933 (m), 2872 (m), 2213 (m), 1614 (s), 1574 (m), 1523 (s), 1445 (m), 1425 (m), 1395 (m), 1359 (w), 1305 (m), 1255 (m), 1237 (m), 1179 (s), 1117 (m), 1028 (w), 890 (s), 867 (s), 835 (m), 801 (m), 779 (m), 737 (m), 699 (m), 634 (m), 576 (s). Anal. calcd. for C$_{21}$H$_{20}$N$_2$O (316.4) : C 79.72, H 6.37, N 8.85. Found: C 79.54, H 6.38, N 8.80.
2.9. 1-(1-Methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-3-phenylprop-2-yn-1-one (3i)

793 mg (61 % yield) as an orange solid. Mp. 107-108 °C. $^1$H NMR (CDCl$_3$, 500 MHz): δ 3.98 (s, 3 H), 7.25-7.29 (m, 1 H), 7.38-7.43 (m, 2 H), 7.43-7.49 (m, 1 H), 7.64-7.68 (m, 2 H), 8.12 (s, 1 H), 8.42 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 8.64 (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 32.3 (CH$_3$), 87.5 (C$_{quat}$), 88.7 (C$_{quat}$), 116.8 (C$_{quat}$), 118.5 (C$_{quat}$), 119.1 (CH), 120.7 (C$_{quat}$), 128.8 (CH), 130.5 (CH), 130.9 (CH), 132.9 (CH), 138.6 (CH), 145.1 (CH), 148.7 (C$_{quat}$), 171.3 (C$_{quat}$). El + MS (m/z (%)): 260 (M$^+$, 72), 232 ((M-CO)$^+$, 100), 231 ((M-CO-H)$^+$, 91), 159 (C$_9$H$_7$N$_2$O$^+$, 21), 131 (15), 129 (23), 116 (14). IR (KBr): ν 3449 (m) cm$^{-1}$, 2198 (m), 1609 (s), 1572 (w), 1524 (m), 1491 (w), 1446 (s), 1406 (w), 1380 (w), 1304 (w), 1274 (w), 1120 (w), 1086 (m), 948 (m), 801 (w), 772 (w), 729 (w), 693 (w). Anal. calcd. for C$_{17}$H$_{12}$N$_2$O (260.3): C 78.44, H 4.65, N 10.76. Found: C 78.21, H 4.44, N 10.87.
2.10. 1-(1-Methyl-1H-pyrrol-2-yl)hept-2-yn-1-one (9a)

\[
\text{C}_{12}\text{H}_{15}\text{NO}
\]

189.25

577 mg (61 % yield) as an orange oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 0.95 (t, \(J = 7.3\) Hz, 3 H), 1.44-1.53 (m, 2 H), 1.58-1.65 (m, 2 H), 2.43 (t, \(J = 7.3\) Hz, 2 H), 3.93 (s, 3 H), 6.15 (dd, \(J = 4.1\) Hz, \(J = 2.5\) Hz, 1 H), 6.83 (t, \(J = 2.2\) Hz, 1 H), 7.15 (dd, \(J = 4.1\) Hz, \(J = 1.9\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 13.5 (CH\(_3\)), 18.7 (CH\(_2\)), 22.0 (CH\(_2\)), 29.9 (CH\(_2\)), 37.3 (CH\(_3\)), 80.2 (C\(_{\text{quat}}\)), 91.8 (C\(_{\text{quat}}\)), 108.8 (CH), 123.5 (CH), 132.1 (CH), 132.3 (C\(_{\text{quat}}\)), 167.4 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 189 (M\(^+\), 22), 160 ((M-C\(_2\)H\(_5\))\(^+\), 28), 147 ((M-C\(_3\)H\(_7\)+H\(^+\)), 53), 146 ((M-C\(_3\)H\(_7\))\(^+\), 52), 132 ((M-C\(_4\)H\(_9\))\(^+\), 17), 121 (15), 120 (58), 119 (C\(_7\)H\(_5\)NO\(^+\), 19), 118 ((M-C\(_4\)H\(_9\)-CH\(_3\))\(^+\), 87), 117 (33), 108 (C\(_6\)H\(_8\)NO\(^+\), 31), 104 (17), 94 (41), 91 (24), 81 (50), 80 (34), 79 (34), 78 (27), 77 (24), 67 (17), 66 (16), 65 (C\(_4\)H\(_3\)N\(^+\), 29), 55 (13), 54 (11), 53 (C\(_3\)HO\(^+\), 88), 52 (21), 51 (27), 43 (24), 42 (38), 41 (C\(_2\)H\(_3\)N\(^+\), 47), 39 (C\(_3\)H\(_3\)\(^+\), 100). IR (Film): \(\tilde{\nu}\) 3109 (w) \text{cm}^{-1}, 2959 (s), 2873 (m), 2251 (m), 2207 (s), 1614 (s), 1525 (m), 1464 (m), 1403 (s), 1328 (m), 1243 (s), 1122 (m), 1090 (w), 1056 (m), 1021 (w), 982 (w), 960 (w), 906 (m), 868 (m), 832 (m), 737 (s), 706 (w), 605 (w). Anal. calcd. for C\(_{12}\)H\(_{15}\)NO (189.3): C 76.16, H 7.99, N 7.40. Found: C 75.97, H 7.95, N 7.35.
2.11. 1-(1-Benzyl-1H-pyrrol-2-yl)hept-2-yne-1-one (9b)

\[
\text{C}_{18}\text{H}_{19}\text{NO}
\]

265.35

574 mg (43 % yield) as an orange oil. \[^1\text{H}\text{NMR (CDCl}_3\text{, 500 MHz): } \delta 0.94 (t, J = 7.6 \text{ Hz, 3 H}), 1.47 (\text{sext, } J = 7.6 \text{ Hz, 2 H}), 1.60 (\text{quint, } J = 7.3 \text{ Hz, 2 H}), 2.41 (t, J = 7.3 \text{ Hz, 2 H}), 5.57 (s, 2 H), 6.19-6.22 (m, 1 H), 6.91-6.94 (m, 1 H), 7.13 (d, J = 7.6 \text{ Hz, 2 H}), 7.21-7.23 (m, 1 H), 7.23-7.31 (m, 3 H). \] \[^{13}\text{C NMR (CDCl}_3\text{, 125 MHz): } \delta 13.5 (\text{CH}_3), 18.7 (\text{CH}_2), 22.0 (\text{CH}_2), 29.9 (\text{CH}_2), 52.4 (\text{CH}_2), 80.3 (\text{C}_{\text{quat}}), 91.9 (\text{C}_{\text{quat}}), 109.4 (\text{CH}), 124.2 (\text{CH}), 127.3 (\text{CH}), 127.6 (\text{CH}), 128.6 (\text{CH}), 131.5 (\text{CH}), 131.7 (\text{C}_{\text{quat}}), 137.7 (\text{C}_{\text{quat}}), 167.2 (\text{C}_{\text{quat}}). \] \] EI + MS (m/z (%)): 265 (M\(^+\), 3), 236 ((M-C\(_2\text{H}_5\))\(^+\), 2), 223 ((M-C\(_3\text{H}_7\)+H\(^+\)), 11), 222 ((M-C\(_3\text{H}_7\))\(^+\), 9), 196 (43), 129 (14), 94 (C\(_6\text{H}_4\text{NO}^+\), 25), 91 (C\(_7\text{H}_7\)+, 100), 65 (C\(_4\text{H}_3\text{N}^+\), 21), 53 (C\(_3\text{HO}^+\), 3), 41 (6). IR (Film): \( \tilde{\nu} 3108 \text{ (w) cm}^{-1}, 3065 \text{ (w), 3032} \text{ (w), 2958} \text{ (m), 2932} \text{ (m), 2872} \text{ (m), 2240} \text{ (m), 2206} \text{ (m), 1614} \text{ (s), 1524} \text{ (m), 1496} \text{ (w), 1466} \text{ (m), 1455} \text{ (m), 1402} \text{ (s), 1358} \text{ (m), 1335} \text{ (s), 1252} \text{ (m), 1237} \text{ (s), 1199} \text{ (w), 1117} \text{ (s), 1080} \text{ (m), 1027} \text{ (w), 982} \text{ (w), 959} \text{ (w), 906} \text{ (m), 867} \text{ (m), 832} \text{ (m), 737} \text{ (s), 694} \text{ (m), 645} \text{ (w), 607} \text{ (w), 570} \text{ (w).} \] Anal. calcd. for C\(_{18}\text{H}_{19}\text{NO} (265.4): C 81.47, H 7.22, N 5.28. Found: C 81.43, H 7.11, N 5.02.
3. Synthesis of 2-Amino Pyrimidines 11

In a screw-cap vessel 1.00 mmol of the alkynone 3 or 9 was dissolved under nitrogen in 2-methoxyethanol (5 mL). Then, potassium carbonate (346 mg, 2.50 mmol) and guanidinium hydrochloride (10) (239 mg, 2.50 mmol) were added and the mixture was stirred at 120°C over night. Then, saturated brine (20 mL) was added and the mixture was extracted with dichloromethane (5 x 20 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with dichloromethane/methanol/aqueous ammonia (For experimental details see Table 2).
**Table 2.** Experimental details of the synthesis of 2-amino pyrimidines 11.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ynone 3 or 9</th>
<th>Guanidinium hydrochloride (10)</th>
<th>2-Amino pyrimidine 11 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>290 mg (1.29 mmol) of 3a</td>
<td>308 mg (3.23 mmol)</td>
<td>277 mg (81 %) of 11a</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1</td>
</tr>
<tr>
<td>2</td>
<td>315 mg (1.00 mmol) of 3b</td>
<td>239 mg (2.50 mmol)</td>
<td>305 mg (86 %) of 11b</td>
<td>DCM → DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>3</td>
<td>303 mg (1.00 mmol) of 3c</td>
<td>239 mg (2.50 mmol)</td>
<td>304 mg (88 %) of 11c</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>4</td>
<td>335 mg (1.00 mmol) of 3d</td>
<td>239 mg (2.50 mmol)</td>
<td>310 mg (82 %) of 11d</td>
<td>DCM-MeOH-NH$_3$ = 200:1:1 → 100:1:1</td>
</tr>
<tr>
<td>5</td>
<td>658 mg (1.99 mmol) of 3e</td>
<td>473 mg (4.95 mmol)</td>
<td>527 mg (88 %) of 11e</td>
<td>DCM → DCM-MeOH-NH$_3$ = 200:1:1 → 100:1:1</td>
</tr>
<tr>
<td>6</td>
<td>255 mg (1.00 mmol) of 3f</td>
<td>239 mg (2.50 mmol)</td>
<td>153 mg (68 %) of 11f</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>7</td>
<td>672 mg (1.76 mmol) of 3g</td>
<td>420 mg (4.40 mmol)</td>
<td>321 mg (68 %) of 11a</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:3:1</td>
</tr>
<tr>
<td>8</td>
<td>907 mg (2.87 mmol) of 3h</td>
<td>685 mg (7.17 mmol)</td>
<td>826 mg (81 %) of 11g</td>
<td>DCM → DCM-MeOH-NH$_3$ = 200:1:1 → 100:1:1</td>
</tr>
<tr>
<td>9</td>
<td>260 mg (1.00 mmol) of 3i</td>
<td>239 mg (2.50 mmol)</td>
<td>258 mg (86 %) of 11h</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>10</td>
<td>503 mg (2.66 mmol) of 9a</td>
<td>635 mg (6.64 mmol)</td>
<td>566 mg (92 %) of 11i</td>
<td>DCM → DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>11</td>
<td>356 mg (1.34 mmol) of 3k</td>
<td>320 mg (3.35 mmol)</td>
<td>384 mg (94 %) of 9j</td>
<td>DCM → DCM-MeOH-NH$_3$ = 100:1:1</td>
</tr>
</tbody>
</table>
3.1. 4-Butyl-6-(1H-indol-3-yl)pyrimid-2-yl-amine (11a)

\[
\begin{align*}
\text{C}_{16}\text{H}_{18}\text{N}_4 \\
266.34
\end{align*}
\]

277 mg (81 % yield from 3a) as a yellow solid. From 3g the same procedure gave 321 mg (68 % yield) as a yellow solid. Mp. 153-158 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 0.91 (t, \(J = 7.3\) Hz, 3 H), 1.35 (sext, \(J = 7.3\) Hz, 2 H), 1.66 (quint, \(J = 7.6\) Hz, 2 H), 2.50 (t, \(J = 7.6\) Hz, 2 H), 6.37 (s, 2 H, \(\text{NH}_2\)), 6.94 (s, 1 H), 7.10-7.15 (m, 1 H), 7.15-7.20 (m, 1 H), 7.45 (d, \(J = 7.9\) Hz, 1 H), 8.19 (d, \(J = 2.8\) Hz, 1 H), 8.60 (d, \(J = 7.9\) Hz, 1 H), 11.6 (br, 1H, \(\text{NH}\)). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 13.9 (CH\(_3\)), 22.0 (CH\(_2\)), 30.6 (CH\(_2\)), 36.9 (CH\(_2\)), 103.9 (CH), 111.8 (CH), 114.0 (C\(_{\text{quat}}\)), 120.2 (CH), 121.9 (CH), 122.4 (CH), 125.5 (C\(_{\text{quat}}\)), 127.9 (CH), 137.0 (C\(_{\text{quat}}\)), 162.7 (C\(_{\text{quat}}\)), 163.6 (C\(_{\text{quat}}\)), 169.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 266 (\(M^+\), 9), 224 ((M-C\(_3\)H\(_7\)H\(_2\))^+, 100). IR (KBr): \(\tilde{\nu}\) 3486 (m) cm\(^{-1}\), 3296 (m), 3127 (m), 2950 (m), 2928 (m), 2861 (m), 1754 (w), 1636 (m), 1575 (s), 1535 (s), 1493 (m), 1456 (m), 1430 (m), 1340 (w), 1319 (w), 1279 (w), 1246 (w), 1215 (m), 1175 (w), 1133 (m), 1110 (w), 1011 (w), 967 (w), 934 (w), 829 (w), 797 (w), 743 (m), 616 (w), 537 (w). Anal. calcd. for C\(_{16}\)H\(_{18}\)N\(_4\) (266.3): C 72.15, H 6.81, N 21.04. Found: C 71.99, H 6.79, N 21.08.
3.2. 4-(1-Benzyl-1H-indol-3-yl)-6-butylpyrimid-2-yl-amine (11b)

![Chemical structure of 4-(1-Benzyl-1H-indol-3-yl)-6-butylpyrimid-2-yl-amine (11b)]

C_{23}H_{24}N_{4}

356.46

305 mg (86 % yield) as a pale yellow solid. Mp. 174-175 °C. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 0.95 (t, $J$ = 7.5 Hz, 3 H), 1.42 (sext, $J$ = 7.5 Hz, 2 H), 1.72 (quint, $J$ = 7.5 Hz, 2 H), 2.60 (t, $J$ = 7.5 Hz, 2 H), 5.05 (s, 2 H, NH$_2$), 5.35 (s, 2 H), 6.89 (s, 1 H), 7.11-7.18 (m, 2 H), 7.18-7.35 (m, 6 H), 7.84 (s, 1 H), 8.33-8.40 (m, 1 H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 14.0 (CH$_3$), 22.6 (CH$_2$), 31.2 (CH$_2$), 37.8 (CH$_2$), 50.5 (CH$_2$), 106.4 (CH), 110.3 (CH), 114.8 (C$_{quat}$), 121.2 (CH), 121.7 (CH), 122.6 (CH), 126.3 (C$_{quat}$), 126.9 (CH), 127.9 (CH), 128.9 (CH), 130.3 (CH), 136.5 (C$_{quat}$), 137.4 (C$_{quat}$), 162.5 (C$_{quat}$), 163.1 (C$_{quat}$), 171.4 (C$_{quat}$). EI + MS (m/z (%)): 356 (M$^+$, 27), 341 ((M-CH$_3$)$^+$, 3), 268 ((M-C$_2$H$_5$)$^+$, 7), 314 ((M-C$_3$H$_7$+H)$^+$, 100), 223 ((M-C$_3$H$_7$+H-C$_7$H$_7$)$^+$, 5), 91 (C$_7$H$_7$$^+$, 14). IR (KBr): $\tilde{\nu}$ 3463 (s) cm$^{-1}$, 3442 (s), 2956 (w), 2927 (w), 2860 (w), 1645 (m), 1628 (m), 1577 (s), 1521 (m), 1469 (m), 1456 (w), 1385 (m), 1175 (w), 743 (m). UV/Vis (CH$_2$Cl$_2$) $\lambda_{max}$ (ε): 246 nm (14200), 264 (10100), 290 (9100), 328 (23500), 340 (18300). Anal. calcd. for C$_{23}$H$_{24}$N$_4$ (356.5): C 77.50, H 6.79, N 15.72. Found: C 77.45, H 6.75, N 15.77.
3.3. 4-(1-Benzyl-1H-indol-3-yl)-6-(methoxymethyl)pyrimid-2-yl-amine (11c)

![Chemical Structure](image)

304 mg (88 % yield) as a pale yellow solid. Mp. 183-188 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 3.51 (s, 3 H), 4.40 (s, 2 H), 5.1 (br, 2 H, NH$_2$), 5.35 (s, 2 H), 7.11 (s, 1 H), 7.13-7.17 (m, 2 H), 7.22-7.33 (m, 6 H), 7.87 (s, 1 H), 8.43-8.46 (m, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 50.5 (CH$_2$), 59.0 (CH$_3$), 74.6 (CH$_2$), 104.0 (CH), 110.2 (CH), 114.6 (C$_{quat}$), 121.4 (CH), 122.1 (CH), 122.7 (CH), 126.3 (C$_{quat}$), 126.9 (CH), 128.0 (CH), 128.9 (CH), 130.6 (CH), 136.4 (C$_{quat}$), 137.5 (C$_{quat}$), 162.9 (C$_{quat}$), 163.4 (C$_{quat}$), 167.3 (C$_{quat}$). El + MS (m/z (%)): 344 (M$^+$, 43), 314 (M-OCH$_3$+H$^+$, 85), 223 ((M-OCH$_3$-C$_7$H$_7$)$^+$, 15), 91 (C$_7$H$_7$+$^+$, 100), 65 (C$_5$H$_5$+$^+$, 14), 58 (22), 43 (68). IR (KBr): $\tilde{\nu}$ 3460 (m) cm$^{-1}$, 3299 (m), 3170 (m), 2925 (w), 2819 (w), 1591 (s), 1546 (s), 1496 (w), 1473 (m), 1454 (m), 1429 (m), 1410 (m), 1389 (m), 1359 (w), 1304 (w), 1231 (w), 1199 (m), 1178 (m), 1130 (m), 1040 (w), 959 (w), 846 (w), 826 (w), 790 (w), 752 (m), 738 (m), 697 (w), 633 (w), 573 (w). Anal. calcd. for C$_{21}$H$_{20}$N$_4$O (344.4) : C 73.23, H 5.85, N 16.27. Found: C 72.99, H 5.87, N 16.42.
3.4. 4-(1-Benzyl-1H-indol-3-yl)-6-phenylpyrimid-2-yl-amine (11d)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{C} \\
\text{C} & \quad \text{H}_2 \\
\end{align*}
\]

C\text{_{25}H_{20}N_{4}}

376.45

310 mg (82 % yield) as a yellow solid (crystallization from dichloromethane/pentane gave citric yellow crystals). Mp. 171-173 °C. \(^1\)H NMR (CDCl\text{\textsubscript{3}}, 500 MHz): \(\delta\) 5.16 (s, 2 H, NH\text{\textsubscript{2}}), 5.37 (s, 2 H), 7.16 (d, \(J = 7.3\) Hz, 2 H), 7.23-7.35 (m, 6 H), 7.43 (s, 1 H), 7.44-7.52 (m, 3 H), 7.92 (s, 1 H), 8.03-8.07 (m, 2 H), 8.43 (d, \(J = 7.3\) Hz, 1 H). \(^13\)C NMR (CDCl\text{\textsubscript{3}}, 125 MHz): \(\delta\) 50.5 (CH\text{\textsubscript{2}}), 104.0 (CH), 110.4 (CH), 114.9 (C\text{\textsubscript{quat}}), 121.4 (CH), 121.8 (CH), 122.7 (CH), 126.3 (C\text{\textsubscript{quat}}), 126.9 (CH), 127.0 (CH), 127.9 (CH), 128.7 (CH), 128.9 (CH), 130.1 (CH), 130.4 (CH), 136.5 (C\text{\textsubscript{quat}}), 137.5 (C\text{\textsubscript{quat}}), 138.1 (C\text{\textsubscript{quat}}), 163.2 (C\text{\textsubscript{quat}}), 163.4 (C\text{\textsubscript{quat}}), 165.2 (C\text{\textsubscript{quat}}). El + MS (m/z (%)): 376 (M\textsuperscript{+}, 100), 285 ((M-C\textsubscript{7}H\textsubscript{7})\textsuperscript{+}, 8), 91 (C\textsubscript{7}H\textsubscript{7}\textsuperscript{+}, 87). IR (KBr): \(\tilde{\nu}\) 3482 (w) cm\(^{-1}\), 3324 (m), 3184 (m), 3184 (m), 3055 (w), 1653 (m), 1566 (s), 1510 (s), 1468 (m), 1439 (m), 1403 (m), 1379 (m), 1357 (w), 1316 (m), 1233 (m), 1180 (m), 1068 (w), 1029 (w), 917 (w), 824 (w), 772 (m), 736 (m), 697 (m), 630 (m). Anal. calcd. for C\textsubscript{25}H\textsubscript{20}N\textsubscript{4} (376.5) : C 79.76, H 5.35, N 14.88. Found: C 79.71, H 5.18, N 14.86.
3.5. 4-(1-Benzyl-1H-indol-3-yl)pyrimid-2-yl-amine (11e)

![Chemical Structure](image)

C_{19}H_{16}N_{4}  
300.36

527 mg (88 % yield) as a pale yellow solid (recrystallization from hot ethylacetate gave upon cooling a colorless solid). Mp. 174-175 °C (Lit.\[5\]: 162-164 °C). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 5.08 (s, 2 H, NH\(_2\)), 5.34 (s, 2 H), 6.97 (dd, \(J = 5.4\) Hz, \(J = 0.6\) Hz, 1 H), 7.14 (d, \(J = 7.3\) Hz, 2 H), 7.22-7.31 (m, 6 H), 7.83 (s, 1 H), 8.22 (dd, \(J = 5.4\) Hz, \(J = 0.6\) Hz, 1 H), 8.39 (d, \(J = 7.6\) Hz, 1 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 50.5 (CH\(_2\)), 107.5 (CH), 110.3 (CH), 114.5 (C\(_{quat}\)), 121.4 (CH), 121.8 (CH), 122.8 (CH), 126.2 (C\(_{quat}\)), 126.9 (CH), 128.0 (CH), 128.9 (CH), 130.5 (CH), 136.4 (C\(_{quat}\)), 137.5 (C\(_{quat}\)), 157.6 (CH), 162.7 (C\(_{quat}\)), 163.1 (C\(_{quat}\)). EI + MS (m/z (%)): 300 (M\(^+\), 100), 91 (C\(_7\)H\(_7^+\), 89), 65 (C\(_5\)H\(_5^+\), 9). IR (KBr): \(\tilde{\nu}\) 3457 (w) cm\(^{-1}\), 3299 (w), 3154 (w), 1624 (m), 1574 (s), 1534 (m), 1455 (s), 1331 (w), 1244 (w), 1221 (w), 1184 (m), 1097 (w), 885 (w), 812 (w), 743 (m), 698 (w), 631 (w), 572 (w). Anal. calcd. for C\(_{19}\)H\(_{16}\)N\(_4\) (300.3): C 75.98, H 5.37, N 18.65. Found: C 75.97, H 5.37, N 18.44.

NMR spectra of 11e in acetone-d\(_6\) and DMSO-d\(_6\) are in agreement with N-benzyl meridianin G\[5\]:

\(^1\)H NMR (acetone-d\(_6\), 500 MHz): \(\delta\) 5.52 (s, 2 H), 5.9 (brs, 2 H, NH\(_2\)), 7.03 (d, \(J = 5.4\) Hz, 1 H), 7.14-7.21 (m, 2 H), 7.25-7.30 (m, 3 H), 7.30-7.35 (m, 2 H), 7.44-7.47 (m, 1 H), 8.15 (d, \(J = 5.4\) Hz, 1 H), 8.22 (s, 1 H), 8.60-8.63 (m, 1 H). \(^13\)C NMR (acetone-d\(_6\), 125 MHz): \(\delta\) 50.9 (CH\(_2\)), 106.9 (CH), 111.4 (CH), 115.2 (C\(_{quat}\)), 121.7 (CH), 123.3 (CH), 123.7 (CH), 127.6 (C\(_{quat}\)), 128.0 (CH), 128.6 (CH), 129.6 (CH), 132.0 (CH), 138.4 (C\(_{quat}\)), 138.6 (C\(_{quat}\)), 158.3 (CH), 163.7 (C\(_{quat}\)), 165.0 (C\(_{quat}\)).

\(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 5.49 (s, 2 H), 6.45 (s, 2 H, NH\(_2\)), 6.98 (d, \(J = 5.4\) Hz, 1 H), 7.13-7.21 (m, 2 H), 7.24-7.30 (m, 3 H), 7.30-7.35 (m, 2 H), 7.52 (d, \(J = 7.6\) Hz, 1 H), 8.13 (d, \(J = 5.4\) Hz, 1 H), 8.37 (s, 1 H), 8.57-8.61 (m, 1 H). \(^13\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 49.5 (CH\(_2\)), 105.3 (CH), 110.7 (CH), 113.4 (C\(_{quat}\)), 120.7 (CH), 122.2 (CH), 122.6 (CH), 126.0 (C\(_{quat}\)), 127.2 (CH), 127.6 (CH), 128.6 (CH), 131.6 (CH), 136.9 (C\(_{quat}\)), 137.5 (C\(_{quat}\)), 157.2 (CH), 162.1 (C\(_{quat}\)), 163.5 (C\(_{quat}\)).
3.6. 4-(1-Methyl-1H-indol-3-yl)pyrimid-2-yl-amine (11f)

\[
\begin{align*}
\text{C}_{13}\text{H}_{12}\text{N}_4 & \quad 224.26 \\
\end{align*}
\]

153 mg (68 % yield) as a colorless solid. Mp. 216-219 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 3.85 (s, 3 H), 6.42 (s, 2 H, NH\(_2\)), 6.94 (d, \(J = 5.4\) Hz, 1 H), 7.15-7.19 (m, 1 H), 7.22-7.26 (m, 1 H), 7.50 (d, \(J = 8.2\) Hz, 1 H), 8.11 (d, \(J = 5.4\) Hz, 1 H), 8.18 (s, 1 H), 8.59 (d, \(J = 7.9\) Hz, 1 H). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 32.8 (CH\(_3\)), 105.0 (CH), 110.1 (CH), 112.5 (C\(_{\text{quat}}\)), 120.4 (CH), 121.9 (CH), 122.4 (CH), 125.6 (C\(_{\text{quat}}\)), 132.0 (CH), 137.4 (C\(_{\text{quat}}\)), 157.0 (CH), 162.1 (C\(_{\text{quat}}\)), 163.4 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 224 (M\(^+\), 100), 183 (86), 172 (14), 168 (16), 155 (34), 139 (35), 127 (16), 118 (15), 113 (20), 101 (15), 91 (12), 77 (31), 63 (20), 51 (13), 42 (40). IR (KBr): \(\tilde{\nu}\) 3455 (m) cm\(^{-1}\), 3292 (w), 3158 (w), 1625 (m), 1575 (s), 1536 (s), 1480 (m), 1458 (s), 1419 (w), 1372 (m), 1327 (w), 1235 (w), 1219 (m), 1155 (w), 1129 (w), 1106 (w), 1017 (w), 886 (w), 816 (w), 743 (m), 677 (w), 567 (w). Anal. calcd. for C\(_{13}\)H\(_{12}\)N\(_4\) (224.3): C 69.62, H 5.39, N 24.98. Found: C 69.53, H 5.56, N 25.11.
3.7. 4-(1-Benzyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-butylpyrimid-2-yl-amine (11g)

826 mg (81 % yield) as a yellow solid (crystallization from dichloromethane/pentane gave upon cooling citric yellow crystals). Mp. 133-135 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.95 (t, $J = 7.3$ Hz, 3 H), 1.41 (sext, $J = 7.6$ Hz, 2 H), 1.70 (quint, $J = 7.6$ Hz, 2 H), 2.58 (t, $J = 7.9$ Hz, 2 H), 5.05 (s, 2 H, NH$_2$), 5.54 (s, 2 H), 6.79 (s, 1 H), 7.22 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.24-7.35 (m, 5 H), 7.87 (s, 1 H), 8.41 (d, $J = 4.4$ Hz, 1 H), 8.68 (d, $J = 7.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 13.9 (CH$_3$), 22.6 (CH$_2$), 31.1 (CH$_2$), 37.8 (CH$_2$), 48.1 (CH$_2$), 105.9 (CH), 113.2 (C$_{quat}$), 117.4 (CH), 118.5 (C$_{quat}$), 127.6 (CH), 127.9 (CH), 128.8 (CH), 129.2 (CH), 130.4 (CH), 137.0 (C$_{quat}$), 143.9 (CH), 148.5 (C$_{quat}$), 162.0 (C$_{quat}$), 163.1 (C$_{quat}$), 171.6 (C$_{quat}$). EI + MS (m/z (%)): 357 (M$^+$, 17), 315 ((M-C$_3$H$_7$+H)$^+$, 100), 91 (C$_7$H$_7$+, 40), 56 (C$_6$H$_5$+, 5). IR (KBr): $\tilde{\nu}$ 3484 (m) cm$^{-1}$, 3296 (m), 3154 (m), 2955 (m), 2926 (m), 2858 (w), 1632 (m), 1579 (s), 1540 (s), 1468 (m), 1455 (m), 1422 (m), 1392 (m), 1358 (w), 1296 (w), 1227 (w), 1186 (w), 1131 (w), 812 (w), 777 (w), 728 (w), 697 (w), 620 (w). Anal. calcd. for C$_{22}$H$_{23}$N$_5$ (357.5) : C 73.92, H 6.49, N 19.59. Found: C 73.95, H 6.65, N 19.51.
3.8. 4-(1-Methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-phenylpyrimid-2-yl-amine (11h)

![Chemical Structure]

C_{18}H_{15}N_5

301.35

258 mg (86 % yield) as a yellow solid (crystallization from dichloromethane/methanol gave yellow crystals). Mp. 186 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 3.93 (s, 3 H), 6.63 (s, 2 H, NH$_2$), 7.26 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.49-7.56 (m, 3 H), 7.63 (s, 1 H), 8.17-8.21 (m, 2 H), 8.37 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 8.63 (s, 1 H), 9.01 (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1 H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 31.3 (CH$_3$), 100.6 (CH), 111.6 (C$_{quat}$), 116.9 (CH), 118.3 (C$_{quat}$), 126.7 (CH), 128.5 (CH), 130.1 (CH), 131.1 (CH), 132.3 (CH), 137.7 (C$_{quat}$), 143.3 (CH), 148.2 (C$_{quat}$), 162.9 (C$_{quat}$), 163.2 (C$_{quat}$), 163.9 (C$_{quat}$). EI + MS (m/z (%)): 301 (M$^+$, 100), 224 ((M-C$_6$H$_5$)$_2^+$, 1), 155 ((C$_{10}$H$_7$N$_2$)$_2^+$, 12), 131 ((C$_8$H$_7$N$_2$)$_2^+$, 19). IR (KBr): $\tilde{\nu}$ 3488 (w) cm$^{-1}$, 3296 (w), 3180 (w), 3180 (w), 1624 (m), 1573 (s), 1534 (s), 1478 (m), 1453 (w), 1419 (w), 1391 (m), 1304 (w), 1222 (w), 1130 (w), 923 (w), 820 (w), 768 (m), 733 (w), 700 (w), 646 (w), 590 (w), 548 (w). Anal. calcd. for C$_{18}$H$_{15}$N$_5$ (301.4): C 71.74, H 5.02, N 23.24. Found: C 71.73, H 5.20, N 22.95.
3.9. 4-Butyl-6-(1-methyl-1H-pyrro-2-yl)pyrimid-2-yl-amine (11i)

\[
\text{C}_{13}\text{H}_{18}\text{N}_{4} \\
230.31
\]

566 mg (92 % yield) as a yellow solid. Mp. 78-79 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 0.94 (t, \(J = 7.6\) Hz, 3 H), 1.39 (sext, \(J = 7.6\) Hz, 2 H), 1.67 (sept, \(J = 7.6\) Hz, 2 H), 2.55 (t, \(J = 7.9\) Hz, 2 H), 4.00 (s, 3 H), 5.07 (s, 2 H, NH\(_2\)), 6.16 (dd, \(J = 3.8\) Hz, \(J = 2.8\) Hz, 1 H), 6.70-6.74 (m, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 13.9 (CH\(_3\)), 22.5 (CH\(_2\)), 31.1 (CH\(_2\)), 37.5 (CH\(_3\)), 37.7 (CH\(_2\)), 106.7 (CH), 108.0 (CH), 113.1 (CH), 128.1 (CH), 130.2 (C\(_{\text{quat}}\)), 159.8 (C\(_{\text{quat}}\)), 162.6 (C\(_{\text{quat}}\)), 171.3 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 230 (M\(^+\), 5), 201 ((M-C\(_2\)H\(_5\))\(^+\), 8), 188 ((M-C\(_3\)H\(_7\)+H)\(^+\), 100), 145 (C\(_8\)H\(_7\)N\(_3\)+, 6), 106 (11), 105 (17), 104 (11), 80 (C\(_4\)H\(_8\)N\(_2\)+, 12), 78 (C\(_4\)H\(_2\)N\(_2\)+, 10), 43 (C\(_3\)H\(_7\)+, 32), 42 (14), 41 (C\(_2\)H\(_3\)N\(^+\), 13). IR (KBr): \(\tilde{\nu}\) 3482 (m) cm\(^{-1}\), 3292 (w), 3151 (w), 2952 (w), 2859 (w), 1627 (m), 1584 (s), 1560 (w), 1544 (m), 1490 (w), 1450 (w), 1418 (w), 1383 (w), 1323 (w), 1235 (w), 1145 (w), 1093 (w), 1070 (w), 832 (w), 791 (w), 723 (m), 683 (w), 607 (w), 548 (w). Anal. calcd. for C\(_{13}\)H\(_{18}\)N\(_4\) (230.3): C 67.80, H 7.88, N 24.33. Found: C 67.66, H 8.00, N 24.07.
3.10. 4-(1-Benzyl-1\textit{H}-pyrrol-2-yl)-6-butylpyrimid-2-yl-amine (11j)

\[
\begin{align*}
\text{C}_{19}\text{H}_{22}\text{N}_{4} \\
306.40
\end{align*}
\]

384 mg (94 % yield) as a yellow solid. Mp. 90 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 0.92 (t, $J$ = 7.3 Hz, 3 H), 1.37 (sext, $J$ = 7.6 Hz, 2 H), 1.60-1.67 (m, 2 H), 2.49-2.54 (m, 2 H), 4.88 (s, 2 H, NH$_2$), 5.76 (s, 2 H), 6.23 (dd, $J$ = 3.8 Hz, $J$ = 2.5 Hz, 1 H), 6.70 (s, 1 H), 6.79 (dd, $J$ = 3.8 Hz, $J$ = 1.9 Hz, 1 H), 6.82 (dd, $J$ = 2.5 Hz, $J$ = 1.9 Hz, 1 H), 7.03-7.07 (m, 2 H), 7.17-7.22 (m, 1 H), 7.23-7.28 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 13.9 (CH$_3$), 22.5 (CH$_2$), 31.0 (CH$_2$), 37.7 (CH$_2$), 52.4 (CH$_2$), 106.7 (CH), 108.7 (CH), 113.5 (CH), 126.6 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 129.8 (C$_{\text{quat}}$), 139.4 (C$_{\text{quat}}$), 159.6 (C$_{\text{quat}}$), 162.4 (C$_{\text{quat}}$), 171.3 (C$_{\text{quat}}$). EI + MS (m/z (%)): 306 (M$^+$, 8), 264 ((M-C$_3$H$_7$+H)$^+$, 17), 229 (18), 187 (9), 156 (C$_3$H$_{16}$N$^+$, 12), 91 (C$_7$H$_{17}^+$, 100), 86 (12), 84 (22), 51 (13), 49 (50), 47 (10). IR (KBr): $\tilde{\nu}$ 3481 (m) cm$^{-1}$, 3290 (w), 3143 (m), 2957 (w), 2930 (w), 2870 (w), 1629 (m), 1578 (s), 1543 (s), 1482 (m), 1453 (m), 1437 (m), 1422 (m), 1414 (m), 1389 (w), 1359 (m), 1283 (w), 1230 (w), 1139 (w), 1088 (m), 1033 (w), 970 (w), 907 (w), 847 (w), 827 (w), 782 (w), 726 (s), 692 (w), 642 (w), 618 (w), 564 (w). Anal. calcd. for C$_{19}$H$_{22}$N$_4$ (306.4) : C 74.48, H 7.24, N 18.29. Found: C 74.29, H 7.18, N 18.45.
4. $^1$H and $^{13}$C MNR Spectra of Compounds 3a-i, 9a-b, and 11a-j

$^1$H NMR of 3a in DMSO-$d_6$ at 298 K ($\delta$ in ppm).

$^1$H NMR of 3a in DMSO-$d_6$ at 298 K ($\delta$ in ppm).
$^{13}$C NMR of 3a in DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3a in DMSO-d$_6$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 3b in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^{13}$C NMR of 3b in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3b in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3c in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of 3c in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3c in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3d in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 3d in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3d in CDCl$_3$ at 297 K ($\delta$ in ppm).
\( ^1H \) NMR of 3e in CDCl\(_3\) at 297 K (\( \delta \) in ppm).
$^{13}\text{C}$ NMR of $3e$ in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}\text{C}$ DEPT 135-NMR of $3e$ in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3f in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of 3f in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3f in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3g in CDCl$_3$ at 297 K ($\delta$ in ppm). *Residual Water in CDCl$_3$. 
$^{13}$C NMR of 3g in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 3g in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 3h in CDCl$_3$ at 297 K (δ in ppm).
$^{13}$C NMR of 3h in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 3h in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 3i in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of 3i in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 3i in CDCl$_3$ at 297 K (δ in ppm).
$^1$H NMR of 9a in CDCl$_3$ at 299 K (δ in ppm).
$^{13}$C NMR of 9a in CDCl$_3$ at 300 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 9a in CDCl$_3$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 9b in CDCl$_3$ at 297 K (δ in ppm). *Residual Water in CDCl$_3$. 

[Chemical structure and NMR spectrum image]
$^{13}$C NMR of 9b in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 9b in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 11a in DMSO-$d_6$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
13C NMR of 11a in DMSO-d6 at 298 K (δ in ppm).

13C DEPT 135-NMR of 11a in DMSO-d6 at 298 K (δ in ppm). *Impurities from residual solvents.
$^1$H NMR of 11b in CDCl$_3$ at 300 K ($\delta$ in ppm).
$^{13}$C NMR of 11b in CDCl$_3$ at 300 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 11b in CDCl$_3$ at 300 K ($\delta$ in ppm).
$^1$H NMR of 11c in CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 11c in CDCl$_3$ at 298 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 11c in CDCl$_3$ at 298 K (δ in ppm).
$^1$H NMR of 11d in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 11d in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 11d in CDCl$_3$ at 297 K (δ in ppm).
$^1$H NMR of 11e in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of **11e** in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT-135 NMR of **11e** in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 11e in DMSO-$d_6$ at 298 K (δ in ppm).
$^{13}$C NMR of 11e in DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 11e in DMSO-d$_6$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 11e in acetone-d$_6$ at 298 K (δ in ppm).
$^{13}$C NMR of 11e in acetone-$d_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 11e in acetone-$d_6$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 11f in DMSO-$d_6$ at 298 K ($\delta$ in ppm).
$^{13}$C NMR of 11f in DMSO-d$_6$ at 298 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 11f in DMSO-d$_6$ at 298 K (δ in ppm).
$^1$H NMR of 11g in CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 11g in CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 11g in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 11h in DMSO-d$_6$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 11h in DMSO-d$_6$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C DEPT 135-NMR of 11h in CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 11i in CDCl$_3$ at 298 K (δ in ppm).
$^{13}$C NMR of 11i in CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 11i in CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 11j in CDCl$_3$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 11j in CDCl$_3$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 11j in CDCl$_3$ at 297 K (δ in ppm).
Table 3. Crystal data and structure refinement for 1-(1-Benzyl-1H-indol-3-yl)hept-2-yn-1-one (3b).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Empirical formula</td>
<td>$C_{22}H_{21}NO$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>315.40</td>
</tr>
<tr>
<td>Temperature</td>
<td>200(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P2_1/n$</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 12.616(1)$ Å</td>
</tr>
<tr>
<td></td>
<td>$\alpha = 90.0$ deg.</td>
</tr>
<tr>
<td></td>
<td>$b = 7.4046(9)$ Å</td>
</tr>
<tr>
<td></td>
<td>$\beta = 104.449(3)$ deg.</td>
</tr>
<tr>
<td></td>
<td>$c = 19.386(2)$ Å</td>
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<td></td>
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<tr>
<td>Density (calculated)</td>
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</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.07 mm$^{-1}$</td>
</tr>
<tr>
<td>Crystal shape</td>
<td>irregular</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.27 x 0.07 x 0.05 mm$^3$</td>
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<tr>
<td>Crystal color</td>
<td>colorless</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.8 to 22.5 deg.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>$-13 \leq h \leq 13$, $-7 \leq k \leq 7$, $-20 \leq l \leq 20$</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>10845</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2278 (R(int) = 0.0456)</td>
</tr>
<tr>
<td>Observed reflections</td>
<td>1771 (I &gt;2$\sigma$(I))</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.00 and 0.98</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
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<td>Goodness-of-fit on $F^2$</td>
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<tr>
<td>Final R indices (I&gt;2$\sigma$(I))</td>
<td>$R1 = 0.039$, $wR2 = 0.083$</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.12 and -0.14 eÅ$^{-3}$</td>
</tr>
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</table>
Table 4. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for 3b. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

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<th>z</th>
<th>U_{eq}</th>
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<td>0.0165(2)</td>
<td>0.6613(1)</td>
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<tr>
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<td>0.8863(1)</td>
<td>0.0375(4)</td>
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<tr>
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<tr>
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<td>0.0317(5)</td>
</tr>
<tr>
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<td>0.0996(2)</td>
<td>0.8163(1)</td>
<td>0.0324(5)</td>
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<tr>
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<td>0.0781(3)</td>
<td>0.8021(1)</td>
<td>0.0389(5)</td>
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<tr>
<td>C6</td>
<td>-0.0675(2)</td>
<td>0.1002(3)</td>
<td>0.8571(1)</td>
<td>0.0460(6)</td>
</tr>
<tr>
<td>C7</td>
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<td>0.9256(1)</td>
<td>0.0483(6)</td>
</tr>
<tr>
<td>C8</td>
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<td>0.1617(3)</td>
<td>0.9414(1)</td>
<td>0.0435(6)</td>
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<tr>
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<td>0.1401(2)</td>
<td>0.8860(1)</td>
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<tr>
<td>C10</td>
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<tr>
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<td>0.0773(3)</td>
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<td>0.0391(5)</td>
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<tr>
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<td>-0.1046(3)</td>
<td>1.0018(1)</td>
<td>0.0490(6)</td>
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<tr>
<td>C13</td>
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<td>0.0571(7)</td>
</tr>
<tr>
<td>C14</td>
<td>0.3924(2)</td>
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<td>0.0593(7)</td>
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<tr>
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<td>0.8480(10)</td>
<td>0.051(6)</td>
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<tr>
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<td>0.9629(11)</td>
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</tr>
<tr>
<td>H8</td>
<td>0.1470(14)</td>
<td>0.188(2)</td>
<td>0.9882(10)</td>
<td>0.039(5)</td>
</tr>
<tr>
<td>H10A</td>
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<td>0.329(3)</td>
<td>0.9628(10)</td>
<td>0.056(6)</td>
</tr>
<tr>
<td>H10B</td>
<td>0.4208(17)</td>
<td>0.206(3)</td>
<td>0.9305(10)</td>
<td>0.054(6)</td>
</tr>
<tr>
<td>H12</td>
<td>0.3165(16)-0.151(3)</td>
<td>0.9555(12)</td>
<td>0.054(6)</td>
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</tr>
<tr>
<td>H13</td>
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</tr>
<tr>
<td>H14</td>
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<tr>
<td>H24B</td>
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<td>0.5877(10)</td>
<td>0.053(6)</td>
</tr>
<tr>
<td>H25A</td>
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</tr>
<tr>
<td>H25B</td>
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<td>0.041(5)</td>
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<tr>
<td>H26A</td>
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<td>0.5795(11)</td>
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<tr>
<td>H26B</td>
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<tr>
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</tr>
<tr>
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<td>0.166(4)</td>
<td>0.7118(15)</td>
<td>0.100(10)</td>
</tr>
<tr>
<td>H27C</td>
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<td>0.080(3)</td>
<td>0.6476(13)</td>
<td>0.082(8)</td>
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Table 5. Hydrogen coordinates and isotropic displacement parameters (Å²) for 3b.

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<th>y</th>
<th>z</th>
<th>Ueq</th>
</tr>
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<tr>
<td>H2</td>
<td>0.3439(16)</td>
<td>0.130(2)</td>
<td>0.8091(9)</td>
<td>0.037(5)</td>
</tr>
<tr>
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<td>0.8480(10)</td>
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<tr>
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<tr>
<td>H8</td>
<td>0.1470(14)</td>
<td>0.188(2)</td>
<td>0.9882(10)</td>
<td>0.039(5)</td>
</tr>
<tr>
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<td>0.9628(10)</td>
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<td>0.083(3)</td>
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<td>0.271(3)</td>
<td>1.0844(10)</td>
<td>0.050(6)</td>
</tr>
<tr>
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</tr>
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<td>H27C</td>
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<td>0.080(3)</td>
<td>0.6476(13)</td>
<td>0.082(8)</td>
</tr>
</tbody>
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**Table 6.** Anisotropic displacement parameters (Å²) for 3b. The anisotropic displacement factor exponent takes the form: -2π²(h²a²U₁₁ + ... + 2hkab¹⁵U₁₂).

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<tr>
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<th>U₁₁</th>
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<th>U₃₃</th>
<th>U₂₃</th>
<th>U₁₃</th>
<th>U₁₂</th>
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<tr>
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<tr>
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<td>0.0009(8)</td>
<td>0.0039(9)</td>
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<tr>
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<td>0.0026(8)</td>
<td>0.0092(10)</td>
<td>0.0020(9)</td>
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<tr>
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<td>0.0494(15)</td>
<td>0.0085(10)</td>
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<td>0.0141(12)</td>
<td>-0.0008(10)</td>
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<tr>
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<td>0.0295(11)</td>
<td>0.0313(12)</td>
<td>0.0031(8)</td>
<td>0.0103(10)</td>
<td>-0.0014(9)</td>
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<td>0.0508(16)</td>
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<td>-0.0002(11)</td>
<td>-0.0004(11)</td>
<td>-0.0156(12)</td>
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<td>0.074(2)</td>
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Table 7. Bond lengths (Å) and angles (deg) for 3b.

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</tr>
<tr>
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<tr>
<td>C2-H2 0.943(19)</td>
<td>C8-C7-C6 121.7(2)</td>
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<td>C3-C4 1.437(3)</td>
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<td>C3-C21 1.442(3)</td>
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<td>C4-C9 1.405(3)</td>
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<td>C5-C6 1.376(3)</td>
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<td>C6-C7 1.392(3)</td>
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<td>C23-C24 1.462(3)</td>
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<td>C11-C16-H16 119.0(11)</td>
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<td>C24-H24B 1.00(2)</td>
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</tr>
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<td>C26-H26B 1.03(2)</td>
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<td>Bond</td>
<td>Angle</td>
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<td>----------------------</td>
<td>-------------</td>
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<td>H26A-C26-H26B</td>
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<td>H27B-C27-H27C</td>
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Figure 1. X-ray analysis of compound 3b.
Table 8. Crystal data and structure refinement for 4-(1-Benzyl-1H-indol-3-yl)-6-butylpyrimid-2-yl-amine (11b).

<table>
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<th>Value</th>
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<td>Temperature</td>
<td>200(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 1</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.4203(3) Å, ( \alpha = 98.244(1) ) deg.</td>
</tr>
<tr>
<td></td>
<td>b = 10.0329(4) Å, ( \beta = 91.059(1) ) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 15.2326(7) Å, ( \gamma = 90.533(1) ) deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>970.82(7) Å^3</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.22 g/cm^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.07 mm(^{-1})</td>
</tr>
<tr>
<td>Crystal shape</td>
<td>polyhedron</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.50 x 0.14 x 0.10 mm(^3)</td>
</tr>
<tr>
<td>Crystal color</td>
<td>colorless</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.0 to 27.5 deg.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-8&lt;h&lt;8, -13&lt;k&lt;12, -19&lt;l&lt;19</td>
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<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
<td>4397 (R(int) = 0.0336)</td>
</tr>
<tr>
<td>Observed reflections</td>
<td>2913 (I &gt;2σ(I))</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.99 and 0.96</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
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<tr>
<td>Goodness-of-fit on F^2</td>
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</tr>
<tr>
<td>Final R indices (I&gt;2σ(I))</td>
<td>R1 = 0.048, wR2 = 0.101</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.24 and -0.17 eÅ(^{-3})</td>
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</table>
Table 9. Atomic coordinates and equivalent isotropic displacement parameters (Å²) for 11b. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
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<td>0.7751(1)</td>
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<td>0.8362(1)</td>
<td>0.0328(4)</td>
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<td>-0.1347(2)</td>
<td>1.0292(1)</td>
<td>0.0440(4)</td>
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<tr>
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<tr>
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<td>1.1769(1)</td>
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<tr>
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<td>0.0741(1)</td>
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<td>0.0282(3)</td>
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<tr>
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<td>0.0305(3)</td>
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<tr>
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Table 10. Hydrogen coordinates and isotropic displacement parameters (Å²) for 11b.

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<th>y</th>
<th>z</th>
<th>U_{eq}</th>
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<td>0.8917</td>
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<tr>
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<tr>
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<td>0.9904</td>
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<tr>
<td>H16</td>
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<td>0.6792</td>
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<tr>
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Table 11. Anisotropic displacement parameters (Å$^2$) for 11b. The anisotropic displacement factor exponent takes the form: -2 pi$^2$ (h$^2$ a$^*^2$ U$_{11}$ + ... + 2 h k a$^*$ b$^*$ U$_{12}$).

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<th>Atom</th>
<th>U$_{11}$</th>
<th>U$_{22}$</th>
<th>U$_{33}$</th>
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<tr>
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<td>0.0319(8)</td>
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<td>0.0025(6)</td>
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<td>0.0016(7)</td>
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<tr>
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### Table 12. Bond lengths (Å) and angles (deg) for 11b.

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Figure 2. X-ray analysis of compound 11b.
Figure 3. Intermolecular hydrogen bond formation in the crystal of 11b.
References:


“Three-component synthesis of N-Boc-4-iodopyrroles and sequential one-pot alkynylation”, Eugen Merkul, Christina Boersch, Walter Frank, Thomas J. J. Müller, 

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Three-Component Synthesis of N-Boc-4-iodopyrroles and Sequential One-Pot Alkynylation\textsuperscript{11}

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ABSTRACT

(Hetero)aryl-, alkenyl-, and selected alkyl-substituted acid chlorides can be efficiently coupled with N-Boc-protected propargylamine to produce ynones which are converted in a one-pot fashion to 2-substituted N-Boc-4-iodopyrroles. Upon addition of a further alkyne, another Sonogashira coupling can be carried out in a one-pot fashion. This sequentially Pd/Cu-catalyzed process represents a very mild and efficient entry to 2,4-disubstituted N-Boc-pyrroles.

Among five-membered heterocycles, pyrroles are the most prominent ones\textsuperscript{1} since they constitute important classes of natural products,\textsuperscript{2} synthetic pharmaceuticals,\textsuperscript{3} and electrically conducting materials such as polypyrroles.\textsuperscript{4} Therefore, the development of new pyrrole syntheses and synthetic strategies has remained an ongoing challenge.\textsuperscript{5} In particular, multicomponent approaches have inevitably become increasingly important due to their elegance and practicability.\textsuperscript{6} Furthermore, the quest for mild synthetic methods for compounds with unusual substitution patterns such as 2,4-disubstituted pyrroles has turned out to be nontrivial.\textsuperscript{7} As part of our program to develop multicomponent syntheses of heterocycles initiated by transition-metal catalysis,\textsuperscript{8} a strategy based upon alkynones via Sonogashira coupling\textsuperscript{9} becomes apparent. Here, we communicate a concise, one-pot synthesis of Boc-protected 2-substituted 4-iodopyrroles and first examples of sequentially Pd/Cu-catalyzed subsequent alkynylations, also in a one-pot fashion.

In the past years, the Sonogashira coupling of acid chlorides with terminal alkynes using only 1 equiv of triethylamine has proven to be a very effective tool for the formation of ynones,\textsuperscript{10} which can be further reacted with various nucleophiles in a one-pot fashion,\textsuperscript{11} opening an entry to many consecutive multicomponent syntheses of hetero-
cycles. Most interestingly, the subsequent additions to alkyrones are restricted to not only Brønsted basic conditions but also Brønsted acid mediated transformations for the one-pot synthesis of halofurans, and oxazoles via the intermediacy of propargyl ketone derivatives can be easily realized as a consequence of the mild reaction conditions of the Sonogashira coupling (Scheme 1).

Scheme 1. Switching Conditions from Brønsted Basic to Brønsted Acidic Conditions Leading to Coupling—Addition—Cyclocondensation and Coupling—Cycloisomerization Sequences via Propargyl Ketone Derivatives


Halopyrroles are valuable synthetic building blocks for synthetic transformations, and therefore, a multicomponent approach would be highly desirable. For the three-component synthesis of the 4-iodopyrroles with a nitrogen protecting group, propargyl amides appear to be the most suitable starting materials. Since the cycloisomerization to an oxazole under acidic conditions could jeopardize this endeavor, the choice of the right nitrogen protecting group plays a key role. The Boc group is a versatile carbamate protecting group for the pyrrole nitrogen atom, useful for many transformations on the pyrrole core and easily removable. Therefore, upon reacting toluoyl chloride (1a) and N-Boc-protected propargylamine (2a) under modified Sonogashira conditions, the intermediate alkynone 3a was obtained. Without isolation, the concluding addition—cyclocondensation furnishes the N-Boc-4-iodo-2-p-tolyopyrrole (4a) (Scheme 2). The final addition—cyclocondensation step was optimized for the sequence by variation of the amount of PTSA • H2O, the added cosolvent, and the reaction time...
Table 1. Optimization of the Final Addition–Cyclocondensation Step within the One-Pot Three-Component Synthesis of 4-Iodopyrrole 4a

<table>
<thead>
<tr>
<th>entry</th>
<th>PTSA · H₂O (equiv)</th>
<th>added cosolvent</th>
<th>reaction time (h)</th>
<th>4-iodopyrrole 4a (isolated yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>MeOH</td>
<td>22a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>t-BuOH</td>
<td>19α</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>t-BuOH</td>
<td>19</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>t-BuOH</td>
<td>1</td>
<td>69</td>
</tr>
</tbody>
</table>

a After 1 h the reaction was not complete according to TLC monitoring.

(Table 1). The best conditions smoothly provided the desired product 4a in 69% isolated yield within 1 h upon applying 2 equiv of PTSA·H₂O and t-BuOH as the alcoholic additive (entry 4). Interestingly, the yields of 4a were higher than that of the isolated intermediate ynone 3a.16

With this mild, quick and practical protocol in hand we set out to screen the scope of this reaction (Scheme 3, Table 2).

Scheme 3. One-Pot Three-Component Synthesis of 4-Iodopyrroles 4


(12) Upon upscaling to a 5 mmol level, an even higher yield of the 4-iodopyrrole 4a can be obtained (Table 2, entry 1 vs Table 1, entry 4). Further upscaling to 30 mmol furnished compound 4d in 77% isolated yield (73% yield on the 5 mmol scale, Table 2, entry 4). The structures of the 4-iodopyrroles 4 were unambiguously assigned by spectroscopic characterization and combustion analysis and later corroborated by an X-ray crystal structure analysis for compound 4d (Figure 1).

The sequence starts with easily accessible starting materials and gives good yields of 4-iodopyrroles 4, and it is easy to perform with a simple catalyst system and under mild conditions.18 It was found to be quite general with respect to the underlying acid chlorides 1. Aromatic substituents bearing electroneutral (entry 5), electron-withdrawing (entries 6 and 7), and electron-donating (entries 1–4) substituents even in the ortho-position (entry 3) are tolerated. Furthermore, heteroaryl (entry 8), alkenyl (entry 9), cyclopropyl (entry 10), and stericly demanding adamantly (entry 11) substituents can be effectively carried through the sequence.

However, for nonaromatic acid chlorides, the reaction times of coupling were slightly longer than 1 h.

![Table 2. One-Pot Three-Component Synthesis of 4-Iodopyrroles 4](image)
The obtained 4-iodopyrroles 4 are highly useful synthetic building blocks, and the first scouting experiments were performed in the sense of a sequentially Pd/Cu-catalyzed reaction since the catalyst system should be still operative after the coupling—addition—cyclocondensation sequence. Therefore, just upon addition of another terminal alkyne to the reaction mixture, N-Boc-2-aryl-4-alkynylpyrroles were obtained in good yields (Scheme 4). The conditions are sufficiently mild to leave the Boc group uncleaved. In comparison to the coupling—addition—cyclocondensation—coupling one-pot synthesis (58% yield), the two-step synthesis of the alkynyl pyrrole furnishes a comparable overall yield (61%).

In conclusion, we disclose an efficient one-pot three-component synthesis of 2-substituted N-Boc-4-iodopyrroles that can easily be upscaled to multigrams, and we also show preliminary examples of a coupling—addition—cyclocondensation—coupling sequence to 4-alkynyl-N-Boc-pyrroles in good yields. This latter principle appears to be quite general and further terminating cross-coupling reactions can be easily envisioned. Studies taking advantage of this versatile one-pot multicomponent strategy to iodopyrroles as valuable building blocks for the synthesis of 2,4-disubstituted pyrrole derivatives are currently underway.

Acknowledgment. The financial support of this work by Merck Serono, Darmstadt, and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds 3a, 3b, 4, and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900581A

(19) Boc as an electron-withdrawing group allows the 4-iodopyrroles, which are notoriously unstable with electron-donating groups at the pyrrole nitrogen, to be handled. They are storable for months in refrigerator under argon without decomposition.

(20) (a) For a review, see e.g.: Müller, T. J. J. Top. Organomet. Chem. 2006, 19, 149. (b) For recent examples, see e.g.: Liao, W.-W.; Müller, T. J. J. Synlett 2006, 3469. (c) See also ref 12b.

Figure 1. ORTEP plot of compound 4d.
Three-Component Synthesis of N-Boc 4-Iodo Pyrroles and Sequential One-Pot Alkynylation

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4. Synthesis of pyrroles 6

4.1. Synthesis of pyrrole 6a by \textit{Sonogashira} coupling of pyrrole 4a

4.1.1. Procedure

4.2. Three-component synthesis of pyrroles 6 by coupling-addition-cyclocondensation-coupling sequence

4.2.1. Procedure

4.3. Spectroscopic and analytical data of compounds 6

4.3.1. tert-Butyl 4-(hex-1-ynyl)-2-\textit{p}-tolyl-1\textit{H}-pyrrole-1-carboxylate (6a)

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4.3.3. tert-Butyl 2-(4-methoxyphenyl)-4-(2-phenylethynyl)-1\textit{H}-pyrrole-1-carboxylate (6c)

5. \textit{\textit{\textit{1}}}H and \textit{\textit{\textit{13}}}C NMR spectra

5.1. \textit{\textit{\textit{1}}}H and \textit{\textit{\textit{13}}}C NMR spectra of compounds 3a and 3b

5.2. \textit{\textit{\textit{1}}}H and \textit{\textit{\textit{13}}}C NMR spectra of compounds 4a-k

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6. Crystallographic data of compound 4d

7. References
1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using MBraun system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased by Sigma-Aldrich Chemie GmbH.

tert-Butyl prop-2-ynylcarbamate (2) was prepared according to literature procedure\(^1\) but is also commercially available by Synthonix. Commercial grade reagents were used as supplied without further purification and were purchased from Acros Organics, Sigma-Aldrich Chemie GmbH, Fluka AG, ABCR GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, Riedel-de Haën, and Merck Serono KGaA.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from Merck Serono KGaA Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F\(_{254}\) 5 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

\(^1\)H, \(^{13}\)C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. TMS was used as reference (\(\delta = 0.0\)) or the resonance of the solvent was locked as internal standard (CDCl\(_3\): \(^1\)H \(\delta 7.24, ^{13}\)C \(\delta 77.2\)). The multiplicities of signals were abbreviated as follows: s: singulett; d: dublett; t: triplett; dd: dublett of dubletts, m: multiplett and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

X-ray structure was measured on Stoe IPDS.
2. Synthesis of Ynones 3 by Modified Sonogashira Coupling

2.1. General Procedure

\[
\begin{align*}
\text{R}^1\text{COCl} & \quad \text{H-N-Boc} \\
\text{1} & \quad \text{2} & \quad \text{3}
\end{align*}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (28 mg, 0.04 mmol) and CuI (16 mg, 0.08 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.28 mL, 2.00 mmol), 2.00 mmol of the acid chloride 1 and tert-butyl prop-2-ynylcarbamate (2) (310 mg, 2.00 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 50 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE) to give the ynones 3.

The experimental details are depicted in Table 1.

**Table 1.** Experimental details of the synthesis of ynones 3 by modified Sonogashira coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid chloride 1 (isolated yield %)</th>
<th>Ynone 3 (isolated yield %)</th>
<th>Chromatographic purification eluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316 mg (2.00 mmol)</td>
<td>295 mg (1.08 mmol, 54 %)</td>
<td>PE-EE = 7:1</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>3a</td>
<td>(R_f) (PE-EE = 7:1 : 0.16)</td>
</tr>
<tr>
<td>2</td>
<td>352 mg (2.00 mmol)</td>
<td>343 mg (1.19 mmol, 59 %)</td>
<td>PE-EE = 5:1 → 4:1 → 3:1</td>
</tr>
<tr>
<td></td>
<td>1d</td>
<td>3b</td>
<td>(R_f) (PE-EE = 3:1 : 0.41)</td>
</tr>
</tbody>
</table>
2.2. Spectroscopic and Analytical Data of Compounds 3a and 3b

2.2.1. tert-Butyl 4-oxo-4-\textit{p}-tolylbut-2-ynylcarbamate (3a)

\[
\begin{align*}
\text{C}_16\text{H}_{19}\text{NO}_3 \\
273.33
\end{align*}
\]

According to the general procedure 295 mg (54 % yield) were obtained as a beige solid. Mp 70-71 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 1.48 (s, 9 H), 2.43 (s, 3 H), 4.22 (d, \(J = 4.1\) Hz, 2 H), 5.0 (br, 1 H), 7.27 (d, \(J = 7.9\) Hz, 2 H), 8.01 (d, \(J = 8.2\) Hz, 2 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 21.8 (CH\textsubscript{3}), 28.3 (CH\textsubscript{3}), 30.8 (CH\textsubscript{2}), 80.5 (C\textsubscript{quat}), 81.0 (C\textsubscript{quat}), 90.1 (C\textsubscript{quat}), 129.3 (CH), 129.8 (CH), 134.1 (C\textsubscript{quat}), 145.5 (C\textsubscript{quat}), 155.2 (C\textsubscript{quat}), 177.4 (C\textsubscript{quat}). EI + MS (\textit{m/z} (%)): 273 (M\textsuperscript{+}, 0.2), 258 ((M-CH\textsubscript{3})\textsuperscript{+}, 0.7), 217 ((M-C\textsubscript{4}H\textsubscript{4}O\textsuperscript{+}), 13), 200 ((M-C\textsubscript{5}H\textsubscript{9}O\textsuperscript{+}), 7), 173 ((M-C\textsubscript{5}H\textsubscript{9}O\textsuperscript{+}), 4), 161 (9), 144 (15), 129 (17), 119 (C\textsubscript{7}H\textsubscript{15}O\textsuperscript{+}, 28), 115 (11), 91 (C\textsubscript{7}H\textsubscript{17}\textsuperscript{+}, 27), 65 (C\textsubscript{3}H\textsubscript{5}\textsuperscript{+}, 12), 59 (19), 57 (C\textsubscript{4}H\textsubscript{9}\textsuperscript{+}, 100), 41 (38), 39 (C\textsubscript{3}H\textsubscript{5}\textsuperscript{+}, 13). IR (KBr): \(\overline{\text{v}}\) 3377 (s) cm\textsuperscript{-1}, 2986 (w), 2968 (m), 2934 (w), 2227 (m), 2187 (w), 1689 (s), 1647 (s), 1607 (s), 1574 (m), 1519 (s), 1461 (w), 1449 (w), 1425 (w), 1394 (w), 1365 (m), 1293 (s), 1266 (s), 1213 (w), 1179 (s), 1115 (w), 1099 (m), 1047 (w), 1020 (w), 926 (m), 896 (m), 866 (m), 837 (m), 790 (w), 768 (w), 740 (m), 680 (m), 594 (m), 505 (w). Anal. calcd for C\textsubscript{16}H\textsubscript{19}NO\textsubscript{3} (273.3): C 70.31, H 7.01, N 5.12. Found: C 70.10, H 7.21, N 5.13.
2.2.2. tert-Butyl 4-(4-methoxyphenyl)-4-oxobut-2-ynylcarbamate (3b)

![Structural formula of the compound](image)

According to the general procedure 343 mg (59 % yield) were obtained as a beige solid. Mp 106-107 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.48 (s, 9 H), 3.89 (s, 3 H), 4.21 (d, $J = 4.1$ Hz, 2 H), 4.9 (br, 1 H), 6.94 (d, $J = 8.8$ Hz, 2 H), 8.09 (d, $J = 8.8$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 28.3 (CH$_3$), 30.8 (CH$_2$), 55.6 (CH$_3$), 80.5 (C$_{quat}$), 81.0 (C$_{quat}$), 89.8 (C$_{quat}$), 113.9 (CH), 129.8 (C$_{quat}$), 132.1 (CH), 155.3 (C$_{quat}$), 164.6 (C$_{quat}$), 176.3 (C$_{quat}$). EI + MS ($m/z$ (%)): 289 (M$^+$, 0.7), 233 ((M-C$_4$H$_9$O$^+$), 32), 216 ((M-C$_4$H$_9$O$_2^+$), 9), 189 ((M-C$_3$H$_5$O$_2$+H)$^+$, 5), 177 (10), 160 (C$_{10}$H$_8$O$_2^+$, 23), 145 (20), 135 (C$_8$H$_7$O$_2^+$, 38), 107 (C$_7$H$_5$O$^+$, 5), 92 (C$_7$H$_8^+$, 13), 77 (C$_6$H$_5^+$, 14), 59 (15), 57 (C$_4$H$_6^+$, 100), 41 (42), 39 (C$_3$H$_3^+$, 10). IR (KBr): $\tilde{v}$ 3330 (s) cm$^{-1}$, 3020 (w), 2978 (m), 2935 (w), 2843 (w), 2232 (m), 1867 (s), 1631 (s), 1598 (s), 1572 (s), 1528 (s), 1456 (w), 1428 (m), 1392 (w), 1368 (w), 1355 (w), 1257 (s), 1169 (s), 1120 (w), 1098 (m), 1053 (w), 1023 (m), 938 (w), 905 (w), 853 (m), 786 (w), 762 (w), 737 (w), 689 (w), 653 (w), 653 (w), 627 (w), 599 (w), 517 (w). Anal. calcd for C$_{16}$H$_{19}$NO$_4$ (289.3): C 66.42, H 6.62, N 4.84. Found: C 66.33, H 6.68, N 4.80.
3. Three-Component Synthesis of Pyrroles 4 by Coupling-Addition-Cyclocondensation Sequence

3.1. General Procedure

\[
\text{R}^1\text{C}=\text{O} \quad 1
\]

\[
\begin{align*}
\text{H} & \quad 2 \\
\text{I} & \quad 4
\end{align*}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (70 mg, 0.10 mmol) and CuI (39 mg, 0.20 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 25 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.69 mL, 5.00 mmol), 5.00 mmol of the acid chloride 1 and tert-butyl prop-2-ynylcarbamate (2) (776 mg, 5.00 mmol) were successively added to the mixture which was stirred at room temperature until the conversion was complete (monitored by TLC). Then, sodium iodide (3.79 g, 25.0 mmol), toluene-4-sulfonic acid monohydrate (1.94 g, 10.0 mmol) and 5 ml of tert-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 50 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petroether (boiling range 40-60 °C)/ethyl acetate (PE-EE) to give the pyrroles 4.

The experimental details are depicted in Table 2.
Table 2. Experimental details of the synthesis of pyrroles 4 by coupling-addition-cyclocondensation sequence.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid chloride 1</th>
<th>Reaction time (1st step)</th>
<th>Pyrole 4 (isolated yield)</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>789 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.40 g (3.65 mmol, 73 %)</td>
<td>R_f (PE/EE = 100:1) = 0.34</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td></td>
<td>4a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>789 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.42 g (3.70 mmol, 74 %)</td>
<td>R_f (PE/EE = 100:1) = 0.27</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td></td>
<td>4b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>773 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.38 g (3.60 mmol, 72 %)</td>
<td>R_f (PE/EE = 100:1) = 0.22</td>
</tr>
<tr>
<td></td>
<td>1c</td>
<td></td>
<td>4c</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>879 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.46 g (3.66 mmol, 73 %)^1</td>
<td>R_f (PE/EE = 100:1) = 0.31</td>
</tr>
<tr>
<td></td>
<td>1d</td>
<td></td>
<td>4d</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>710 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.32 g (3.58 mmol, 72 %)</td>
<td>R_f (PE/EE = 100:1) = 0.23</td>
</tr>
<tr>
<td></td>
<td>1e</td>
<td></td>
<td>4e</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>875 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.24 g (3.08 mmol, 62 %)</td>
<td>R_f (PE/EE = 100:1) = 0.32</td>
</tr>
<tr>
<td></td>
<td>1f</td>
<td></td>
<td>4f</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>793 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.49 g (3.84 mmol, 75 %)</td>
<td>R_f (PE/EE = 100:1) = 0.22</td>
</tr>
<tr>
<td></td>
<td>1g</td>
<td></td>
<td>4g</td>
<td></td>
</tr>
</tbody>
</table>

1. When the reaction was performed on 30 mmol scale, 9.23 g (23.1 mmol, 77 % yield) of the pyrrole 4e could be isolated.
Continuation of Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid chloride 1</th>
<th>Reaction time (1st step)</th>
<th>Pyrrole 4 (isolated yield)</th>
<th>Chromatographic purification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R_f (eluent)</td>
</tr>
<tr>
<td>8</td>
<td>733 mg (5.00 mmol)</td>
<td>1 h</td>
<td>1.19 g (3.17 mmol, 63 %)</td>
<td>PE/EE = 100:1</td>
</tr>
<tr>
<td></td>
<td>1h</td>
<td></td>
<td></td>
<td>R_f (PE/EE = 100:1) = 0.31</td>
</tr>
<tr>
<td>9</td>
<td>859 mg (5.00 mmol)</td>
<td>21 h</td>
<td>1.38 g (3.48 mmol, 70 %)</td>
<td>PE/EE = 100:1</td>
</tr>
<tr>
<td></td>
<td>1i</td>
<td></td>
<td></td>
<td>R_f (PE/EE = 100:1) = 0.21</td>
</tr>
<tr>
<td>10</td>
<td>533 mg (5.00 mmol)</td>
<td>3 h</td>
<td>1.15 g (3.46 mmol, 69 %)</td>
<td>PE/EE = 100:1</td>
</tr>
<tr>
<td></td>
<td>1j</td>
<td></td>
<td></td>
<td>R_f (PE/EE = 100:1) = 0.35</td>
</tr>
<tr>
<td>11</td>
<td>1.02 g (5.00 mmol)</td>
<td>21 h</td>
<td>1.31 g (3.07 mmol, 61 %)</td>
<td>PE</td>
</tr>
<tr>
<td></td>
<td>1k</td>
<td></td>
<td></td>
<td>R_f (PE) = 0.27</td>
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3.2. Spectroscopic and Analytical Data of Compounds 4a-k

3.2.1. tert-Butyl 4-iodo-2-p-tolyl-1H-pyrrole-1-carboxylate (4a)

\[
\text{C}_{{16}}\text{H}_{{18}}\text{INO}_2
\]

According to the general procedure 1.40 g (73 % yield) were obtained as a colorless solid. Mp 57 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 1.38 (s, 9 H), 2.37 (s, 3 H), 6.21 (d, \(J = 1.9\) Hz, 1 H), 7.15 (d, \(J = 7.9\) Hz, 2 H), 7.20 (d, \(J = 8.2\) Hz, 2 H), 7.40 (d, \(J = 1.9\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 21.3 (CH\(_3\)), 27.6 (CH\(_3\)), 64.4 (C\(_{\text{quat}}\)), 84.2 (C\(_{\text{quat}}\)), 120.4 (CH), 126.8 (CH), 128.4 (CH), 129.0 (CH), 129.9 (C\(_{\text{quat}}\)), 136.8 (C\(_{\text{quat}}\)), 137.5 (C\(_{\text{quat}}\)), 147.9 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 383 (M\(^+\), 16), 327 ((M-C\(_4\)H\(_9\)+H\(^+\), 30), 283 ((M-C\(_3\)H\(_9\)O\(_2\)+H\(^+\), 77), 191 (12), 155 ((M-C\(_3\)H\(_9\)O\(_2\)-I\(^+\), 11), 154 (17), 57 (C\(_4\)H\(_9\)+, 100), 41 (43), 39 (12). IR (KBr): \(\tilde{\nu}\) 3144 (w) cm\(^{-1}\), 2988 (w), 1734 (s), 1686 (m), 1655 (m), 1638 (w), 1561 (w), 1544 (w), 1510 (m), 1475 (m), 1370 (s), 1335 (s), 1297 (s), 1250 (m), 1152 (s), 987 (m), 901 (w), 848 (m), 829 (w), 807 (m), 766 (m), 583 (w). Anal. calcd for C\(_{16}\)H\(_{18}\)INO\(_2\) (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.36, H 4.85, N 3.59.
3.2.2. tert-Butyl 4-iodo-2-m-tolyl-1H-pyrrole-1-carboxylate (4b)

According to the general procedure 1.42 g (74 % yield) were obtained as a colorless solid. Mp 52 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \( \delta \) 1.35 (s, 9 H), 2.36 (s, 3 H), 6.22-6.24 (m, 1 H), 7.08-7.15 (m, 3 H), 7.21-7.25 (m, 1 H), 7.40-7.42 (m, 1 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \( \delta \) 21.3 (CH\textsubscript{3}), 27.5 (CH\textsubscript{3}), 64.3 (C\textsubscript{quat}), 84.2 (C\textsubscript{quat}), 120.5 (CH), 126.2 (CH), 126.9 (CH), 127.6 (CH), 128.4 (CH), 129.8 (CH), 132.8 (C\textsubscript{quat}), 136.7 (C\textsubscript{quat}), 137.1 (C\textsubscript{quat}), 147.9 (C\textsubscript{quat}). EI + MS (\( m/z \) (%)): 383 (M\textsuperscript{+}, 0.2), 327 ((M-C\textsubscript{6}H\textsubscript{5}+H)\textsuperscript{+}, 1), 283 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}+H)\textsuperscript{+}, 5), 156 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}-I+H)\textsuperscript{+}, 1), 155 ((M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}-I)\textsuperscript{+}, 3), 57 (C\textsubscript{4}H\textsubscript{9}+, 100), 41 (22). IR (KBr): \( \tilde{\nu} \) 3134 (w) cm\textsuperscript{-1}, 2981 (m), 1728 (s), 1612 (w), 1587 (w), 1554 (w), 1494 (w), 1467 (m), 1363 (s), 1335 (s), 1295 (s), 1248 (s), 1147 (s), 1094 (m), 1047 (m), 1025 (m), 983 (w), 903 (m), 886 (m), 844 (s), 820 (m), 789 (s), 766 (s), 704 (s), 659 (w), 616 (w), 590 (m), 535 (m). Anal. calcd for C\textsubscript{16}H\textsubscript{18}INO\textsubscript{2} (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.18, H 4.63, N 3.72.
3.2.3. tert-Butyl 4-iodo-2-otolyl-1H-pyrrole-1-carboxylate (4c)

According to the general procedure 1.38 g (72 % yield) were obtained as a pale yellow oil. 

\[ C_{16}H_{18}INO_2 \]

383.22

\[ \begin{align*}
\text{H} & \quad \text{NMR (CDCl}_3, 500 \text{ MHz)} \delta 1.25 (s, 9 \text{ H}), 2.12 (s, 3 \text{ H}), 6.14-6.15 (m, 1 \text{ H}), 7.14-7.20 (m, 3 \text{ H}), 7.23-7.28 (m, 1 \text{ H}), 7.46 (d, J = 1.3 \text{ Hz}, 1 \text{ H}). \\
\text{C} & \quad \text{NMR (CDCl}_3, 125 \text{ MHz)} \delta 19.9 (\text{CH}_3), 27.4 (\text{CH}_3), 64.3 (\text{C}_{\text{quat}}), 83.9 (\text{C}_{\text{quat}}), 120.0 (\text{CH}), 125.2 (\text{CH}), 126.0 (\text{CH}), 128.3 (\text{CH}), 129.3 (\text{CH}), 130.0 (\text{CH}), 133.3 (\text{C}_{\text{quat}}), 135.2 (\text{C}_{\text{quat}}), 137.7 (\text{C}_{\text{quat}}), 147.8 (\text{C}_{\text{quat}}). \\
\text{EI + MS (m/z (%))): 383 (M}^+\text{, 2), 327 ((M-C}_4\text{H}_9\text{+H})^+, 4), 283 ((M-C}_3\text{H}_5\text{O}_2\text{+H})^+, 9), 156 ((M-C}_3\text{H}_5\text{O}_2\text{-I+H})^+, 15), 155 ((M-C}_3\text{H}_5\text{O}_2\text{-I}^+\text{, 20), 154 (34), 127 (19), 89 (18), 78 (16), 57 (C}_4\text{H}_9^+, 100), 41 (30).} \\
\text{IR (Film): } \tilde{\nu} \text{ 3148 (m) cm}^{-1}, 3062 (m), 2980 (s), 2932 (m), 1744 (s), 1605 (w), 1556 (m), 1501 (m), 1474 (s), 1395 (m), 1367 (s), 1334 (s), 1293 (s), 1246 (s), 1151 (s), 1113 (s), 1077 (m), 1047 (w), 986 (s), 942 (w), 905 (s), 846 (s), 814 (m), 798 (m), 764 (s), 725 (m), 667 (w), 604 (w), 589 (m), 520 (w).} \\
\text{Anal. calcd for } C_{16}H_{18}INO_2 \text{ (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.10, H 4.73, N 3.55.} \]
3.2.4. *tert*-Butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (4d)

![Chemical Structure](C_16H_18INO_3_399.22)

According to the general procedure 1.46 g (73 % yield) were obtained as a colorless solid. Mp 71–72 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, $J = 1.9$ Hz, 1 H), 6.88 (d, $J = 8.8$ Hz, 2 H), 7.24 (d, $J = 8.8$ Hz, 2 H), 7.39 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 27.6 (CH$_3$), 55.3 (CH$_3$), 64.4 (C$_{quat}$), 84.2 (C$_{quat}$), 113.1 (CH), 120.3 (CH), 125.3 (C$_{quat}$), 126.7 (CH), 130.4 (CH), 136.5 (C$_{quat}$), 147.9 (C$_{quat}$), 159.3 (C$_{quat}$). EI + MS (m/z (%)):

- 399 (M$^+$, 3), 343 ((M-C$_4$H$_9$+H)$^+$, 11), 299 ((M-C$_3$H$_5$O$_2$+H)$^+$, 16), 298 ((M-C$_3$H$_5$O$_2$)$^+$, 13), 171 ((M-C$_3$H$_5$O$_2$-I)$^+$, 6), 156 (12), 128 (11), 57 (C$_4$H$_9$+$^+$, 100), 41 (34).

IR (KBr): $\tilde{\nu}$ 3145 (m) cm$^{-1}$, 2986 (m), 2934 (w), 2832 (w), 1734 (s), 1609 (m), 1576 (w), 1557 (w), 1511 (s), 1476 (m), 1460 (m), 1435 (w), 1370 (s), 1337 (s), 1293 (s), 1251 (s), 1180 (s), 1151 (s), 1108 (m), 1032 (s), 985 (m), 904 (m), 847 (s), 833 (m), 808 (s), 771 (m), 675 (w), 629 (w), 615 (w), 594 (m), 528 (w), 511 (w).

Anal. calcd for C$_{16}$H$_{18}$INO$_3$ (399.2):

- C 48.14, H 4.54, N 3.51.
- Found: C 48.36, H 4.37, N 3.34.
3.2.5. tert-Butyl 4-iodo-2-phenyl-1H-pyrrole-1-carboxylate (4e)

According to the general procedure 1.32 g (72 % yield) were obtained as a colorless solid. Mp 65-66 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.34 (s, 9 H), 6.24 (d, $J = 1.9$ Hz, 1 H), 7.29-7.37 (m, 5 H), 7.42 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 27.5 (CH$_3$), 64.4 (C$_{\text{quat}}$), 84.3 (C$_{\text{quat}}$), 120.7 (CH), 127.0 (CH), 127.7 (CH), 127.7 (CH), 129.2 (CH), 132.9 (C$_{\text{quat}}$), 136.6 (C$_{\text{quat}}$), 147.9 (C$_{\text{quat}}$). EI + MS (m/z (%)): 369 (M$^+$, 2), 313 ((M-C$_4$H$_9$+H)$^+$, 3), 269 ((M-C$_5$H$_9$O$_2$)$^+$, 8), 141 ((M-C$_5$H$_9$O$_2$-I)$^+$, 12), 114 (11), 57 (C$_4$H$_9^+$, 100), 41 (32). IR (KBr): $\tilde{\nu}$ 3150 (w) cm$^{-1}$, 2969 (w), 1749 (s), 1474 (w), 1445 (w), 1370 (m), 1296 (s), 1261 (m), 1148 (s), 1081 (w), 1032 (w), 986 (w), 903 (w), 849 (w), 820 (w), 771 (w), 745 (w), 693 (w), 664 (w), 593 (w). Anal. calcd for C$_{15}$H$_{16}$INO$_2$ (369.2): C 48.80, H 4.37, N 3.79. Found: C 48.68, H 4.57, N 3.62.
3.2.6. tert-Butyl 4-iodo-2-(p-chlorophenyl)-1H-pyrrole-1-carboxylate (4f)

\[
\begin{align*}
\text{C}_{15}\text{H}_{15}\text{ClINO}_2 \\
403.64
\end{align*}
\]

According to the general procedure 1.24 g (62 % yield) were obtained as a colorless solid. Mp 64 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 1.39 (s, 9 H), 6.24 (d, \(J = 1.9\) Hz, 1 H), 7.23-7.26 (m, 2 H), 7.31-7.34 (m, 2 H), 7.42 (d, \(J = 1.9\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 27.6 (CH\(_3\)), 64.4 (C\(_{\text{quat}}\)), 84.7 (C\(_{\text{quat}}\)), 121.0 (CH), 127.3 (CH), 127.9 (CH), 130.5 (CH), 131.3 (C\(_{\text{quat}}\)), 133.8 (C\(_{\text{quat}}\)), 135.3 (C\(_{\text{quat}}\)), 147.7 (C\(_{\text{quat}}\)). EI + MS \((m/\text{z} (%)\)): 405 (M\((^{37}\text{Cl})^+\), 0.2), 403 (M\((^{35}\text{Cl})^+\), 1.0), 349 ((M\((^{37}\text{Cl})\)-C\(_4\text{H}_9\)+H\)\(^+\), 0.4), 347 ((M\((^{35}\text{Cl})\)-C\(_4\text{H}_9\)+H\)\(^+\), 1.7), 305 ((M\((^{37}\text{Cl})\)-C\(_5\text{H}_9\text{O}_2\)+H\)\(^+\), 2.0), 303 ((M\((^{35}\text{Cl})\)-C\(_5\text{H}_9\text{O}_2\)+H\)\(^+\), 6.3), 177 ((M\((^{37}\text{Cl})\)-C\(_5\text{H}_9\text{O}_2\)-I\)\(^+\), 0.5), 175 ((M\((^{35}\text{Cl})\)-C\(_5\text{H}_9\text{O}_2\)-I\)\(^+\), 1.4), 57 (C\(_4\text{H}_9\)\(^+\), 100), 41 (16). IR (KBr): \(\tilde{\nu}\) 3145 (m) cm\(^{-1}\), 2988 (w), 1735 (s), 1638 (w), 1498 (w), 1467 (w), 1398 (w), 1369 (s), 1339 (m), 1297 (s), 1252 (w), 1153 (s), 1090 (w), 1016 (w), 987 (w), 904 (w), 847 (m), 808 (m), 768 (m), 596 (w). Anal. calcd for C\(_{15}\)H\(_{15}\)ClINO\(_2\) (403.6): C 44.63, H 3.75, N 3.47. Found: C 44.74, H 3.84, N 3.41.
3.2.7. tert-Butyl 4-iodo-2-(p-fluorophenyl)-1H-pyrrole-1-carboxylate (4g)

![Chemical Structure]

According to the general procedure 1.49 g (75 % yield) were obtained as a colorless solid. Mp 74°C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.38 (s, 9 H), 6.23 (d, $J = 1.9$ Hz, 1 H), 7.01-7.07 (m, 2 H), 7.26-7.30 (m, 2 H), 7.42 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 27.6 (CH$_3$), 64.3 (C$_\text{quat}$), 84.5 (C$_\text{quat}$), 114.7 (d, $J = 21.1$ Hz, CH), 120.9 (CH), 127.0 (CH), 128.9 (C$_\text{quat}$), 130.9 (d, $J = 8.2$ Hz, CH), 135.5 (C$_\text{quat}$), 147.8 (C$_\text{quat}$), 162.5 (d, $J = 247.4$ Hz, C$_\text{quat}$). EI + MS (m/z (%)): 387 (M$^+$, 2), 331 ((M-C$_5$H$_9$H$^+$), 3), 287 ((M-C$_5$H$_9$O$_2$H$^+$), 9), 159 ((M-C$_5$H$_9$O$_2$I$^+$), 9), 57 (C$_4$H$_9^+$, 100), 41 (28). IR (KBr): $\tilde{\nu}$ 3147 (w) cm$^{-1}$, 3135 (w), 2984 (w), 1733 (s), 1593 (w), 1552 (w), 1508 (m), 1474 (w), 1370 (s), 1337 (s), 1297 (s), 1250 (m), 1224 (m), 1160 (s), 1096 (w), 1017 (w), 990 (w), 904 (w), 849 (m), 812 (m), 766 (m), 720 (w), 611 (w), 585 (w), 524 (w). Anal. calcd for C$_{15}$H$_{13}$FINO$_2$ (387.2): C 46.53, H 3.90, N 3.62. Found: C 46.52, H 3.96, N 3.44.
3.2.8. tert-Butyl 2-(2-thienyl)-4-iodo-1H-pyrrole-1-carboxylate (4h)

According to the general procedure 1.19 g (63 % yield) were obtained as a colorless solid. Mp 55 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.41 (s, 9 H), 6.37 (d, $J = 1.9$ Hz, 1 H), 7.01 (dd, $J = 5.0$ Hz, $J = 3.5$ Hz, 1 H), 7.05 (dd, $J = 3.5$ Hz, $J = 1.3$ Hz, 1 H), 7.32 (dd, $J = 5.0$ Hz, $J = 1.3$ Hz, 1 H), 7.44 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 27.6 (CH$_3$), 64.1 (C$_{quat}$), 84.5 (C$_{quat}$), 122.6 (CH), 126.2 (CH), 126.5 (CH), 127.7 (CH), 128.3 (CH), 128.5 (C$_{quat}$), 133.0 (C$_{quat}$), 147.6 (C$_{quat}$). EI + MS ($m/z$ (%)): 375 (M$^+$, 2), 319 ((M-C$_4$H$_9$+H)$^+$, 5), 275 ((M-C$_5$H$_9$O$_2$+H)$^+$, 9), 147 ((M-C$_3$H$_9$O$_2$-I)$^+$, 2), 57 (C$_4$H$_9^+$, 100), 41 (20). IR (KBr): $\tilde{\nu}$ 3152 (w) cm$^{-1}$, 2979 (w), 1750 (s), 1655 (w), 1638 (w), 1560 (w), 1543 (w), 1509 (w), 1475 (w), 1420 (w), 1371 (m), 1345 (w), 1305 (s), 1295 (s), 1255 (w), 1219 (w), 1158 (m), 1141 (m), 1081 (w), 932 (w), 903 (w), 850 (w), 818 (w), 768 (w), 699 (w), 592 (w). Anal. calcd for C$_{13}$H$_{14}$INO$_2$S (375.2): C 41.61, H 3.76, N 3.73. Found: C 41.75, H 3.82, N 3.48.
3.2.9. tert-Butyl 2-(phenylethenyl)-4-iodo-1H-pyrrole-1-carboxylate (4i)

According to the general procedure 1.38 g (70 % yield) were obtained as a colorless solid. Mp 84 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.61 (s, 9 H), 6.60 (s, 1 H), 6.87 (d, $J$ = 16.4 Hz, 1 H), 7.21-7.26 (m, 1 H), 7.30-7.36 (m, 3 H), 7.46 (d, $J$ = 7.3 Hz, 2 H), 7.67 (d, $J$ = 16.4 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 28.0 (CH$_3$), 65.3 (C$_{quat}$), 84.7 (C$_{quat}$), 117.2 (CH), 118.3 (CH), 126.5 (CH), 126.7 (CH), 127.7 (CH), 128.6 (CH), 129.6 (CH), 136.0 (C$_{quat}$), 137.1 (C$_{quat}$), 148.1 (C$_{quat}$). EI + MS ($m/z$ (%)): 395 (M$^+$, 2), 339 ((M-C$_4$H$_9$+H)$^+$, 15), 295 ((M-C$_3$H$_5$O$_2$+H)$^+$, 11), 167 ((M-C$_3$H$_5$O$_2$-I)$^+$, 13), 57 (C$_4$H$_9^+$, 100), 41 (18). IR (KBr): $\tilde{\nu}$ 3160 (m) cm$^{-1}$, 3123 (w), 3078 (w), 3024 (w), 2978 (m), 2929 (w), 1813 (w), 1752 (s), 1624 (w), 1596 (w), 1575 (w), 1493 (m), 1471 (m), 1454 (m), 1384 (s), 1370 (s), 1301 (s), 1259 (s), 1237 (s), 1155 (s), 1109 (s), 1077 (s), 1029 (s), 984 (w), 962 (s), 906 (s), 848 (s), 804 (s), 770 (s), 747 (s), 694 (s), 645 (w), 610 (m), 586 (m), 546 (w), 514 (w). Anal. calcd for C$_{17}$H$_{18}$INO$_2$ (395.2): C 51.66, H 4.59, N 3.54. Found: C 51.60, H 4.75, N 3.51.
3.2.10. tert-Butyl 2-(cyclopropyl)-4-iodo-1H-pyrrole-1-carboxylate (4j)

According to the general procedure 1.15 g (69 % yield) were obtained as a colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.56-0.60 (m, 2 H), 0.83-0.88 (m, 2 H), 1.59 (s, 9 H), 2.14-2.21 (m, 1 H), 5.89 (dd, $J$ = 1.9 Hz, $J$ = 1.3 Hz, 1 H), 7.25 (d, $J$ = 1.9 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 7.1 (CH$_2$), 9.4 (CH), 28.0 (CH$_3$), 63.7 (C$_{\text{quat}}$), 84.0 (C$_{\text{quat}}$), 116.2 (CH), 125.7 (CH), 139.7 (C$_{\text{quat}}$), 148.1 (C$_{\text{quat}}$). EI + MS (m/z (%)): 333 (M$^+$, 4), 277 ((M-C$_5$H$_9$I$^+$, 15), 233 ((M-C$_5$H$_9$O$_2$)+, 8), 106 ((M-C$_5$H$_9$O$_2$-I$^+$, 13), 105 ((M-C$_5$H$_9$O$_2$-I$^+$, 5), 57 (C$_5$H$_9^+$, 100), 41 (19). IR (Film): $\tilde{\nu}$ 3157 (m) cm$^{-1}$, 3087 (m), 3007 (s), 2980 (s), 2933 (s), 1744 (s), 1560 (s), 1478 (s), 1458 (s), 1352 (s), 1303 (s), 1283 (s), 1159 (s), 1118 (s), 1080 (s), 1048 (s), 908 (s), 885 (s), 849 (s), 802 (s), 757 (s), 667 (w), 647 (w), 590 (s). Anal. calcd for C$_{12}$H$_{16}$INO$_2$ (333.2): C 43.26, H 4.84, N 4.20. Found: C 43.49, H 5.03, N 3.91.
3.2.11. tert-Butyl 2-(1-adamantyl)-4-iodo-1H-pyrrole-1-carboxylate (4k)

According to the general procedure 1.31 g (61 % yield) were obtained as a colorless solid. Mp 151 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.58 (s, 9 H), 1.68-1.78 (m, 6 H), 2.0 (br, 3 H), 2.05-2.08 (m, 6 H), 6.07-6.09 (m, 1 H), 7.24-7.27 (m, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 28.2 (CH$_3$), 28.9 (CH), 35.7 (C$_{quat}$), 36.9 (CH$_2$), 40.7 (CH$_2$), 63.6 (C$_{quat}$), 83.9 (C$_{quat}$), 117.6 (CH), 128.0 (CH), 147.7 (C$_{quat}$), 148.3 (C$_{quat}$). EI + MS (m/z (%)): 427 (M$^+$, 2), 371 ((M-C$_4$H$_9$+H)$^+$, 6), 327 ((M-C$_3$H$_7$O$_2$+H)$^+$, 18), 270 (4), 57 (C$_4$H$_9^+$, 100), 41 (7). IR (KBr): $\tilde{\nu}$ 3166 (w) cm$^{-1}$, 2980 (m), 2908 (s), 2849 (s), 2677 (w), 1748 (s), 1543 (w), 1489 (m), 1452 (m), 1395 (w), 1368 (s), 1316 (s), 1297 (s), 1255 (s), 1234 (s), 1163 (s), 1137 (s), 1105 (m), 1089 (s), 1011 (s), 976 (w), 937 (w), 899 (m), 849 (m), 819 (w), 804 (s), 764 (m), 679 (w), 644 (w), 590 (w), 533 (w). Anal. calcd for C$_{19}$H$_{26}$INO$_2$ (427.3): C 53.40, H 6.13, N 3.28. Found: C 53.46, H 6.22, N 3.11.
4. Synthesis of Pyrroles 6

4. 1. Synthesis of Pyrrole 6a by Sonogashira Coupling of Pyrrole 4a

4.1.1. Procedure

\[
PdCl_2(PPh_3)_2 \quad \text{(28 mg, 0.04 mmol)} \quad \text{and} \quad CuI \quad \text{(16 mg, 0.08 mmol)} \quad \text{were placed under argon in a}
\]

screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Cesium carbonate (2.63 g, 8.00 mmol), \( \text{tert-Butyl 4-iodo-2-}p\text{-tolyl-1H-pyrrole-1-carboxylate (4a)} \quad \text{(766 mg, 2.00 mmol)} \quad \text{and} \quad \text{1-hexyne (5a)} \quad \text{(0.47 ml, 4.00 mmol)} \quad \text{were successively added to the mixture}
\]

which was stirred at 70 °C for 1 h until the conversion was complete (monitored by TLC). The reaction mixture was diluted with 20 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petroether (boiling range 40-60 °C)/ethyl acetate

\[
= 200:1 \quad \text{to give 598 mg (89 \% yield) of 6a as a brown oil. R}_f(\text{PE-EE} = 150:1) : 0.23.
\]
4.2. Three-Component Synthesis of Pyrroles 6 by Coupling-Addition-Cyclocondensation-Coupling Sequence

4.2.1. Procedure

\[
\text{R}^1\text{Cl} \quad \begin{array}{c}
\text{H} \\
\text{N-Boc}
\end{array} \\
\text{2} \quad "\text{Hl}" \quad \begin{array}{c}
\text{=N} \\
\text{R}^2
\end{array}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (28 mg, 0.04 mmol) and CuI (16 mg, 0.08 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.28 mL, 2.00 mmol), acid chloride 1 (2.00 mmol) and tert-butyl prop-2-ynylcarbamate (2) (310 mg, 2.00 mmol) were successively added to the mixture which was stirred at room temperature until the conversion was complete (monitored by TLC). Then, sodium iodide (1.51 g, 10.0 mmol), toluene-4-sulfonic acid monohydrate (776 mg, 4.00 mmol) and 2 ml of tert-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). After that, cesium carbonate (2.63 g, 8.00 mmol) and terminal alkyne 5 (4.00 mmol) were successively added to the mixture which was stirred at 70 °C for 1 h until the conversion was complete (monitored by TLC). The reaction mixture was diluted with 20 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel.

The experimental details are depicted in Table 3.
Table 3. Experimental details of the synthesis of pyrroles 6 by Coupling-Addition-Cyclocondensation-Coupling Sequence.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid chloride 1</th>
<th>Terminal alkyne 5</th>
<th>Pyrrole 6 (isolated yield %)</th>
<th>Chromatographic purification</th>
<th>R_f (elucent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316 mg (2.00 mmol)</td>
<td>0.47 mL (4.00 mmol)</td>
<td>391 mg (1.16 mmol, 58 %)</td>
<td>PE</td>
<td>R_f (PE) : 0.13</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>5a</td>
<td>6a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>352 mg (2.00 mmol)</td>
<td>0.89 mL (4.00 mmol)</td>
<td>481 mg (1.06 mmol, 53 %)</td>
<td>PE → PE-EE = 100:1</td>
<td>R_f (PE-EE = 100:1) : 0.10</td>
</tr>
<tr>
<td></td>
<td>1d</td>
<td>5b</td>
<td>6b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>352 mg (2.00 mmol)</td>
<td>0.45 mL (4.00 mmol)</td>
<td>502 mg (1.34 mmol, 67 %)</td>
<td>PE-EE = 100:1 → 90:1 → 80:1 → 70:1</td>
<td>R_f (PE-EE = 20:1) : 0.20</td>
</tr>
<tr>
<td></td>
<td>1d</td>
<td>5c</td>
<td>6c</td>
<td></td>
<td></td>
</tr>
</tbody>
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4.3. Spectroscopic and Analytical Data of Compounds 6

4.3.1. tert-Butyl 4-(hex-1-ynyl)-2-p-tolyl-1H-pyrrole-1-carboxylate (6a)

According to the general procedure 391 mg (58 % yield) were obtained as an orange oil. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$0.94 (t, $J$ = 7.3 Hz, 3 H), 1.38 (s, 9 H), 1.41-1.50 (m, 2 H), 1.53-1.60 (m, 2 H), 2.36-2.40 (m, 5 H), 6.16 (d, $J$ = 1.9 Hz, 1 H), 7.13-7.16 (m, 2 H), 7.19-7.22 (m, 2 H), 7.40 (d, $J$ = 1.9 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 13.7 (CH$_3$), 19.2 (CH$_2$), 21.3 (CH$_3$), 22.0 (CH$_2$), 27.6 (CH$_3$), 30.9 (CH$_2$), 73.9 (C$_{quat}$), 83.9 (C$_{quat}$), 90.3 (C$_{quat}$), 107.4 (C$_{quat}$), 116.6 (CH), 124.9 (CH), 128.3 (CH), 129.1 (CH), 130.6 (C$_{quat}$), 135.0 (C$_{quat}$), 137.3 (C$_{quat}$), 148.6 (C$_{quat}$). EI + MS (m/z (%)): 337 (M$^+$, 0.5), 281 ((M-C$_4$H$_9$+H)$^+$, 2), 237 ((M-C$_5$H$_7$O$_2$+H)$^+$, 2), 57 (C$_4$H$_9^+$, 100), 41 (20). IR (Film): $\tilde{\nu}$ 3149 (w) cm$^{-1}$, 2959 (s), 2933 (s), 2872 (s), 1739 (s), 1532 (m), 1488 (m), 1456 (m), 1394 (m), 1368 (s), 1337 (s), 1256 (s), 1219 (m), 1156 (s), 1121 (s), 1025 (m), 989 (m), 847 (m), 813 (s), 765 (m), 718 (w), 635 (w), 610 (m). Anal. calcd for C$_{22}$H$_{27}$NO$_2$ (337.5): C 78.30, H 8.06, N 4.15. Found: C 78.12, H 8.19, N 4.34.
4.3.2. tert-Butyl 4-(2-(triisopropylsilyl)ethynyl)-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (6b)

According to the general procedure 481 mg (53 % yield) were obtained as a yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.11 (s, 21 H), 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, $J = 1.9$ Hz, 1 H), 6.86-6.90 (m, 2 H), 7.22-7.26 (m, 2 H), 7.48 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 11.6 (CH), 18.9 (CH$_3$), 27.9 (CH$_3$), 55.5 (CH$_3$), 84.3 (C$_{quat}$), 90.8 (C$_{quat}$), 100.9 (C$_{quat}$), 107.3 (C$_{quat}$), 113.3 (CH), 116.8 (CH), 126.1 (C$_{quat}$), 126.3 (CH), 130.6 (CH), 135.0 (C$_{quat}$), 148.7 (C$_{quat}$), 159.4 (C$_{quat}$). EI + MS (m/z (%)): 453 (M$^+$, 2), 397 ((M-C$_4$H$_9$+H)$^+$, 2), 354 ((M-C$_3$H$_7$O$_2$+H)$^+$, 2), 285 ((M-CH$_3$-TIPS+4H)$^+$, 95), 241 ((M-C$_4$H$_9$-TIPS+2H)$^+$, 13), 191 (10), 185 (12), 135 (18), 131 (19), 129 (27), 125 (12), 113 (11), 112 (10), 111 (20), 105 (26), 103 (16), 99 (15), 98 (15), 97 (34), 96 (13), 95 (13), 87 (11), 85 (36), 84 (15), 83 (35), 82 (12), 81 (11), 77 (38), 75 (16), 73 (47), 71 (57), 70 (19), 69 (42), 67 (11), 61 (22), 60 (37), 59 (12), 57 (C$_4$H$_9$+), 100). IR (Film): $\tilde{\nu}$ 2943 (s) cm$^{-1}$, 2866 (s), 2156 (m), 1744 (s), 1614 (w), 1578 (w), 1529 (w), 1489 (m), 1464 (m), 1367 (s), 1330 (s), 1249 (s), 1154 (s), 1109 (m), 1039 (m), 1016 (w), 995 (m), 981 (w), 920 (w), 883 (m), 848 (m), 819 (m), 798 (w), 765 (m), 742 (w), 677 (m), 607 (w), 517 (w). Anal. calcd for C$_{27}$H$_{39}$NO$_3$Si (453.7): C 71.48, H 8.66, N 3.09. Found: C 71.25, H 8.55, N 3.02.
4.3.3. tert-Butyl 2-(4-methoxyphenyl)-4-(2-phenylethynyl)-1H-pyrrole-1-carboxylate (6c)

According to the general procedure 502 mg (67% yield) were obtained as an orange oil. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.40 (s, 9 H), 3.82 (s, 3 H), 6.26 (d, $J = 1.9$ Hz, 1 H), 6.87-6.91 (m, 2 H), 7.25-7.34 (m, 5 H), 7.47-7.51 (m, 2 H), 7.55 (d, $J = 1.9$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 27.8 (CH$_3$), 55.4 (CH$_3$), 83.6 (C$_{quat}$), 84.3 (C$_{quat}$), 89.6 (C$_{quat}$), 106.9 (C$_{quat}$), 113.3 (CH), 116.4 (CH), 123.8 (C$_{quat}$), 125.7 (CH), 126.0 (C$_{quat}$), 128.1 (CH), 128.5 (CH), 130.7 (CH), 131.6 (CH), 135.3 (C$_{quat}$), 148.7 (C$_{quat}$), 159.4 (C$_{quat}$). EI + MS (m/z (%)): 373 (M$^+$, 0.5), 317 ((M-C$_4$H$_9$+H)$^+$, 0.7), 284 ((M-CH$_3$-Ph+3H)$^+$, 27), 241 ((M-C$_4$H$_9$-Ph+2H)$^+$, 4), 191 (10), 135 (6), 97 (10), 88 (13), 85 (15), 73 (16), 71 (18), 70 (18), 61 (20), 57 (C$_4$H$_9^+$, 30), 55 (11), 45 (C$_2$H$_5$O$^+$, 17), 43 (C$_2$H$_3$O$^+$, 100). IR (KBr): $\tilde{\nu}$ 3146 (w) cm$^{-1}$, 2979 (w), 2836 (w), 2217 (w), 1741 (s), 1616 (m), 1578 (w), 1533 (m), 1483 (s), 1459 (w), 1442 (m), 1366 (s), 1346 (s), 1280 (s), 1248 (s), 1177 (m), 1148 (s), 1098 (m), 1035 (m), 991 (m), 975 (m), 847 (m), 819 (m), 755 (m), 690 (m), 632 (w), 610 (w), 583 (w), 525 (w). Anal. calcd for C$_{24}$H$_{23}$NO$_3$ (373.4): C 77.19, H 6.21, N 3.75. Found: C 77.18, H 6.38, N 3.53.
5. $^1$H and $^{13}$C NMR Spectra

5.1. $^1$H and $^{13}$C NMR Spectra of Compounds 3a and 3b

$^1$H NMR of 3a in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of 3a in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of 3a in CDCl$_3$ at 297 K
$^1$H NMR of 3b in CDCl$_3$ at 297 K
$^{13}$C NMR of 3b in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of 3b in CDCl$_3$ at 297 K
5.2. $^1$H and $^{13}$C NMR Spectra of Compounds 4a-k

$^1$H NMR of 4a in CDCl$_3$ at 297 K
$^{13}$C NMR of 4a in CDCl$_3$ at 297 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of 4a in CDCl$_3$ at 296 K
$^1$H NMR of 4b in CDCl$_3$ at 296 K
$^{13}$C NMR of 4b in CDCl$_3$ at 296 K

$^{13}$C DEPT 135 of 4b in CDCl$_3$ at 296 K
$^1$H NMR of 4c in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of 4c in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of 4c in CDCl$_3$ at 297 K
$^1$H NMR of 4d in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of 4d in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of 4d in CDCl$_3$ at 297 K
$^1$H NMR of 4e in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of 4e in CDCl$_3$ at 297 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of 4e in CDCl$_3$ at 298 K

*Impurities from residual solvents.
$^1$H NMR of 4f in CDCl$_3$ at 297 K
$^{13}$C NMR of 4f in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of 4f in CDCl$_3$ at 297 K
$^1$H NMR of 4g in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of $4g$ in CDCl$_3$ at 298 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of $4g$ in CDCl$_3$ at 298 K

*Impurities from residual solvents.
$^1$H NMR of 4h in CDCl$_3$ at 298 K

*Impurities from residual solvents.
$^{13}$C NMR of 4h in CDCl$_3$ at 297 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of 4h in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^1$H NMR of 4i in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^{13}$C NMR of 4i in CDCl$_3$ at 297 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of 4i in CDCl$_3$ at 297 K

*Impurities from residual solvents.
$^1$H NMR of 4j in CDCl$_3$ at 297 K
$^{13}$C NMR of $4j$ in CDCl$_3$ at 297 K

$^{13}$C DEPT 135 of $4j$ in CDCl$_3$ at 297 K
$^1$H NMR of 4k in CDCl$_3$ at 298 K
$^{13}$C NMR of 4k in CDCl$_3$ at 298 K

$^{13}$C DEPT 135 of 4k in CDCl$_3$ at 298 K
5.3. $^1$H and $^{13}$C NMR Spectra of Compounds 6

$^1$H NMR of 6a in CDCl$_3$ at 297 K
$^{13}$C NMR of 6a in CDCl$_3$ at 296 K

$^{13}$C DEPT 135 of 6a in CDCl$_3$ at 296 K
$^1$H NMR of 6b in CDCl$_3$ at 298 K
$^{13}$C NMR of $6b$ in CDCl$_3$ at 298 K

$^{13}$C DEPT 135 of $6b$ in CDCl$_3$ at 298 K
$^1$H NMR of 6c in CDCl$_3$ at 296 K
$^{13}$C NMR of $6c$ in CDCl$_3$ at 296 K

*Impurities from residual solvents.

$^{13}$C DEPT 135 of $6c$ in CDCl$_3$ at 296 K

*Impurities from residual solvents.
6. Crystallographic Data of Compound 4d

Figure 1. Molecular structure of tert-Butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (4d) in the crystal (50% probability ellipsoids).

(4d): yellow crystal (cube), dimensions 0.15 x 0.15 x 0.15 mm³, crystal system triclinic, space group P-1, Z=2, a= 9.3344(8) Å, b= 9.5233(8) Å, c= 10.9791(9) Å, alpha= 77.329(9) deg, beta= 68.367(9) deg, gamma= 69.877(10) deg, V= 847.06(14) Å³, rho= 1.565 g/cm³, T=223(2) K, 2Theta max= 25.00 deg, radiation Mo Kα, lambda=0.71073 Å, μ=0.189 mm⁻¹ STOE IPDS, 12191 reflections measured, 2864 unique (R(int)=0.040), 2570 observed (I >2σ(I)), intensities were corrected for Lorentz and polarization effects., μ=0.18mm⁻¹, structure solved by direct methods and refined against F² with a full-matrix least-squares algorithm using SHELXS-97 and SHELXL-97, respectively, 194 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.147, final residual values R1(F)=0.030, wR(F²)=0.081 for observed reflections, residual electron density -0.32 to 0.80 eÅ⁻³. CCDC 723307 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
Table 1: Crystal data and structure refinement for 4d.

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Table 2: Atomic coordinates (x 10<sup>4</sup>) and equivalent isotropic displacement parameters (Å<sup>2</sup>x 10<sup>3</sup>) for 4d. U<sub>eq</sub> is defined as one third of the trace of the orthogonalized U<sub>ij</sub> tensor.

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Table 4: Anisotropic displacement parameters (Å$^2$ x 10$^3$) for 4d. The anisotropic displacement factor exponent takes the form: $-2\pi^2 (h^2 a^2 U_{11} + ... + 2h k a^* b^* U_{12})$

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<th>Atom</th>
<th>U$_{11}$</th>
<th>U$_{22}$</th>
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<th>U$_{23}$</th>
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Table 5: Bond lengths (Å) and angles (deg) for 4d.

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Table 6: Torsion angles (deg) for 4d.

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7. References


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http://pubs.rsc.org/en/content/articlelanding/2011/ob/c1ob05310h
Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation–Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G†‡ §

Eugen Merkul, Elisabeth Schäfer and Thomas J. J. Müller*

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3-(Hetero)aryl substituted indoles, 7-azaindoles, and pyrroles can be obtained in a very concise fashion via a one-pot Masuda borylation–Suzuki coupling sequence. The concise total syntheses of the marine natural products meridianins A (5) and G (4i) nicely illustrate the utility of this methodology. Indoles and pyrroles belong to the most important heterocycles. They are widespread in nature1 and represent privileged structures found in a plethora of biologically and pharmacologically active compounds.2 In particular, indoles with 5- or 6-membered heterocyclic substituents in the 3-position have aroused considerable attention due to a remarkable spectrum of biological activity. For example, meridianins1 and variolins2 (Fig. 1) are small marine alkaloids consisting of indole and 7-azaindole frameworks connected to a 2-aminopyrimidine ring, the essential structural element for the kinase inhibitory activity of these natural products.

Fig. 1 3-Substituted indoles as natural products and bioactive compounds.

Recently, we synthesized some members of the meridianin family using the carbonylative Sonogashira coupling reaction as a key step.3 The simplified 7-azaindole analogue of variolin B (later called merelinin 1)b has attracted our attention because it is very active on kinases and human cancer cell lines with IC50 values (i.e. concentration reducing cell proliferation by 50%) of 0.18 and 0.14 μM against HCT116 (colon carcinoma) and A2780 (ovarian carcinoma), respectively. 7-Azaindole is an increasingly important structural motif due to its strong ability to bind to the hinge region of kinases and act as a kinase inhibitor. We are particularly interested in investigating the structure–activity relationship of 3-heteroaryl substituted 7-azaindoles. Therefore, a robust and general synthetic methodology to decorate (aza)indoles with diverse heterocyclic residues is highly desirable.

The Suzuki–Miyaura cross-coupling reaction4 is an extremely important tool for the construction of biaryl, as emphasized by awarding the Nobel Prize 2010 to Akira Suzuki in recognition of the enormous utility of this Pd-catalyzed transformation. As the nucleophilic component of this coupling, pinacol boronic esters5 are stable reagents and can be also accessed via Pd-catalyzed approaches such as Miyaura (Bpin/PdCl2/dpdf/KOAc)6 and Masuda (HBPin/PdCl2/dpdf/NET3)7 borylations. The Masuda protocol utilizes pinacolborane,8 thus being a more elegant and atom economical approach. The catenation of Masuda and Suzuki reactions into a one-pot fashion has been described by several groups pioneered by the work of Baudoin in 2000.9 However, the strategy has never been generalized and no simple catalytic system has been disclosed for the flexible introduction of various heterocycles on pharmaceutically relevant heterocyclic scaffolds such as indoles or related systems.10 Herein, we report a strikingly simple one-pot procedure which was established to efficiently synthesize a variety of 3-(hetero)aryl substituted (7-aza)indoles, pyrroles, and other electron-rich (hetero)aryls.

N-Boc protected (aza)indolyl11 iodides 1 are easily accessible, stable to storage and can be successfully used as valuable building blocks in cross-coupling reactions. The direct Suzuki coupling of 1 with heteroaryl boronic acids or esters is strongly limited by the accessibility of the latter. We reasoned that iodides 1 could be converted to the corresponding pinacol esters12 and then reacted en route with heterocyclic halides 3, which are readily available (Scheme 1).

According to this strategy, the iodides 1 are reacted with pinacolborane and triethylamine as a base in 1,4-dioxane. After completed transformation (as monitored by TLC), methanol is added which scavenges excess of pinacolborane. One equivalent of mostly commercially available halide 3 is added followed by caesium carbonate to promote the Suzuki coupling. Concurrently,
This methodology exemplifies sequential catalysis, since a single Pd-precatalyst promotes both transformations. No exotic ligands are required and no additional catalyst portion has to be added in the second reaction step. The yield did not increase upon addition of further 3 mol% Pd(PPh₃)₄, which performed best for the described substrates. PdCl₂(PPh₃)₂ was only slightly less efficient (64% vs. 61% for 4f), but the typical precatalyst for Masuda borylations, PdCl₂(dppf), failed to give the desired product in a good yield (39% for 4f). K₂CO₃ can be used instead of Cs₂CO₃ with slightly decreased efficiency.

Interestingly, in a related approach to substituted 7-azaindolyl pyrimidines, a stepwise protocol consisting of Miyaura borylation and Suzuki coupling with two different (!) Pd-precatalysts was utilized, and the protective phenylsulfonyl group remained uncleaved. The scope of the presented sequence is remarkable since it allows the introduction of a great variety of different 6-membered aryl substituents or nitrogen heterocycles (Fig. 2). Functional groups including cyano, free hydroxy and amino groups on (hetero)aryl halides are tolerated and give good yields. (Hetero)aromatic iodides, bromides and chlorides (see the color code of Fig. 2) can be reacted according to the expected oxidative addition tendency of the halide and its position in the (hetero)cycle. Pharmacophore motifs such as 2-aminopyrimidine, 2-aminopyridine, and even 2,6-diaminopyridine can be introduced without difficulties. It should be emphasized that upon using the reverse approach, i.e. the direct coupling with heteroaryl boronic acids or pinacol esters, the observed functional and structural diversity can hardly be realized: especially ortho-nitrogen atom containing boronic reagents are particularly challenging coupling partners. Not only indoles and 7-azaindoles but also iodo pyrazoles, 3-iodo thiophene, 2,5-disubstituted 4-iodo furan as well as 2-amino 5-iodo pyridine, 2-amino 5-iodo pyrimidine and electron-rich iodo arenes can be functionalized with (hetero)aryl substituents with comparable efficiency (4o–4u). Free hydroxy and amino groups on the substrates are well tolerated (4r–4t). The yields of the isolated products are fair to very good and the compounds can be obtained analytically pure by simple flash chromatography.

With this practical and versatile methodology in hand, we set out to perform very concise total syntheses of meridianins A (5) and G (4i) in order to illustrate the utility in alkaloid synthesis. Starting from commercially available 4-methoxy-1H-indole, the former natural product was obtained in four steps and 54% total yield. The one-pot Masuda borylation–Suzuki coupling sequence was used as a key step to prepare O-Me-meridianin A (4j), which was then demethylated by PyHCl in the final step (Scheme 3). It is worth mentioning that this strategy represents the first targeted synthesis of this natural product since the sole approach by Fresneda and Molina delivered 15% (19 mg) of meridianin A in 5 steps from 4-benzoyloxy-7-bromo-1H-indole, which is not commercially available. The presented procedure gives also access to other interesting hydroxylated 3-aryl and 3-heteroaryl substituted indoles. Syntheses of further natural products can be easily envisioned and are currently underway.

The presented sequence consisting of Masuda borylation and Suzuki coupling is tailored to efficiently synthesize 3-(hetero)aryl substituted (aza)indoles, many of them are biologically active compounds. Moreover, the obtained 2,4-di(hetero)aryl substituted pyrroles represent a new promising scaffold. The most exciting feature of this preparatively extremely simple transformation is the possibility to directly connect readily available heterocyclic halides in a one-pot fashion without the need for sophisticated catalysts, ligands or additives. Considering the huge pool of
commercially available or easily accessible heteroaromatic halides, this methodology is a quite general concept.

The full scope of the structure as well as structure–activity studies and the biological data of analogues based on 7-azaindole will be reported in near future.

Notes and references


2 For a recent minireview on indole alkaloid marine natural products as a source of drug leads, see: W. Gu and M. T. Hamann, Life Sci., 2005, 78, 447.


Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation - Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G **

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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using MBraun system MB-SPS-800, and triethylamine was refluxed under argon atmosphere over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from Sigma-Aldrich Chemie GmbH.

4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolborane) was purchased from Sigma-Aldrich Chemie GmbH and used as supplied. Tetrakis(triphenylphosphane)-palladium(0) and cesium carbonate were purchased from Merck Serono KGaA.

Commercial grade reagents were used as supplied without further purification and were purchased from Acros Organics, Sigma-Aldrich Chemie GmbH, Fluka AG, ABCR GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, Aces Pharma Inc., Interchim Inc., Synthonix Inc., Synchem OHG and Merck Serono KGaA.

Compounds 1h-1i, 1k-1n and 3a-3q are commercially available (see Table 1). Compounds 1a-1c,[1] 1d-1g,[2] and 1j[3] were prepared according to the literature procedures.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from Merck Serono KGaA Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F254 5 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.
$^1$H, $^{13}$C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. Acetone-d$_6$, CDCl$_3$ and DMSO-d$_6$ were used as deuterated solvents. TMS was used as reference ($\delta = 0.0$) or the resonances of the solvents were locked as internal standards (acetone-d$_6$: $^1$H $\delta$ 2.05, $^{13}$C $\delta$ 30.8; CDCl$_3$: $^1$H $\delta$ 7.26, $^{13}$C $\delta$ 77.0; DMSO-d$_6$: $^1$H $\delta$ 2.50, $^{13}$C $\delta$ 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, td: triplet of doublets, tt: triplet of triplets, q: quartet, quint: quintet, sext: sextet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.
2. Preparation of Starting Materials 1a, 1c, 1f and 1j

2.1. Preparation of tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1a)[1]

A solution of iodine (25.7 g, 101 mmol) in 180 mL DMF was dropped to the solution of 7-azaindole (12.1 g, 100 mmol) and potassium hydroxide (16.5 g, 250 mmol) in 180 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poured on 1 L ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 23.7 g (97.2 mmol, 97 % yield) of a yellow solid.

The obtained solid was used without further purification for the next step. It was suspended in 180 mL dichloromethane, 4-dimethylaminopyridine (1.21 g, 9.72 mmol) was added and di-tert-butyl dicarbonate (32.8 g, 146 mmol), dissolved in 180 mL dichloromethane, was added dropwise for 30 min. The mixture was stirred for 30 min. at room temperature, washed with 200 mL 0.1 N HCl, and the aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1, Rf (PE-EtOAc = 20:1): 0.14) to give 31.6 g (91.8 mmol, 94 % yield; 92 % total yield over two steps) of 1a as an orange oil, which solidifies upon storage in refrigerator.

**tert-Butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1a)**

![Chemical Structure](image)

{\text{C}_{12}\text{H}_{13}\text{IN}_{2}\text{O}_{2}}

344.15

31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 79 °C. $^1$H NMR (acetone-d$_6$, 300 MHz): $\delta$ 1.67 (s, 9 H), 7.36 (dd, $J = 8.1$ Hz, $J = 4.8$ Hz, 1 H), 7.75 (dd, $J = 8.1$ Hz, $J = 1.5$ Hz, 1 H), 7.99 (s, 1 H), 8.44 (dd, $J = 4.8$ Hz, $J = 1.5$ Hz, 1 H). $^{13}$C NMR (acetone-d$_6$, 75 MHz): $\delta$ 28.1 (CH$_3$), 61.9 (C$_{\text{quat}}$), 84.8 (C$_{\text{quat}}$), 120.1 (CH), 125.8 (C$_{\text{quat}}$), 130.1 (CH), 132.1 (CH), 146.6 (CH), 147.8 (C$_{\text{quat}}$), 147.9 (C$_{\text{quat}}$). EI + MS ($m/z$ (%)): 344 (M$^+$, 7), 271 ((M-C$_4$H$_9$O)$^+$, 3), 245 (10), 244 ((M-C$_5$H$_9$O$_2$+H)$^+$, 100), 217 ((M-I)$^+$, 5), 162 (C$_8$H$_8$N$_2$O$_2$$^+$, 13), 144 (C$_8$H$_4$N$_2$O$^+$, 1), 127 (I$^+$, 2), 117 (C$_7$H$_6$N$_2$$^+$, 14), 116 (C$_7$H$_4$N$_2$$^+$, 8), 57 (C$_4$H$_9$$^+$, 22).

Data reported in the literature:


$^1$H NMR (CDCl$_3$): $\delta$ 1.70 (s, 9 H), 7.28 (dd, $J = 8.5$ Hz, 1 H), 7.72 (dd, $J = 8.1$ Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, $J = 5.1$ Hz, 1 H).
2.2. Preparation of tert-butyl 3-iodo-4-methoxy-1H-indole-1-carboxylate (1c)[1]

A solution of iodine (2.57 g, 10.1 mmol) in 15 mL DMF was dropped to the solution of 4-methoxy-1H-indole (1.50 g, 10.0 mmol) and potassium hydroxide (1.65 g, 25.0 mmol) in 15 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poured on 200 mL ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 3.34 g (8.58 mmol, 86 % yield) of a gray solid.

The obtained solid was used without further purification for the next step. It was suspended in 15 mL dichloromethane, 4-dimethylaminopyridine (106 mg, 0.86 mmol) was added and di-tert-butyl dicarbonate (2.90 g, 12.9 mmol), dissolved in 15 mL dichloromethane, was added dropwise for 25 min. The mixture was stirred for 30 min at room temperature, washed with 15 mL 0.1 N HCl, and the aqueous phase was extracted with dichloromethane (4 x 15 mL, monitored by TLC). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1 → 50:1 (stepwise gradient), Rf (PE-EtOAc = 50:1): 0.21) to give 3.08 g (8.24 mmol, 96 % yield; 82 % total yield over two steps) of 1c as a pale yellow oil, which solidifies upon storage in refrigerator to a pale yellow amorphous solid.

**tert-Butyl 3-iodo-4-methoxy-1H-indole-1-carboxylate (1c)**

![Chemical Structure](image)

C_{14}H_{16}INO_3  
373.19

3.08 g (8.24 mmol, 82 % yield over two steps) as a pale yellow oil (solidified upon storage in refrigerator). Mp 68 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.64 (s, 9 H), 3.92 (s, 3 H), 6.67 (d, $J = 8.2$ Hz, 1 H), 7.24 (t, $J = 8.2$ Hz, 1 H), 7.61 (s, 1 H), 7.80 (d, $J = 8.2$ Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 28.1 (CH$_3$), 55.4 (CH$_3$), 57.6 (C$_{quat}$), 84.2 (C$_{quat}$), 104.0 (CH), 108.0 (CH), 119.6 (C$_{quat}$), 125.9 (CH), 130.0 (CH), 136.5 (C$_{quat}$), 148.5 (C$_{quat}$), 153.2 (C$_{quat}$). EI + MS ($m/z$ (%)): 373 (M$^+$, 33), 317 ((M-C$_4$H$_9$+H)$^+$, 100), 273 ((M-C$_4$H$_9$+H-CO$_2$)$^+$, 56), 258 ((M-C$_4$H$_9$+H-CO$_2$-CH$_3$)$^+$, 23), 57 (C$_4$H$_9^+$, 83). IR (film): $\tilde{\nu}$ 3151 (w) cm$^{-1}$, 2979 (s), 2937 (m), 2837 (w), 1732 (s), 1606 (m), 1586 (s), 1494 (s), 1427 (s), 1394 (m), 1370 (s), 1339 (s), 1286 (s), 1153 (s), 1124 (s), 1046 (s), 955 (w), 903 (w), 852 (m), 819 (w), 775 (m), 735 (m), 696 (w), 668 (w), 597 (w). Anal. calcd for C$_{14}$H$_{16}$INO$_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.11, N 3.56.
2.3. Preparation of tert-butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1f)

\[
\begin{align*}
\text{MeO-} & \quad \text{Cl} \\
\text{H} & \quad \text{N-Boc} \\
\text{C} \quad \text{H} & \quad \text{I} \\
\end{align*}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (425 mg, 0.60 mmol, 2 mol %) and Cul (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to room temperature (water bath). Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and tert-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 ml of tert-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite\textsuperscript{®} and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (1f) as a colorless solid.

2.4. Preparation of 2-ethyl-3-iodo-5-(thiophen-2-yl)furan (1j)[3]

\[
\text{PdCl}_2(\text{PPh}_3)_2 \quad (142 \text{ mg, } 0.20 \text{ mmol, } 2 \text{ mol } \%) \quad \text{and} \quad \text{Cul} \quad (78 \text{ mg, } 0.40 \text{ mmol, } 4 \text{ mol } \%)
\]
were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to room temperature (water bath). Then, 50 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol), thiophene-2-carbonyl chloride (1.50 g, 10.0 mmol), and tetrahydro-2-(pent-1-yn-3-yl)oxy)-2H-pyran (4.66 g, 10.0 mmol) were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). Then, sodium iodide (7.57 g, 50.0 mmol), toluene-4-sulfonic acid monohydrate (2.14 g, 11.0 mmol) and 30 ml of methanol were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 10:1) to give 2.72 g (8.93 mmol, 89 % yield) of 1j as an orange oil.


3. Preparation of \textit{tert}-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1\textit{H}-pyrrolo[2,3-\textit{b}]pyridine-1-carboxylate (2a)

\[
\begin{align*}
\text{1a} & \quad \text{I} \\
& \quad \text{H-B-O} \\
& \quad \text{2a} \\
& \quad \text{Boc} \\
& \quad \text{Boc}
\end{align*}
\]

Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and \textit{tert}-butyl 3-ido-1\textit{H}-pyrrolo[2,3-\textit{b}]pyridine-1-carboxylate (1a) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), the solvent was removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically* on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1) to give 291 mg (0.85 mmol, 85 % yield) of 2a as a yellow solid. Recrystallization from \textit{n}-pentane gave colorless crystals.

*The purification was performed on Biotage SP-1 system using a 50 g silica gel SNAP cartridge.
tert-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1\textit{H}-pyrrolo[2,3-\textit{b}]pyridine-1-carboxylate (2a)

\[
\begin{align*}
\text{C}_{18}\text{H}_{25}\text{BN}_{2}\text{O}_{4} & \\
344.21
\end{align*}
\]

291 mg (0.85 mmol, 85 \% yield) as a yellow solid. \(R_f\) (PE-EtOAc = 5:1): 0.30. Mp 97-98 °C. \(\text{\textit{H}}\) NMR (acetone-\textit{d}\textsubscript{6}, 500 MHz): \(\delta\) 1.37 (s, 12 H), 1.68 (s, 9 H), 7.28 (dd, \(J = 7.6\) Hz, \(J = 4.7\) Hz, 1 H), 8.05 (s, 1 H), 8.21 (dd, \(J = 7.9\) Hz, \(J = 1.9\) Hz, 1 H), 8.40 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H). \(\text{\textit{C}}\) NMR (acetone-\textit{d}\textsubscript{6}, 125 MHz): \(\delta\) 26.2 (CH\textsubscript{3}), 29.2 (CH\textsubscript{3}), 85.3 (C\textsubscript{quat}), 85.6 (C\textsubscript{quat}), 120.7 (CH), 127.7 (C\textsubscript{quat}), 132.2 (CH), 137.6 (CH), 146.5 (CH), 149.5 (C\textsubscript{quat}), 150.8 (C\textsubscript{quat}), 207.1 (C\textsubscript{quat}). EI + MS (m/z (%)): 344 (M\textsuperscript{+}, 10), 244 (100), 229 (28), 185 (10), 171 (9), 158 (37), 144 (62), 118 (12), 57 (13). Anal. calcd for C\textsubscript{18}H\textsubscript{25}BN\textsubscript{2}O\textsubscript{4} (344.2): C 62.81, H 7.32, N 8.14. Found: C 62.75, H 7.39, N 8.10.

Data reported in the literature:


White solid. Mp 115-117 °C. \(\text{\textit{H}}\) NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 1.33 (br s, 12 H), 1.62 (br s, 9 H), 7.16-7.18 (dd, \(J = 7.8\) Hz, \(J = 4.6\) Hz, 1 H), 8.01 (br s, 1 H), 8.20-8.22 (dd, \(J = 7.8\) Hz, \(J = 1.7\) Hz, 1 H), 8.45-8.46 (dd, \(J = 4.9\) Hz, \(J = 1.7\) Hz, 1 H). \(\text{\textit{C}}\) NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 24.8 (CH\textsubscript{3}), 28.1 (CH\textsubscript{3}), 83.5 (C\textsubscript{quat}), 84.3 (C\textsubscript{quat}), 118.8 (CH), 126.1 (C\textsubscript{quat}), 130.9 (CH), 135.4 (CH), 145.1 (CH), 147.6 (C\textsubscript{quat}), 149.3 (C\textsubscript{quat}), 207.1 (C\textsubscript{quat}). GCMS (EI) (m/z (%)): 244 (100), 229 (38), 187 (35), 158 (37), 144 (46), 117 (11). \(\text{\textsuperscript{11}}\text{B}\) NMR (CDCl\textsubscript{3}, 96 MHz): \(\delta\) 30.2. Anal. calcd for C\textsubscript{18}H\textsubscript{25}BN\textsubscript{2}O\textsubscript{4} (344.2): C 62.81, H 7.32, N 8.14. Found: C 63.18, H 7.59, N 8.09.
4. Preparation of Compounds 4a-u by the *Masuda* Borylation – *Suzuki* Coupling Sequence

### 4.1. General Procedure

Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and *tert*-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1a) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1.00 mmol of (hetero)aryl halide 3 and cesium carbonate (823 mg, 2.50 mmol, 2.50 equiv) were successively added and the mixture was stirred at 100 °C overnight (preheated oil bath; for exact reaction times, see Table 2). Then, after cooling to room temperature (water bath) the solvents were removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia (isocratic or stepwise gradient). The obtained bis(hetero)aryls 4 can be further purified by suspending in dichloromethane, sonication in ultrasound bath for 0.5-1.0 h, filtration and drying in vacuo overnight.

*For the preparation of compounds 4r-4t, 3.00 equiv (0.44 mL, 3.00 mmol) of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane) were used.

The experimental details are given in Table 1.
Table 1. Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tert-Butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate</td>
<td>4-Chloropyrimidin-2-amine (Synchem) 134 mg (1.00 mmol)</td>
<td>Pale yellow solid 134 mg (0.63 mmol, 63 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:4:1 → 100:6:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>344 mg (1.00 mmol) 1a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>6-Chloropyrazin-2-amine (Synthonix) 132 mg (1.00 mmol)</td>
<td>Green-brown solid 112 mg (0.53 mmol, 53 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:4:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>3</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>5-Iodo-pyrimidin-2-amine (Alfa Aesar) 228 mg (1.00 mmol)</td>
<td>Pale yellow solid 139 mg (0.66 mmol, 66 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>4</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>2-Chloropyrimidin-4-amine (Aldrich) 134 mg (1.00 mmol)</td>
<td>Beige solid 79 mg (0.37 mmol, 37 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 98.1 %</td>
</tr>
</tbody>
</table>
**Table 1 (continuation).** Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>tert-Butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate</td>
<td>6-Bromo-pyridin-2-amine (ABCR)</td>
<td>Pale yellow solid 170 mg (0.81 mmol, 81 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>344 mg (1.00 mmol) 1a</td>
<td>177 mg (1.00 mmol) 3e</td>
<td>4e</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>4-Bromo-pyridin-2-amine (Interchim)</td>
<td>Yellow solid 135 mg (0.64 mmol, 64 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>173 mg (1.00 mmol) 3f</td>
<td>4f</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>2-Iodo-benzen-amine (Merck)</td>
<td>Pale yellow solid 154 mg (0.74 mmol, 74 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>221 mg (1.00 mmol) 3g</td>
<td>4g</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>344 mg (1.00 mmol) 1a</td>
<td>4-Iodo-phenol (Alfa Aesar)</td>
<td>Beige solid 120 mg (0.57 mmol, 57 %)</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 97.5 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>222 mg (1.00 mmol) 3h</td>
<td>4h</td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>tert-Butyl 3-iodo-1H-indole-1-carboxylate</td>
<td>4-Chloropyrimidin-2-amine (Synchem)</td>
<td>Pale yellow solid 154 mg (0.73 mmol, 73 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:4:1 → 100:5:1 → HT-LC-MS: 99.6 %</td>
</tr>
<tr>
<td></td>
<td>343 mg (1.00 mmol)</td>
<td>134 mg (1.00 mmol)</td>
<td>3a</td>
<td>4i</td>
</tr>
<tr>
<td>10</td>
<td>tert-Butyl 3-iodo-4-methoxy-1H-indole-1-carboxylate</td>
<td>3a</td>
<td>Colorless solid 185 mg (0.77 mmol, 77 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:4:1 → 100:6:1 → HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>373 mg (1.00 mmol)</td>
<td></td>
<td>3a</td>
<td>4j</td>
</tr>
<tr>
<td>11</td>
<td>tert-Butyl 4-iodo-2-phenyl-1H-pyrrole-1-carboxylate</td>
<td>3a</td>
<td>Rosa solid 190 mg (0.80 mmol, 80 %)</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → HT-LC-MS: 98.2 %</td>
</tr>
<tr>
<td></td>
<td>369 mg (1.00 mmol)</td>
<td></td>
<td>3a</td>
<td>4k</td>
</tr>
</tbody>
</table>
Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R_f (eluent) UV purity</td>
</tr>
<tr>
<td>12</td>
<td>tert-Butyl 2- (4-chloro-phenyl)-4- iodo-1H-pyrrole-1-carboxylate</td>
<td>5-Iodo-1,3-dimethyl-pyrimidine-2,4(1H,3H)-dione (5-Iodo-1,3-dimethyl-uracil) (Aldrich)</td>
<td>Rosa solid 202 mg (0.64 mmol, 64 %)</td>
<td>PE-EtOAc = 2:1 → 1:1 R_f (PE-EtOAc = 1:1): 0.32 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>tert-Butyl 4-iodo-2-(4-methoxy-phenyl)-1H-pyrrole-1-carboxylate</td>
<td>4-Iodo-pyridine (ABCR)</td>
<td>Beige solid 151 mg (0.60 mmol, 60 %)</td>
<td>DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>tert-Butyl 4-iodo-2-(thiophen-2-yl)-1H-pyrrole-1-carboxylate</td>
<td>1-Fluoro-4-iodobenzene (ABCR)</td>
<td>Pale gray solid 170 mg (0.70 mmol, 70 %)</td>
<td>PE-EtOAc = 10:1 R_f (PE-EtOAc = 10:1): 0.21 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1-Benzyl-4-iodo-1H-pyrazole (ABCR)</td>
<td>1-(Trifluoromethyl)-4-iodobenzene (Alfa Aesar)</td>
<td>Colorless solid 106 mg (0.35 mmol, 35 %)</td>
<td>PE-EtOAc = 7:1 Rf (PE-EtOAc = 7:1): 0.17 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>284 mg (1.00 mmol)</td>
<td>278 mg (1.00 mmol)</td>
<td>4o</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>3-Iodothiophene (Alfa Aesar)</td>
<td>1-Iodoisoquinoline (Aldrich)</td>
<td>Colorless solid 161 mg (0.76 mmol, 76 %)</td>
<td>PE-EtOAc = 5:1 Rf (PE-EtOAc = 5:1): 0.35 HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>219 mg (1.00 mmol)</td>
<td>263 mg (1.00 mmol)</td>
<td>4p</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2-Ethyl-3-iodo-5-(thiophen-2-yl)furan</td>
<td>4-Iodo-benzonitrile (ABCR)</td>
<td>Pale yellow solid 221 mg (0.79 mmol, 79 %)</td>
<td>PE-EtOAc = 20:1 Rf (PE-EtOAc = 20:1): 0.36 Crystallization by suspension in n-pentane, sonication in ultrasound bath, filtration and drying in vacuo overnight HT-LC-MS: 100 %</td>
</tr>
<tr>
<td></td>
<td>304 mg (1.00 mmol)</td>
<td>234 mg (1.00 mmol)</td>
<td>4q</td>
<td></td>
</tr>
</tbody>
</table>


Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
<th>UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>5-iodo-pyridin-2-amine (Alfa Aesar) 227 mg (1.00 mmol) 1k</td>
<td>1-Iodo-4-(trifluoromethoxy)benzene (Alfa Aesar) 294 mg (1.00 mmol) 3o</td>
<td>Colorless solid 233 mg (0.92 mmol, 92 %)[c]</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>19</td>
<td>5-iodopyrimidin-2-amine (Alfa Aesar) 228 mg (1.00 mmol) 1l</td>
<td>1-(Trifluoromethyl)-4-iodobenzene (Alfa Aesar) 278 mg (1.00 mmol) 3l</td>
<td>Colorless solid 105 mg (0.44 mmol, 44 %)[c]</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>20</td>
<td>4-Iodophenol (Alfa Aesar) 225 mg (1.00 mmol) 1m</td>
<td>4-Bromopyridazine hydrochloride[d] (Aces Pharma) 212 mg (1.00 mmol) 3p</td>
<td>Rosa solid 121 mg (0.70 mmol, 70 %)[c]</td>
<td>DCM-MeOH-NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
</tbody>
</table>

[c] 3.00 equiv of HBpin have been used in the Masuda borylation step.
[d] Since the bromide 3p was used as a hydrochloride, 3.00 equiv of Cs$_2$CO$_3$ were applied in the Suzuki coupling step.
Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>(Hetero)aryl halide 3</th>
<th>Bis(hetero)aryl 4 (isolated yield %)</th>
<th>Chromatographic purification (eluent) UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>5-Iodo-1,2,3-trimethoxybenzene (Alfa Aesar) 300 mg (1.00 mmol)</td>
<td>4-Bromopyridine-2,6-diamine (ABCR) 192 mg (1.00 mmol)</td>
<td>Orange solid 136 mg (0.44 mmol, 44 %)[e]</td>
<td>DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1</td>
</tr>
</tbody>
</table>

Purified by dissolving in 1.25 M HCl in EtOH (Fluka), precipitation with n-pentane, filtration and drying in vacuo overnight at 70 °C

HT-LC-MS: 98.5 %

[e] The yield was determined after formation of the hydrochloride with solution of HCl in EtOH.
Table 2. Reaction times\textsuperscript{[a]} in the synthesis of bis(hetero)aryls 4.

<table>
<thead>
<tr>
<th>Bis(hetero)aryl</th>
<th>\textit{Masuda} borylation step</th>
<th>\textit{Suzuki} coupling step</th>
<th>Bis(hetero)aryl</th>
<th>\textit{Masuda} borylation step</th>
<th>\textit{Suzuki} coupling step</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>3 h</td>
<td>49 h</td>
<td>4l</td>
<td>4 h</td>
<td>23 h</td>
</tr>
<tr>
<td>4b</td>
<td>3 h</td>
<td>24 h</td>
<td>4m</td>
<td>4 h</td>
<td>19 h</td>
</tr>
<tr>
<td>4c</td>
<td>3 h</td>
<td>24 h</td>
<td>4n</td>
<td>4 h</td>
<td>19 h</td>
</tr>
<tr>
<td>4d</td>
<td>3 h</td>
<td>67 h</td>
<td>4o</td>
<td>4 h</td>
<td>18 h</td>
</tr>
<tr>
<td>4e</td>
<td>3 h</td>
<td>20 h</td>
<td>4p</td>
<td>4 h</td>
<td>17 h</td>
</tr>
<tr>
<td>4f</td>
<td>3 h</td>
<td>24 h</td>
<td>4q</td>
<td>4 h</td>
<td>23 h</td>
</tr>
<tr>
<td>4g</td>
<td>3 h</td>
<td>24 h</td>
<td>4r</td>
<td>4 h</td>
<td>17 h</td>
</tr>
<tr>
<td>4h</td>
<td>3 h</td>
<td>24 h</td>
<td>4s</td>
<td>4 h</td>
<td>18 h</td>
</tr>
<tr>
<td>4i</td>
<td>3 h</td>
<td>24 h</td>
<td>4t</td>
<td>3 h</td>
<td>19 h</td>
</tr>
<tr>
<td>4j</td>
<td>3 h</td>
<td>15 h</td>
<td>4u</td>
<td>4 h</td>
<td>18 h</td>
</tr>
<tr>
<td>4k</td>
<td>4 h</td>
<td>17 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} The reaction times for the \textit{Suzuki} coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times of the \textit{Masuda} borylation step may also be shorter in some cases.
4.2. Spectroscopic Data of the Compounds 4a-u

4.2.1. 4-(1H-Pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-2-amine (Meriolin 1, 4a)

![Structure of Meriolin 1](image)

N\_N\_NH

\[\text{C}_{11}\text{H}_9\text{N}_5\]

134 mg (0.63 mmol, 63 % yield) as a pale yellow solid. Mp 258-271 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 6.50 (s, 2 H, NH\_2), 7.06 (d, \(J = 5.4\) Hz, 1 H), 7.19 (dd, \(J = 7.9\) Hz, 1 H), 8.14 (d, \(J = 5.4\) Hz, 1 H), 8.29 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H), 8.35 (d, \(J = 2.8\) Hz, 1 H), 8.93 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 12.2 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 104.9 (CH), 112.4 (C\text{quat}), 116.6 (CH), 117.7 (C\text{quat}), 128.3 (CH), 130.7 (CH), 143.3 (CH), 149.1 (C\text{quat}), 157.2 (CH), 162.0 (C\text{quat}), 163.5 (C\text{quat}). EI + MS (\(m/z\) (%)): 212 (16), 211 (M\(^+\)), 210 ((M-H)\(^+\), 38), 195 ((M-NH\_2)\(^+\), 2), 170 (14).

Data reported in the literature:


Yellow prisms. Mp 286-289 °C. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz): \(\delta\) 6.47 (s, 2 H, NH\_2), 7.05 (d, \(J = 5.13\) Hz, 1 H, H-5'), 7.13 (dd, \(J = 8.12\) Hz, \(J = 4.7\) Hz, 1 H, H-5), 8.14 (d, \(J = 5.13\) Hz, 1 H, H-6'), 8.28 (dd, \(J = 8.12\) Hz, \(J = 1.28\) Hz, 1 H, H-6), 8.33 (s, 1 H, H-2), 8.92 (dd, \(J = 4.7\) Hz, \(J = 1.28\) Hz, 1 H, H-4), 12.17 (s, 1 H, NH). \(^{13}\)C NMR (DMSO-\(d_6\), 75 MHz): \(\delta\) 105.0 (C-5'), 112.5 (C-3), 116.6 (C-5), 117.8 (C-3a), 128.3 (C-2), 130.6 (C-6), 143.4 (C-4), 143.4 (C-7a), 157.2 (C-6'), 162.0 (C-4'), 163.5 (C-2'). EI + MS (\(m/z\) (%)): 212 (M\(^+\)+1, 35), 211 (M\(^+\), 100), 210 (68), 195 (11), 170 (48), 142 (31). IR (nujol): \(\tilde{\nu}\) 3473 (m) cm\(^{-1}\), 3294 (m), 3133 (m), 1670 (s), 1565 (s), 1223 (m). Anal. calcd for C\(_{11}\)H\(_9\)N\(_5\) (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.73, H 4.45, N 33.22.
4.2.2. 6-(1H-Pyrrolo[2,3-b]pyridin-3-yl)pyrazin-2-amine (4b)

\[
\begin{align*}
\text{C}_{11}\text{H}_9\text{N}_5 \\
211.22
\end{align*}
\]

112 mg (0.53 mmol, 53 % yield) as a green-brown solid. Mp 241-243 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 6.36 (s, 2 H, \(\text{NH}_2\)), 7.17 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.67 (s, 1 H), 8.22 (d, \(J = 2.5\) Hz, 1 H), 8.27-8.30 (m, 2 H), 8.82 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 12.1 (br, 1 H, \(\text{NH}\)). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 111.6 (C\(\text{quat}\)), 116.3 (CH), 117.8 (C\(\text{quat}\)), 125.8 (CH), 127.6 (CH), 127.9 (CH), 130.1 (CH), 143.2 (CH), 147.7 (C\(\text{quat}\)), 149.0 (C\(\text{quat}\)), 155.0 (C\(\text{quat}\)). EI + MS (m/z (%)): 211 (M\(^{+}\), 100), 184 (C\(_{10}\)H\(_8\)N\(_4^+\), 23), 58 (13), 43 (32), 41 (10). IR (KBr): \(\tilde{\nu}\) 3317 (s) cm\(^{-1}\), 3146 (s), 1645 (m), 1575 (w), 1541 (s), 1522 (m), 1495 (m), 1470 (m), 1434 (s), 1366 (w), 1323 (w), 1295 (m), 1280 (w), 1245 (w), 1218 (w), 1139 (w), 1121 (w), 1030 (w), 1001 (w), 886 (w), 825 (w), 796 (w), 772 (w), 697 (w), 633 (w), 586 (w), 528 (w). Anal. calcd for C\(_{11}\)H\(_9\)N\(_5\) (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.47, H 4.38, N 32.92.
4.2.3. 5-(1H-Pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-2-amine (4c)

139 mg (0.66 mmol, 66 % yield) as a pale yellow solid. Mp 272 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 6.61 (s, 2 H, NH$_2$), 7.13 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.80 (d, $J = 2.5$ Hz, 1 H), 8.20 (dd, $J = 7.9$ Hz, $J = 1.3$ Hz, 1 H), 8.27 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 8.60 (s, 2 H), 11.9 (br, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 108.9 (C$_{quat}$), 115.7 (CH), 117.0 (C$_{quat}$), 117.6 (C$_{quat}$), 122.3 (CH), 127.3 (CH), 142.8 (CH), 148.7 (C$_{quat}$), 155.4 (CH), 161.9 (C$_{quat}$). EI + MS ($m/z$ (%)): 211 (M$^+$, 100), 184 (10), 170 (12), 156 (13), 142 (22). IR (KBr): $\tilde{\nu}$ 3136 (s) cm$^{-1}$, 1670 (m), 1618 (m), 1534 (s), 1492 (s), 1423 (w), 1335 (w), 1293 (w), 1272 (w), 1219 (w), 1132 (w), 961 (w), 895 (w), 797 (w), 770 (m), 609 (w). Anal. calcd for C$_{11}$H$_9$N$_5$ (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.73, H 4.13, N 32.99.
4.2.4. 2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-amine (4d)

\[
\begin{align*}
\text{C}_{11}\text{H}_{9}\text{N}_{5} \\
211.22
\end{align*}
\]

79 mg (0.37 mmol, 37 % yield) as a beige solid. Mp 239 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 6.23 (d, \(J = 6.0\) Hz, 1 H), 6.7 (br, 2 H, NH\(_2\)), 7.16 (dd, \(J = 7.9\) Hz, \(J = 4.4\) Hz, 1 H), 8.08-8.11 (m, 2 H), 8.25 (dd, \(J = 4.4\) Hz, \(J = 1.6\) Hz, 1 H), 8.87 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 12.0 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 101.4 (CH), 114.2 (C\(_{\text{quat}}\)), 116.3 (CH), 118.2 (C\(_{\text{quat}}\)), 128.0 (CH), 130.4 (CH), 142.9 (CH), 149.0 (C\(_{\text{quat}}\)), 155.0 (CH), 162.4 (C\(_{\text{quat}}\)), 163.1 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 211 (M\(^+\), 100), 210 ((M-H\(^+\), 11), 195 ((M-NH\(_2\))\(^+\), 4), 144 (19), 58 (25), 43 (49). IR (KBr): \(\tilde{\nu}\) 3418 (m) cm\(^{-1}\), 3316 (m), 3210 (m), 1632 (m), 1579 (s), 1557 (m), 1533 (s), 1467 (s), 1435 (m), 1398 (w), 1369 (m), 1340 (w), 1297 (w), 1238 (w), 1124 (w), 1050 (w), 1019 (w), 984 (w), 901 (w), 828 (m), 803 (w), 777 (w), 671 (w), 599 (w), 530 (w). Anal. calcd for C\(_{11}\)H\(_9\)N\(_5\) (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.48, H 4.37, N 32.99.
4.2.5. 6-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-pyridin-2-amine (4e)

![Chemical Structure](image)

C_{12}H_{10}N_{4}

170 mg (0.81 mmol, 81 % yield) as a pale yellow solid. Mp 157-158 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 5.87 (s, 2 H, NH$_2$), 6.26 (dd, $J = 8.2$ Hz, $J = 0.6$ Hz, 1 H), 7.00 (dd, $J = 7.6$ Hz, $J = 0.6$ Hz, 1 H), 7.12 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.36 (t, $J = 7.9$ Hz, 1 H), 8.04 (d, $J = 2.5$ Hz, 1 H), 8.24 (dd, $J = 4.4$ Hz, $J = 1.6$ Hz, 1 H), 8.86 (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1 H), 11.9 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 104.2 (CH), 107.3 (CH), 114.6 (C$_{quat}$), 115.9 (CH), 117.8 (C$_{quat}$), 125.0 (CH), 130.3 (CH), 137.3 (CH), 142.7 (CH), 149.0 (C$_{quat}$), 152.8 (C$_{quat}$), 159.1 (C$_{quat}$). EI + MS ($m/z$ (%)): 210 (M$^+$, 100), 209 ((M-H)$^+$, 15), 194 ((M-NH$_2$)$^+$, 5), 183 (26), 182 (15), 155 (16), 39 (11). IR (KBr): $\tilde{\nu}$ 3139 (m) cm$^{-1}$, 2892 (m), 1633 (m), 1595 (m), 1578 (s), 1528 (s), 1493 (w), 1469 (s), 1454 (s), 1412 (w), 1369 (w), 1339 (w), 1311 (w), 1295 (m), 1273 (w), 1186 (w), 1157 (w), 1129 (w), 895 (w), 819 (w), 800 (s), 771 (m), 733 (w), 675 (w), 630 (w), 582 (w), 525 (w). Anal. calcd for C$_{12}$H$_{10}$N$_{4}$ (210.2): C 68.56, H 4.79, N 26.65. Found: C 68.32, H 4.87, N 26.86.
4.2.6. 4-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-pyridin-2-amine (4f)

\[ \text{C}_{12}\text{H}_{10}\text{N}_4 \]

135 mg (0.64 mmol, 64 % yield) as a yellow solid. Mp 263-270 °C.\(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 5.85 (s, 2 H, NH\(_2\)), 6.87 (dd, \(J = 5.4\) Hz, \(J = 1.6\) Hz, 1 H), 6.89 (s, 1 H), 7.20 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.90 (d, \(J = 5.4\) Hz, 1 H), 8.00 (d, \(J = 2.5\) Hz, 1 H), 8.30 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H), 8.33 (dd, \(J = 8.2\) Hz, \(J = 1.6\) Hz, 1 H), 12.1 (br, 1 H, NH). \(^13\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 104.0 (CH), 109.6 (CH), 112.3 (C\(_{\text{quat}}\)), 116.2 (CH), 117.0 (C\(_{\text{quat}}\)), 125.2 (CH), 127.6 (CH), 143.0 (C\(_{\text{quat}}\)), 143.0 (CH), 147.9 (CH), 149.1 (C\(_{\text{quat}}\)), 160.3 (C\(_{\text{quat}}\)). El + MS (m/z (%)): 210 (M\(^+\), 100), 210 ((M-H\(^+\), 25), 183 (33), 182 (20), 170 (32), 155 (25), 142 (10), 63 (11), 41 (10), 39 (10). IR (KBr): \(\tilde{\nu}\) 3314 (m) cm\(^{-1}\), 3191 (m), 1639 (m), 1607 (s), 1538 (m), 1525 (m), 1507 (w), 1421 (s), 1365 (w), 1323 (w), 1289 (s), 1243 (w), 1174 (w), 1146 (w), 1071 (w), 992 (w), 881 (w), 835 (w), 802 (m), 778 (m), 627 (w), 579 (w). Anal. calcd for C\(_{12}\)H\(_{10}\)N\(_4\) (210.2): C 68.56, H 4.79, N 26.65. Found: C 68.36, H 4.82, N 26.89.
4.2.7. 2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-benzenamine (4g)

![Chemical Structure](image)

\[C_{13}H_{11}N_3\]

209.25

154 mg (0.74 mmol, 74 % yield) as a pale yellow solid. Mp 147 °C. \(^1\)H NMR (DMSO-d$_6$, 500 MHz): \(\delta\) 4.77 (s, 2 H, NH$_2$), 6.64 (td, \(J = 7.6\) Hz, \(J = 1.3\) Hz, 1 H), 6.80 (dd, \(J = 8.2\) Hz, \(J = 1.3\) Hz, 1 H), 7.01-7.05 (m, 1 H), 7.08 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.16 (dd, \(J = 7.6\) Hz, \(J = 1.6\) Hz, 1 H), 7.58 (d, \(J = 2.5\) Hz, 1 H), 7.87 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 8.26 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H), 11.8 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d$_6$, 125 MHz): \(\delta\) 111.9 (C$_{quat}$), 115.0 (CH), 115.4 (CH), 116.4 (CH), 118.3 (C$_{quat}$), 118.8 (C$_{quat}$), 124.1 (CH), 127.3 (CH), 127.7 (CH), 130.2 (CH), 142.7 (CH), 145.7 (C$_{quat}$), 148.6 (C$_{quat}$). EI + MS (m/z (%)): 209 (M$^+$, 100), 208 ((M-H)$^+$, 93), 193 (C$_{13}$H$_9$N$_2$$^+$, 12), 181 (39), 154 (33), 128 (22), 127 (35), 117 (C$_7$H$_5$N$_2$$^+$, 11), 77 (20). IR (KBr): \(\tilde{\nu}\) 3364 (m) cm$^{-1}$, 3142 (s), 3029 (m), 2913 (m), 1614 (s), 1581 (m), 1536 (m), 1490 (m), 1448 (m), 1418 (w), 1339 (w), 1290 (m), 1265 (m), 1152 (w), 1107 (w), 963 (m), 937 (w), 896 (w), 797 (m), 774 (s), 750 (s), 645 (w), 621 (m), 590 (w), 514 (w). Anal. calcd for C$_{13}$H$_{11}$N$_3$ (209.3): C 74.62, H 5.30, N 20.08. Found: C 74.43, H 5.14, N 19.95.
4.2.8. 4-(1H-Pyrrolo[2,3-b]pyridin-3-yl)phenol (4h)

![Chemical structure](image)

C_{13}H_{10}N_{2}O

210.23

120 mg (0.57 mmol, 57 % yield) as a beige solid. Mp 244 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 6.85-6.89 (m, 2 H), 7.12 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 7.50-7.54 (m, 2 H), 7.69 (d, $J = 2.2$ Hz, 1 H), 8.21 (dd, $J = 8.2$ Hz, $J = 1.3$ Hz, 1 H), 8.26 (dd, $J = 4.7$ Hz, $J = 1.6$ Hz, 1 H), 9.39 (s, 1 H, OH), 11.76 (s, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 114.5 (C$_{quat}$), 115.6 (CH), 115.6 (CH), 117.3 (C$_{quat}$), 122.2 (CH), 125.8 (C$_{quat}$), 127.3 (CH), 127.4 (CH), 142.6 (CH), 148.9 (C$_{quat}$), 155.5 (C$_{quat}$). EI + MS (m/z (%)): 210 (M$^+$, 100), 209 ((M-H)$^+$, 10), 182 (14), 181 (12), 154 (13), 127 (10), 105 (14), 97 (10), 71 (11), 57 (11). IR (KBr): $\tilde{\nu}$ 3387 (m) cm$^{-1}$, 3000 (m), 2673 (m), 1604 (m), 1583 (m), 1548 (s), 1504 (m), 1488 (m), 1461 (s), 1438 (s), 1386 (w), 1340 (w), 1324 (m), 1299 (w), 1256 (s), 1169 (m), 1142 (m), 1097 (s), 1043 (w), 964 (m), 836 (s), 817 (m), 797 (m), 774 (m), 578 (m), 540 (m), 503 (w). Anal. calcd for C$_{13}$H$_{10}$N$_2$O (210.2): C 74.27, H 4.79, N 13.33. Found: C 74.04, H 4.86, N 13.62.
4.2.9. 4-(1H-Indol-3-yl)-pyrimidin-2-amine (*Meridianin G, 4i*)

![Chemical Structure](image)

$\text{C}_{12}\text{H}_{10}\text{N}_{4}$

210.23

154 mg (0.73 mmol, 73 % yield) as a pale yellow solid. Mp 195-197 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 6.42 (s, 2 H, NH$_2$), 7.02 (dd, $J = 5.4$ Hz, $J = 0.6$ Hz, 1 H), 7.10-7.15 (m, 1 H), 7.15-7.20 (m, 1 H), 7.43-7.46 (m, 1 H), 8.10 (d, $J = 5.4$ Hz, 1 H), 8.20 (d, $J = 2.5$ Hz, 1 H), 8.59 (d, $J = 7.9$ Hz, 1 H), 11.7 (br, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 105.2 (CH), 111.7 (CH), 113.6 (C$_{quat}$), 120.1 (CH), 121.8 (CH), 122.3 (CH), 125.2 (C$_{quat}$), 128.1 (CH), 136.9 (C$_{quat}$), 156.9 (CH), 162.6 (C$_{quat}$), 163.4 (C$_{quat}$). EI + MS (m/z (%)): 211 (15), 210 (M$^+$, 100), 209 ((M-H)$^+$, 34), 169 (60), 141 (10), 140 (14), 105 (12), 97 (12), 85 (10), 83 (10), 71 (12), 57 (14).
Data reported in the literature:


Mp 262.2-264.3 °C (EtOAc/MeOH). $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 6.39 (br s, 2 H), 7.02 (d, $J = 5.3$ Hz, 1 H), 7.15 (m, 2 H), 7.45 (d, $J = 7.9$ Hz, 1 H), 8.11 (d, $J = 5.3$ Hz, 1 H), 8.19 (s, 1 H), 8.59 (d, $J = 7.4$ Hz, 1 H), 11.65 (br s, 1 H). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$: 105.2, 111.7, 113.6, 120.2, 121.9, 122.3, 125.3, 128.1, 136.9, 156.9, 162.6, 163.4. El + MS (m/z (%)): 210 (M$^+$, 100), 209 (35), 169 (48), 155 (4), 140 (9), 114 (8), 89 (4). IR (KBr): $\tilde{\nu}$ 3408 cm$^{-1}$, 3329, 3174, 1661, 1568, 1453, 1414, 1246, 1119. HRMS calcd for C$_{12}$H$_{10}$N$_4$: 210.0923. Found: 210.0914.


Mp 263-265 °C. $^1$H NMR (DMSO-d$_6$, 270 MHz): $\delta$ 6.4 (br s, 2 H, NH$_2$), 7.03 (d, 1 H, H-5$'$), 7.15 (m, 2 H, H-5, H-6), 7.44-7.46 (d, 1 H, H-7), 8.11 (d, 1 H, H-6$'$), 8.19 (s, 1 H, H-2), 8.58-8.61 (d, 1 H, H-4), 11.65 (br s, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 300 MHz): $\delta$: 105.2 (C-5$'$), 111.71 (C-7), 113.70 (C-3), 120.21 (C-3a), 121.85 (C-6), 122.32 (C-5), 125.30 (C-4), 128.10 (C-2), 136.90 (C-7a), 156.91 (C-6$'$), 162.62 (C-4$'$), 163.40 (C-2$'$). El + MS (m/z (%)): 210 (M$^+$, 100), 209 (36), 169 (49), 155 (4), 140 (10), 114 (8). IR (KBr): $\tilde{\nu}$ 3409 (NH$_2$) cm$^{-1}$, 3329 (NH$_2$), 3172 (NH), 1659, 1569, 1454, 1416, 1241, 1129, 808, 741, 684. Anal. calcd for C$_{12}$H$_{10}$N$_4$: 210.2: C 68.56, H 4.79, N 26.79. Found: C 68.72, H 4.76, N 26.47.


Yellow powder. Mp 183-185 °C. $^1$H NMR (acetone-d$_6$): $\delta$ 5.91 (br s, NH$_2$), 7.04 (d, $J = 5.3$ Hz, 1 H, H-5$'$), 7.10-7.22 (m, 2 H, H-5, H-6), 7.46 (d, $J = 7.3$ Hz, 1 H, H-7), 8.12 (m, 2 H, H-6$'$, H-2), 8.58 (d, $J = 7.7$ Hz, 1 H, H-4), 10.86 (br s, NH). $^{13}$C NMR (acetone-d$_6$): $\delta$: 111.5 (C-5$'$), 117.2 (C-7), 120.2 (C-3), 126.0/127.7/128.0 (C-4/C-5/C-6), 131.4 (C-3a), 133.0 (C-2), 143.0 (C-7a), 162.7 (C-6$'$), 168.7/169.5 (C-2$'$/C-4$'$). IR (KBr): $\tilde{\nu}$ 3408 cm$^{-1}$, 3329, 3173, 1660, 1568, 1520, 1452, 1413, 1246, 751, 735. Anal. calcd for C$_{12}$H$_{10}$N$_4$: 210.2: C 68.56, H 4.79. Found: C 68.45, H 4.78.


Beige powder.

Dark-brown solid. Mp 183 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 6.40 (br, 2H), 7.01 (d, $J = 5.3$ Hz, 1 H), 7.18-7.19 (m, 2 H), 7.42 (d, $J = 7.9$ Hz, 1 H), 8.08 (d, $J = 5.3$ Hz, 1 H), 8.18 (d, $J = 2.9$ Hz, 1 H), 8.56 (d, $J = 7.9$ Hz, 1 H), 11.64 (br, 1H). MS (Cl): $m/z$ 211 (M+1). Anal. calcd for C$_{12}$H$_{10}$N$_4$: C 68.56, H 4.79, N 26.65. Found: C 68.47, H 4.81, N 26.72.


$^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ 6.38 (s, NH$_2$), 7.00 (d, $J = 5.3$ Hz, 1 H, H-5´), 7.10 (t, $J = 6.8$ Hz, 1 H, H-6), 7.16 (t, $J = 6.8$ Hz, 1 H, H-5), 7.42 (d, $J = 7.9$ Hz, 1 H, H-7), 8.08 (d, $J = 5.3$ Hz, 1 H, H-6´), 8.17 (d, $J = 2.4$ Hz, 1 H, H-2), 8.56 (d, $J = 7.8$ Hz, 1 H, H-4), 11.93 (br s, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 300 MHz): $\delta$ 105.3 (d, C-5´), 111.8 (d, C-7), 113.2 (s, C-3), 120.2 (d, C-6), 121.9 (d, C-4), 122.4 (d, C-5), 125.2 (s, C-7a), 128.2 (d, C-2), 137.0 (s, C-3a), 157.0 (d, C-6´).

The NMR spectra are in good agreement with those reported in the literature. However, the melting point deviates immensely from the melting point reported by *Jiang* and *Radwan*. 

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4.2.10. 4-(4-Methoxy-1H-indol-3-yl)pyrimidin-2-amine (4j)

\[
\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}
\]

240.26

185 mg (0.77 mmol, 77 % yield) as a colorless solid. Mp 221-222 °C. \(^1\)H NMR (DMSO-\text{d}_6, 500 MHz): \(\delta\) 3.87 (s, 3 H), 6.27 (s, 2 H, NH\(_2\)), 6.63 (d, \(J = 6.9\) Hz, 1 H), 7.06-7.12 (m, 2 H), 7.26 (dd, \(J = 5.4\) Hz, \(J = 0.9\) Hz, 1 H), 7.85 (d, \(J = 2.5\) Hz, 1 H), 8.15 (d, \(J = 5.4\) Hz, 1 H), 11.6 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-\text{d}_6, 125 MHz): \(\delta\) 55.0 (CH\(_3\)), 101.2 (CH), 105.5 (CH), 109.7 (CH), 114.4 (C\(_{\text{quat}}\)), 115.4 (C\(_{\text{quat}}\)), 122.7 (CH), 127.5 (CH), 138.8 (C\(_{\text{quat}}\)), 153.2 (C\(_{\text{quat}}\)), 157.0 (CH), 161.8 (C\(_{\text{quat}}\)), 163.2 (C\(_{\text{quat}}\)). EI + MS (\(m/z\) (%)): 240 (M\(^+\), 50), 239 ((M-H\(^+\)), 21), 211 ((M-CH\(_3\)O+H\(^+\)), 20), 202 ((M-C\(_2\)H\(_2\)N+2H\(^+\)), 11), 58 (CH\(_4\)N\(_3\)^+), 43 (C\(_2\)H\(_3\)O\(^+\)), 100. IR (KBr): \(\tilde{\nu}\) 3465 (m) cm\(^{-1}\), 3313 (m), 3165 (m), 1644 (m), 1624 (m), 1575 (s), 1555 (s), 1506 (s), 1459 (s), 1414 (m), 1359 (w), 1320 (m), 1275 (w), 1245 (m), 1212 (w), 1168 (w), 1130 (w), 1088 (m), 970 (w), 884 (w), 815 (w), 778 (w), 733 (m), 706 (w), 630 (w). Anal. calcd for C\(_{13}\)H\(_{12}\)N\(_4\)O (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.86, H 4.85, N 23.25.
4.2.11. 4-(5-Phenyl-1H-pyrrol-3-yl)pyrimidin-2-amine (4k)

190 mg (0.80 mmol, 80 % yield) as a rosa solid. Mp 257 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 6.35 (s, 2 H, NH$_2$), 6.87 (d, $J$ = 5.0 Hz, 1 H), 7.06-7.08 (m, 1 H), 7.18-7.23 (m, 1 H), 7.37-7.41 (m, 2 H), 7.58-7.60 (m, 1 H), 7.66-7.70 (m, 2 H), 8.12 (d, $J$ = 5.0 Hz, 1 H), 11.7 (br, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 104.0 (CH), 104.9 (CH), 120.7 (CH), 123.5 (CH), 123.9 (C$_{quat}$), 126.0 (CH), 128.7 (CH), 132.1 (C$_{quat}$), 132.4 (C$_{quat}$), 157.5 (CH), 161.2 (C$_{quat}$), 163.5 (C$_{quat}$). EI + MS (m/z (%)): 237 (16), 236 (M$^+$, 100), 235 ((M-H)$^+$, 22), 195 (35), 133 (13). IR (KBr): $\tilde{\nu}$ 3408 (m) cm$^{-1}$, 3141 (w), 1631 (m), 1567 (s), 1543 (s), 1509 (w), 1455 (s), 1416 (m), 1369 (w), 1281 (w), 1203 (m), 1156 (w), 1110 (w), 1071 (w), 1031 (w), 990 (w), 926 (w), 900 (w), 874 (w), 815 (m), 793 (w), 751 (s), 694 (m), 593 (w), 528 (w). Anal. calcd for C$_{14}$H$_{12}$N$_4$ (236.3): C 71.17, H 5.12, N 23.71. Found: C 71.30, H 5.30, N 23.98.
4.2.12. 5-(5-(4-Chlorophenyl)-1H-pyrrol-3-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4I)

![Chemical Structure](image)

C_{16}H_{14}ClN_{3}O_{2}

315.75

202 mg (0.64 mmol, 64 \% yield) as a rosa solid. Mp 256 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 3.25 (s, 3 H), 3.38 (s, 3 H), 6.93 (dd, \(J = 2.5\) Hz, \(J = 1.6\) Hz, 1 H), 7.41-7.45 (m, 2 H), 7.49 (dd, \(J = 2.5\) Hz, \(J = 1.6\) Hz, 1 H), 7.61-7.64 (m, 2 H), 8.04 (s, 1 H), 11.4 (br, 1 H, NH). \(^13\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 27.6 (CH\(_3\)), 36.3 (CH\(_3\)), 103.3 (CH), 107.3 (C\(_{\text{quat}}\)), 116.7 (C\(_{\text{quat}}\)), 118.7 (CH), 124.8 (CH), 128.7 (CH), 129.8 (C\(_{\text{quat}}\)), 131.4 (C\(_{\text{quat}}\)), 137.8 (CH), 150.5 (C\(_{\text{quat}}\)), 161.5 (C\(_{\text{quat}}\)). EI + MS \((m/z)\): 317 ((M\(^{37}\)Cl\(^+\)), 36), 316 (20), 315 ((M\(^{35}\)Cl\(^+\)), 100), 258 (22), 229 (11), 217 (27), 203 (13), 201 (28), 189 (18), 154 (13), 140 (14), 116 (10). IR (KBr): \(\tilde{\nu}\) 3378 (m) cm\(^{-1}\), 1694 (s), 1653 (s), 1627 (s), 1565 (w), 1515 (w), 1443 (m), 1404 (w), 1357 (w), 1231 (w), 1130 (m), 1048 (w), 928 (w), 828 (w), 800 (w), 754 (w), 726 (w), 608 (w), 540 (w). Anal. calcd for C\(_{16}\)H\(_{14}\)ClN\(_3\)O\(_2\) (315.8): C 60.86, H 4.47, N 13.31. Found: C 60.93, H 4.71, N 13.11.
4.2.13. 4-(5-(4-Methoxyphenyl)-1H-pyrrol-3-yl)pyridine (4m)

151 mg (0.60 mmol, 60 % yield) as a beige solid. Mp 181-183 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 3.77 (s, 3 H), 6.93-7.00 (m, 3 H), 7.53-7.59 (m, 3 H), 7.60-7.65 (m, 2 H), 8.40-8.45 (m, 2 H), 11.6 (br, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 55.0 (CH$_3$), 102.0 (CH), 114.1 (CH), 118.2 (CH), 118.8 (CH), 121.8 (C$_{quat}$), 124.9 (CH), 125.1 (C$_{quat}$), 133.0 (C$_{quat}$), 142.9 (C$_{quat}$), 149.6 (CH), 157.7 (C$_{quat}$). EI + MS (m/z (%)): 251 (21), 250 (M$^+$, 100), 236 (13), 235 ((M-CH$_3$)$^+$, 89), 207 (39), 206 (20), 205 (15), 180 (11), 179 (11), 178 (13), 153 (11), 152 (35), 151 (18), 128 (11), 127 (15), 126 (12), 125 (11), 102 (10), 89 (13), 77 (19), 76 (12), 63 (15), 51 (15). IR (KBr): $\tilde{\nu}$ 3114 (m) cm$^{-1}$, 3065 (m), 2991 (m), 2893 (m), 2834 (m), 1602 (s), 1543 (m), 1533 (w), 1505 (s), 1464 (m), 1440 (w), 1429 (m), 1376 (w), 1306 (w), 1287 (m), 1251 (s), 1216 (m), 1180 (m), 1165 (w), 1111 (w), 1094 (w), 1066 (w), 1038 (m), 1001 (m), 935 (w), 834 (m), 795 (s), 750 (w), 738 (w), 691 (m), 667 (w), 638 (w), 610 (w), 525 (m). Anal. calcd for C$_{16}$H$_{14}$N$_2$O (250.3): C 76.78, H 5.64, N 11.19. Found: C 76.51, H 5.80, N 11.20.
4.2.14. 4-(4-Fluorophenyl)-2-(thiophen-2-yl)-1H-pyrrole (4n)

![Chemical Structure](image)

C\textsubscript{14}H\textsubscript{10}FNS  
243.30

170 mg (0.70 mmol, 70 % yield) as a pale gray solid. Mp 163 °C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \(\delta\) 6.67-6.69 (m, 1 H), 7.05 (dd, \(J = 5.0\) Hz, \(J = 3.8\) Hz, 1 H), 7.11-7.16 (m, 2 H), 7.26 (dd, \(J = 3.5\) Hz, \(J = 0.9\) Hz, 1 H), 7.29 (dd, \(J = 2.5\) Hz, \(J = 1.9\) Hz, 1 H), 7.35 (dd, \(J = 5.0\) Hz, \(J = 0.9\) Hz, 1 H), 7.58-7.64 (m, 2 H), 11.48 (s, 1 H, NH). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \(\delta\) 103.3 (CH), 115.2 (d, \(J = 21.1\) Hz, CH), 116.1 (CH), 120.9 (CH), 122.7 (CH), 123.5 (C\textsubscript{quat}), 126.0 (d, \(J = 8.2\) Hz, CH), 127.1 (C\textsubscript{quat}), 127.7 (CH), 131.9 (d, \(J = 2.7\) Hz, C\textsubscript{quat}), 135.9 (C\textsubscript{quat}), 160.2 (d, \(J = 241.9\) Hz, C\textsubscript{quat}). EI + MS (m/z (%)): 244 (18), 243 (M\textsuperscript{+}, 100), 242 ((M-H)\textsuperscript{+}, 14), 215 (14), 183 (11), 133 (18), 122 (19). IR (KBr): \(\tilde{\nu}\) 3412 (s) cm\textsuperscript{-1}, 3123 (w), 1655 (w), 1578 (w), 1535 (w), 1501 (m), 1420 (w), 1300 (w), 1224 (m), 1161 (w), 1130 (m), 1098 (w), 1047 (w), 1010 (w), 924 (w), 840 (s), 811 (w), 793 (s), 770 (m), 685 (s), 662 (m), 597 (w), 577 (w), 538 (m), 515 (s). Anal. calcd for C\textsubscript{14}H\textsubscript{10}FNS (243.3): C 69.11, H 4.14, N 5.76. Found: C 69.29, H 4.35, N 5.68.
4.2.15. 1-Benzyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole (4o)

\[
\begin{align*}
\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2 \\
302.29
\end{align*}
\]

106 mg (0.35 mmol, 35 % yield) as a colorless solid. Mp 106 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 5.35 (s, 2 H), 7.26-7.30 (m, 2 H), 7.31-7.40 (m, 3 H), 7.52-7.56 (m, 2 H), 7.56-7.60 (m, 2 H), 7.67 (s, 1 H), 7.86 (s, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 56.3 (CH\(_2\)), 122.2, 124.2 (q, \(J = 272.2\) Hz, C\(_{\text{quat}}\)), 125.4, 125.8 (q, \(J = 3.7\) Hz, CH), 126.6, 127.8, 128.2 (q, \(J = 33.0\) Hz, C\(_{\text{quat}}\)), 128.3, 128.9, 136.0, 136.1 (q, \(J = 1.8\) Hz, CH), 137.1. EI + MS (m/z (%)): 303 (10), 302 (M\(^+\), 49), 301 ((M-H\(^+\), 51), 91 (C\(_7\)H\(_7\)^+\), 100), 65 (C\(_5\)H\(_5\)^+\), 11). IR (KBr): \(\tilde{\nu}\) 3106 (w) cm\(^{-1}\), 2925 (w), 2852 (w), 1620 (m), 1456 (w), 1432 (w), 1337 (s), 1229 (w), 1158 (s), 1113 (s), 1080 (m), 1062 (m), 1000 (w), 953 (w), 842 (m), 729 (m), 693 (w), 597 (w), 510 (w), 453 (w). Anal. calcd for C\(_{17}\)H\(_{13}\)F\(_3\)N\(_2\) (302.3): C 67.54, H 4.33, N 9.27. Found: C 67.70, H 4.31, N 9.02.
4.2.16. 1-(Thiophen-3-yl)isoquinoline (4p)

\[
\text{C}_{13}\text{H}_9\text{NS}
\]

161 mg (0.76 mmol, 76 % yield) as a colorless solid. Mp 91-92 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.49 (dd, \(J = 5.0\) Hz, \(J = 2.8\) Hz, 1 H), 7.54 (dd, \(J = 5.0\) Hz, \(J = 1.3\) Hz, 1 H), 7.55-7.59 (m, 1 H), 7.61 (d, \(J = 5.7\) Hz, 1 H), 7.67-7.71 (m, 1 H), 7.72 (dd, \(J = 2.8\) Hz, \(J = 1.3\) Hz, 1 H), 7.87 (d, \(J = 8.2\) Hz, 1 H), 8.28 (d, \(J = 8.5\) Hz, 1 H), 8.57 (d, \(J = 5.7\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 119.9 (CH), 125.7 (CH), 126.1 (CH), 126.9 (C\(_{\text{quat}}\)), 127.0 (CH), 127.2 (CH), 127.3 (CH), 129.2 (CH), 130.0 (CH), 136.8 (C\(_{\text{quat}}\)), 140.7 (C\(_{\text{quat}}\)), 142.2 (CH), 155.9 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 212 (12), 211 (M\(^+\), 57), 210 ((M-H\(^+\)), 100), 166 (C\(_9\)H\(_8\)N\(^+\)), 139 (9), 128 (C\(_9\)H\(_8\)N\(^+\)), 126 (C\(_4\)H\(_3\)S\(^+\)), 10, 83 (C\(_4\)H\(_3\)S\(^+\)), 4). IR (KBr): \(\tilde{\nu}\) 3047 (w) cm\(^{-1}\), 1614 (w), 1579 (w), 1552 (m), 1524 (w), 1494 (w), 1452 (w), 1415 (m), 1333 (m), 1306 (m), 1215 (w), 1192 (w), 1138 (w), 1061 (w), 1018 (w), 988 (w), 963 (w), 901 (m), 867 (m), 833 (m), 810 (s), 792 (m), 774 (m), 753 (s), 708 (w), 683 (s), 661 (w), 639 (w), 612 (w), 567 (w), 514 (w). Anal. calcd for C\(_{13}\)H\(_9\)NS (211.3): C 73.90, H 4.29, N 6.63. Found: C 73.79, H 4.25, N 6.62.

Data reported in the literature:


Yellow solid. Mp 74-75 °C. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.49 (ddd, \(J = 6\) Hz, \(J = 3\) Hz, \(J = 1\) Hz, 1 H), 7.55 (dt, \(J = 1.6\) Hz, 1 H), 7.57 (dt, \(J = 1.8\) Hz, 1 H), 7.62 (d, \(J = 6\) Hz, 1 H), 7.69 (dt, \(J = 1.8\) Hz, 1 H), 7.72 (dt, \(J = 1.3\) Hz, 1 H), 7.87 (d, \(J = 8\) Hz, 1 H), 8.29 (d, \(J = 8\) Hz, 1 H), 8.58 (d, \(J = 6\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 119.8, 125.6, 126.0, 126.9, 127.1, 127.3, 129.1, 130.1, 130.0, 130.5, 136.7, 140.6, 142.1, 155.8. IR (neat): \(\tilde{\nu}\) 3105 cm\(^{-1}\), 3049, 1620, 1582, 1555, 1498, 1418, 1337, 1309. Anal. calcd for C\(_{13}\)H\(_9\)NS (211.3): C 73.90, H 4.29. Found: C 73.79, H 4.25.
4.2.17. 4-(2-Ethyl-5-(thiophen-2-yl)furan-3-yl)benzonitrile (4q)

221 mg (0.79 mmol, 79 % yield) as a pale yellow solid (after crystallization by suspension in n-pentane, sonication in ultrasound bath, filtration and drying in vacuo overnight). Mp 108 °C. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.34 (t, $J = 7.6$ Hz, 3 H), 2.85 (q, $J = 7.6$ Hz, 2 H), 6.60 (s, 1 H), 7.05 (dd, $J = 5.0$ Hz, $J = 3.8$ Hz, 1 H), 7.24 (dd, $J = 5.0$ Hz, $J = 0.9$ Hz, 1 H), 7.27 (dd, $J = 3.5$ Hz, $J = 0.9$ Hz, 1 H), 7.47-7.51 (m, 2 H), 7.66-7.70 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 12.8 (CH$_3$), 20.6 (CH$_2$), 105.6 (CH), 110.0 (C$_{quat}$), 119.0 (C$_{quat}$), 121.0 (C$_{quat}$), 122.6 (CH), 124.2 (CH), 127.7 (CH), 128.0 (CH), 132.4 (CH), 133.2 (C$_{quat}$), 138.7 (C$_{quat}$), 147.9 (C$_{quat}$), 153.5 (C$_{quat}$). EI + MS (m/z (%)): 280 (12), 279 (M$^+$, 59), 265 (18), 264 ((M-CH$_3$)$^+$, 100), 166 (22), 164 (17), 131 (13), 129 (13), 111 (23). IR (KBr): $\tilde{\nu}$ 2975 (w) cm$^{-1}$, 2222 (s), 1606 (s), 1503 (w), 1203 (w), 1177 (w), 1133 (w), 1060 (m), 983 (m), 947 (w), 840 (m), 799 (m), 707 (s), 567 (m), 549 (m). Anal. calcd for C$_{17}$H$_{13}$NOS (279.4): C 73.09, H 4.69, N 5.01. Found: C 72.99, H 4.43, N 4.91.
4.2.18. 5-(4-(Trifluoromethoxy)phenyl)pyridin-2-amine (4r)

\[
\begin{align*}
\text{OC}_3F_3 \\
\text{H}_2N \\
\text{C}_{12}H_9F_3N_2O \\
254.21
\end{align*}
\]

233 mg (0.92 mmol, 92 % yield) as a colorless solid. Mp 98-101 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 6.12 (s, 2 H, NH\(_2\)), 6.54 (d, \(J = 8.5\) Hz, 1 H), 7.34-7.38 (m, 2 H), 7.65-7.68 (m, 2 H), 7.70 (dd, \(J = 8.5\) Hz, \(J = 2.5\) Hz, 1 H), 8.24 (d, \(J = 2.5\) Hz, 1 H). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 108.1 (CH), 120.2 (q, \(J = 255.7\) Hz, C\(_{\text{quat}}\)), 121.6 (CH), 122.6 (C\(_{\text{quat}}\)), 127.1 (CH), 135.6 (CH), 137.6 (C\(_{\text{quat}}\)), 146.0 (CH), 147.0 (q, \(J = 1.8\) Hz, C\(_{\text{quat}}\)), 159.5 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 255 (13), 254 (M\(^+\), 100), 185 ((M-CF\(_3\))\(^+\), 30), 158 (12). IR (KBr): \(\tilde{\nu}\) 3490 (w) cm\(^{-1}\), 3466 (w), 3298 (w), 3150 (w), 1638 (s), 1634 (s), 1603 (m), 1562 (w), 1494 (s), 1423 (w), 1389 (m), 1249 (s), 1147 (s), 1017 (w), 997 (w), 857 (w), 827 (w), 806 (w), 671 (w), 537 (w), 509 (w). Anal. calcd for C\(_{12}H_9F_3N_2O\) (254.2): C 56.70, H 3.57, N 11.02. Found: C 56.64, H 3.57, N 10.75.
4.2.19. 5-(4-(Trifluoromethyl)phenyl)pyrimidin-2-amine (4s)

\[
\begin{align*}
\text{CF}_3 \\
\text{H}_2\text{N} \\
\text{N} \\
\text{N} \\
\text{C} \\
\text{H}_8 \\
\text{F}_3 \\
\text{N}_3
\end{align*}
\]

\[C_{11}H_8F_3N_3 \quad 239.20\]

105 mg (0.44 mmol, 44 % yield) as a colorless solid. Mp < 176 °C (subl.)*. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 6.93 (s, 2 H, NH\(_2\)), 7.73-7.76 (m, 2 H), 7.82-7.86 (m, 2 H), 8.65 (s, 2 H). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 120.6 (C\(_{\text{quat}}\)), 124.5 (q, \(J = 272.2\) Hz, C\(_{\text{quat}}\)), 125.8 (CH), 125.9 (q, \(J = 3.7\) Hz, CH), 127.3 (q, \(J = 32.1\) Hz, C\(_{\text{quat}}\)), 139.5 (C\(_{\text{quat}}\)), 156.5 (CH), 163.3 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 240 (13), 239 (M\(^+\), 100), 238 ((M-H)\(^+\), 26), 211 (10), 198 (13), 170 (28), 169 (12), 151 (12), 120 (17). IR (KBr): \(\tilde{\nu}\) 3478 (w) cm\(^{-1}\), 3321 (w), 3165 (w), 1661 (m), 1638 (m), 1599 (m), 1550 (w), 1528 (w), 1482 (m), 1424 (w), 1382 (w), 1324 (s), 1300 (m), 1224 (w), 1174 (m), 1133 (m), 1112 (m), 1071 (m), 1013 (w), 838 (m), 799 (w), 721 (w), 664 (w), 639 (w), 599 (w), 517 (w). Anal. calcd for C\(_{11}H_8F_3N_3\) (239.2): C 55.23, H 3.37, N 17.57. Found: C 55.23, H 3.44, N 17.46.

*Slow sublimation with not clearly detectable sublimation point.
4.2.20. 4-(Pyridazin-4-yl)phenol (4t)

\[
\begin{align*}
\text{C}_{10}
\text{H}_{8}
\text{N}_2
\text{O} \\
\text{172.18}
\end{align*}
\]

121 mg (0.70 mmol, 70 % yield) as a rosa solid. Mp 242 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 6.91-6.95 (m, 2 H), 7.76-7.80 (m, 2 H), 7.88 (dd, \(J = 5.4\) Hz, \(J = 2.5\) Hz, 1 H), 9.14 (dd, \(J = 5.4\) Hz, \(J = 1.3\) Hz, 1 H), 9.55 (dd, \(J = 2.5\) Hz, \(J = 1.3\) Hz, 1 H), 10.2 (br, 1 H, OH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 116.4 (CH), 122.0 (CH), 124.2 (C\(_{quat}\)), 128.7 (CH), 137.2 (C\(_{quat}\)), 149.0 (CH), 151.5 (CH), 159.6 (C\(_{quat}\)). EI + MS (m/z (%)): 173 (13), 172 (M\(^+\), 100), 118 (41), 115 (30), 91 (10), 89 (16). IR (KBr): \(\nu\) 3448 (w) cm\(^{-1}\), 3073 (w), 1615 (w), 1574 (s), 1515 (m), 1444 (w), 1390 (w), 1360 (w), 1285 (s), 1242 (w), 1177 (m), 1111 (w), 1046 (w), 979 (w), 839 (w), 812 (m), 789 (w), 745 (w), 665 (w), 571 (w). Anal. calcd for C\(_{10}\)H\(_8\)N\(_2\)O (172.2): C 69.76, H 4.68, N 16.27. Found: C 69.49, H 4.91, N 16.10.

Data reported in the literature:


4.2.21. 4-(3,4,5-Trimethoxyphenyl)pyridine-2,6-diamine hydrochloride (4u)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{HCl} \\
\text{N} & \quad \text{NH}_2 \\
\text{MeO} & \quad \text{MeO} \\
\text{OMe} & \\
\text{C}_14\text{H}_{18}\text{ClN}_3\text{O}_3 & \\
311.76
\end{align*}
\]

136 mg (0.44 mmol, 44 % yield) as an orange solid (after crystallization with \(n\)-pentane from 1.25 \(M\) HCl in EtOH, filtration, washing with \(n\)-pentane, and drying in vacuo overnight at 70 °C). Mp 128-135 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 1.34 (t, \(J = 7.6\) Hz, 3 H), 2.85 (q, \(J = 7.6\) Hz, 2 H), 6.60 (s, 1 H), 7.05 (dd, \(J = 5.0\) Hz, \(J = 3.8\) Hz, 1 H), 7.24 (dd, \(J = 5.0\) Hz, \(J = 0.9\) Hz, 1 H), 7.27 (dd, \(J = 3.5\) Hz, \(J = 0.9\) Hz, 1 H), 7.47-7.51 (m, 2 H), 7.66-7.70 (m, 2 H). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 12.8 (CH\(_3\)), 20.6 (CH\(_2\)), 105.6 (CH), 110.0 (C\(_{\text{quat}}\)), 119.0 (C\(_{\text{quat}}\)), 121.0 (C\(_{\text{quat}}\)), 122.6 (CH), 124.2 (CH), 127.7 (CH), 128.0 (CH), 132.4 (CH), 133.2 (C\(_{\text{quat}}\)), 138.7 (C\(_{\text{quat}}\)), 147.9 (C\(_{\text{quat}}\)), 153.5 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 276 (17), 275 ((M-HCl)+, 100), 260 ((M-HCl-CH\(_3\))+, 17), 217 (C\(_{14}\)H\(_{11}\)N\(_3\)O\(_2\)+, 20), 108 (C\(_9\)H\(_6\)N\(_3\)+, 5). IR (KBr): \(\tilde{\nu}\) 3410 (m) cm\(^{-1}\), 3334 (m), 3207 (m), 2941 (w), 2837 (w), 2741 (w), 1645 (s), 1588 (m), 1518 (w), 1492 (w), 1463 (w), 1413 (w), 1378 (m), 1325 (m), 1267 (w), 1245 (w), 1169 (w), 1127 (s), 999 (m), 965 (w), 831 (w), 807 (w), 757 (w), 720 (w), 562 (w), 524 (w). Anal. calcd for C\(_{14}\)H\(_{18}\)ClN\(_3\)O\(_3\) (311.8): C 53.93, H 5.82, N 13.48. Found: C 53.73, H 6.03, N 13.35.
4.3. Synthesis of Meridianin A (5)

Synthesis of 3-(2-aminopyrimidin-4-yl)-1H-indol-4-ol (Meridianin A, 5)

Pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 4-(4-methoxy-1H-indol-3-yl)pyrimidin-2-amine (4j) (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min, the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The mixture was adsorbed on Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH₃ = 100:1:1 → 100:2:1 → 100:3:1→ 100:4:1 (stepwise gradient). After drying in vacuo, meridianin A (5) was obtained as a bright yellow fine crystalline solid.
Spectroscopic data of 3-(2-aminopyrimidin-4-yl)-1H-indol-4-ol (Meridianin A, 5)

\[
\text{C}_{12}\text{H}_{10}\text{N}_{4}\text{O}
\]

226.23

96 mg (0.43 mmol, 85 % yield) as a bright yellow fine crystalline solid. Mp 264-276 °C. (Lit.: 164-168 °C). \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta 6.39\) (dd, \(J = 7.9\) Hz, \(J = 0.9\) Hz, 1 H), 6.76 (s, 2 H, NH\(_2\)), 6.82 (dd, \(J = 8.2\) Hz, \(J = 0.9\) Hz, 1 H), 7.00 (t, \(J = 7.9\) Hz, 1 H), 7.14 (d, \(J = 5.4\) Hz, 1 H), 8.14 (d, \(J = 5.4\) Hz, 1 H), 8.25 (d, \(J = 3.2\) Hz, 1 H), 11.8 (br, 1 H, NH), 13.62 (s, 1 H, OH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta 102.3\) (CH), 104.3 (CH), 105.5 (CH), 113.7 (C\(_{quat}\)), 114.3 (C\(_{quat}\)), 124.4 (CH), 128.4 (CH), 139.2 (C\(_{quat}\)), 152.0 (C\(_{quat}\)), 158.4 (CH), 160.4 (C\(_{quat}\)), 161.7 (C\(_{quat}\)). El + MS (m/z (%)): 226 (M\(^+\), 100), 225 ((M-H)\(^+\), 13), 209 ((M-OH)\(^+\), 2), 197 ((M-COH)\(^+\), 6), 185 ((M-CH\(_2\)N\(_2\)+H)\(^+\), 18), 158 ((M-C\(_3\)H\(_4\)N\(_2\))\(^+\), 6). IR (KBr): \(\tilde{\nu}\) 3429 (m) cm\(^{-1}\), 3342 (m), 1638 (m), 1593 (s), 1562 (m), 1532 (m), 1469 (m), 1444 (m), 1401 (m), 1321 (m), 1272 (w), 1227 (m), 1194 (w), 1167 (w), 820 (w), 802 (w), 775 (w), 719 (m), 617 (w). Anal. calcd for C\(_{12}\)H\(_{10}\)N\(_4\)O (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.48, H 4.61, N 24.72.


\(^1\)H NMR (DMSO-d\(_6\), 400 MHz): \(\delta 6.38\) (dd, \(J = 0.7\) Hz, \(J = 0.7\) Hz, 1 H), 6.68 (br s, 2 H, NH\(_2\)), 6.81 (dd, \(J = 7.7\) Hz, \(J = 0.7\) Hz, 1 H), 7.08 (dd, \(J = 7.7\) Hz, \(J = 7.7\) Hz, 1 H), 7.12 (d, \(J = 5.4\) Hz, 1 H), 8.12 (br d, \(J = 5.4\) Hz, 1 H), 8.22 (d, \(J = 2.5\) Hz, 1 H), 11.75 (br s, 1 H, NH), 13.55 (s, 1 H, OH). \(^{13}\)C NMR (DMSO-d\(_6\), 100 MHz): \(\delta 102.3, 104.3, 105.4, 113.7, 114.3, 124.3, 128.3, 139.2, 152.0, 158.3, 160.7, 161.7.\)
Data reported in the literature:


Yellow needles (MeOH-H$_2$O). Mp 164-168 °C. $^1$H NMR (DMSO-d$_6$, 200 MHz): $\delta$ 6.36 (dd, $J = 7.1$ Hz, $J = 0.7$ Hz, H-5), 6.69 (s, NH$_2$), 6.78 (dd, $J = 7.5$ Hz, $J = 0.7$ Hz, H-7), 6.96 (dd, $J = 7.5$ Hz, $J = 7.1$ Hz, H-6), 7.09 (d, $J = 5.4$ Hz, H-5’), 8.10 (d, $J = 5.4$ Hz, H-6’), 8.20 (d, $J = 1.2$ Hz, H-2), 11.71 (brs, NH), 13.55 (s, OH). $^{13}$C NMR (DMSO-d$_6$, 50 MHz): $\delta$ 102.4 (C-7), 104.5 (C-5’), 105.6 (C-5), 113.8 (C-3), 114.5 (C-3a), 124.4 (C-6), 128.5 (C-2), 139.4 (C-7a), 152.1 (C-4), 158.5 (C-6’), 160.6 (C-4’), 161.9 (C-2’). HREIMS calcd for C$_{12}$H$_{10}$N$_4$O: 226.0855. Found: 226.0857. IR (KBr): $\tilde{\nu}$ 3437 cm$^{-1}$, 3351, 3200, 2924, 1647, 1605, 1533, 1469, 1326, 820, 721. UV (CH$_3$Cl) $\lambda_{max}$ (log$\varepsilon$) 248 (3.68), 356 (3.58) nm.

NMR spectra of *meridianin A* are in good agreement with those given by Palermo.


Yellow prisms (EtOH-hexane). Mp 164-168 °C. $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 7.13 (dd, $J = 7.8$ Hz, $J = 0.9$ Hz, 1 H, H-5), 7.48 (brs, 2 H, NH$_2$), 7.57 (dd, $J = 8.1$ Hz, $J = 0.9$ Hz, 1 H, H-5’), 7.74 (dd, $J = 7.8$ Hz, 1 H, H-6), 7.88 (d, $J = 5.7$ Hz, 1 H, H-5’), 8.88 (d, $J = 5.7$ Hz, 1 H, H-6’), 9.0 (s, 1 H, H-2), 11.8 (s, 1 H, NH), 13.9 (s, 1 H, OH). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 102.3 (C-7), 104.4 (C-5’), 105.4 (C-5), 113.7 (C-3), 114.4 (C-3a), 124.4 (C-6), 128.4 (C-2), 139.2 (C-7a), 152.0 (C-4), 158.4 (C-6’), 160.5 (C-4’), 161.7 (C-2’). IR (nujol): $\tilde{\nu}$ 3456 (m) cm$^{-1}$, 3416 (m), 3340 (m), 3181 (m), 1586 (s), 1532 (s), 1270 (s), 1124 (s), 1072 (s). EI + MS (m/z (%)): 226 (M$^+$, 100), 185 (26), 167 (16), 149 (59). Anal. calcd for C$_{12}$H$_{10}$N$_4$O (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.57, H 4.31, N 24.93.

The $^{13}$C NMR values are in good agreement with those given by Fresneda and Molina, but the $^1$H NMR values deviate considerably.

However, the melting point deviates immensely from the melting point reported both by Palermo as well as Fresneda and Molina.
5. $^1$H and $^{13}$C NMR Spectra of Compounds 4a-u and 5

$^1$H NMR of 4a (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4a (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4a (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm).
$^1$H NMR of 4b (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4b (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4b (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
$^1$H NMR of 4c (15 mg) in 0.7 mL DMSO-d$_6$ at 299 K (δ in ppm).
$^{13}$C NMR of $4c$ (15 mg) in 0.7 mL DMSO-d$_6$ at 299 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of $4c$ (15 mg) in 0.7 mL DMSO-d$_6$ at 299 K ($\delta$ in ppm).
$^1$H NMR of 4d (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm).
$^{13}$C NMR of 4d (15 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4d (15 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 4e (15 mg) in 0.7 mL DMSO-$d_6$ at 299 K ($\delta$ in ppm).
\(^{13}\)C NMR of 4e (15 mg) in 0.7 mL DMSO-d\(_6\) at 299 K (\(\delta\) in ppm).

\(^{13}\)C DEPT 135-NMR of 4e (15 mg) in 0.7 mL DMSO-d\(_6\) at 299 K (\(\delta\) in ppm).
$^1$H NMR of 4f (15 mg) in 0.7 mL DMSO-d$_6$ at 298 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4f (15 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4f (15 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4g (15 mg) in 0.7 mL DMSO-d$_6$ at 298 K (δ in ppm). *Impurity from residual solvents.
$^{13}$C NMR of 4g (15 mg) in 0.7 mL DMSO-$d_6$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4g (15 mg) in 0.7 mL DMSO-$d_6$ at 298 K (δ in ppm).
$^1$H NMR of 4h (30 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
$^{13}$C NMR of 4h (30 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4h (30 mg) in 0.7 mL DMSO-$d_6$ at 295 K ($\delta$ in ppm).
$^1$H NMR of 4i (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 4i (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4i (15 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
$^1$H NMR of 4j (30 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
$^{13}$C NMR of $4j$ (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of $4j$ (30 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 4k (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 4k (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4k (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 4I (20 mg) in 0.7 mL DMSO-d$_6$ at 298 K (δ in ppm).
$^{13}$C NMR of 4I (20 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4I (20 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4m (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm). *Impurities from residual solvents.
\(^{13}\)C NMR of 4m (15 mg) in 0.7 mL DMSO-d\(_6\) at 297 K (\(\delta\) in ppm). *Impurities from residual solvents.

\(^{13}\)C DEPT 135-NMR of 4m (15 mg) in 0.7 mL DMSO-d\(_6\) at 297 K (\(\delta\) in ppm). *Impurities from residual solvents.
$^1$H NMR of 4n (20 mg) in 0.7 mL DMSO-$d_6$ at 298 K (δ in ppm).
\(^{13}\)C NMR of 4n (20 mg) in 0.7 mL DMSO-\(d_6\) at 299 K (\(\delta\) in ppm).

\(^{13}\)C DEPT 135-NMR of 4n (20 mg) in 0.7 mL DMSO-\(d_6\) at 298 K (\(\delta\) in ppm).
$^1$H NMR of 4o (50 mg) in 0.7 mL CDCl$_3$ at 297 K ($\delta$ in ppm). *Impurities from residual solvents.
\(^{13}\)C NMR of 4o (50 mg) in 0.7 mL CDCl\(_3\) at 298 K (\(\delta\) in ppm). *Impurities from residual solvents.

\(^{13}\)C DEPT 135-NMR of 4o (50 mg) in 0.7 mL CDCl\(_3\) at 297K (\(\delta\) in ppm). *Impurities from residual solvents.
$^1$H NMR of 4p (20 mg) in 0.7 mL CDCl$_3$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4p (20 mg) in 0.7 mL CDCl$_3$ at 296 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4p (20 mg) in 0.7 mL CDCl$_3$ at 296 K (δ in ppm).
$^1$H NMR of 4q (20 mg) in 0.7 mL CDCl$_3$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4q (20 mg) in 0.7 mL CDCl$_3$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4q (20 mg) in 0.7 mL CDCl$_3$ at 298 K ($\delta$ in ppm).
$^1$H NMR of 4r (30 mg) in 0.7 mL CDCl$_3$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 4r (30 mg) in 0.7 mL CDCl$_3$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4r (30 mg) in 0.7 mL CDCl$_3$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 4s (15 mg) in 0.7 mL CDCl$_3$ at 297 K (δ in ppm).
$^{13}$C NMR of 4s (15 mg) in 0.7 mL CDCl$_3$ at 297 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4s (15 mg) in 0.7 mL CDCl$_3$ at 297 K ($\delta$ in ppm).
$^1$H NMR of 4t (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 4t (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm).

$^{13}$C DEPT 135-NMR of 4t (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K (δ in ppm).
$^1$H NMR of 4u (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^{13}$C NMR of 4u (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 4u (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^1$H NMR of 5 (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 5 (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C DEPT 135-NMR of 5 (30 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
6. Appendix

6.1. UV Purity of Compounds 4a-u and 5

HT-LC-MS Spectrum (SOP 2200) of 4a. UV purity: 100 %
Peak ID | Compound | Time | Mass Found
--- | --- | --- | ---
2 | (Time: 3.88) Combine (916:814) | 3.88 | 2.0e+03

Peak ID | Compound | Time | Mass Found
--- | --- | --- | ---
3 | (Time: 7.22) Combine (1568:1512) | 7.22 | 1.3e+03
HT-LC-MS Spectrum (SOP 2200) of 4b. UV purity: 100%

3: UV Detector: 254 Smooth (Ms, 2x3)

1.947e-1
Range: 1.944e-1

1: MS ESI+ (BPI Smooth (SG, 2x4))

1.4e+066

1: MS ESI+ :212.09+234.09 Smooth (SG, 2x4)

1.9e+066

1: MS ESI+ :423.18+445.18 Smooth (SG, 2x4)

3.9e+064

2: MS ESI- :BPI Smooth (SG, 2x4)

2.9e+065
### Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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#### 2: MS ES- @210.09 Smooth (SG, 2x4)

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Range: 271.633

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1.7e+006

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2: MS ES-  
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HT-LC-MS Spectrum (SOP 2200) of 4c. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 4d. UV purity: 98.1 %

### UV Detector: 254 Smooth (Mn, 2x3)

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### MS ES+ / 423.18+445.10 Smooth (8G, 2x4)

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HT-LC-MS Spectrum (SOP 2200) of 4f. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2222) of 4g. UV purity: 100 %
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1: MG ES+ 4.7e+006
2: MG ES+ 2.5e+005
HT-LC-MS Spectrum (SOP 2200) of 4h. UV purity: 97.5 %

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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HT-LC-MS Spectrum (SOP 2200) of 4i. UV purity: 99.6 %
HT-LC-MS Spectrum (SOP 2200) of 4j. UV purity: 100%
HT-LC-MS Spectrum (SOP 2200) of 4k. UV purity: 98.2 %

1: MS ES+ :BFI Smooth (5G, 2x4)

1: MS ES+ :237.11+259.11 Smooth (5G, 2x4)

1: MS ES+ :473.22+495.22 Smooth (5G, 2x4)

2: MS ES- :BFI Smooth (5G, 2x4)
HT-LC-MS Spectrum (SOP 2200) of 4l. UV purity: 100 %
2: MS ES-: 114.08 Smooth (GO, 2x4)

Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found
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3.2e+03

(1) ESDG Signal Smooth (Mg, 2x3)

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071.470

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Time

Peak ID | Compound | Time | Mass Found
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1: MS ES+ 4.3e+06

Peak ID | Compound | Time | Mass Found
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1: (Time: 3.56) Combine (742-746) | 395.0 | 352.9 & 396.0

2: MS ES- 1.1e+05

Peak ID | Compound | Time | Mass Found
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1: (Time: 3.56) Combine (742-746) | 822.8 & 863.5
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HT-LC-MS Spectrum (SOP 2200) of 4n. UV purity: 100 %
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HT-LC-MS Spectrum (SOP 2200) of 4o. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 4p. UV purity: 100 %

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3: UV Detector: 254 Smooth (Nh, 2x3)

Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found
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4 1.47 300342.2 8.15 0.3 175174.6
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10 7.23 38216.9 1.04 0.1 947226.8

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Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2011
HT-LC-MS Spectrum (SOP 2200) of 4q. UV purity: 100 %

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1: MS ES+ 286.07+392.07 Smooth (SG, 2x4)

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1: MS ES+ 286.07+392.07 Smooth (SG, 2x4)

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<th>Width</th>
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<tbody>
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<td>1</td>
<td>MS ES+ 286.07+392.07 Smooth (SG, 2x4)</td>
<td>2.9e+04</td>
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1: MS ES+ 286.07+392.07 Smooth (SG, 2x4)

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<th>Compound</th>
<th>Time</th>
<th>AreaAbs</th>
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<th>Mass Found</th>
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HT-LC-MS Spectrum (SOP 2200) of 4r. UV purity: 100 %
HP-LC-MS Spectrum (SOP 2200) of 4s. UV purity: 100 %
HP-LC-MS Spectrum (SOP 2200) of 4t. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 4u. UV purity: 98.5 %

1. MS ES+ 1DPI Smooth (SO, 2x4).

2. MS ES+ 1DPI Smooth (SO, 2x3).

3. UV Detector, 254 Smooth (Mn, 2x3).

Range: 3.992e-1

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2011
HT-LC-MS Spectrum (SOP 2200) of 5 (meridianin A). UV purity: 99.5 %
### 6.2. HT-LC-MS Methods for the Control of Identity and Purity of Compounds 4a-u and 5

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<th>Identity and Purity</th>
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<td>Methods</td>
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<tr>
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<td>B: 99.9 % water + 0.1 % TFA</td>
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<tr>
<td>Gradient</td>
<td>time (min)</td>
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<tr>
<td>Injection volume</td>
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<tr>
<td>Sample Preparation</td>
<td>Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasonic bath, so that the concentration was 0.5 mM.</td>
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<td>If necessary, the sample was additionally diluted: 100 μl in 500 μl acetonitrile + water 5/95.</td>
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<td>Problem Definition</td>
<td>Identity and Purity</td>
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<td>-------------------</td>
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<td>SOP</td>
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<td>1 x Waters 2488 Mux-UV Detector</td>
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<td>Eluent</td>
<td>A: 99.9 % acetonitrile + 0.1 % formic acid</td>
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<td>B: 99.9 % water + 0.1 % formic acid</td>
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<td>Throughput</td>
<td>416 samples: approx. 11 hours</td>
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7. References


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Dedicated to Prof. em. Dr. Leonhard Birkofier on the occasion of his 100th birthday

Keywords: Alkaloids / Arylation / Boron / C–C coupling / Multicomponent reactions / Palladium

Diazine-bridged bisindoles are readily obtained from N-Boc-protected 3-iodoindoles and 3-iodo-7-azaindole in a pseudo three-component reaction involving a one-pot Masuda borylation–Suzuki arylation sequence. Some of the title compounds display promising cytotoxic properties. The versatility of this methodology is illustrated by a very concise total synthesis of the marine alkaloid hyrtinadine A.

Introduction

Heterocycles bridging two identical indole substituents are common scaffolds in many pharmaceutically interesting natural products,[1] such as hamacanthins,[2] nortopsentin,[3] and lynamins.[4] Inspired by marine alkaloids of the meridianin and variolin family,[5,6] we identified the structurally related, novel bisindole alkaloid hyrtinadine A (Scheme 1)[7] as a suitable target to scrutinize the scope of the Masuda borylation–Suzuki coupling sequence[8] of nitrogen heterocycles, which we applied recently in a concise synthesis of meridianin A and 7-azaindole analogues. Hyrtinadine A, isolated from an Okinawan marine sponge of the *Hyrtios* genus, was found to be highly cytotoxic against murine leukemia L1210 and human epidermoid carcinoma KB cell lines. The sole total synthesis of hyrtinadine A was realized by a Pd-catalyzed coupling of indiumorganyls as a key step.[9] Although a twofold cross-coupling with heterocyclic substrates and an unsymmetrical substitution of the pyrimidyl core were achieved, this methodology appears to be very limited. A major drawback is the overstoichiometrical use of the precious indolyl organoindium reagent, which is also associated with the need for organolithium or organomagnesium precursors not tolerant towards functional groups. Herein we report the adaptation of the Masuda borylation–Suzuki coupling sequence to diheteroaryl-substituted diazines and its application to a concise total synthesis of hyrtinadine A.

Results and Discussion

The Suzuki–Miyaura cross-coupling reaction is one of the most versatile tools for the preparation of biaryls in a short and efficient manner.[10] Pinacolboronates[11] are stable esters and can be readily applied as coupling partners in Suzuki coupling reactions. Most advantageously, their preparation proceeds by palladium-catalyzed Miyaura[12] or Masuda[13] borylation under mild conditions and tolerates a lot of polar functionality. The Masuda borylation has the advantage of using pinacolborane as a borylating agent, which is definitely more atom economical and elegant than applying bispinacolato diboron. Therefore, the advantages of performing a Masuda borylation and a subsequent Suzuki coupling in a one-pot sequence lie at hand. Prior to our studies, this sequence has not generally been used for the preparation of heteroaromatic biaryls.[14] Just recently, we established this conceptually elegant sequence for N-heterocycles, such as indoles and pyrroles,[8] which are both ubiquitous in nature and constitute important building blocks.

Scheme 1. Retrosynthetic analysis of hyrtinadine A.
blocks of many biologically active compounds with significant relevance in medicinal chemistry.\[15\]

Our retrosynthetic analysis of hyrtinadine A suggests the Masuda borylation–Suzuki coupling as a key transform (Scheme 1), which is projected as a one-pot reaction in the sense of a sequentially palladium-catalyzed process.\[16\]

Moreover, the Boc protecting group is concomitantly cleaved under the terminal Suzuki conditions, accounting for the efficiency of the sequence. As a consequence, \(N\)-Boc-3-iodo-5-methoxyindole and 5-bromo-2-iodopyrimidine are the electrophilic coupling partners; the former is readily available from commercially available starting materials.\[17\]

According to this strategy, we first scouted the applicability of the sequence to the synthesis of structural subunits 3a–c, using the standard conditions for the sequence (Scheme 2).

Scheme 2. One-pot Masuda borylation–Suzuki arylation synthesis of heteroaryl-substituted indoles 3.

| 1a: R\(^1\) = H, X = NBoc, Y = CH, R\(^2\) = H |
| 1b: R\(^1\) = H, X = Nboc, Y = N, R\(^2\) = H |
| 1c: R\(^1\) = 5-Cl, X = Nboc, Y = CH, R\(^2\) = H |
| 1d: R\(^1\) = 5-F, X = Nboc, Y = CH, R\(^2\) = H |
| 1e: R\(^1\) = 4-OMe, X = Nboc, Y = CH, R\(^2\) = H |
| 1f: R\(^1\) = 5-OME, X = Nboc, Y = CH, R\(^2\) = H |
| 1g: R\(^1\) = 6-OME, X = Nboc, Y = CH, R\(^2\) = H |
| 1h: R\(^1\) = 5-thien-2-yl, X = O, R\(^2\) = Et |
| 1i: R\(^1\) = 2-(p-anisyl), X = NBoc, R\(^2\) = H |

According to this strategy, we first scouted the applicability of the sequence to the synthesis of structural subunits 3a–c, using the standard conditions for the sequence (Scheme 2).

Scheme 3. Synthesis of isomeridianin A (4) by demethylation of 3c.

Scheme 4. One-pot Masuda borylation–Suzuki arylation synthesis of diazine-bridged bis(heteroaryl) 6.
After generating the boronate intermediate by Masuda borylation of indoles 1 with pinacolborane, methanol, 2-bromopyrimidine (2a), 5-bromopyrimidine (2b), or 4-chloro-2-aminoopyrimidine (2c), and cesium carbonate were subsequently added to the reaction mixture to give, after the Suzuki arylation step, 3-pyrimidyl-substituted indoles 3 in good to excellent isolated yields. For quenching the excess amount of pinacolborane, the addition of anhydrous methanol has proven to furnish highest yields in the two-step sequence. For demethylation of 3c, heating in the melt of pyridinium chloride (PyHCl)[18] was applied to give the literature unknown isomeridianin A (4) in a very good yield (Scheme 3).

With this convenient sequential Masuda borylation–Suzuki arylation protocol in hand we set out to perform the sequence as a pseudo-three-component synthesis, that is, the ratio of the in situ generated heterocyclic pinacolester to the dihalodiazine was chosen as 2:1. Starting from 3-iodo-substituted heterocycles such as indoles 1a, 1c–g, 7-azaindole (1b), 2-ethyl-5-thien-2-yl-furane (1h),[19] and 5-(p-anisyl)pyrrole (1i)[20] after Masuda borylation with pinacolborane the Suzuki arylation step with various diodo-, dibromo-, or bromoiodo-substituted diazines 5 furnishes bis(heteroaryl) substituted diazines 6 in a one-pot fashion in moderate to good yields (Scheme 4).

In particular, 2,5-bis(methoxyindol-3-yl)pyrimidines 6e–g can be readily obtained by this one-pot procedure, with the literature unknown compound 6f being O,O′-dimethyl hyrtinadine A, a precursor of the natural product. Thus, by virtue of the one-pot Masuda borylation–Suzuki arylation sequence as a key step, the total synthesis of hyrtinadine A can be conducted in a very concise fashion. Starting from commercially available 5-methoxy-1H-indole, after iodination, Boc protection, and Masuda borylation–Suzuki coupling sequence, dimethyl hyrtinadine A (6f) is accessible in good yield.

However, unexpectedly the final demethylation with PyHCl furnished hyrtinadine A (7) in only 39% yield. Therefore, we sought an alternative deprotection method.[21] Gratifyingly, demethylation of 6f using BBr₃ gave hyrtinadine A in 78% yield (Scheme 5).

Scheme 5. Synthesis of hyrtinadine A (7) by demethylation of O,O′-dimethyl hyrtinadine A (6f).

The biological activities of O-methyl isomeridianin A (3c), isomeridianin A (4), selected diazine-bridged bisheteroaryls 6, and hyrtinadine A (7) were evaluated by screening against a broad panel of 102–121 kinases at the Division of Signal Transduction Therapy (DSTT), University of Dundee, UK, and by determining the IC₅₀ values in viability assays with HCT116 (colon carcinoma) and A2780 (ovarian carcinoma) cell lines (Table 1).[22] Interestingly, O,O′-dimethyl hyrtinadine A (6f) as well as the chloro analogue (6c) show a low micromolar activity in viability assays, which however seems not to be correlated with kinase inhibitory activity. Fascinatingly, precursor 6f was more active than the natural product in viability assays.

Table 1. Biological data of selected compounds 3, 4, 6, and 7.

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<th>IC₅₀ (HCT116) [μM]</th>
<th>IC₅₀ (A2780) [μM]</th>
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<tr>
<td>Number of kinases tested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>7/110</td>
<td>&gt;10</td>
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<td>4</td>
<td>8/110</td>
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<tr>
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</tr>
<tr>
<td>6m</td>
<td>0/121</td>
<td>&gt;10</td>
</tr>
<tr>
<td>7</td>
<td>3/121</td>
<td>&gt;10</td>
</tr>
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</table>

[a] IC₅₀: concentration reducing cell proliferation by 50%.

Conclusions

In summary we have successfully adapted the one-pot Masuda borylation–Suzuki arylation sequence to a general synthesis of diazine-bridged bisheteroaryls in the sense of a one-pot pseudo-three-component reaction. The procedure is another showcase for sequential Pd-catalyzed processes, which can be easily performed without the need for exotic ligands or the excessive use of expensive reagents. Besides the concise total synthesis of the marine alkaloid hyrtinadine A, several bisheteroaryl analogues have been efficiently prepared in a straightforward fashion. Studies directed towards the syntheses of structurally more complex marine alkaloids, kinase inhibitors, and oligomeric heteroarenes using the Masuda borylation–Suzuki arylation are currently underway.

Experimental Section

Synthesis of 6f: Tetrakis(triphenylphosphane)palladium(0) (69 mg, 0.06 mmol, 3 mol-%) and tert-butyl 3-ido-5-methoxy-1H-indole-1-carboxylate (1f, 746 mg, 2.00 mmol) were placed under an argon atmosphere in a dry screw-cap vessel with a septum. Then, dry 1,4-dioxane (10 mL) was added, and the mixture was degassed with argon (5 min). Dry triethylamine (1.0 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolan (0.45 mL, 3.00 mmol) were successively added to the mixture, which was then stirred at 80°C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), dry methanol (10 mL), 5-bromo-2-iodopyrimidine (5a, 289 mg, 1.00 mmol), and cesium carbonate (1.63 g, 5.00 mmol) were successively added. The mixture was stirred at 100°C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give compound 6f as a yellow solid (238 mg, 0.64 mmol, 64% yield). For full analytical details, see the Supporting Information.
Synthesis of 7 (Demethylation of Compound 6; Synthesis of Hyrtidine A): 3,3′-(Pyrimidine-2,5-diyl)bis(5-methoxy-1H-indole) (66; 185 mg, 0.50 mmol) was dissolved in a dry screw-cap vessel under an argon atmosphere. Then, dry dichloromethane (15 mL) was added. The suspension was cooled to −78 °C (acetone/dry ice bath) and tribromoborane (0.58 mL, 6.00 mmol) was slowly added. The mixture was allowed to reach room temperature and continuously stirred for 20 h. The reaction progress was monitored by TLC.

Then the mixture was cooled to 0 °C (water/ice bath), and water (3 mL) followed by saturated potassium carbonate solution (3 mL) were slowly added. The resulting yellow precipitate was filtered and purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give hyrtidine A (7) as a yellow solid [147 mg, 0.43 mmol, 78% yield (contained one molecule of MeOH)]. For full analytical details, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data and copies of the NMR spectra of compounds 3, 4, 6, and 7.

Acknowledgments

The authors cordially thank Merck KGaA, Darmstadt and the Fonds der Chemischen Industrie (scholarship to B.O. A.T.) for financial support and Dr. Dieter Dorsch and Dr. Christian Sirenberg (Merck Serono R&D, Merck KGaA Darmstadt) for providing biological tests.


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Published Online: July 13, 2011
SUPPORTING INFORMATION

DOI: 10.1002/ejoc.201100680
Title: One-Pot Synthesis of Diazine-Bridged Bisindoles and Concise Synthesis of the Marine Alkaloid Hyrtinadine A
Author(s): Boris O. A. Tasch, Eugen Merkul, Thomas J. J. Müller*
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1 General Considerations  
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1 General Considerations

All cross-coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using an MBraun system MB-SPS-800. Triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from Sigma-Aldrich Chemie GmbH. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolyl borane) was purchased from Sigma-Aldrich Chemie GmbH. Tetrakis(triphenylphosphane)palladium(0) and cesium carbonate were purchased from Merck Serono KGaA. Commercial grade reagents were used as supplied without further purification and were purchased from Sigma-Aldrich Chemie GmbH, Acros Organics N. V., ABCR GmbH & Co. KG, Alfa Aesar GmbH & Co. KG, Merck Serono KGaA, Jiangsu and Synthonix Inc..

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from Merck Serono KGaA using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from Merck Serono KGaA before chromatographic purification. The reaction progress was monitored qualitatively using TLC Silica gel 60 F254 x 7.5 cm aluminium sheets obtained by Merck Serono KGaA. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

\(^{1}\)H, \(^{13}\)C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. CDCl₃ and DMSO-d₆ were used as deuterated solvents. TMS was used as reference (\(\delta 0.0\)) or the resonances of the solvents were locked as internal standards (acetone-d₆: \(^{1}\)H \(\delta 2.05\), \(^{13}\)C \(\delta 30.8\); CDCl₃: \(^{1}\)H \(\delta 7.26\), \(^{13}\)C \(\delta 77.0\); DMSO-d₆: \(^{1}\)H \(\delta 2.50\), \(^{13}\)C \(\delta 39.4\)). The multiplicities of the signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets; ddd: doublet of doublets of doublets; dt: doublet of triplets; td: triplet of doublets; tt: triplet of triplets; q: quartet; quint: quintet; sext: sextet; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. HT-LC-MS spectra were measured in the Molecule Analytics laboratory of Central Analytical Services, Merck Serono KGaA Darmstadt. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf. Kinase assays were performed at the Division of Signal Transduction Therapy (DSTT),
University of Dundee, UK. Viability assays were performed at Merck Serono KGaA, Darmstadt.
2 Preparation of Starting Materials

2.1 Synthesis of N-Boc 3-iodo-indoles 1

2.1.1 Preparation of tert-butyl 3-iodo-5-methoxy-1H-indole-1-carboxylate (1f)

A solution of iodine (5.14 g, 20.2 mmol, 1.01 equiv) in 30 mL DMF was dropped to the solution of 5-methoxy-1H-indole (2.97 g, 20.0 mmol) and potassium hydroxide (3.30 g, 50.0 mmol, 2.50 equiv) in 30 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poured on 400 mL of ice water containing 0.5 % ammonia and 0.1 % sodium disulfite. The mixture was placed in a refrigerator to ensure the complete precipitation. The precipitate was filtered, washed with 200 mL ice water and dried in vacuo to obtain 5.12 g (18.8 mmol, 94 % yield) of a beige solid. It was used without further purification for the next step.

The obtained solid was suspended in 35 mL dichloromethane. 4-Dimethylaminopyridine (231 mg, 188 mmol, 10 mol %) and di-tert-butyl dicarbonate (6.33 g, 28.1 mmol, 1.50 equiv), dissolved in 35 mL dichloromethane, were added and the mixture was stirred for 30 min at room temperature, washed with 35 mL 0.1 N HCl and the aqueous phase was extracted with dichloromethane (3 x 35 mL, monitored by TLC). The combined organic layers were dried with sodium sulfate, the solvents were removed under reduced pressure, the residue was adsorbed onto Celite® and purified chromatographically on silica gel with n-hexane/ethyl acetate (He/EtOAc = 50:1), (Rf (He/EtOAc = 50:1): 0.27) to give 6.79 g (18.2 mmol, 97 % yield, 91 % total yield over two steps) of 1f as a colorless solid.

The experimental details are given in Table 1.


---

1
<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>3-Iodo indole</th>
<th>(N)-Boc 3-Iodo indole 1 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0 g (171 mmol) (1H)-Indole (Acros)</td>
<td>Yellow solid</td>
<td>Pale brown oil</td>
<td>He/EtOAc = 50:1  (R_f) (He/EtOAc = 50:1): 0.38</td>
</tr>
<tr>
<td>1</td>
<td>12.1 g (100 mmol) (1H)-Pyrrlo[2,3-b]pyridine (7-Azaindole) (ABCR)</td>
<td>Yellow solid</td>
<td>Yellow oil</td>
<td>He/EtOAc = 20:1 (R_f) (He/EtOAc = 20:1): 0.14</td>
</tr>
<tr>
<td>1</td>
<td>0.93 g (6.00 mmol) 5-Chloro-(1H)-indole (Aldrich)</td>
<td>Yellow solid</td>
<td>Colorless solid</td>
<td>He/EtOAc = 50:1 (R_f) (He/EtOAc = 50:1): 0.41</td>
</tr>
<tr>
<td>1</td>
<td>0.82 g (6.00 mmol) 5-Fluoro-(1H)-indole (Aldrich)</td>
<td>Yellow solid</td>
<td>Colorless solid</td>
<td>He/EtOAc = 50:1 (R_f) (He/EtOAc = 50:1): 0.41</td>
</tr>
<tr>
<td></td>
<td>Mass (mmol)</td>
<td>Color</td>
<td>Mass (mmol)</td>
<td>Color</td>
</tr>
<tr>
<td>---</td>
<td>------------</td>
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</tr>
</tbody>
</table>
| 5 | 1.50       | Grey solid | 3.34       | Pale yellow oil | He/EtOAc = 50:1  
|   | (10.0)     |           | (8.58, 86 %)|           | R<sub>f</sub> (He/EtOAc = 50:1): 0.21  
|   | 4-Methoxy-1H-indole (ABCR) |  
|   | 3.08       | Pale yellow oil | 8.24 mmol, 96 % | Total yield: 82 % |  
| 6 | 2.97       | Beige solid | 5.12       | Colorless solid | He/EtOAc = 50:1  
|   | (20.0)     |           | (18.8 mmol, 94 %)|           | R<sub>f</sub> (He/EtOAc = 50:1): 0.27  
|   | 5-Methoxy-1H-indole (ABCR) |  
|   | 6.79       | Colorless solid | 18.2 mmol, 97 % | Total yield: 91 % |  
| 7 | 0.80       | Yellow solid | 1.27       | Pale yellow solid | He/EtOAc = 20:1  
|   | (5.40)     |           | (4.67 mmol, 86 %)|           | R<sub>f</sub> (He/EtOAc = 20:1): 0.38  
|   | 6-Methoxy-1H-indole (Merck)<sup>1</sup> |  
|   | 1.61       | Pale yellow solid | 4.32 mmol, 94 % | Total yield: 81 % |  

<sup>1</sup> 6-Methoxy-1H-indole was prepared in the laboratories of Merck Serono KGaA, Darmstadt, and chromatographically purified with n-hexane/ethyl acetate (He/EtOAc = 1:1) before use.
2.2 Spectroscopic Data of N-Boc 3-Iodo-indoles 1

2.2.1 tert-Butyl 3-ido-1H-indole-1-carboxylate (1a)

\[
\begin{array}{c}
\text{I} \\
\text{C}_{13}\text{H}_{14}\text{INO}_2 \\
343.16
\end{array}
\]

11.3 g (32.9 mmol, 63 % yield over two steps) as a pale brown oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.66 (s, 9 H), 7.28-7.32 (m, 1 H), 7.33-7.36 (m, 1 H), 7.36-7.40 (m, 1 H), 7.72 (s, 1 H), 8.12 (d, \(J = 7.3\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 28.1 (CH\(_3\)), 65.4 (C\(_{\text{quat}}\)), 84.2 (C\(_{\text{quat}}\)), 115.0 (CH), 121.4 (CH), 123.3 (CH), 125.3 (CH), 130.0 (CH), 132.0 (C\(_{\text{quat}}\)), 134.8 (C\(_{\text{quat}}\)), 148.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 343 (M\(^+\), 14), 287 ((M-C\(_4\)H\(_9\)+H\(^+\)), 59), 270 ((M-C\(_6\)H\(_5\)O+H\(^+\)), 6), 243 ((M-C\(_5\)H\(_9\)O\(_2\)+H\(^+\)), 79), 116 (C\(_6\)H\(_5\)N\(^+\), 30), 115 (C\(_6\)H\(_5\)N\(^+\), 22), 88 (10), 57 (C\(_4\)H\(_9\)+, 100), 41 (13). IR (film): \(\tilde{\nu}\) 3151 (w), 3052 (w), 2979 (m), 2932 (w), 1747 (s), 1731 (s), 1606 (w), 1528 (w), 1476 (m), 1449 (s), 1375 (s), 1358 (s), 1336 (m), 1311 (m), 1249 (m), 1211 (m), 1148 (m), 1112 (m), 1054 (m), 1016 (w), 938 (w), 854 (w), 800 (w), 769 (m), 745 (m), 672 (w), 589 (w) cm\(^{-1}\). Anal. calcd. for C\(_{13}\)H\(_{14}\)INO\(_2\) (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.24, H 4.30, N 3.89.

Data reported in the literature:\(^1\)

Colorless solid (n-pentane), mp: 36-40 °C. \(^1\)H NMR (400 MHz): \(\delta\) 1.68 (s, 9 H), 7.29-7.43 (m, 3 H), 7.73 (s, 1 H), 8.13 (d, \(J = 8.1\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 28.1 (q), 65.4 (s), 115.1 (d), 121.5 (d), 123.3 (d), 125.3 (d), 130.1 (d), 132.0 (s), 134.9 (s), 148.7 (s). EI + MS (m/z (%)): 343 (M\(^+\), 69), 287 (100), 270 (13), 243 (98), 116 (28), 57 (98). Anal. calcd. for C\(_{13}\)H\(_{14}\)INO\(_2\) (343.16): C 45.50, H 4.11, N 4.08. Found C 45.37, H 3.66, N 3.96.

Data reported in the literature:\(^2\)

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.69 (s, 9 H), 7.20-7.41 (m, 3 H), 7.72 (s, 1 H), 8.15 (d, \(J = 5.0\) Hz, 1 H).

---

2.2.2  tert-Butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1b)

\[
\text{C}_{12}\text{H}_{13}\text{IN}_{2}\text{O}_{2}
\]

344.15

31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator), mp: 79 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.66 (s, 9 H), 7.22 (dd, \(J = 7.9\) Hz, \(J = 4.7\) Hz, 1 H), 7.61 (dd, \(J = 7.9\) Hz, \(J = 1.6\) Hz, 1 H), 7.78 (s, 1 H), 8.50 (dd, \(J = 4.7\) Hz, \(J = 1.6\) Hz, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 27.4 (CH\(_3\)), 61.3 (C\(_{\text{quat}}\)), 83.8 (C\(_{\text{quat}}\)), 118.5 (CH), 124.3 (C\(_{\text{quat}}\)), 128.9 (CH), 129.9 (CH), 145.3 (CH), 146.0 (C\(_{\text{quat}}\)), 146.6 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 344 (M\(^+\), 4), 245 (8), 244 ((M-C\(_5\)H\(_9\)O\(_2\)+H)\(^+\), 100), 117 (C\(_7\)H\(_5\)N\(_2\)+, 23), 116 (C\(_7\)H\(_4\)N\(_2\)+, 10), 90 (10), 57 (C\(_4\)H\(_9\)+, 26).

Data reported in the literature:\(^3\)

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.70 (s, 9 H), 7.28 (dd, \(J = 8.5\) Hz, 1 H), 7.72 (dd, \(J = 8.1\) Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, \(J = 5.1\) Hz, 1 H).

2.2.3  **tert-Butyl 5-chloro-3-iodo-1\textit{H}\textsubscript{2} indole-1-carboxylate (1c)**

![Chemical Structure](image)

C\textsubscript{13}H\textsubscript{13}ClINO\textsubscript{2}

377.61

1.39 g (3.67 mmol, 61 % yield over two steps) as a colorless solid, mp: 106 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 1.66 (s, 9 H), 7.31 (dd, \(J = 8.8\) Hz, \(J = 2.0\) Hz, 1 H), 7.38 (d, \(J = 2.0\) Hz, 1 H), 7.73 (s, 1 H), 8.03-8.08 (m, 1 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta\) 28.1 (CH\textsubscript{3}), 64.0 (C\textsubscript{quat}), 84.8 (C\textsubscript{quat}), 116.2 (CH), 121.2 (CH), 125.6 (CH), 129.2 (C\textsubscript{quat}), 131.3 (CH), 133.3 (C\textsubscript{quat}), 133.4 (C\textsubscript{quat}), 148.3 (C\textsubscript{quat}). EI + MS (m/z (%)): 377 (M\textsuperscript{+}, 8), 320 (29), 279 (14), 278 (6), 277 (M-C\textsubscript{5}H\textsubscript{9}O\textsubscript{2}+H\textsuperscript{+}, 43), 150 (16), 114 (20), 57 (100), 41 (15). IR (KBr): \(\tilde{\nu}\) 3001 (w), 2970 (w), 2932 (w), 2916 (w), 2866 (w), 1749 (w), 1732 (s), 1475 (w), 1460 (w), 1445 (m), 1394 (w), 1358 (s), 1339 (w), 1308 (w), 1267 (m), 1248 (s), 1203 (m), 1151 (s), 1121 (m), 1053 (s), 1038 (m), 953 (m), 937 (w), 856 (m), 839 (w), 810 (w), 793 (s), 760 (m), 721 (m), 633 (m) cm\textsuperscript{-1}. Anal. calcd. for C\textsubscript{13}H\textsubscript{13}ClINO\textsubscript{2} (377.6): C 41.35, H 3.47, N 3.71. Found: C 41.49, H 3.57, N 3.64.
2.2.4 tert-Butyl 5-fluoro-3-iodo-1H-indole-1-carboxylate (1d)

\[
\begin{align*}
\text{F} & \quad \text{I} \\
\text{C}_\text{Boc} & \quad \text{H}
\end{align*}
\]

C\text{_{13}H_{13}FNO_{2}}

361.15

1.25 g (3.47 mmol, 58 % yield over two steps) as a colorless solid, mp: 76 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.66 (s, 9 H), 7.05-7.10 (m, 2 H), 7.75 (s, 1 H), 8.09 (br, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 28.1 (CH\(_3\)), 64.4 (d, \(J = 4.1\) Hz, C\(_{\text{quat}}\)), 84.6 (C\(_{\text{quat}}\)), 107.2 (d, \(J = 24.9\) Hz, CH), 113.3 (d, \(J = 25.1\) Hz, CH), 116.3 (d, \(J = 9.0\) Hz, CH), 131.2 (C\(_{\text{quat}}\)), 131.6 (CH), 133.3 (d, \(J = 10.1\) Hz, C\(_{\text{quat}}\)), 148.4 (C\(_{\text{quat}}\)), 159.9 (d, \(J = 240.6\) Hz, C\(_{\text{quat}}\)). EI + MS (m/z (%)): 361 (M\(^+\), 10), 305 (32), 261 ((M-C\text{\textsubscript{5}H\textsubscript{9}O\textsubscript{2}+H})\(^+\), 51), 134 (24), 133 (21), 57 (C\(_4\)H\(_9\)\(^+\), 100). IR (KBr): \(\nu\) 2980 (m), 2887 (w), 2357 (w), 2332 (w), 1730 (m), 1603 (w), 1589 (w), 1472 (m), 1456 (w), 1441 (m), 1396 (w), 1366 (s), 1348 (m), 1337 (w), 1308 (w), 1252 (s), 1240 (m), 1202 (m), 1148 (s), 1105 (m), 1072 (w), 1053 (m), 1036 (m), 972 (m), 945 (w), 843 (s), 812 (m), 795 (s), 758 (m), 744 (m), 698 (w), 685 (w), 662 (m), 648 (w), 611 (m) cm\(^{-1}\). Anal. calcd. for C\text{\textsubscript{13}H\textsubscript{13}FNO\textsubscript{2}} (361.2): C 43.23, H 3.63, N 3.88. Found: C 43.15, H 3.82, N 3.78.
2.2.5 *tert-*Butyl 3-iodo-4-methoxy-1H-indole-1-carboxylate (1e)

\[ \text{C}_{14}\text{H}_{16}\text{INO}_3 \]

3.08 g (8.24 mmol, 82 % yield over two steps) as a pale yellow oil (solidified upon storage in refrigerator), mp: 68 °C. $^1$H NMR (CDCl$_3$, 500 MHz): \( \delta \) 1.64 (s, 9 H), 3.92 (s, 3 H), 6.67 (d, \( J = 8.2 \) Hz, 1 H), 7.24 (t, \( J = 8.2 \) Hz, 1 H), 7.61 (s, 1 H), 7.80 (d, \( J = 8.2 \) Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): \( \delta \) 28.1 (CH$_3$), 55.4 (CH$_3$), 57.6 (C$_{quat}$), 84.2 (C$_{quat}$), 104.0 (CH), 108.0 (CH), 119.6 (C$_{quat}$), 125.9 (CH), 130.0 (CH), 136.5 (C$_{quat}$), 148.5 (C$_{quat}$), 153.2 (C$_{quat}$). EI + MS (m/z (%)): 373 (M$^+$, 33), 317 ((M-C$_{4}$H$_9$+H)$^+$, 100), 273 ((M-C$_{4}$H$_9$O$_2$+H)$^+$, 56), 258 ((M-C$_{4}$H$_9$O$_2$-CH$_3$+H)$^+$, 23), 57 (C$_{4}$H$_5^+$, 83). IR (film): \( \tilde{\nu} \) 3151 (w), 2979 (s), 2937 (m), 2837 (w), 1732 (s), 1606 (m), 1586 (s), 1494 (s), 1427 (s), 1394 (m), 1370 (s), 1339 (s), 1286 (s), 1153 (s), 1124 (s), 1046 (s), 955 (w), 903 (w), 852 (m), 819 (w), 775 (m), 735 (m), 696 (w), 668 (w), 597 (w) cm$^{-1}$. Anal. calcd. for C$_{14}$H$_{16}$INO$_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.11, N 3.56.
2.2.6 tert-Butyl 3-iodo-5-methoxy-1H-indole-1-carboxylate (1f)

![Chemical Structure](image)

\[ C_{14}H_{16}INO_3 \]

373.19

6.79 g (18.2 mmol, 91 % yield over two steps) as a colorless solid, mp: 114 °C. \(^1\)H NMR (CDCl$_3$, 500 MHz): \( \delta \) 1.65 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, \( J = 2.5 \) Hz, 1 H), 6.96 (dd, \( J = 8.8 \) Hz, \( J = 2.5 \) Hz, 1 H), 7.70 (s, 1 H), 8.0 (br, 1 H). \(^13\)C NMR (CDCl$_3$, 125 MHz): \( \delta \) 28.1 (CH$_3$), 55.7 (CH$_3$), 65.1 (C$_{quat}$), 84.1 (C$_{quat}$), 103.6 (CH), 114.5 (CH), 116.0 (CH), 129.4 (C$_{quat}$), 130.5 (CH), 132.9 (C$_{quat}$), 148.6 (C$_{quat}$), 156.5 (C$_{quat}$). EI + MS (m/z (%)): 373 (M$^+$, 41), 317 ((M-C$_4$H$_9$O$_2$)$^+$, 100), 273 ((M-C$_4$H$_9$O$_2$-CH$_3$)$^+$, 65), 258 ((M-C$_4$H$_9$O$_2$-CH$_3$)$^+$, 22). IR (KBr): \( \tilde{\nu} \) 3158 (w), 3003 (w), 2978 (w), 2934 (w), 2836 (w), 1855 (w), 1729 (w), 1656 (w), 1622 (w), 1579 (w), 1528 (w), 1482 (m), 1439 (m), 1372 (s), 1280 (m), 1250 (s), 1204 (m), 1161 (s), 1120 (m), 1054 (m), 1028 (m), 959 (w), 931 (w), 845 (m), 802 (m), 783 (m), 753 (m), 669 (m), 626 (w), 558 (w) cm$^{-1}$. Anal. calcd. for C$_{14}$H$_{16}$INO$_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.20, H 4.43, N 4.00.

Data reported in the literature:

\(^1\)H NMR (CDCl$_3$): \( \delta \) 1.63 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, \( J = 1.0 \) Hz, 1 H), 7.00 (dd, \( J = 5.1 \) Hz, 1 H), 7.69 (s, 1 H), 8.01 (d, \( J = 5.0 \) Hz, 1 H). MS (CI) (m/z (%)) 374 ((M+H)$^+$, 65), 318 (100).
2.2.7  *tert*-Butyl 3-iodo-6-methoxy-1H-indole-1-carboxylate (1g)

\[
\begin{align*}
\text{C}_{14}\text{H}_{16}\text{INO}_3 \\
373.19
\end{align*}
\]

1.61 g (4.32 mmol, 81 % yield over two steps) as a pale yellow solid, mp: 135 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.66 (s, 9 H), 3.88 (s, 3 H), 6.93 (dd, \(J = 8.6\) Hz, \(J = 2.3\) Hz, 1 H), 7.25-7.26 (m, 1 H), 7.59 (s, 1 H), 7.73 (br, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 28.1 (CH\(_3\)), 55.7 (CH\(_3\)), 65.2 (C\(_{quat}\)), 84.1 (C\(_{quat}\)), 98.2 (CH), 112.8 (CH), 122.0 (CH), 125.9 (C\(_{quat}\)), 128.7 (CH), 135.7 (C\(_{quat}\)), 148.8 (C\(_{quat}\)), 158.6 (C\(_{quat}\)). EI + MS (m/z (%)): 373 (M\(^+\), 14), 318 ((M-C\(_4\)H\(_9\)+2H)\(^+\), 10), 317 ((M-C\(_4\)H\(_9\)+H)\(^+\), 100), 273 ((M-C\(_4\)H\(_9\)O\(_2\)+H)\(^+\), 67), 272 (12), 258 ((M-C\(_4\)H\(_9\)O\(_2\)-CH\(_3\)+H)\(^+\), 51), 57 (C\(_4\)H\(_9\)\(^+\), 72). IR (KBr): \(\tilde{\nu}\) 3165 (w), 3009 (w), 2988 (w), 2968 (w), 2930 (w), 2905 (w), 2887 (w), 2831 (w), 1726 (s), 1618 (w), 1541 (w), 1526 (w), 1487 (m), 1456 (w), 1441 (m), 1369 (s), 1327 (s), 1306 (w), 1288 (w), 1259 (m), 1223 (s), 1159 (s), 1148 (s), 1136 (m), 1105 (m), 1049 (m), 1032 (s), 960 (m), 924 (w), 887 (w), 858 (w), 833 (m), 797 (m), 762 (m), 735 (w), 633 (w), 623 (w) cm\(^{-1}\). Anal. calcd. for C\(_{14}\)H\(_{16}\)INO\(_3\) (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.56, N 3.57.
2.3 Preparation of tert-butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1i)\(^4\)

\[
\begin{align*}
\text{MeO} &-\text{CHCl} \\
&\quad \text{N-Boc} \\
&\quad \text{MeO} \\
&\quad \text{I} \\
\text{Boc} \\
1i
\end{align*}
\]

PdCl\(_2\)(PPh\(_3\))\(_2\) (425 mg, 0.60 mmol, 2 mol %) and Cul (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a dry screw-cap vessel. Then, 150 mL of dry THF were added and the mixture was degassed with argon (5 min). Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and tert-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture, which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 mL of tert-butanol were successively added to the mixture, which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After filtration and removal of the solvents under reduced pressure, the residue was absorbed onto Celite\(^\circledR\) and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE/EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (1i) as a colorless solid.

3 Preparation of Compounds 3 and 6 by the Masuda Borylation–Suzuki Coupling Sequence

3.1 Synthesis of Biaryls 3a-c by the Masuda Borylation–Suzuki Coupling Sequence

Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1a) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry 1,4-dioxane were added and the mixture was degassed with argon (5 min). Dry triethylamine (1.39 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture, which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1.00 mmol of heteroaryl halide 2, and cesium carbonate (823 mg, 2.50 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure, the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia. The obtained compounds 3 can be further purified by suspending in dichloromethane, sonication for 0.5-1 h in an ultrasound bath, filtration and drying under reduced pressure overnight.

The experimental details are given in Table 2 and Table 3.
Table 2: Experimental details for the synthesis of biaryls 3a-c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1</th>
<th>Heteroarylhalide 2</th>
<th>Biaryl 3 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>343 mg (1.00 mmol) 1a</td>
<td>162 mg (1.00 mmol) 2a</td>
<td>Pale beige solid 146 mg (0.75 mmol, 75 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>2</td>
<td>343 mg (1.00 mmol) 1a</td>
<td>161 mg (1.00 mmol) 2b</td>
<td>Pale yellow solid 178 mg (0.91 mmol, 91 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>3</td>
<td>746 mg (2.00 mmol) 1f</td>
<td>259 mg (2.00 mmol) 2c</td>
<td>Yellow solid 413 mg (1.72 mmol, 86 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %</td>
</tr>
</tbody>
</table>
Table 3: Reaction times in the synthesis of biaryls 3a-c.[1]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Biaryl 3</th>
<th>Masuda borylation step</th>
<th>Suzuki coupling step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>3 h</td>
<td>24 h</td>
</tr>
</tbody>
</table>

[1] The reaction times for the Suzuki coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times for the Masuda borylation step may also be shorter in some cases.
3.2 Spectroscopic Data of Biaryls 3

3.2.1 3-(Pyrimidin-2-yl)-1H-indole (3a)

146 mg (0.75 mmol, 75 % yield) as a pale beige solid, mp: 158 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 7.12-7.13 (m, 3 H), 7.45-7.49 (m, 1 H), 8.22 (d, \(J = 2.5\) Hz, 1 H), 8.51-8.54 (m, 1 H), 8.76 (d, \(J = 5.0\) Hz, 2 H), 11.7 (br, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 111.9 (CH), 114.7 (C\(_{\text{quat}}\)), 177.0 (CH), 120.4 (CH), 121.9 (CH), 121.9 (CH), 125.5 (C\(_{\text{quat}}\)), 129.2 (CH), 137.0 (C\(_{\text{quat}}\)), 157.0 (CH), 163.7 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 195 (M\(^+\), 100), 168 (5), 167 (6), 142 ((M-C\(_3\)H\(_3\)N\(^+\)), 48), 115 (14), 88 (6), 57 (6). IR (KBr): \(\tilde{\nu}\) 3141 (w), 2906 (w), 1618 (w), 1578 (m), 1539 (s), 1453 (m), 1422 (m), 1357 (m), 1271 (w), 1235 (w), 1175 (w), 1130 (w), 1102 (w), 1010 (w), 975 (w), 804 (w), 757 (m), 642 (w), 578 (w) cm\(^{-1}\). Anal. calcd. for C\(_{12}\)H\(_9\)N\(_3\) (195.2): C 73.83, H 4.65, N 21.52. Found: C 73.86, H 4.63, N 21.51.
3.2.2 3-(Pyrimidin-5-yl)-1H-indole (3b)

178 mg (0.91 mmol, 91 % yield) as a pale yellow solid, mp: 218 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 7.12-7.17 (m, 1 H), 7.18-7.23 (m, 1 H), 7.48-7.52 (m, 1 H), 7.92 (d, \(J = 7.9\) Hz, 1 H), 7.99 (d, \(J = 2.5\) Hz, 1 H), 9.04 (s, 1 H), 9.16 (s, 2 H), 11.7 (br, 1 H, NH). \(^13\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 108.5 (C\(_\text{quat}\)), 112.2 (CH), 118.9 (CH), 120.4 (CH), 122.0 (CH), 124.5 (C\(_\text{quat}\)), 125.1 (CH), 130.0 (C\(_\text{quat}\)), 136.9 (C\(_\text{quat}\)), 153.6 (CH), 155.1 (CH). El + MS (m/z (%)): 195 (M\(^+\), 100), 194 ((M-H)\(^+\), 21), 141 (23), 140 (22), 117 (11), 114 (11), 113 (13), 111 (16), 109 (11), 97 (25), 95 (16), 85 (19), 83 (21), 81 (15), 71 (30), 70 (15), 69 (17), 57 (26), 55 (16), 43 (9).

IR (KBr): \(\tilde{\nu}\) 3166 (m), 3107 (s), 3064 (m), 2979 (m), 2938 (m), 1620 (w), 1581 (m), 1556 (m), 1536 (s), 1454 (m), 1418 (w), 1312 (w), 1275 (w), 1252 (w), 1168 (s), 1123 (w), 1094 (w), 1016 (w), 959 (w), 879 (w), 766 (w), 732 (s), 717 (w), 641 (w), 622 (w) cm\(^{-1}\). Anal. calcd. for C\(_{12}\)H\(_9\)N\(_3\) (195.2): C 73.83, H 4.65, N 21.52. Found: C 73.57, H 4.94, N 21.23.
3.2.3 4-(5-Methoxy-1H-indol-3-yl)pyrimidin-2-amine (3c)

![Chemical Structure](image)

\[ C_{13}H_{12}N_2O \]

240.26

413 mg (1.72 mmol, 86 % yield) as a colorless solid, mp: 204 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 3.84 (s, 3 H), 6.44 (s, 2 H, \(\text{NH}_2\)), 6.82 (dd, \(J = 8.5\) Hz, \(J = 2.5\) Hz, 1 H), 6.99 (d, \(J = 5.4\) Hz, 1 H), 7.33 (d, \(J = 8.8\) Hz, 1 H), 8.09 (d, \(J = 5.4\) Hz, 1 H), 8.12 (d, \(J = 2.5\) Hz, 1 H), 8.15 (d, \(J = 2.8\) Hz, 1 H), 11.6 (br, 1 H, \(\text{NH}\)). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 55.4 (CH\(_3\)), 104.4 (CH), 105.0 (CH), 111.8 (CH), 112.2 (CH), 113.2 (C\(_\text{quat}\)), 125.8 (C\(_\text{quat}\)), 128.6 (CH), 131.9 (C\(_\text{quat}\)), 154.3 (C\(_\text{quat}\)), 156.7 (CH), 162.7 (C\(_\text{quat}\)), 163.4 (C\(_\text{quat}\)). EI + MS (m/z (%)): 240 (M\(^+\), 100), 239 ((M-H)\(^+\), 34), 225 ((M-CH\(_3\))\(^+\), 13), 211 ((M-CH\(_3\)-\(\text{NH}_2\))\(^+\), 11), 210 ((M-CH\(_3\)-\(\text{NH}_2\))\(^+\), 8), 197 (38), 155 (11), 112 (10), 111 (10), 97 (14), 85 (16), 71 (18), 69 (12), 57 (18), 55 (9), 43 (C\(_2\)H\(_3\)O\(^+\), 8). IR (KBr): \(\tilde{\nu}\) 3360 (m), 3129 (w), 1626 (m), 1575 (s), 1530 (m), 1482 (m), 1456 (s), 1338 (w), 1293 (w), 1269 (w), 1211 (w), 1163 (w), 1070 (w), 1037 (w), 819 (w), 694 (w), 630 (w) cm\(^{-1}\). Anal. calcd. for C\(_{13}\)H\(_{12}\)N\(_2\)O (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.94, H 4.97, N 23.56.
3.3 \(^1\)H NMR and \(^{13}\)C NMR Spectra of Biaryls 3

3.3.1 3-(Pyrimidin-2-yl)-1H-indole (3a)

\(^1\)H NMR of 3a (15 mg) in 0.7 mL DMSO-d\(_6\) at 299 K (\(\delta\) in ppm).

\(^{13}\)C NMR of 3a (15 mg) in 0.7 mL DMSO-d\(_6\) at 299 K (\(\delta\) in ppm).
$^{13}$C 135-DEPT NMR of 3a (15 mg) in 0.7 mL DMSO-d$_6$ at 299 K ($\delta$ in ppm).
3.3.2 3-(Pyrimidin-5-yl)-1H-indole (3b)

\[ \text{NMR of 3b (15 mg) in 0.7 mL DMSO-d}_6 \text{ at 296 K (}\delta\text{ in ppm).} \]

\[ \text{13C NMR of 3b (15 mg) in 0.7 mL DMSO-d}_6 \text{ at 297 K (}\delta\text{ in ppm).} \]
$^{13}$C 135-DEPT NMR of 3b (15 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
3.3.3 4-(5-Methoxy-1H-indol-3-yl)pyrimidin-2-amine (3c)

$^1$H NMR of 3c (30 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C NMR of 3c (30 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of $3c$ (30 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
3.4 Synthesis of Bisindoles and Analogues 6 by the *Masuda* Borylation-Suzuki Coupling Sequence

Tetrakis(triphenylphosphane)-palladium(0) (69 mg, 0.06 mmol, 3 mol %) and iodide 1 (2.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 10 mL of dry 1,4-dioxane were added and the mixture was degassed with argon (5 min). Dry triethylamine (1.0 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 mL, 3.00 mmol) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 10 mL of dry methanol, 1.00 mmol of linker 5 and cesium carbonate (1.63 g, 5.00 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure. The residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia. The product was then dried at 70 °C under reduced pressure overnight, or dried in a drying closet at 100 °C for 24 to 48 h under normal pressure, in order to obtain the correct elemental analyses. The obtained compounds 6 can be further purified by suspending in dichloromethane, sonication for 0.5-1 h in an ultrasound bath, filtration and drying in vacuo overnight.

The experimental details are given in Table 4 and Table 5.
Table 4: Experimental details for the synthesis of bisindoles and their analogues 6a-n.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Linker 5</th>
<th>Bisindole 6 (isolated yield %)</th>
<th>Chromatographic purification (eluent)</th>
<th>UV purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>686 mg (2.00 mmol) 1a</td>
<td>289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>Pale yellow solid 240 mg (0.77 mmol, 77 %)</td>
<td>DCM/MeOH/NH₃ = 100:1:1 → 100:2:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>2</td>
<td>688 mg (2.00 mmol) 1b</td>
<td>289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>Pale yellow solid 134 mg (0.43 mmol, 43 %)</td>
<td>DCM/MeOH/NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1</td>
<td>HT-LC-MS: 100 %</td>
</tr>
<tr>
<td>3</td>
<td>755 mg (2.00 mmol) 1c</td>
<td>289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>Yellow solid 155 mg (0.41 mmol, 41 %)</td>
<td>DCM/MeOH/NH₃ = 100:1:1</td>
<td>HT-LC-MS: 100 %</td>
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<tr>
<td>4</td>
<td>722 mg (2.00 mmol)</td>
<td>289 mg (1.00 mmol)</td>
<td>Yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</strong></td>
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<tr>
<td>5</td>
<td>1.49 mg (4.00 mmol)</td>
<td>578 mg (2.00 mmol)</td>
<td>Yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1 \rightarrow 100:2:1 \rightarrow 100:3:1 \rightarrow 100:4:1 \rightarrow 100:5:1 \rightarrow 100:6:1 \rightarrow 100:7:1</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</strong></td>
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<tr>
<td>6</td>
<td>746 mg (2.00 mmol)</td>
<td>289 mg (1.00 mmol)</td>
<td>Yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
<td></td>
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<tr>
<td></td>
<td><strong>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</strong></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>289 mg (1.00 mmol)</td>
<td>Pale yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1 HT-LC-MS:100%</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>746 mg (2.00 mmol)</td>
<td>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>201 mg (0.54 mmol, 54 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Image](https://example.com/image1.png)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>289 mg (1.00 mmol)</th>
<th>Yellow solid</th>
<th>DCM/MeOH/NH$_3$ = 100:1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>608 mg (2.00 mmol)</td>
<td>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>242 mg (0.56 mmol, 56 %)</td>
<td></td>
</tr>
</tbody>
</table>

![Image](https://example.com/image2.png)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>289 mg (1.00 mmol)</th>
<th>Pale red solid</th>
<th>DCM/MeOH/NH$_3$ = 100:1:1</th>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>798 mg (2.00 mmol)</td>
<td>5-Bromo-2-iodopyrimidine (Jiangsu) 5a</td>
<td>215 mg (0.51 mmol, 51 %)</td>
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</tbody>
</table>

![Image](https://example.com/image3.png)
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mass (g)</th>
<th>Molar Mass (mmol)</th>
<th>Product</th>
<th>Yield</th>
<th>Solvent Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>686 mg (2.00 mmol) 1a</td>
<td>339 mg (1.00 mmol)</td>
<td>Pale yellow solid</td>
<td>75 mg (0.24 mmol, 24 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>11</td>
<td>686 mg (2.00 mmol) 1a</td>
<td>342 mg (1.00 mmol)</td>
<td>Yellow solid</td>
<td>237 mg (0.76 mmol, 76 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
</tr>
<tr>
<td>12</td>
<td>686 mg (2.00 mmol) 1a</td>
<td>242 mg (1.00 mmol)</td>
<td>Yellow solid</td>
<td>207 mg (0.67 mmol, 67 %)</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
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<td>---</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>686 mg (2.00 mmol)</td>
<td>342 mg (1.00 mmol)</td>
<td>3,6-Diiodopyridazine $(\text{Aldrich} \ 5e)$</td>
<td>Yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>HT-LC-MS: 100 %</td>
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<tr>
<td>14</td>
<td>686 mg (2.00 mmol)</td>
<td>245 mg (1.00 mmol)</td>
<td>2,5-Dibromopyrazine $(\text{Synthonix} \ 5f)$</td>
<td>Yellow solid</td>
<td>DCM/MeOH/NH$_3$ = 100:1:1</td>
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</tbody>
</table>
Table 5: Reaction times in the synthesis of bisindoles and their analogues 6a-n.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bisindole 6</th>
<th>Masuda borylation step</th>
<th>Suzuki coupling step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>5</td>
<td>6e</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>6</td>
<td>6f</td>
<td>3 h</td>
<td>24 h</td>
</tr>
<tr>
<td>7</td>
<td>6g</td>
<td>3 h</td>
<td>20 h</td>
</tr>
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<td>8</td>
<td>6h</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>9</td>
<td>6i</td>
<td>3 h</td>
<td>19 h</td>
</tr>
<tr>
<td>10</td>
<td>6j</td>
<td>3 h</td>
<td>19 h</td>
</tr>
<tr>
<td>11</td>
<td>6k</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>12</td>
<td>6l</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>13</td>
<td>6m</td>
<td>3 h</td>
<td>20 h</td>
</tr>
<tr>
<td>14</td>
<td>6n</td>
<td>3 h</td>
<td>19 h</td>
</tr>
</tbody>
</table>

[a] The reaction times for the Suzuki coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times for the Masuda borylation step may also be shorter in some cases.
3.5 Spectrological Data of Bisindoles and Analogues 6

3.5.1 3-3’-(Pyrimidin-2,5-diyl)bis(1H-indole) (6a)

\[ \text{C}_{20}\text{H}_{14}\text{N}_{4} \] 310.35

240 mg (0.77 mmol, 77 % yield) as a pale yellow, scaly solid, mp: 318 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 7.13-7.25 (m, 4 H), 7.46-7.55 (m, 2 H), 7.90-8.00 (m, 2 H), 8.25 (s, 1 H), 8.60-8.63 (m, 1 H), 9.14 (s, 2 H), 11.6 (br, 1 H, NH), 11.7 (br, 1 H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 109.4 (C$\text{quat}$), 111.9 (CH), 112.1 (CH), 114.9 (C$\text{quat}$), 119.0 (CH), 120.1 (CH), 120.3 (CH), 121.8 (CH), 121.9 (CH), 121.9 (CH), 124.0 (CH), 124.7 (C$\text{quat}$), 125.1 (C$\text{quat}$), 125.5 (C$\text{quat}$), 128.6 (CH), 136.8 (C$\text{quat}$), 137.1 (C$\text{quat}$), 153.9 (CH), 160.6 (C$\text{quat}$). EI + MS ($m/z$ (%)): 310 (M$^+$, 80), 204 (8), 155 (15), 141 (23), 97 (10), 85 (10), 71 (14), 57 (24), 55 (11), 44 (100). IR (KBr): $\tilde{\nu}$ 3389 (s), 1614 (w), 1546 (m), 1454 (m), 1326 (w), 1229 (w), 1178 (w), 1118 (w), 1092 (w), 801 (w), 745 (m), 590 (w), 546 (w), 515 (w) cm$^{-1}$. Anal. calcd. for C$_{20}$H$_{14}$N$_{4}$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.22, H 4.47, N 18.02.
3.5.2 3,3’-(Pyrimidine-2,5-diyl)bis(1H-pyrrolo[2,3-b]pyridine) (6b)

134 mg (0.43 mmol, 43 % yield) as a pale yellow solid, mp: > 370 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 7.22 (dd, $J = 7.9$ Hz, $J = 4.4$ Hz, 1 H), 7.27 (dd, $J = 7.9$ Hz, $J = 4.7$ Hz, 1 H), 8.16 (d, $J = 2.2$ Hz, 1 H), 8.33-8.36 (m, 3 H), 8.44 (d, $J = 7.9$ Hz, 1 H), 8.87 (dd, $J = 7.9$ Hz, $J = 1.3$ Hz, 1 H), 9.21 (s, 2 H), 12.2 (br, 1 H, NH), 12.3 (br, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 108.0 (C$_{quat}$), 113.5 (C$_{quat}$), 116.3 (CH), 116.8 (CH), 116.9 (C$_{quat}$), 117.9 (C$_{quat}$), 124.5 (CH), 124.9 (C$_{quat}$), 127.7 (CH), 128.6 (CH), 129.9 (CH), 143.3 (CH), 143.3 (CH), 149.0 (C$_{quat}$), 149.2 (C$_{quat}$), 153.8 (CH), 160.1 (C$_{quat}$). EI + MS (m/z (%)): 313 (23), 312 (M$^+$, 100), 156 (14), 143 (18), 142 (79), 115 (14). IR (KBr): $\tilde{\nu}$ 3448 (w), 3141 (m), 3091 (m), 3039 (m), 2883 (m), 2823 (m), 1585 (w), 1537 (s), 1498 (m), 1468 (m), 1436 (w), 1415 (w), 1368 (w), 1335 (w), 1314 (w), 1277 (s), 1188 (w), 1130 (w), 1034 (w), 992 (m), 956 (w), 926 (w), 896 (m), 795 (m), 768 (s), 659 (w), 632 (w), 586 (w), 513 (w) cm$^{-1}$. Anal. calcd. for C$_{18}$H$_{12}$N$_6$ (312.3): C 68.24, H 3.98, N 26.53. Found: C 68.01, H 3.99, N 26.45.
3.5.3 3,3’-(Pyrimidine-2,5-diyl)bis(5-chloro-1H-indole) (6c)

![Chemical Structure]

C₂₀H₁₂Cl₂N₄  
379.24

155 mg (0.41 mmol, 41 % yield) as a yellow solid, mp: 265-268 °C. ¹H NMR (DMSO-d₆, 500 MHz): δ 7.15-7.25 (m, 2 H), 7.50 (d, J = 3.0 Hz, 1 H), 7.52 (d, J = 3.1 Hz, 1 H), 7.96 (s, 1 H), 8.01 (d, J = 1.7 Hz, 1 H), 8.30 (d, J = 1.7 Hz, 1 H), 8.61-8.62 (m, 1 H), 9.129 (s, 1 H), 9.131 (s, 1 H), 11.80 (s, 1 H, NH), 11.86 (s, 1 H, NH). ¹³C NMR (DMSO-d₆, 125 MHz): δ 109.6 (Cₜₐₜ), 113.8 (CH), 113.9 (CH), 114.7 (Cₜₐₜ), 118.6 (CH), 121.3 (CH), 122.1 (CH), 122.2 (CH), 124.9 (Cₜₐₜ), 125.1 (Cₜₐₜ), 125.3 (Cₜₐₜ), 125.9 (Cₜₐₜ), 126.1 (CH), 126.8 (Cₜₐₜ), 130.3 (CH), 135.5 (Cₜₐₜ), 135.8 (Cₜₐₜ), 154.3 (CH), 160.5 (Cₜₐₜ). EI + MS (m/z (%)): 382 (M⁺(C³⁷Cl³⁷)+, 12), 381 (15), 380 (M⁺(C³⁷C³⁵)+, 66), 379 (25), 378 (M⁺(C³⁵Cl³⁵)+, 100), 337 (19), 277 (22), 176 (34), 175 (72), 149 (51), 140 (49). IR (KBr): ν 2361 (w), 2332 (w), 1543 (s), 1520 (m), 1447 (s), 1420 (w), 1379 (w), 1362 (w), 1302 (m), 1223 (w), 1179 (w), 1157 (w), 1132 (m), 1099 (m), 1072 (w), 1036 (w), 995 (w), 930 (w), 889 (m), 879 (m), 845 (m), 787 (s), 748 (w), 714 (w), 619 (m) cm⁻¹. Anal. calcd. for C₂₀H₁₂Cl₂N₄ (379.2): C 63.34, H 3.19, N 14.77. Found: C 63.50, H 3.46, N 14.51.
3.3.4 3,3’-(Pyrimidine-2,5-diyl)bis(5-fluoro-1H-indole) (6d)

$$\text{C}_{20}\text{H}_{12}\text{F}_{2}\text{N}_{4}$$

346.33

137 mg (0.40 mmol, 40 % yield) as a yellow solid, mp: 288-289 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 7.08-7.16 (m, 2 H), 7.46-7.52 (m, 2 H), 7.72 (dd, $J = 10.2$ Hz, $J = 2.3$ Hz, 1 H), 8.02 (d, $J = 2.6$ Hz, 1 H), 8.26-8.32 (m, 2 H), 9.12 (s, 2 H), 11.70 (s, 1 H, NH), 11.78 (s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 104.3 (d, $J = 24.1$ Hz, CH), 106.8 (d, $J = 24.5$ Hz, CH), 110.0 (d, $J = 32.5$ Hz, CH), 110.1 (d, $J = 32.1$ Hz, CH), 110.4 (d, $J = 4.0$ Hz, C$_{\text{quat}}$), 113.2-113.4 (m, 2 CH), 115.1 (d, $J = 4.5$ Hz, C$_{\text{quat}}$), 124.9-125.1 (m, 2 C$_{\text{quat}}$), 126.1 (d, $J = 11.1$ Hz, C$_{\text{quat}}$), 126.3 (CH), 130.5 (CH), 133.7 (C$_{\text{quat}}$), 133.9 (C$_{\text{quat}}$), 154.1 (CH), 157.8 (d, $J = 232.4$ Hz, C$_{\text{quat}}$), 158.0 (d, $J = 232.3$ Hz, C$_{\text{quat}}$), 160.6 (C$_{\text{quat}}$). EI + MS ($m/z$ (%)): 347 (23), 346 (M$^+$, 100), 173 (24), 160 (20), 159 (76), 158 (32), 133 (10), 132 (19). IR (KBr): $\tilde{\nu}$ 3447 (m), 3288 (w), 3115 (w), 2357 (w), 2336 (w), 1844 (w), 1626 (w), 1582 (w), 1545 (s), 1522 (w), 1487 (m), 1448 (s), 1383 (w), 1311 (w), 1306 (w), 1263 (m), 1221 (w), 1176 (w), 1159 (w), 1144 (s), 1123 (m), 1090 (w), 1036 (w), 995 (w), 974 (w), 930 (s), 920 (s), 878 (m), 835 (s), 789 (s), 746 (s), 669 (w), 636 (s), 621 (m) cm$^{-1}$. Anal. calcd. for C$_{20}$H$_{12}$F$_2$N$_4$ (346.3): C 69.36, H 3.49, N 16.18. Found: C 69.13, H 3.68, N 16.07.
3.5.5 3,3’-(Pyrimidine-2,5-diyl)bis(4-methoxy-1H-indole) (6e)

\[
\begin{align*}
N & \quad N \\
\text{MeO} & \quad \text{OMe} \\
\text{H} & \quad \text{H} \\
C_{22}H_{18}N_4O_2 & \\
370.40
\end{align*}
\]

465 mg (1.25 mmol, 63 % yield) as a yellow solid, mp: 300 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta 3.79\) (s, 3 H), 3.86 (s, 3 H), 6.59-6.64 (m, 2 H), 7.06-7.14 (m, 4 H), 7.61 (d, \(J = 2.5\) Hz, 1 H), 7.74 (d, \(J = 2.5\) Hz, 1 H), 8.93 (s, 2 H), 11.53 (d, \(J = 2.2\) Hz, 1 H, NH), 11.58 (d, \(J = 1.9\) Hz, 1 H, NH). \(^13\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta 54.9\) (CH\(_3\)), 55.2 (CH\(_3\)), 100.0 (CH), 101.2 (CH), 105.0 (CH), 105.2 (CH), 109.6 (C\(_{\text{quat}}\)), 114.7 (C\(_{\text{quat}}\)), 115.4 (C\(_{\text{quat}}\)), 116.6 (C\(_{\text{quat}}\)), 122.5 (CH), 122.6 (CH), 123.6 (CH), 125.5 (C\(_{\text{quat}}\)), 127.1 (CH), 138.4 (C\(_{\text{quat}}\)), 138.4 (C\(_{\text{quat}}\)), 153.5 (C\(_{\text{quat}}\)), 154.1 (C\(_{\text{quat}}\)), 155.3 (CH), 160.3 (C\(_{\text{quat}}\)). \(\text{EI } + \text{ MS (m/z (%))}: 371 (25), 370 (M^+, 100), 369 ((M-H)^+, 32), 341 (34), 326 (25), 325 (15), 199 (13), 185 (20), 184 (21), 183 (25), 171 (23), 170 (22), 169 (48), 162 (13), 157 (17), 156 (36), 155 (32), 143 (11), 142 (23), 141 (11), 130 (11), 129 (23), 128 (26), 115 (11). \(\text{IR (KBr)}: \tilde{\nu} 3422 (\text{w}), 3120 (\text{w}), 1617 (\text{w}), 1584 (\text{w}), 1540 (\text{s}), 1508 (\text{m}), 1461 (\text{s}), 1383 (\text{w}), 1355 (\text{w}), 1319 (\text{m}), 1280 (\text{m}), 1252 (\text{m}), 1235 (\text{m}), 1183 (\text{w}), 1092 (\text{s}), 992 (\text{w}), 969 (\text{w}), 939 (\text{w}), 801 (\text{w}), 777 (\text{m}), 731 (\text{s}), 692 (\text{w}), 626 (\text{w}) \text{ cm}^{-1}. \) Anal. calcd. for C\(_{22}\)H\(_{18}\)N\(_4\)O\(_2\) (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.15, H 5.15, N 15.15.
3.5.6 3,3′-(Pyrimidine-2,5-diyl)bis(5-methoxy-1H-indole) (6f)

238 mg (0.64 mmol, 64 % yield) as a yellow solid, mp: 220 °C. 1H NMR (DMSO-d₆, 500 MHz): δ 3.85 (s, 6 H), 6.85-6.86 (m, 1 H), 6.86-6.88 (m, 1 H), 7.38-7.40 (m, 2 H), 7.41 (d, J = 4.4 Hz, 1 H), 7.90 (d, J = 2.8 Hz, 1 H), 8.15 (d, J = 2.5 Hz, 1 H), 8.21 (d, J = 2.8 Hz, 1 H), 9.14 (s, 2 H), 11.46 (d, J = 2.2 Hz, 1 H, NH), 11.56 (d, J = 2.2 Hz, 1 H, NH). 13C NMR (DMSO-d₆, 125 MHz): δ 55.3 (CH₃), 55.3 (CH₃), 100.5 (CH), 103.8 (CH), 109.3 (Cquat), 111.7 (CH), 112.1 (CH), 112.5 (CH), 112.7 (CH), 114.6 (Cquat), 124.5 (CH), 124.9 (Cquat), 125.0 (Cquat), 126.0 (Cquat), 128.9 (CH), 131.8 (Cquat), 132.1 (Cquat), 153.7 (CH), 154.2 (Cquat), 154.3 (Cquat), 160.6 (Cquat). EI + MS (m/z (%)): 370 (M⁺, 100), 369 ((M-H)⁺, 12), 355 ((M-CH₃)⁺, 9), 327 (16), 240 (20), 185 (19), 163 (14), 156 (17), 142 (25), 128 (14). IR (KBr): ν 3291 (m), 1624 (m), 1585 (m), 1544 (s), 1487 (s), 1447 (s), 1367 (w), 1327 (w), 1306 (w), 1281 (m), 1259 (w), 1212 (m), 1156 (m), 1131 (w), 1031 (m), 993 (w), 919 (m), 861 (w), 798 (m), 735 (w), 641 (w), 526 (w) cm⁻¹. Anal. calcd. for C₂₂H₁₈N₄O₂ (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.19, H 5.03, N 15.20.
3.5.7 3,3′-(Pyrimidine-2,5-diyl)bis(6-methoxy-1H-indole) (6g)

\[ \text{C}_{22}\text{H}_{18}\text{N}_{4}\text{O}_{2} \]

201 mg (0.54 mmol, 54 % yield) as a pale yellow solid, mp: 291-293 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \( \delta \) 3.80 (s, 6 H), 6.79 (dd, \( J = 8.7 \text{ Hz}, \ J = 2.3 \text{ Hz}, 1 \text{ H} \)), 6.82 (dd, \( J = 8.7 \text{ Hz}, \ J = 2.3 \text{ Hz}, 1 \text{ H} \)), 6.96-6.98 (m, 2 H), 7.78 (d, \( J = 2.5 \text{ Hz}, 1 \text{ H} \)), 7.81 (d, \( J = 8.7 \text{ Hz}, 1 \text{ H} \)), 8.08 (d, \( J = 2.7 \text{ Hz}, 1 \text{ H} \)), 8.43 (d, \( J = 8.7 \text{ Hz}, 1 \text{ H} \)), 9.07 (s, 2 H), 11.37 (d, \( J = 1.8 \text{ Hz}, 1 \text{ H, NH} \)), 11.44 (d, \( J = 2.0 \text{ Hz}, 1 \text{ H, NH} \)). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \( \delta \) 55.3 (CH\(_3\)), 55.4 (CH\(_3\)), 95.0 (CH), 95.2 (CH), 109.6 (C\(_\text{quat}\)), 110.4 (CH), 110.5 (CH), 115.1 (C\(_\text{quat}\)), 119.1 (C\(_\text{quat}\)), 119.9 (C\(_\text{quat}\)), 120.0 (CH), 122.7 (CH), 122.8 (CH), 125.3 (C\(_\text{quat}\)), 127.5 (CH), 138.0 (C\(_\text{quat}\)), 138.04 (C\(_\text{quat}\)), 153.8 (CH), 156.1 (C\(_\text{quat}\)), 160.7 (C\(_\text{quat}\)). EI + MS \((m/z \%): 371 \text{ (25)}, 370 \text{ (M}^+\text{, 100)}, 355 \text{ (M-CH}_3\text{)}^+, 38\), 185 (18), 177 (14), 170 (11), 156 (16), 142 (17). IR (KBr): \( \tilde{\nu} \) 3530 (w), 3381 (m), 2963 (w), 2885 (w), 2831 (w), 2324 (w), 1622 (m), 1541 (s), 1499 (m), 1450 (m), 1435 (m), 1412 (w), 1352 (m), 1327 (m), 1288 (m), 1263 (m), 1232 (m), 1200 (s), 1165 (m), 1149 (s), 1119 (s), 1090 (m), 1024 (s), 991 (m), 939 (s), 874 (w), 858 (w), 808 (s), 752 (w), 729 (w), 702 (m), 642 (m), 617 (m) cm\(^{-1}\). Anal. calcd. for \( \text{C}_{22}\text{H}_{18}\text{N}_{4}\text{O}_{2} \) (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.43, H 5.15, N 15.37.
3.5.8  2,5-Bis(2-ethyl-5-(thiophen-2-yl)furan-3-yl)pyrimidine (6h)

242 mg (0.56 mmol, 56 % yield) as a yellow solid, mp: 158-159 °C. EI + MS (m/z (%)): 432 (M⁺, 9), 262 (32), 255 ((M-C₁₀H₅OS)⁺, 10), 254 (61), 240 (17), 239 (100), 230 (23), 201 (54), 183 (30), 178 (19), 172 (22), 163 (18), 152 (10), 149 (12). IR (KBr): ν 2972 (w), 2932 (w), 2922 (w), 2855 (w), 2357 (w), 1568 (w), 1468 (m), 1427 (m), 1394 (m), 1362 (w), 1315 (w), 1256 (w), 1198 (m), 1119 (m), 1045 (m), 1016 (m), 989 (m), 928 (w), 847 (m), 800 (s), 685 (s), 646 (m), 633 (m) cm⁻¹. Anal. calcd. for C₂₄H₂₀N₂O₂S₂ (432.6): C 66.64, H 4.66, N 6.48. Found: C 66.82, H 4.79, N 6.32.

After drying the compound was found to be insoluble in common deuterated solvents.
3.5.9 2,5-Bis(5-(4-methoxyphenyl)-1H-pyrrol-3-yl)pyrimidine (6i)

215 mg (0.51 mmol, 51 % yield) as a pale red solid, mp: 320-323 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 3.77 (brs, 6 H), 6.90-7.00 (m, 6 H), 7.43-7.54 (m, 2 H), 7.58-7.64 (m, 4 H), 8.92 (s, 2 H), 11.49 (m, 1 H, NH), 11.55 (m, 1 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 55.29 (CH$_3$), 55.31 (CH$_3$), 101.7 (CH), 103.8 (CH), 114.41 (CH), 114.42 (CH) 116.5 (CH), 118.5 (C$_{quat}$), 120.7 (CH), 125.13 (CH), 125.15 (CH), 125.3 (C$_{quat}$), 125.46 (C$_{quat}$), 125.47 (C$_{quat}$), 125.51 (C$_{quat}$), 132.7 (C$_{quat}$), 133.1 (C$_{quat}$), 152.6 (CH), 157.94 (C$_{quat}$), 157.96 (C$_{quat}$), 159.7 (C$_{quat}$). EI + MS (m/z (%)): 423 (29), 422 (M$^+$, 100), 407 ((M-CH$_3$)$^+$, 27), 211 (17), 203 (13), 182 (13), 168 (12). IR (KBr): $\tilde{\nu}$ 2962 (w), 2838 (w), 1719 (w), 1686 (w), 1655 (w), 1638 (w), 1609 (w), 1570 (m), 1354 (w), 1492 (s), 1459 (w), 1439 (m), 1396 (w), 1280 (m), 1248 (s), 1211 (w), 1181 (m), 1114 (m), 1024 (m), 941 (m), 924 (w), 830 (s), 807 (s), 667 (w), 640 (w), 620 (w), 553 (m), 518 (w) cm$^{-1}$. Anal. calcd. for C$_{26}$H$_{22}$N$_4$O$_2$ (422.5): C 73.92, H 5.25, N 13.26. Found: C 73.63, H 5.15, N 13.53.
3.5.10 4,6-Di(1H-indol-3-yl)pyrimidine (6j)

$$\begin{align*}
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{N} & \\
\text{H} & \\
\text{C} & \\
\text{H} & \\
\text{H} & \\
\text{N} & \\
\text{H} & \\
\text{C}_{20}\text{H}_{14}\text{N}_{4} & \\
310.35
\end{align*}$$

75 mg (0.24 mmol, 24 %) as a yellow solid, mp: 275–276 °C. $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 7.13–7.25 (m, 4 H), 7.45–7.52 (m, 2 H), 8.25 (s, 1 H), 8.48 (d, $J$ = 7.3 Hz, 2 H), 8.59 (d, $J$ = 8.2 Hz, 2 H), 9.07 (s, 1 H), 11.82 (s, 2 H, NH). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 109.8 (CH), 112.2 (CH), 113.8 (C$_{\text{quat}}$), 120.7 (CH), 122.2 (CH), 122.3 (CH), 125.5 (C$_{\text{quat}}$), 128.8 (CH), 137.3 (C$_{\text{quat}}$), 158.8 (CH), 161.3 (C$_{\text{quat}}$). EI + MS (m/z (%)): 311 (22), 310 (M$^+$, 100), 309 (59), 282 (13), 194 ((M-C$_8$H$_6$N)$^+$, 11), 155 (23), 141 (23), 140 (19), 128 (13), 114 (18). IR (KBr): $\tilde{\nu}$ 2284 (s), 3144 (w), 1655 (w), 1586 (s), 1541 (m), 1503 (m), 1432 (s), 1334 (w), 1290 (m), 1231 (m), 1209 (w), 1125 (m), 1009 (w), 991 (w), 869 (m), 772 (m), 749 (s), 617 (w), 598 (w), 586 (w), 569 (w), 534 (m) cm$^{-1}$. Anal. calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_{4}$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.31, H 4.80, N 18.16.
3.5.11 2,6-Di(1H-indol-3-yl)pyrazine (6k)

![Chemical Structure]

**C<sub>20</sub>H<sub>14</sub>N<sub>4</sub>**

310.35

237 mg (0.76 mmol, 76 % yield) as a yellow solid, mp: 283-285 °C. ¹H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 7.16-7.25 (m, 4 H), 7.53 (d, J = 7.8 Hz, 2 H), 8.31 (d, J = 2.7 Hz, 2 H), 8.54 (d, J = 7.8 Hz, 2 H), 8.88 (s, 2 H), 11.72 (s, 2 H, NH). ¹³C NMR (DMSO-d<sub>6</sub>, 125 MHz): δ 112.3 (CH), 113.2 (C<sub>quat</sub>), 120.5 (CH), 121.4 (CH), 122.2 (CH), 125.5 (C<sub>quat</sub>), 126.9 (CH), 136.9 (CH), 137.3 (C<sub>quat</sub>), 150.1 (C<sub>quat</sub>). EI + MS (m/z (%)): 311 (25), 310 (M⁺, 100), 309 (26), 155 (C₁₀H₇N₂⁺, 14), 141 (C₁₀H₇N⁺, 32), 140 (22). IR (KBr): ν 3089 (w), 1686 (w), 1655 (w), 1587 (w), 1541 (s), 1510 (s), 1491 (m), 1439 (s), 1407 (w), 1323 (w), 1302 (w), 1238 (m), 1141 (m), 1123 (m), 1039 (w), 1006 (w), 961 (w), 822 (w), 789 (w), 750 (m), 735 (m), 623 (w), 581 (m), 524 (m) cm⁻¹. Anal. calcd. for C<sub>20</sub>H<sub>14</sub>N<sub>4</sub> (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.21, H 4.67, N 18.05.
3.5.12 2,6-Di(1H-indol-3-yl)pyridine (6l)

\[
\begin{align*}
\text{C}_{21}\text{H}_{15}\text{N}_3 & \quad \text{309.36} \\
\end{align*}
\]

207 mg (0.67 mmol, 67 % yield) as a yellow solid, mp: 297-298 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta 7.12-7.24 (m, 4 H), 7.51 (d, J = 7.9 Hz, 2 H), 7.62 (d, J = 7.8 Hz, 2 H), 7.76 (t, J = 7.8 Hz, 1 H), 8.14 (d, J = 2.6 Hz, 2 H), 8.54 (d, J = 7.9 Hz, 2 H), 11.52 (s, 2 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta 111.9 (\text{CH}), 115.8 (\text{CH}), 116.2 (\text{C}_{\text{quat}}), 119.8 (\text{CH}), 121.4 (\text{CH}), 121.6 (\text{CH}), 125.3 (\text{C}_{\text{quat}}), 125.8 (\text{CH}), 136.6 (\text{CH}), 137.1 (\text{C}_{\text{quat}}), 154.6 (\text{C}_{\text{quat}}).\) EI + MS (m/z (%)): 310 (24), 309 (M\(^+\), 100), 308 (38), 154 (18), 141 (14), 140 (21), 127 (11), 126 (11). IR (KBr): \(\tilde{\nu} 3054 (w), 1787 (w), 1685 (w), 1655 (w), 1593 (m), 1563 (m), 1546 (m), 1484 (w), 1456 (m), 1420 (w), 1338 (w), 1333 (w), 1311 (w), 1263 (w), 1239 (m), 1157 (w), 1143 (w), 1118 (w), 1093 (s), 1011 (m), 939 (w), 852 (m), 801 (s), 742 (s), 662 (w), 640 (w), 616 (w), 589 (m), 527 (s) cm\(^{-1}\). Anal. calcd. for \(\text{C}_{21}\text{H}_{15}\text{N}_3\) (309.4): C 81.53, H 4.89, N 13.58. Found: C 81.41, H 4.64, N 13.80.
3.5.13 3,6-Di(1H-indol-3-yl)pyridazine (6m)

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{C} \\
\text{20} & \quad \text{H} \\
\text{14} & \quad \text{N} \\
\text{4} & \quad 310.35
\end{align*}
\]

150 mg (0.48 mmol, 48 % yield) as a yellow solid, mp: > 300 °C. \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 7.17-7.24 (m, 4 H), 7.47-7.51 (m, 2 H), 8.07 (s, 2 H), 8.25 (d, \(J = 2.8\) Hz, 2 H), 8.59-8.63 (m, 2 H), 11.66 (s, 2 H, NH). \(^1\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 112.0 (CH), 113.1 (C\text{quat}), 120.5 (CH), 122.3 (CH), 122.5 (CH), 123.6 (CH), 125.2 (C\text{quat}), 126.8 (CH), 137.4 (C\text{quat}), 154.5 (C\text{quat}). EI + MS (\(m/z\) (%)): 310 (M\(^+\), 7), 170 (37), 150 (12), 149 (100), 141 (15), 113 (13), 83 (11). IR (KBr): \(\tilde{\nu}\) 1614 (w), 1562 (m), 1537 (w), 1512 (w), 1454 (m), 1437 (m), 1366 (w), 1325 (w), 1263 (m), 1234 (m), 1119 (m), 1084 (m), 1074 (m), 1040 (w), 1005 (m), 976 (m), 932 (w), 866 (m), 824 (m), 741 (s), 640 (m) cm\(^{-1}\). Anal. calcd. for C\(_{20}\)H\(_{14}\)N\(_4\) (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.17, H 4.54, N 17.93.
3.5.14 2,5-Di(1H-indol-3-yl)pyrazine (6n)

\[
\begin{align*}
\text{C}_{20}\text{H}_{14}\text{N}_4 & \\
310.35
\end{align*}
\]

120 mg (0.39 mmol, 39 % yield) as a yellow solid, mp: > 300 °C. \( ^1 \)H NMR (DMSO-\( d_6 \), 500 MHz): \( \delta \) 6.27-6.36 (m, 4 H), 6.62 (d, \( J = 7.8 \) Hz, 2 H), 7.38 (d, \( J = 2.7 \) Hz, 2 H), 7.59 (d, \( J = 7.8 \) Hz, 2 H), 8.28 (s, 2 H), 10.77 (s, 2 H, NH). \( ^{13} \)C NMR (DMSO-\( d_6 \), 125 MHz): \( \delta \) 112.1 (CH), 112.9 (C\(_{\text{quat}}\)), 120.3 (CH), 121.6 (CH), 122.1 (CH), 125.4 (C\(_{\text{quat}}\)), 125.8 (CH), 137.1 (C\(_{\text{quat}}\)), 140.3 (CH), 146.8 (C\(_{\text{quat}}\)). EI + MS (m/z (%)): 311 (23), 310 (M\(^+\), 100), 309 (13), 155 (21), 141 (42), 140 (13). IR (KBr): \( \tilde{\nu} \) 1614 (w), 1545 (m), 1483 (w), 1456 (m), 1421 (m), 1340 (m), 1263 (w), 1232 (m), 1173 (m), 1142 (m), 1117 (m), 1099 (m), 1063 (w), 1028 (m), 1005 (w), 972 (m), 908 (w), 839 (m), 825 (m), 742 (s), 642 (w) cm\(^{-1}\). Anal. calcd. for C\(_{20}\)H\(_{14}\)N\(_4\) (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.25, H 4.55, N 17.80.
3.6 $^1$H NMR and $^{13}$C NMR Spectra of Bisindoles and Analogues

3.6.1 3-3’-(Pyrimidin-2,5-diyl)bis(1H-indole) (6a)

$^1$H NMR of 6a (20 mg) in 0.7 mL DMSO-d$_6$ at 299 K (δ in ppm).

$^{13}$C NMR of 6a (20 mg) in 0.7 mL DMSO-d$_6$ at 299 K (δ in ppm).
$^{13}$C 135-DEPT NMR of 6a (20 mg) in 0.7 mL DMSO-d$_6$ at 299 K ($\delta$ in ppm).
3.6.2 3,3’-(Pyrimidine-2,5-diyl)bis(1H-pyrrolo[2,3-b]pyridine) (6b)

$^1$H NMR of 6b (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C NMR of 6b (20 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of $6b$ (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
3.6.3 3,3’-(Pyrimidine-2,5-diyl)bis(5-chloro-1H-indole) (6c)

$^1$H NMR of 6c (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).

$^{13}$C NMR of 6c (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K (δ in ppm).
$^{13}$C 135-DEPT NMR of 6c (20 mg) in 0.7 mL DMSO-$d_6$ at 296 K (δ in ppm).
3.6.4 3,3′-(Pyrimidine-2,5-diyl)bis(5-fluoro-1\textit{H}-indole) (6d)

$^1$H NMR of 6d (15 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm). *Impurities from residual solvents.
$^{13}$C NMR of 6d (15 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).

$^{13}$C 135-DEPT NMR of 6d (15 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).
3.6.5 3,3’-(Pyrimidine-2,5-diyl)bis(4-methoxy-1H-indole) (6e)

$^1$H NMR of 6e (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm). *Impurities from residual solvents.

$^{13}$C NMR of 6e (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6e (20 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
3.6.6 3,3''-(Pyrimidine-2,5-diyl)bis(5-methoxy-1H-indole) (6f)

$^1$H NMR of 6f (30 mg) in 0.7 mL DMSO-d$_6$ at 295 K ($\delta$ in ppm).

$^{13}$C NMR of 6f (30 mg) in 0.7 mL DMSO-d$_6$ at 295 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6f (30 mg) in 0.7 mL DMSO-$d_6$ at 295 K ($\delta$ in ppm).
3.6.7 3,3’-(Pyrimidine-2,5-diyl)bis(6-methoxy-1H-indole) (6g)

$^1$H NMR of 6g (16 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C NMR of 6g (16 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

63
$^{13}$C 135-DEPT NMR of $6g$ (16 mg) in 0.7 mL DMSO-d$_6$ at 296 K ($\delta$ in ppm).
3.6.8 2,5-Bis(5-(4-methoxyphenyl)-1H-pyrrol-3-yl)pyrimidine (6i)

$^1$H NMR of 6i (20 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).

$^{13}$C NMR of 6i (20 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6i (20 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).
3.6.9 4,6-Di(1H-indol-3-yl)pyrimidine (6j)

$^1$H NMR of 6j (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).

$^{13}$C NMR of 6j (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6j (30 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).
3.6.10 2,6-Di(1H-indol-3-yl)pyrazine (6k)

$^1$H NMR of 6k (30 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).

$^{13}$C NMR of 6k (30 mg) in 0.7 mL DMSO-$d_6$ at 298 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6k (30 mg) in 0.7 mL DMSO-d$_6$ at 298 K ($\delta$ in ppm).
3.6.11 2,6-Di(1H-indol-3-yl)pyridine (6l)

$^1$H NMR of 6l (25 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).

$^{13}$C NMR of 6l (25 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6I (25 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
3.6.12 3,6-Di(1H-indol-3-yl)pyridazine (6m)

$^1$H NMR of 6m (20 mg) in 0.7 mL DMSO-d$_6$ at 299 K (δ in ppm).

$^{13}$C NMR of 6m (20 mg) in 0.7 mL DMSO-d$_6$ at 299 K (δ in ppm).
$^{13}$C 135-DEPT NMR of 6m (20 mg) in 0.7 mL DMSO-$d_6$ at 299 K ($\delta$ in ppm).
3.6.13 2,5-Di(1H-indol-3-yl)pyrazine (6n)

$^{1}H$ NMR of 6n (15 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).

$^{13}$C NMR of 6n (15 mg) in 0.7 mL DMSO-$d_6$ at 297 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 6n (15 mg) in 0.7 mL DMSO-d$_6$ at 297 K ($\delta$ in ppm).
4 Synthesis of *Isomeridianin A* (4)

Pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 4-(5-methoxy-1H-indol-3-yl)pyrimidin-2-amine (3c) (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The reaction mixture was adsorbed onto Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia (DCM/MeOH/NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 (stepwise gradient)). After drying under reduced pressure *isomeridianin A* (4) was obtained as a pale rose solid. HT-LC-MS: 100 %. 
4.1 3-(2-Aminopyrimidin-4-yl)-1H-indol-5-ol (Isomeridianin A, 4)

\[
\begin{align*}
\text{C}_{12}\text{H}_{10}\text{N}_{4}\text{O} & & 226.23 \\
\end{align*}
\]

100 mg (0.44 mmol, 89% yield) as a pale rose scaly solid, mp: 293 °C (dec.). \(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \(\delta\) 6.31 (s, 2 H, \(\text{NH}_2\)), 6.72 (dd, \(J = 8.5\) Hz, \(J = 2.5\) Hz, 1 H), 6.94 (d, \(J = 5.4\) Hz, 1 H), 7.24 (d, \(J = 8.8\) Hz, 1 H), 7.84 (d, \(J = 2.2\) Hz, 1 H), 8.07 (d, \(J = 2.8\) Hz, 1 H), 8.10 (d, \(J = 5.4\) Hz, 1 H), 8.80 (s, 1 H, \(\text{OH}\)), 11.44 (d, \(J = 2.5\) Hz, 1 H, \(\text{NH}\)). \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 105.2 (CH), 106.4 (CH), 112.0 (CH), 112.0 (CH), 112.9 (C quat), 126.2 (C quat), 128.4 (CH), 131.4 (C quat), 151.7 (C quat), 156.8 (CH), 162.8 (C quat), 163.4 (C quat). EI + MS (\(m/z\) (%)): 226 (M\(^+\), 100), 225 ((M-H\(^+\)), 18), 197 ((M-COH\(^+\)), 7), 185 ((M-CH\(_2\)N\(_2\)H\(^+\)), 57), 158 ((M-C\(_3\)H\(_4\)N\(_2\)H\(^+\)), 4). IR (KBr): \(\tilde{\nu}\) 3387 (m), 3278 (m), 1591 (s), 1543 (m), 1526 (m), 1497 (w), 1472 (s), 1457 (m), 1429 (m), 1367 (w), 1332 (w), 1285 (w), 1263 (w), 1232 (m), 1121 (m), 1172 (m), 1057 (w), 988 (w), 942 (w), 896 (w), 868 (w), 822 (m), 795 (w), 698 (m), 636 (w), 585 (w), 559 (w) cm\(^{-1}\). Anal. calcd. for \(\text{C}_{12}\text{H}_{10}\text{N}_{4}\text{O}\) (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.77, H 4.57, N 24.84.
$^1$H NMR of 4 (30 mg) in 0.7 mL DMSO-d$_6$ at 295 K (δ in ppm).

$^{13}$C NMR of 4 (30 mg) in 0.7 mL DMSO-d$_6$ at 295 K (δ in ppm).
$^{13}$C 135-DEPT NMR of 4 (30 mg) in 0.7 mL DMSO-d$_6$ at 295 K ($\delta$ in ppm).
5 Synthesis of *Hyrtinadine A* (7)

5.1 Synthesis of 3,3'-(Pyrimidine-2,5-diyl)bis(1H-indol-5-ol) (*Hyrtinadine A*, 7), Method I

Pyridinium hydrochloride (2.36 g, 20.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 3,3'-(pyrimidine-2,5-diyl)bis(5-methoxy-1H-indole) (6f) (185 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The reaction mixture was adsorbed onto Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia (DCM/MeOH/NH₃ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 (stepwise gradient)). After drying under reduced pressure *hyrtinadine A* (7) was obtained as a yellow solid (65 mg, 0.19 mmol, 38 % yield). HT-LC-MS: 100 %.
5.2 Synthesis of 3,3’-(Pyrimidine-2,5-diyl)bis(1H-indol-5-ol) (Hyrtinadine A, 7), Method II

![Chemical structures](image)

3,3’-(Pyrimidine-2,5-diyl)bis(5-methoxy-1H-indole) (6f) (185 mg, 0.50 mmol) was placed in a dry screw-cap vessel under nitrogen atmosphere. Then, 15 mL of dry dichloromethane were added. The suspension was cooled to -78 °C (acetone/dry ice bath) and tribromoborane (0.58 mL, 6.00 mmol) was slowly added. The mixture was allowed to reach room temperature and continuously stirred for 20 h. The reaction progress was monitored by TLC. Then the mixture was cooled to 0 °C (water/ice bath) and 3 mL of water followed by 30 mL of saturated potassium carbonate solution were slowly added. The resulting yellow precipitate was filtered, dried under reduced pressure and purified chromatographically on silica with dichloromethane/methanol/ammonia (DCM/MeOH/NH$_3$ = 100:7:1 → 100:8:1 → 100:9:1 → 100:10:1 (stepwise gradient)). After drying under reduced pressure hyrtinadine A (7) was obtained as a yellow solid (147 mg, 0.43 mmol, 78 % (contained 1 molecule MeOH)).
5.2.1 3,3’-(Pyrimidine-2,5-diyl)bis(1H-indol-5-ol) (Hyrtinadine A, 7)

\[
\text{HO-}\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{N} \\
\text{HO-}
\end{array}
\begin{array}{c}
\text{H} \\
\text{H}
\end{array}

c_{20}h_{14}n_4o_2
342.35
\]

147 mg (0.43 mmol, 78 % yield) as a yellow solid, mp: 296 °C. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 6.68 (dd, \(J = 8.6\) Hz, \(J = 2.4\) Hz, 1 H), 6.71 (dd, \(J = 8.7\) Hz, \(J = 2.1\) Hz, 1 H), 7.19 (d, \(J = 2.0\) Hz, 1 H), 7.25 (d, \(J = 8.6\) Hz, 1 H), 7.28 (d, \(J = 8.7\) Hz, 1 H), 7.80 (d, \(J = 2.6\) Hz, 1 H), 7.96 (d, \(J = 2.3\) Hz, 1 H), 8.11 (d, \(J = 2.8\) Hz, 1 H), 8.84 (brs, 2 H), 8.98 (s, 2 H), 11.30 (d, \(J = 2.0\) Hz, 1 H, NH), 11.39 (d, \(J = 2.2\) Hz, 1 H, NH). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 102.8 (CH), 106.4 (CH), 108.7 (C\(_{quat}\)), 112.2 (CH), 112.3 (CH), 112.4 (CH), 112.8 (CH), 114.9 (C\(_{quat}\)), 124.5 (CH), 125.2 (C\(_{quat}\)), 125.6 (C\(_{quat}\)), 126.6 (C\(_{quat}\)), 129.0 (CH), 131.5 (C\(_{quat}\)), 131.6 (C\(_{quat}\)), 151.9 (C\(_{quat}\)), 152.0 (C\(_{quat}\)), 153.7 (CH), 160.8 (C\(_{quat}\)). EI + MS (m/z (%)): 343 (23), 342 (M\(^+\), 100), 171 (18), 157 (29). IR (KBr): \(\tilde{v}\) 3387 (m), 3127 (w), 1715 (w), 1624 (m), 1582 (m), 1547 (s), 1535 (s), 1493 (m), 1468 (m), 1448 (s), 1369 (m), 1313 (w), 1283 (m), 1252 (m), 1227 (m), 1203 (m), 1153 (m), 1128 (w), 1099 (w), 1045 (w), 993 (w), 978 (w), 922 (s), 860 (w), 822 (m), 791 (s), 764 (w), 742 (w), 696 (w), 681 (w), 663 (m), 625 (s), 607 (m) cm\(^{-1}\).


ESIMS (pos) (m/z (%)): 343 (M+H)^+. HRESIMS calcd for C_{20}H_{14}N_{4}O_{2} 343.1195 (M+H)^+, found 343.1191. IR (KBr): ν 3390 cm^{-1}. UV (MeOH): λ_{max} (ε_{max}) 339 nm (3100), 277 (7600).

Data reported in the literature:6

White solid, mp: > 220 °C (dec.). \(^1\)H NMR (DMSO-d\(_6\), 500 MHz, dual cryoprobe \(^1\)H/\(^{13}\)C): δ 6.69 (dd, J = 8.6 Hz, J = 2.2 Hz, 1 H), 6.72 (dd, J = 8.6 Hz, J = 2.2 Hz, 1 H), 7.20 (br s, 1 H), 7.26 (d, J = 8.6 Hz, 1 H), 7.29 (d, J = 8.6 Hz, 1 H), 7.80 (d, J = 2.5 Hz, 1 H), 7.97 (d, J = 2.2 Hz, 1 H), 8.11 (d, J = 2.5 Hz, 1 H), 8.86 (br s, 2 H), 8.99 (s, 2 H), 11.31 (br s, 1 H), 11.39 (br s, 1 H). \(^{13}\)C NMR (DMSO-d\(_6\), 125 MHz, dual cryoprobe \(^1\)H/\(^{13}\)C): δ 102.7 (CH), 106.2 (CH), 108.5 (C_{quat}), 110.0 (CH), 110.6 (CH), 112.6 (CH), 112.1 (CH), 125.0 (C_{quat}), 125.4 (C_{quat}), 126.4 (C_{quat}), 128.8 (CH), 131.3 (C_{quat}), 131.4 (C_{quat}), 151.7 (C_{quat}), 151.8 (C_{quat}), 153.5 (2 CH), 160.6 (C_{quat}). El + MS (m/z (%)): 342 (M^+, 100), 317 (7), 171 (11), 157 (16), 84 (10). IR (ATR): ν 3420 (br), 1659 (br), 1049, 1001 (s), 823, 760 cm^{-1}. HRMS calcd. for C_{20}H_{14}N_{4}O_{2}. Found: 342.1099. UV (MeOH): λ_{max} (ε_{max}) 339 nm (4295), 277 (6644).

---

$^1$H NMR of 7 (16 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).

$^{13}$C NMR of 7 (16 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
$^{13}$C 135-DEPT NMR of 7 (16 mg) in 0.7 mL DMSO-$d_6$ at 296 K ($\delta$ in ppm).
6 Appendix

6.1 UV Purity of Compounds 3, 4, 6, and 7

HT-LC-MS Spectrum (SOP 2200) of 3c (O-Methyl isomeridianin A). UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 4(Isomeridianin A). UV purity: 100%
HT-LC-MS Spectrum (SOP 2200) of 6a. UV purity: 100 %

1: MS ES+ :602.24-643.24
   Peak Number  Compound  Time  AreaAbs  Area %Total  Width  Height  Mass Found
   1: Found  3.87  294253.2  0.14  0.1  30230.5  310.12

2: MS ES− :681.24+643.24
   Peak Number  Compound  Time  AreaAbs  Area %Total  Width  Height  Mass Found
   1: Found  3.71  31028.7  10.43  0.1  57452.0  310.12

3: UV Detector: 254
   Range: 2.536e-1
HT-LC-MS Spectrum (SOP 2200) of 6b. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 6c. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 6e. UV purity: 100%

1: MS ES+: $370.1\pm1\%$ Smooth (SG, 2x4)

2: MS ES+: $741.2\pm1\%$ Smooth (SG, 2x4)

3: MS ES+: $570.1\pm1\%$ Smooth (SG, 2x4)
### Table: 2: (Time: 3.20) Combine (669, 673)

<table>
<thead>
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<th>Compound</th>
<th>Time</th>
<th>Mass Found</th>
</tr>
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<td>7.9e-05</td>
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<td>2</td>
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<td>371.1</td>
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<td>479.1</td>
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<td>480.2</td>
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<tr>
<td>2</td>
<td></td>
<td></td>
<td>909.3</td>
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</tbody>
</table>

### Table: 2: (Time: 3.20) Combine (668, 673)

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<th>Time</th>
<th>Mass Found</th>
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HT-LC-MS Spectrum (SOP 2200) of 6f. UV purity: 100 %
HT-LC-MS Spectrum (SOP 2200) of 6g. UV purity: 100 %

<table>
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<tr>
<th>Peak Number</th>
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<th>AreaAbs</th>
<th>Area %Total</th>
<th>Width</th>
<th>Height</th>
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<tbody>
<tr>
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<td>0.1</td>
<td>493613.5</td>
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</table>

1. MS ES+: EPI Smooth (SG, 2x4)
HT-LC-MS Spectrum (SOP 2200) of 6m. UV purity: 100%
<table>
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<th>Compound</th>
<th>Time</th>
<th>AreaAbs</th>
<th>Area %Total</th>
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<th>Height</th>
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<tr>
<td>0</td>
<td></td>
<td>3.88</td>
<td>11570.7</td>
<td>100.00</td>
<td>0.1</td>
<td>265554.9</td>
<td>5.5e+03</td>
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<tr>
<td>2: MS ES+ 1309.12 Smooth (95, 2x%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: MS ES+ 1619.24 Smooth (95, 2x%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>(1) ELSD Signal Smooth (Mn, 2x3)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1: Found 2.77</td>
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<td>39678.6</td>
<td>100.00</td>
<td>970720.3</td>
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<td>1: (Time: 2.77) Combine (578:582)</td>
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</table>

**Peak ID**

1. Found 2.78 | 310.12 | 1: MS ES+ 4.6e+06

**m/z**

- 311.1
- 313.2
- 621.2
- 789.2
<table>
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<th>Time</th>
<th>Mass Found</th>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>(Time: 2.03) Combine (697, 595)</td>
<td>2.03</td>
<td>310.12</td>
</tr>
<tr>
<td>3</td>
<td>(Time: 2.92) Combine (608, 612)</td>
<td>2.92</td>
<td>310.12</td>
</tr>
<tr>
<td>4</td>
<td>(Time: 3.03) Combine (631, 635)</td>
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</tr>
<tr>
<td>5</td>
<td>(Time: 3.88) Combine (809, 013)</td>
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</tr>
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</table>
HT-LC-MS Spectrum (SOP 2200) of 7 (Hyrtinadine A). UV purity: 100 %
Peak ID | Compound | Time | Mass Found
--- | --- | --- | ---
2 | Found 205 | 342.11
2: (Time: 2.06) Combine (430:434) | MS ES+ | 1.9e+05

Peak ID | Compound | Time | Mass Found
--- | --- | --- | ---
3 | 3.87 | 3.87
3: (Time: 3.87) Combine (408:812) | MS ES- | 2.6e+05
### 6.2 HT-LC-MS Methods for the Control of Identity and Purity of Compounds 3, 4, 6 and 7

<table>
<thead>
<tr>
<th>Problem Definition</th>
<th>Identity and Purity</th>
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<tr>
<td><strong>SOP</strong> (Standart Operation Procedure)</td>
<td>2200</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>HT-LC-MS</td>
</tr>
<tr>
<td><strong>System</strong></td>
<td>Waters Acquity UPLC® with PDA and ELSD</td>
</tr>
<tr>
<td></td>
<td>Waters SQD (ESI+/− and APCI+/−)</td>
</tr>
<tr>
<td><strong>Software</strong></td>
<td>MassLynx with OpenLynx</td>
</tr>
<tr>
<td><strong>Column</strong></td>
<td>Waters XBridge™ C8 3.5 µm</td>
</tr>
<tr>
<td></td>
<td>4.6 x 50 mm Column</td>
</tr>
<tr>
<td></td>
<td>Part No. 186003053</td>
</tr>
<tr>
<td><strong>Eluent</strong></td>
<td>A: 99.9 % acetonitrile + 0.1 % TFA</td>
</tr>
<tr>
<td></td>
<td>B 99.9 % water + 0.1 % TFA</td>
</tr>
<tr>
<td><strong>Gradient</strong></td>
<td>time (min)</td>
</tr>
<tr>
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<td>11.00</td>
</tr>
<tr>
<td><strong>Column temperature</strong></td>
<td>Room temperature</td>
</tr>
<tr>
<td><strong>Injection volume</strong></td>
<td>3 µL</td>
</tr>
<tr>
<td><strong>Sample preparation</strong></td>
<td>Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasound bath, so that the concentration was 0.5 mM.</td>
</tr>
<tr>
<td></td>
<td>If necessary, the sample was additionally diluted: 100 µL in 500 µL acetonitrile + water 5/95.</td>
</tr>
</tbody>
</table>
6.3 Biological Data

6.3.1 DSTT Kinase Assays\textsuperscript{7}

The kinase assays were carried out at room temperature. Compounds were pre-incubated in the presence of the enzyme and peptide/protein substrate for 5 min before initiation of the reaction by adding ATP. Assays were incubated at room temperature before termination by the addition of 5 µL orthophosphoric acid. The assays were then harvested onto P81 Unifilter Plates (wash buffer was 50 mM orthophosphoric acid) and dried in air. The dry Unifilter plates were then sealed on the addition of MicroScint O and were counted in Packard Topcount NXT scintillation counters.

6.3.2 Viability Assays\textsuperscript{8}

A2780 (ovarian tumor cell line; European Collection of Cell Culture (ECACC) 93112519) or HCT116 (colon tumor cell line, ATCC CCL-247) cells were plated in 96-well plates at 2000 cells per well and incubated for 24 h at 37 °C in DMEM (Dulbecco’s modified Eagle medium) supplemented with FCS (fetal calf serum or fetal bovine serum). The test compounds were diluted in DMSO, added to the culture plates and incubation was continued for 72 h. At the end of the compound incubation period AlamarBlue reagent (BUF012B, Serotec) was added and the 96-well plates were further incubated. The plates were measured with a fluorescence reader.


There is no substitute for hard work.

*Thomas Alva Edison*