Inaugural-Dissertation

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Multi-component Reactions Initiated via Sonogashira Coupling

Gutachter: Prof. Dr. Thomas J. J. Müller
Prof. Dr. Dr. h. c. Rolf Gleiter

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne unerlaubte Hilfsmittel durchgeführt habe.

Heidelberg, im Februar 2005

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Parts of this thesis have already been published or submitted for publication:

Publications

[1] "A Novel Three-component Synthesis of 2,5-Disubstituted *β*-halofurans", A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, **2005**, submitted.

[2] "A Novel One-pot Four-component Access to Tetrahydro-*β*-carbolines by a Coupling-amination-aza-annulation-Pictet-Spengler Sequence (CAAPS)", A. S. Karpov, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2004**, 1502-1503.

[3] "Straightforward Novel One-Pot Enaminone and Pyrimidine Syntheses by Coupling-Addition-Cyclocondensation Sequences", A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815-2826.

[4] "New Entry to a Three-Component Pyrimidine Synthesis by TMS-Ynones via Sonogashira Coupling", A. S. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451-3454.

[5] "Facile One-Pot Coupling-Aminovinylation Approach to Push-Pull Chromophores: Alkyne Activation by Sonogashira Coupling", A. S. Karpov, F. Rominger, T. J. J. Müller, *J. Org. Chem.* **2003**, *68*, 1503-1511.

[6] „Synthese von substituierten Heterocyclen, Carbocyclen und Enaminonen mittels einer neuartigen Ein-Topf-Reaktion", T. J. J. Müller, A. S. Karpov, Deutsches Patent, Anmeldung 25. 6. **2003**; DE 103 28 400.1.

Additionally, parts of this thesis were presented in form of oral contributions or posters:

Oral Contributions

[1] "Multi-component Reactions Initiated via Sonogashira Coupling", Weihnachtskolloquium, 13.12.2004, Heidelberg, Germany.

[2] "Alkynones via Sonogashira Coupling as An Entry to The Synthesis of Heterocycles", Tag der Organischen Chemie der Universität Stuttgart (Doktorandenseminar), 15.10.2004, Stuttgart, Germany.

Posters

[1] "A Novel One-pot Four-component Coupling-amination-aza-annulation-Pictet-Spengler (CAAPS) Sequence", A. S. Karpov, T. J. J. Müller; 14th International Symposium on Homogeneous Catalysis, München, Germany, **2004**, Abstracts, p. 365.

[2] "Straightforward Novel One-Pot Enaminone and Pyrimidine Syntheses by Coupling-Addition-Cyclocondensation Sequences", A. S. Karpov, T. J. J. Müller; Heidelberg Forum of Molecular Catalysis, Heidelberg, Germany, **2003**, Abstracts, p. 81.

[3] "A Multicomponent Approach to Novel Push-Pull Chromophores", A. S. Karpov, T. J. J. Müller; XXXVth International Conference on Coordination Chemistry, Heidelberg, Germany, **2002**, Abstracts, p. 973.

[4] "A Multicomponent Approach to Novel Push-Pull Chromophores", A. S. Karpov, T. J. J. Müller; Fifth International Symposium on Functional π-Electron Systems, Ulm, Germany, **2002**, Abstracts, p. 200.

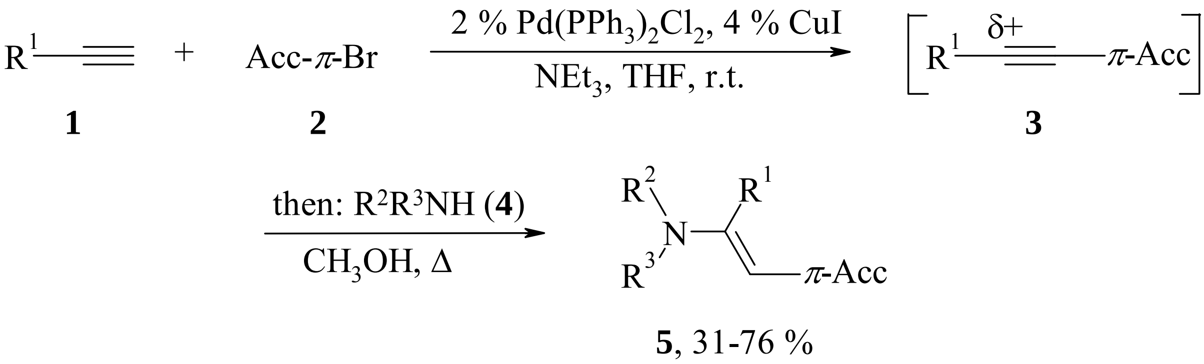
Abbreviations

Acc-π	acceptor-substituted conjugate π -system
Bn	benzyl
^{n}Bu	*n*-butyl
Boc	*tert*-butoxycarbonyl
br	broad
Cbz	benzyloxycarbonyl
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dspt	doublet of septets
dt	doublet of triplets
de	diastereomeric excess
dr	diastereomeric ratio
ee	enantiomeric excess
DFT	density functional theory
DHP	3,4-dihydro-*2H*-pyran
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	diphenylphosphinoferrocene
EA	ethyl acetate
ee	enantiomeric excess
equiv	equivalent
ESP	electrostatic potential
EWG	electron-withdrawing group
HE	hexane
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
m	multiplet
NBO	natural bonding orbital
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
q	quartet
s	singlet
spt	septet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
TMSA	trimethylsilyl acetylene

Table of Contents

1 Summary

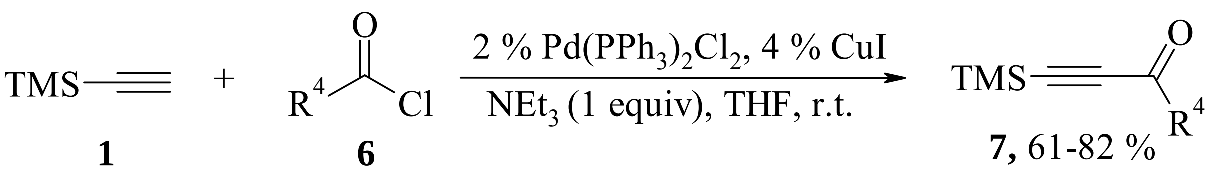
Subjecting of heteroarylbromides **2** bearing EWG in appropriate positions to Sonogashira coupling with terminal alkynes **1** furnishes internal alkynes **3** that can now undergo a Michael addition with suitable secondary amines **4**. This coupling-aminovinylation sequence can be performed in a one-pot fashion providing a straightforward access to push-pull chromophores **5** **(**Scheme 1**)**.



Scheme 1. Coupling-Aminovinylation Sequence to *β*-Amino Vinyl Heteroarenes

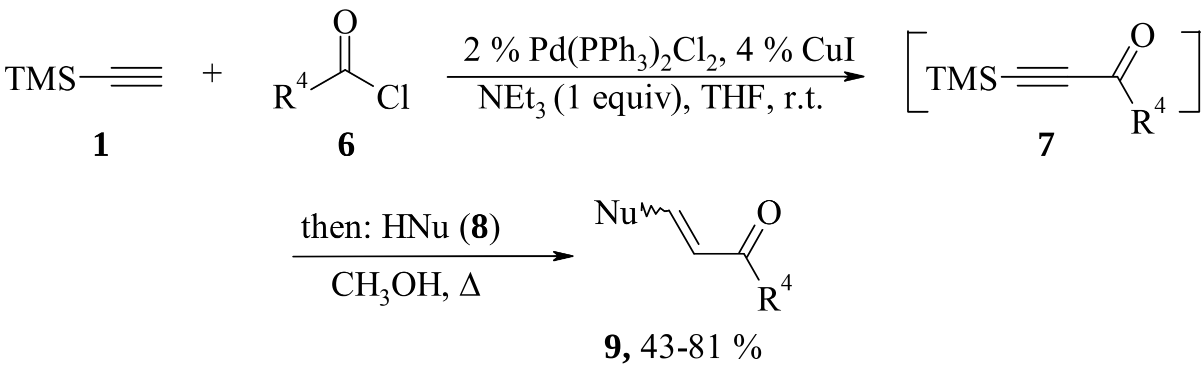
The *π*-electron system that conjugates the acetylene fragment with the acceptor moiety plays a key role for the opening of this additional Michael type reactivity. Interestingly, only the relative LUMO energies reveal a satisfactory picture and rationalize the observed reactivity. The lower the LUMO of the electron-deficient alkyne **3** the more likely the aminovinylation will proceed.

Since acetylenic ketones are known to be highly reactive towards Michael addition, I extended this methodology by subjecting acid chlorides **6** instead of arylbromides **2** to Sonogashira coupling. First, I modified the original Sonogashira conditions and reduced the amount of triethylamine to only one equivalent. This gave an essentially neutral reaction medium after the first cross-coupling step when the base scavenged the hydrochloric acid which is the side-product of the Sonogashira coupling. Unexpectedly, even (TMS)-acetylene (**1f**) was involved in the cross-coupling under these altered, extremely mild conditions providing an access to (TMS)-ynones **7** (Scheme 2).



Scheme 2. Synthesis of (TMS)-ynones by Sonogashira Coupling

(TMS)-ynones are synthetic equivalents of β-keto aldehydes that in their own right are well-established three-carbon building blocks in heterocyclic chemistry. They can be synthesized according to my procedure with very good yields and furthermore they can be subjected in a one-pot fashion to the reaction with nucleophiles and binucleophiles (Scheme 3).

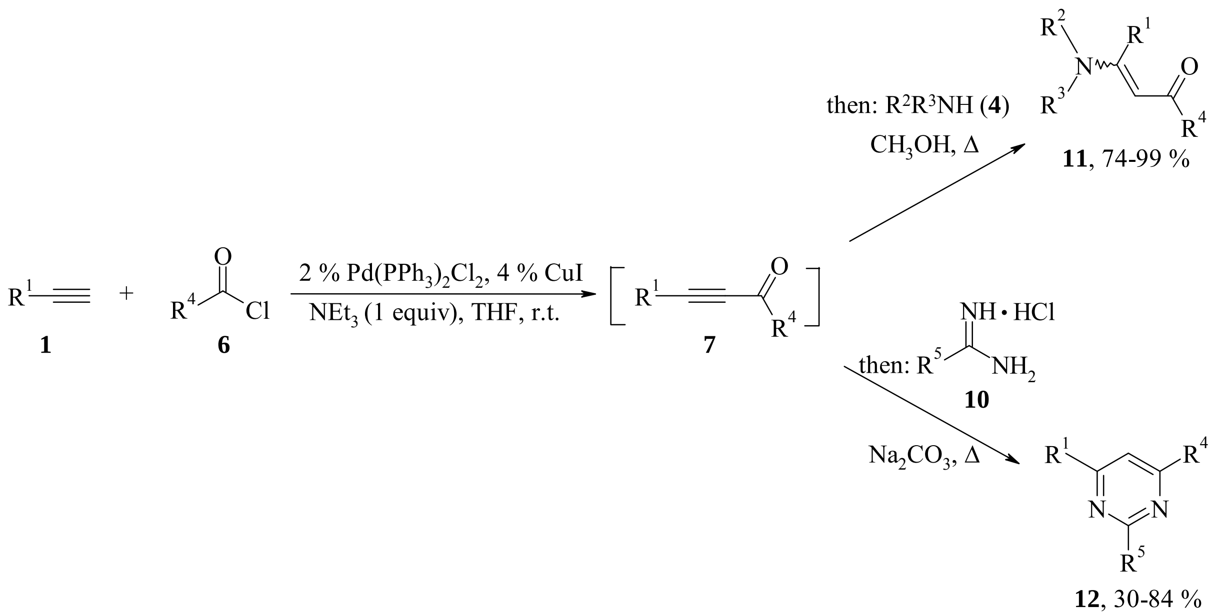


Scheme 3. One-Pot Coupling-Addition Sequence

As expected, all these additions proceeded with the concomitant loss of the TMS group. However, among all the binucleophiles the cyclization occurred only in the case of guanidine providing one-pot access to pyrimidine.

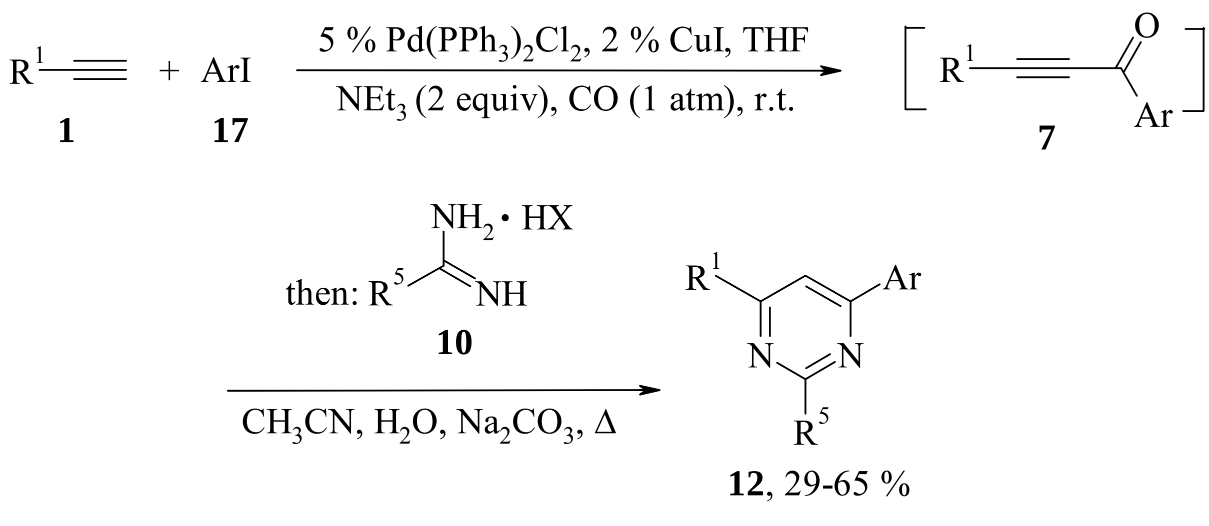
Since the reaction with amines and guanidinium salt worked smoothly, I extended this methodology to other alkynes and acid chlorides.

As before, in the sense of a consecutive three-component reaction, the intermediate ynones **7** were not isolated, but converted directly to β-enaminones **11** and pyrimidines **12** through the reaction with amines **4** and amidinium salts **10** (Scheme 4).



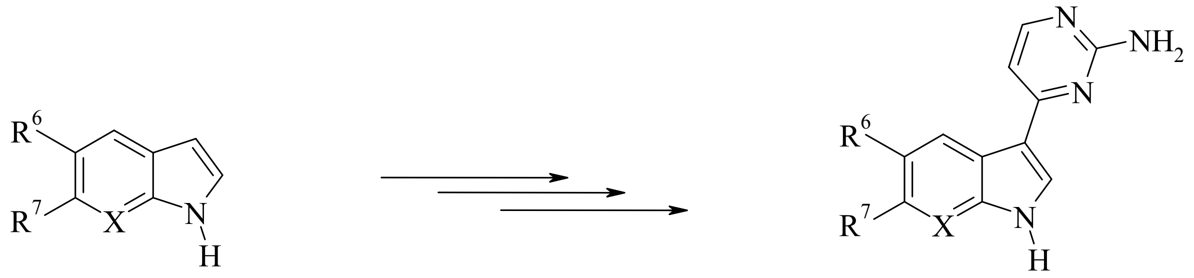
Scheme 4. Synthesis of *β*-Enaminones and Pyrimidines via Sonogashira Coupling

In the case of inaccessible acid chlorides, carbonylative coupling of alkynes **1** and aryl iodides **17** represents a complementary approach to ynones **7**. The intermediate ynones can be transformed in a one-pot four-component fashion to pyrimidines **12** (Scheme 5).



Scheme 5. Synthesis of Pyrimidines via Carbonylative Coupling

Based upon this methodology, the naturally occuring meridianins **16** were synthesized starting from the readily available indoles **13** (Scheme 6).

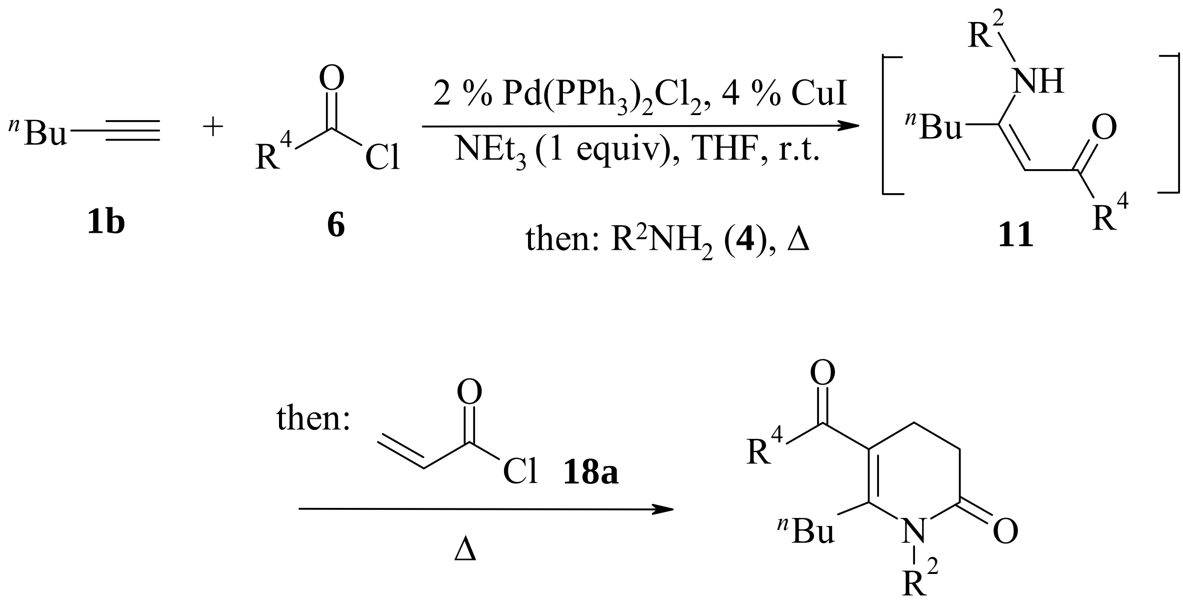


13a $R^6 = H$, $R^7 = H$, X = CH
13b $R^6 = Br$, $R^7 = H$, X = CH
13c $R^6 = H$, $R^7 = Br$, X = CH
13d $R^6 = H$, $R^7 = H$, X = N

Meridianin G (**16a**) 28 %
Meridianin C (**16b**) 41 %
Meridianin D (**16c**) 38 %
Variolin analog (**16d**) 25 %

Scheme 6. Synthesis of Meridianins (Overall Yields on Four-Step Sequence)

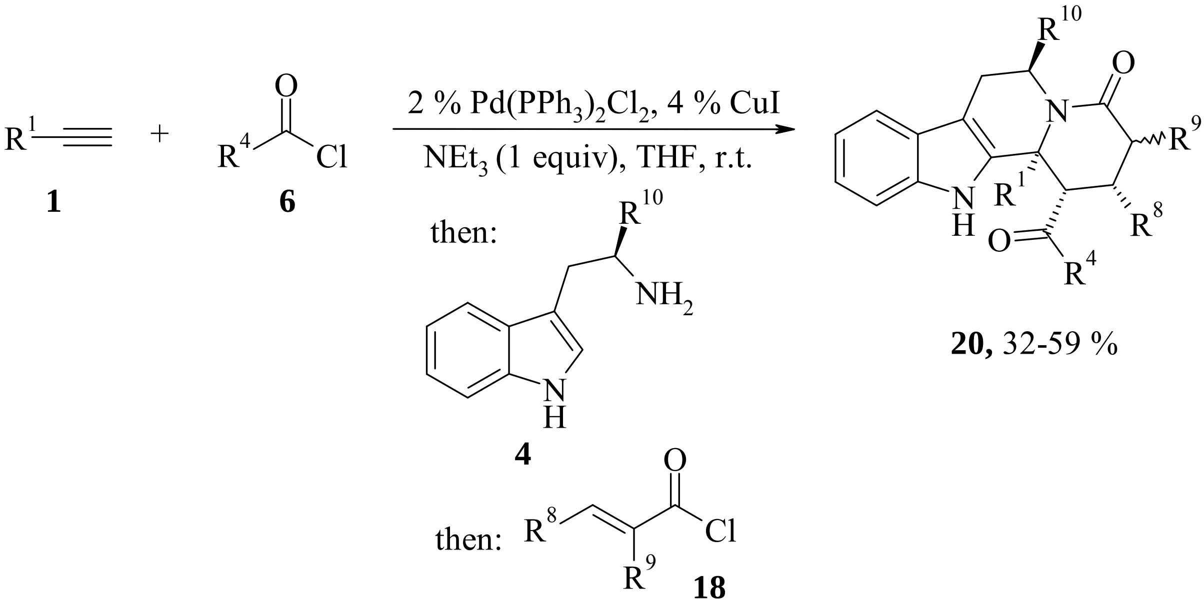
β-Enaminones **11** obtained via coupling-addition sequence can be subjected to the subsequent aza-annulation reaction with *α,β*-unsaturated chlorides **18** providing one-pot four-component access to lactams **19** (Scheme 7).



19, 31-69 %

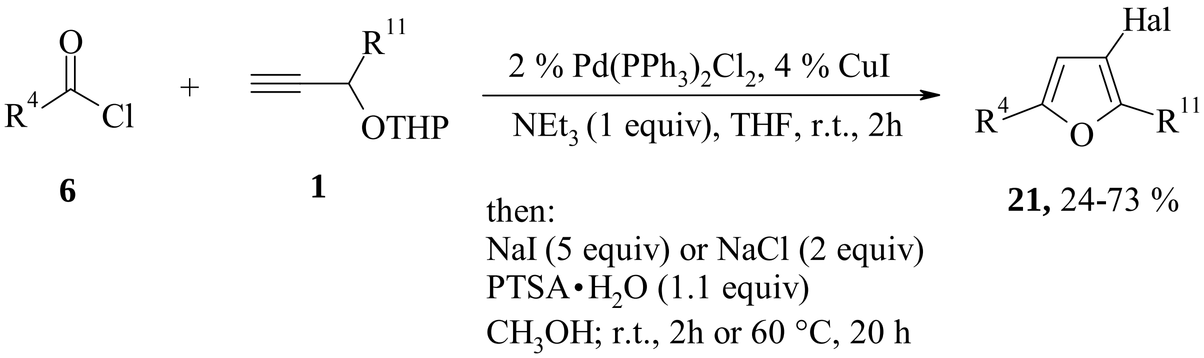
Scheme 7. Coupling-Amination-Aza-Annulation (CAA) Sequence

However, upon applying tryptamine (**4g**) or (*S*)-(−)-tryptophane methyl ester (**4i**) as primary amines in the CAA sequence, a Pictet-Spengler reaction completed the sequence resulting in the formation of indolo[2,3-a]quinolizin-4-ones **20** (Scheme 8).



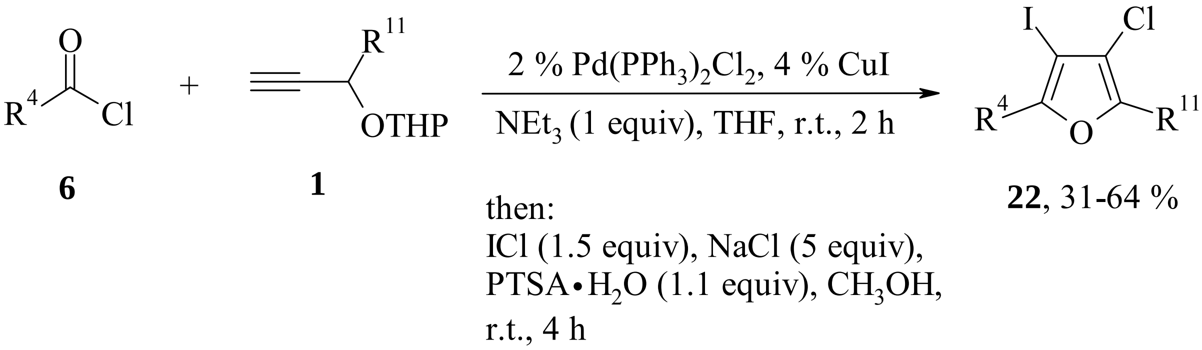
Scheme 8. Coupling-Addition-Aza-Annulation-Pictet-Spengler (CAAPS) Sequence

Subjecting THP-protected alcohols **1** to the Sonogashira coupling with acid chlorides **6** upon sequential treatment with the mixture of NaX and PTSA·H_2O led to the formation of *β*-halofurans **21** (Scheme 9).



Scheme 9. Synthesis of 2,5-Disubstituted 3-Halofurans

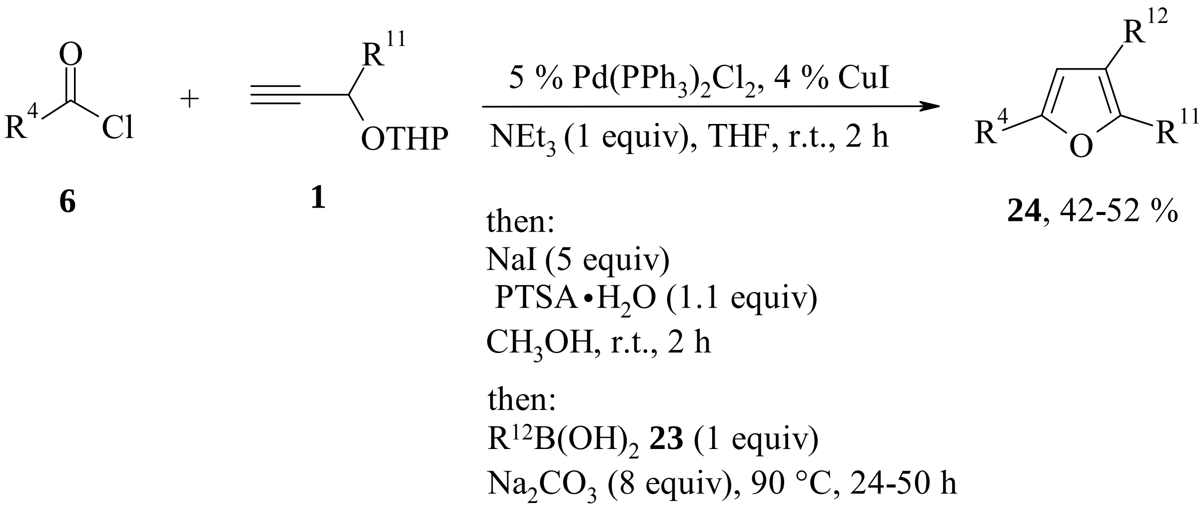
The use of ICl instead of sodium salts on the second step provided one-pot access to 3-chloro 4-iodofurans **22** (Scheme 10).



Scheme 10. Synthesis of 3-Chloro-4-iodofurans

Amazingly, 3-chloro-4-iodofurans represent an hitherto unknown class of organic compounds.

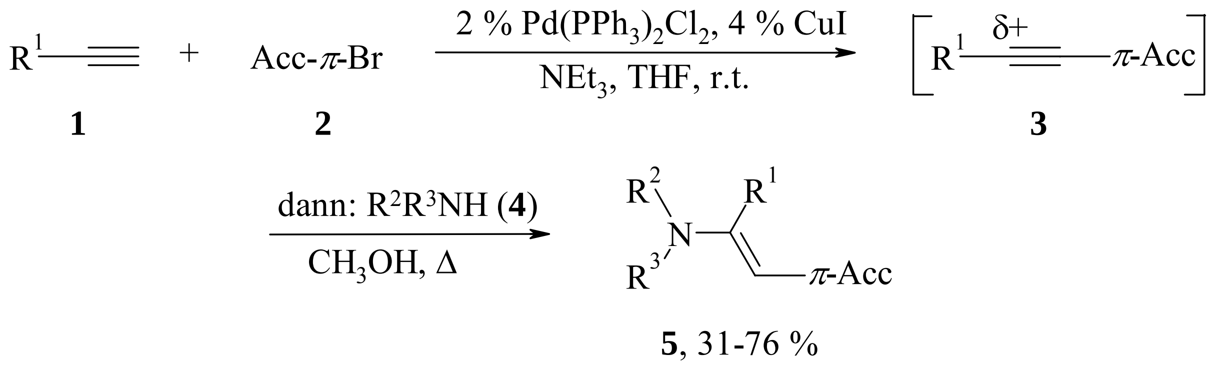
I reasoned that the halogen atom in *β*-halofurans **21** can be used for the subsequent transformation preferentially in a one-pot fashion. Therefore, after the usual formation of *β*-iodofurans the boronic acids **23** with excess of sodium carbonate were added to the reaction mixture giving rise to 2,3,5-trisubstituted furans **24** (Scheme 11).



Scheme 11. One-pot Three-component Synthesis of 2,3,5-Trisubstituted Furans

2 Zusammenfassung

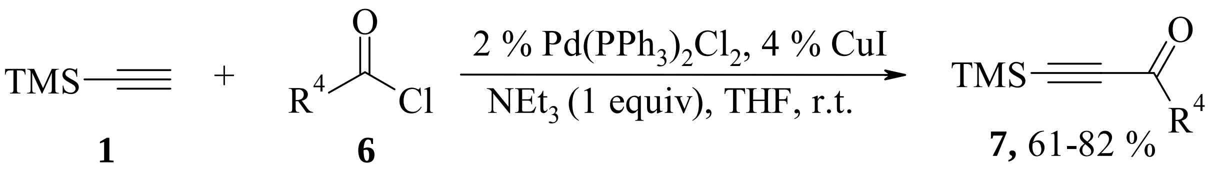
Die Sonogashira-Reaktion von terminalen Alkinen **1** mit akzeptorsubstituierten Heteroarylbromiden **2** liefert die entsprechenden Alkine **3**. Erfolgt die Umsetzung der *in-situ* generierten internen Alkine **3** mit sekundären Aminen **4** im Sinne einer Michael-Addition, ist ein bequemer Zugang zu Enaminen **5** geschaffen. Unter Verwendung der hier vorgestellten Kupplungs-Aminovinylierungs-Reaktion sind wir in der Lage, im Ein-Topf-Verfahren Push-Pull-Chromophore **5** in mäßigen bis guten Ausbeuten zu erhalten (Schema 12).



Schema 12. Kupplungs-Aminovinylierungs-Reaktion unter Erhalt von *β*-Amino Vinyl Heteroarenen 5

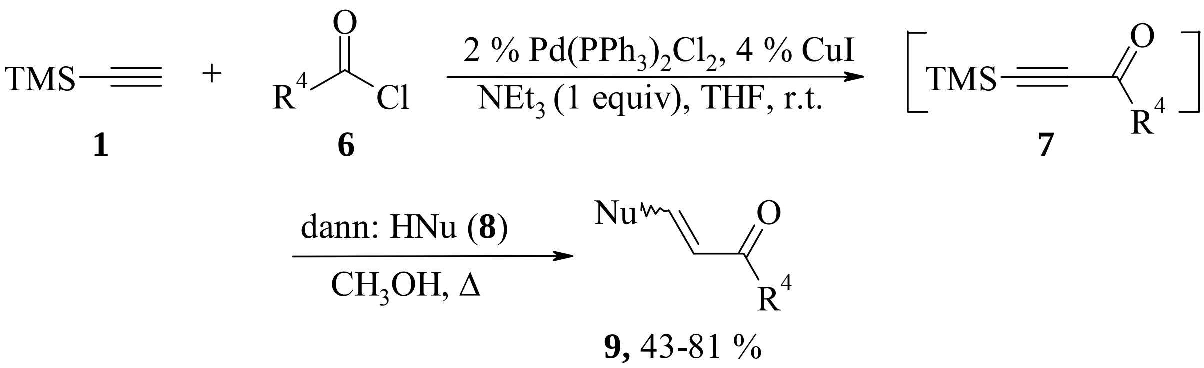
Wir haben festgestellt, dass die Polarisation des *π*-Elektronsystems, die in unserem Fall durch den elektronenziehenden Effekt einer benachbarten Gruppe erfolgt, eine Schlüsselrolle für die Zugänglichkeit dieser anschließenden Michael Typ Reaktivität spielt. Erwähnenswert ist, dass nur die relative LUMO Energie eine zufriedenstellende Erklärung für die beobachtete Reaktivität liefert; je niedriger die LUMO Energie desto wahrscheinlicher findet die Aminovinylierungs-Sequenz statt.

Da Alkinone Michael-Additionen leicht eingehen, haben wir uns entschieden, unsere Methodik auf die Verwendung von Säurechloriden **6** anstelle von Heteroarylbromiden **2** auszuweiten. Hierzu war es allerdings notwendig, das Reaktionsprotokoll der Sonogashira-Kupplung zu modifizieren, da ein Überschuss an Triethylamin weiteren Transformationen im Wege stehen würde. In der Verwendung von äquimolaren Mengen an Triethylamin lag der Schlüssel zum Erfolg. So ergibt sich im Wesentlichen nach dem ersten Kreuzkupplungs-Schritt ein neutrales Medium, denn die Base bindet die als Nebenprodukt entstehende Salzsäure. Sogar der Zugang zu extrem sensitiven (TMS)-Inonen **7** aus Trimethylsilylacetylen (**1f**) wurde unter diesen veränderten extrem milden Bedingungen ermöglicht (Schema 13).



Schema 13. Synthese der (TMS)-Inone 7

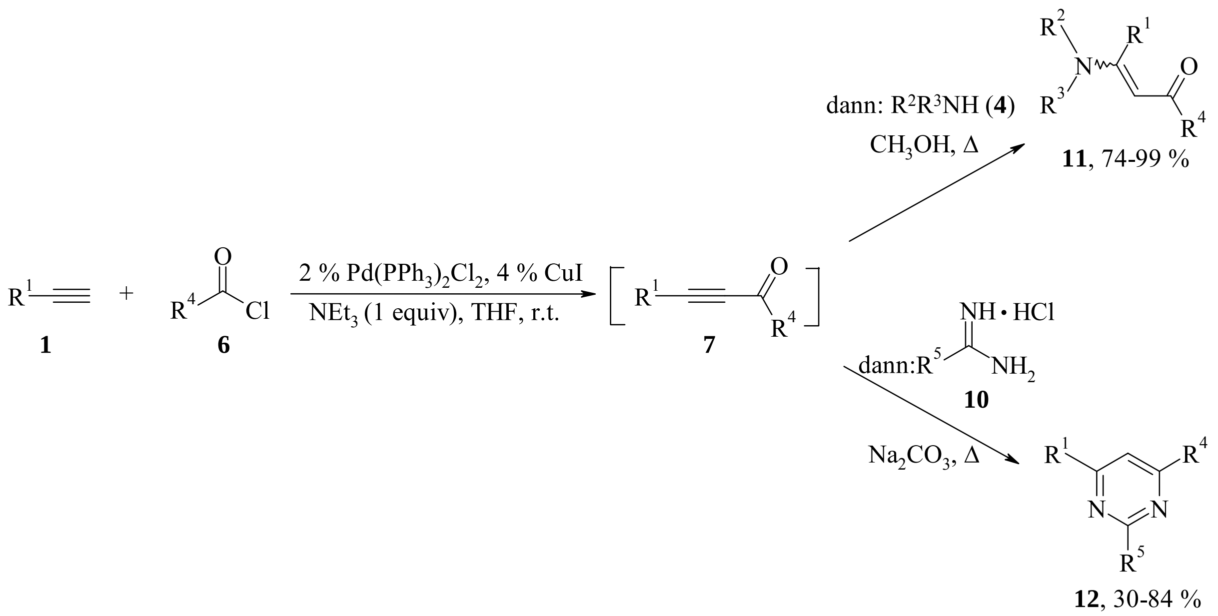
(TMS)-Inone sind synthetische Äquivalente für β-Ketoaldehyde; unter Verwendung des von uns entwickelten Protokolls kann diese Substanzklasse erstmals in sehr guten Ausbeuten synthetisiert werden. Zusätzlich können diese direkt bei der Reaktion mit Nucleophilen und Binucleophilen im Ein-Topf-Verfahren eingesetzt werden (Schema 14).



Schema 14. Ein-Topf Kupplungs-Additions-Reaktion

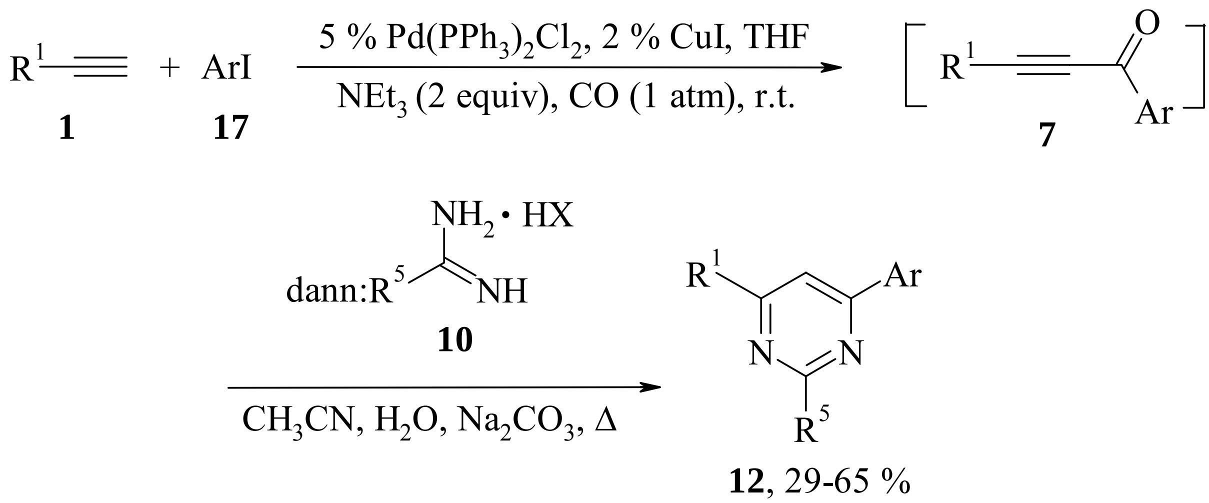
Wie erwartet, führten alle diese Additionen zum begleitenden Verlust der (TMS)-Gruppe. Nach der vollzogenen Reaktion der Säurechloride wurde die Reaktionslösung mit äquimolaren Mengen stickstoffhaltiger Nukleophile wie Diethylamin, Hydroxylamin, *o*-Aminophenol, *o*-Phenylendiamin oder Guanidin versetzt. An dieser Stelle sei jedoch erwähnt, dass lediglich Guanidin eine zweifache nucleophile Addition einging, was jedoch den Zugang zu Pyrimidinen bereitstellt.

Wie zuvor, im Sinne einer konsekutiven Drei-Komponenten-Reaktion, wurden die als Zwischenstufe auftretenden Alkinone **7** nicht isoliert, sondern direkt mit den Aminen **4** bzw. Amidinen **10** zu β-Enaminonen **11** bzw zu Pyrimidinen **12** umgesetzt (Schema 15).



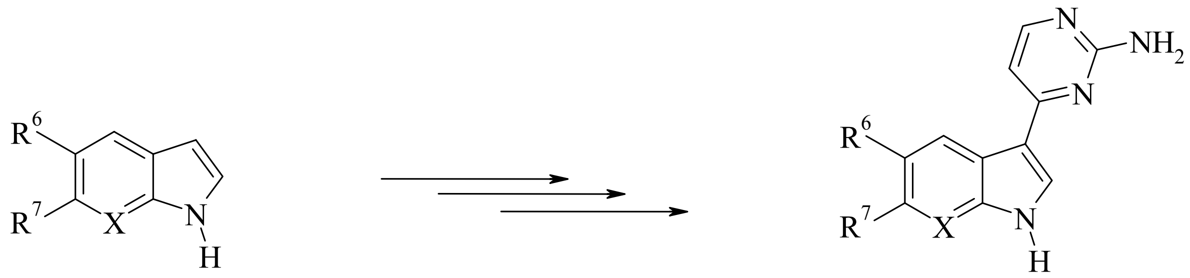
Schema 15. Synthese von *β*-Enaminonen 11 und Pyrimidinen 12

Im Fall von nicht verfügbaren Säurechloriden wurde eine carbonylierende Kreuzkupplung von terminalen Alkinen **1** und Aryliodiden **17** entwickelt. Mit Hilfe dieser Methodik konnten Alkinone **7** in einem Ein-Topf-Vier-Komponenten-Verfahren zu den entsprechenden Pyrimidinen **12** funktionalisiert werden (Schema 16).



Schema 16. Synthese von Pyrimidinen 12 durch die carbonylierende Kreuzkupplungs-Reaktion

Auf der Basis dieser Methodik gelang es uns, die natürlich vorkommenden Meridianine **16**, ausgehend von den leicht zugänglichen Indolen **13**, zu synthetisieren (Schema 17).



13a R^6 = H, R^7 = H, X = CH
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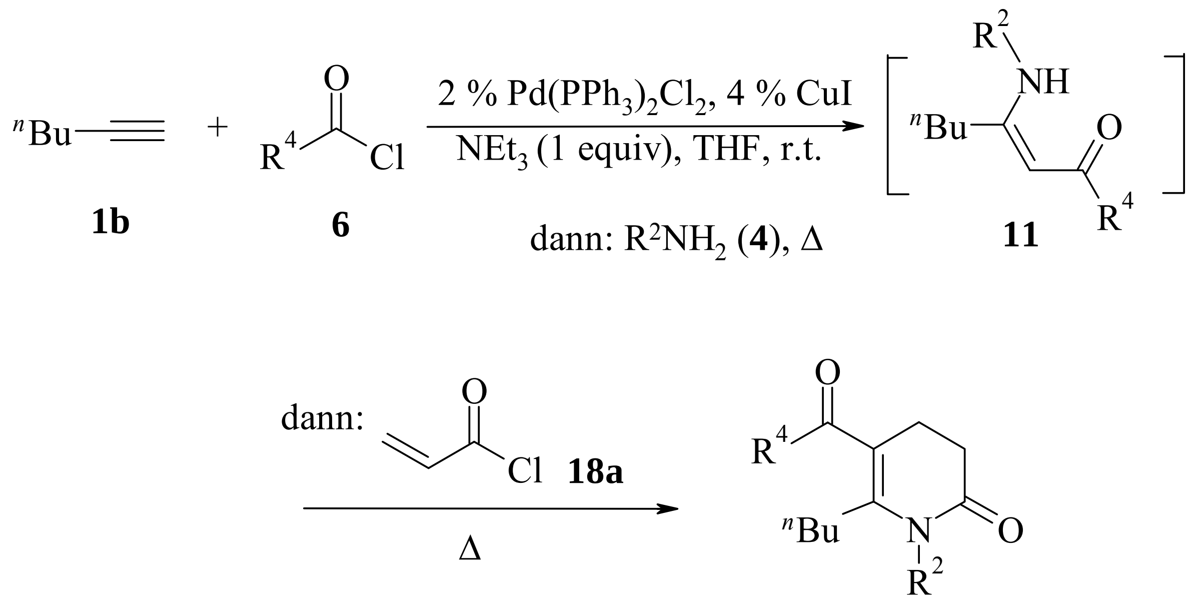
13d R^6 = H, R^7 = H, X = N

Meridianin G (**16a**) 28 %
Meridianin C (**16b**) 41 %
Meridianin D (**16c**) 38 %
Variolin analog (**16d**) 25 %

Schema 17. Synthese der Meridianinen 16a-d

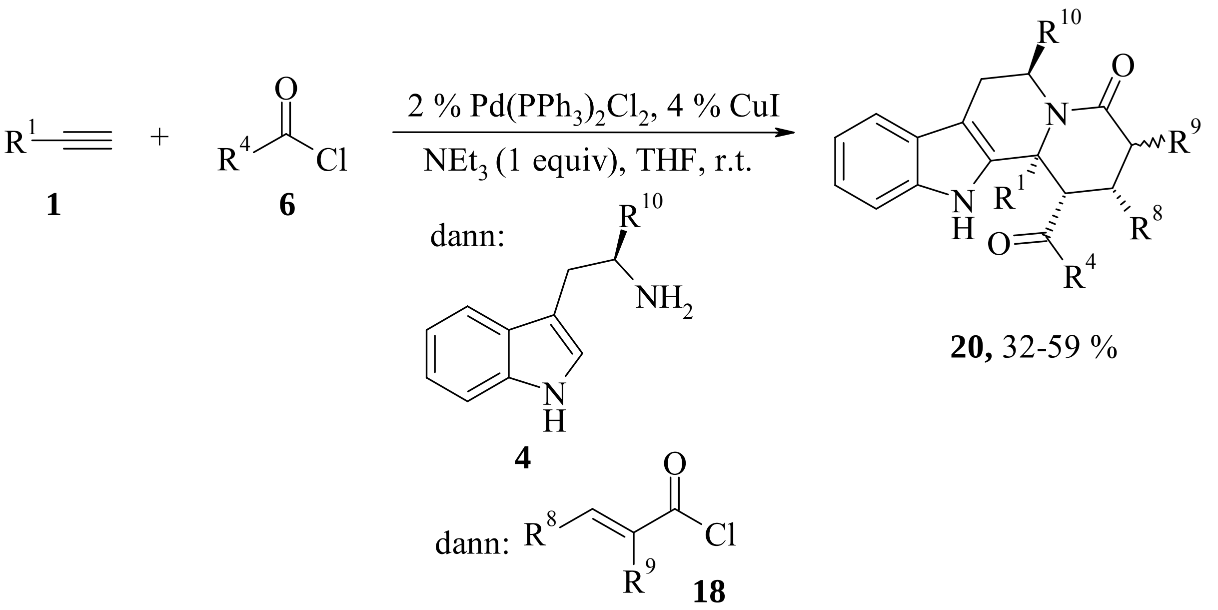
Die über die Kupplungs-Addition erhaltenen *β*-Enaminone **11** können anschließend einer Aza-Anellierungs-Reaktion mit *α,β*-ungesättigten Säurechloriden **18** unterworfen werden. Hiermit ist der synthetische Pfad einer Vier-Komponenten-Reaktion zu Lactamen **19** geebnet (Schema 18).



19, 31-69 %

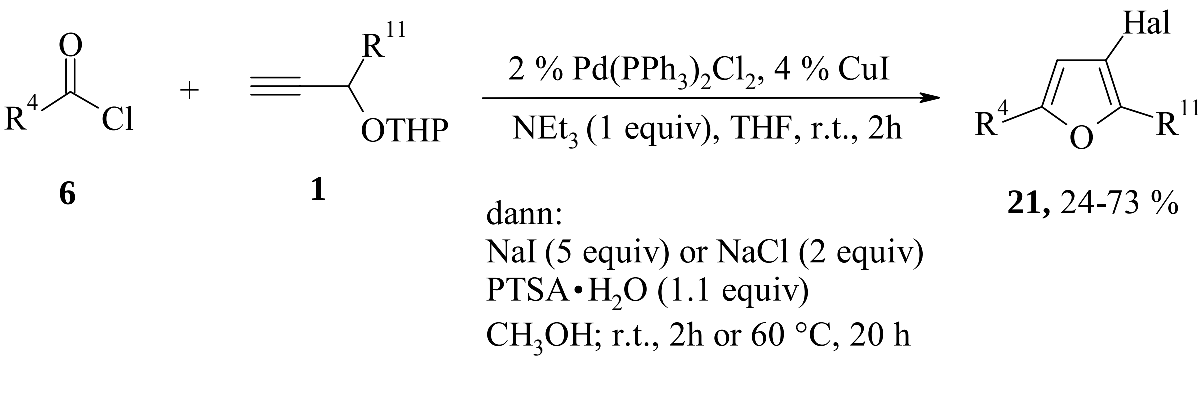
Schema 18. Kupplungs-Aminierungs-Aza-Anellierungs (KAA)-Reaktion

Unter der Verwendung von Tryptamin (**4g**) oder (*S*)-(−)-Tryptophanmethylester (**4i**) als primäre Amine in der KAA-Reaktion wurden jedoch die Indolo[2,3-a]quinolizin-4-one **20** als Produkte der anschließenden Pictet-Spengler-Cyclisierung isoliert (Schema 19).



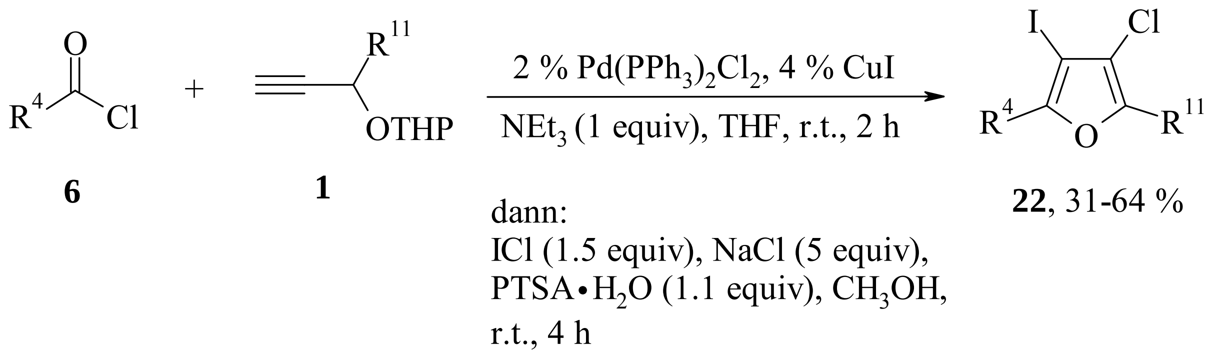
Schema 19. Kupplungs-Aminierungs-Aza-Annulierungs-Pictet-Spengler-Reaktion

Die Sonogashira-Kupplung der THP-geschützten Alkohole **1** mit den Saürechloriden **6** und anschließender Zugabe einer Mischung bestehend aus NaI oder NaCl und PTSA·H_2O führt zur Bildung von *β*-Halogenfuranen **21** (Schema 20).



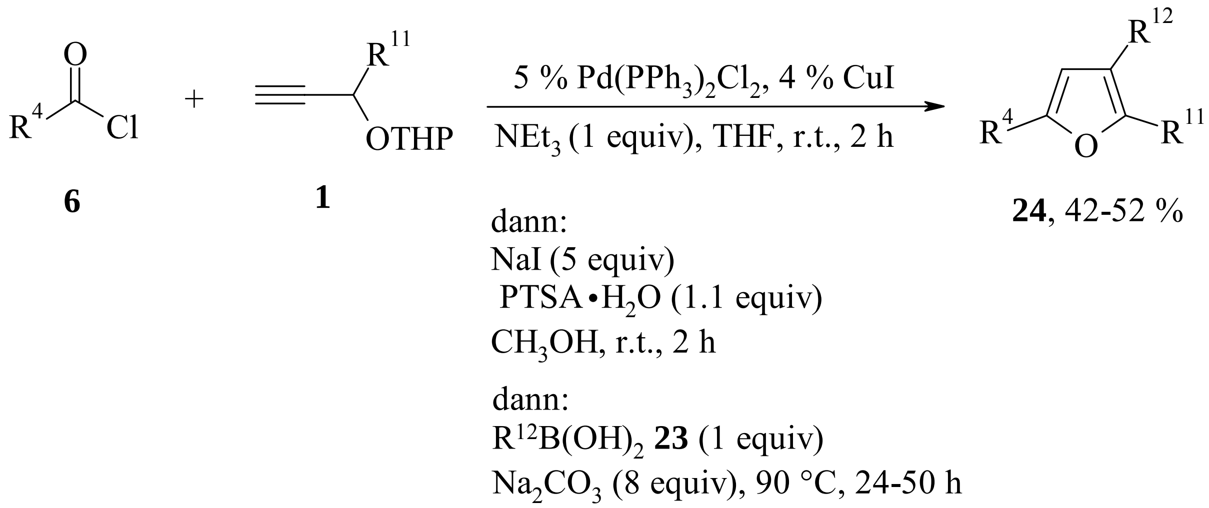
Schema 20. Synthese von 3-Halogenfuranen 21

Der Einsatz von ICl anstelle von Natriumsalzen im zweiten Schritt bietet einen Ein-Topf-Zugang zu 3-Chlor-4-iodfuranen **22** (Schema 21).



Schema 21. Synthese von 3-Chlor-4-iodfuranen 22

Wir haben angenommen, dass die Halogenatome in *β*-Halogenfuranen **21** für die konsekutive Umwandlung im Sinne einer Ein-Topf-Synthese von Nutzen sein könnten. Deshalb wurde nach der Bildung von *β*-Iodfuranen die Boronsäure **23** zusammen mit einem Überschuss an Natriumcarbonat zur Reaktionsmischung gegeben, wodurch ein Ein-Topf-Drei-Komponenten-Zugang zu 2,3,5-trisubstituierten Furanen **24** ermöglicht wird (Schema 22).



Schema 22. Ein-Topf-Drei-Komponenten Synthese von 2,3,5-trisubstituierten Furanen 24

4 General Part – Results and Discussion

4.1 Synthesis of Push-Pull Chromophores

4.1.1 Michael Addition – Literature Review

In this thesis the term "Michael addition" is defined as the addition of any type of nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group (EWG). Additionally, it shall be restricted only to alkynes as the unsaturated functionality, since alkynes can be generated *in-situ* via Sonogashira coupling (Fig. 1).

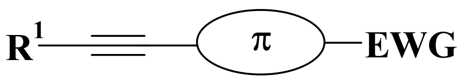


Fig. 1 Michael Acceptor

Michael was the first to report an example of this type of transformation, namely the addition of ethoxide to diethyl acetylenedicarboxylate.[9] Since that time many other examples of *π*-conjugated-EWG systems have been used to activate the alkyne moiety (Fig. 2).

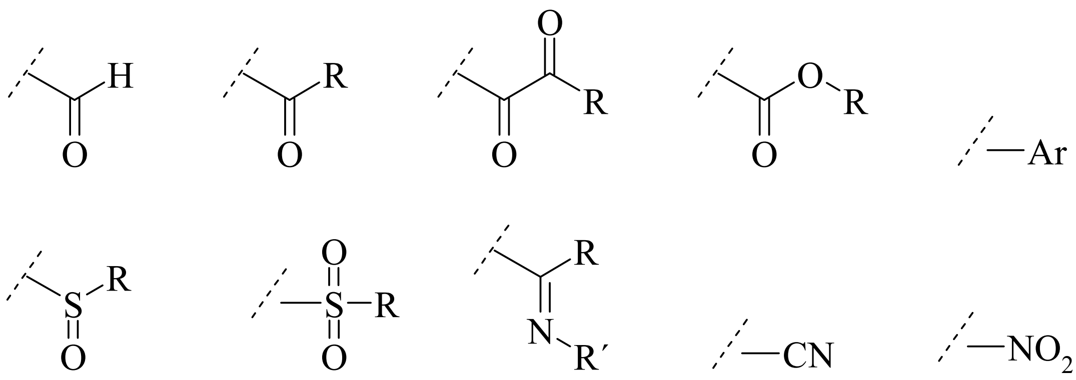


Fig. 2. Activating Groups

The relative strength of the activating power of these groups was qualitatively established and it can be correlated with their ability to stabilize a carbanion. The order is delineated at Fig. 3.[10]

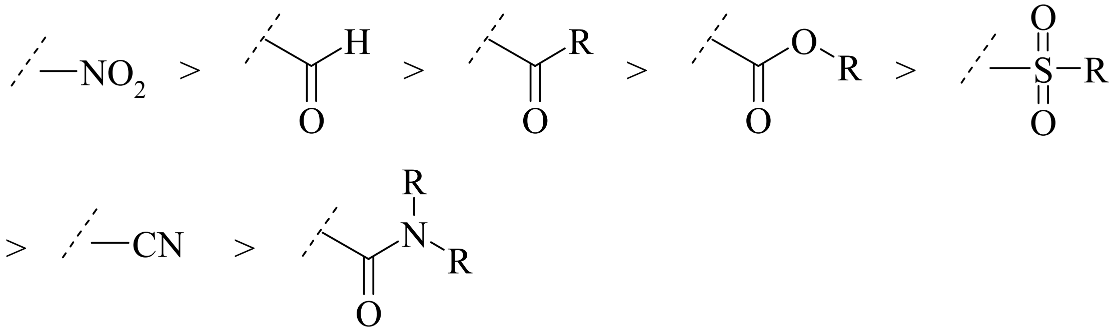


Fig. 3. The Relative Strength of Activating Groups

The power of an Ar group is hitherto not completely predictable and is dependent on the substituent on the aromatic ring and on the polarizability of the π-electron system.

The number of nucleophiles that have been used in the conjugate addition is quite extensive. Some of them are listed below (Fig. 4).

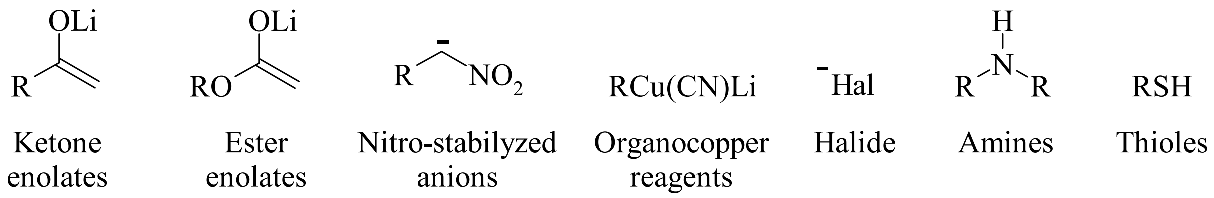
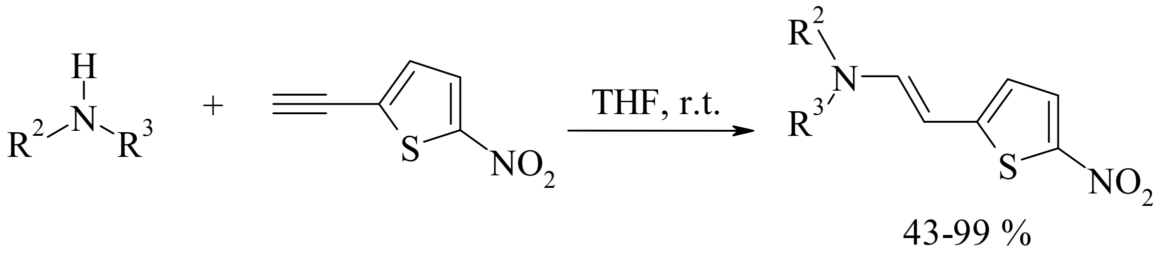


Fig. 4. Nucleophiles in Michael Addition

The thermodynamics of Michael addition usually favours a conjugate adduct over the starting material. The gain in energy is represented by difference in energy between a carbon-carbon single bond and a carbon-carbon double (formed in the product) and a carbon-carbon triple bond (broken in the starting material).

The mechanism of the base-catalyzed addition of heteronucleophiles consists of a slow, rate-determining addition of the conjugate base, followed by rapid protonation of the intermediate carbanion.

Recently, Professor Müller et al has shown that the electron-withdrawing effect of the nitro group can be efficiently transmitted through the thiophene core, thus making an appended triple bond activated towards Michael-type addition (Scheme 28).[11]

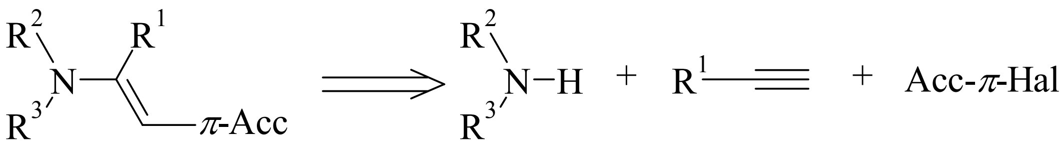


Scheme 28. Aminovinylation of 5-Ethynyl 2-nitrothiophene

The products of this aminovinylation reaction represent a novel class of push-pull chromophores with remarkable NLO responses and favourable glass-forming properties.

Since the development of short chromophores with high dipole moments and, therefore, high β-values, overcoming the disadvantage of long and extended π-systems (i.e., bathochromic absorption, efficiency-transparency trade-off) remains a challenge. I decided to extend this facile β-aminovinylation reaction to a one-pot Sonogashira coupling-aminovinylation sequence.

A retrosynthetic analysis of push-pull chromophores leads to a cross-coupling of a terminal alkyne with an electron-deficient aromatic or heteroaromatic π-electron system, furnishing an activated electron-deficient alkyne that could now undergo a Michael addition with a suitable secondary amine in a one-pot fashion (Scheme 29).



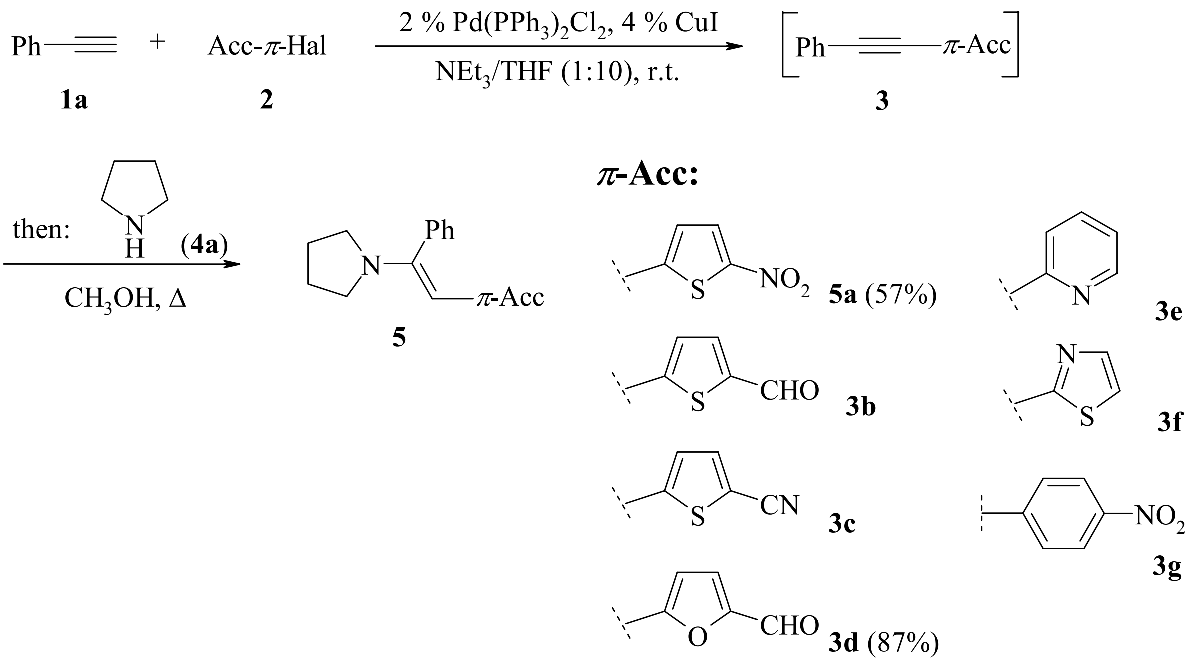
Scheme 29. Retrosynthetic Analysis of Push-pull Chromophores

4.1.2 Synthesis of Push-Pull Chromophores

A survey of the literature reveals that although the Michael addition to acceptor-substituted acetylenes is a known transformation,[12] this straightforward concept of an *in-situ* alkyne activation remains unexplored.

This new concept takes advantage of the extremely mild Sonogashira synthesis of internal alkynes, which simultaneously tolerates a wide range of functional groups. However, quite a number of electron-deficient arenes and heteroarenes such as pyridines can be coupled with alkynes in the presence of secondary amines without Michael-type product formation. Presumably, the polarizability of the π–electron system plays a key role for opening the additional Michael-type reactivity.

Therefore, phenylacetylene (**1a**) and several electron-deficient heteroaryl halides **2** were subjected to typical Sonogashira coupling conditions. Upon complete conversion to the corresponding coupling product **3**, the subsequent addition of pyrrolidine (**4a**) allowed an evaluation of the electrophilic reactivity in Michael-type aminations to be carried out (Scheme 30).

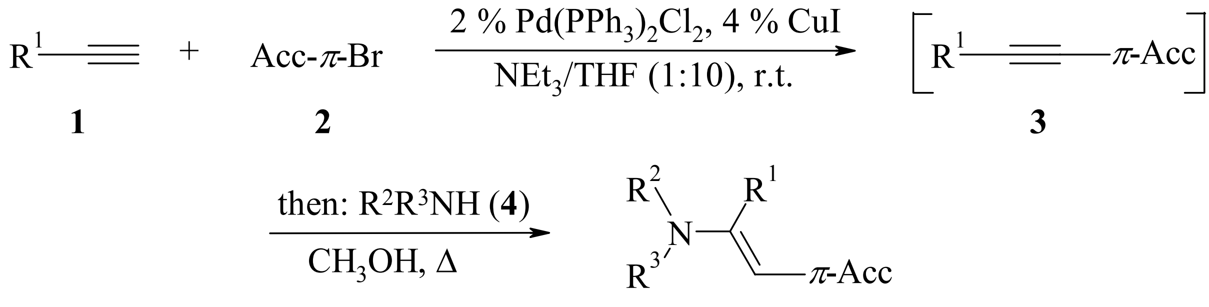


Scheme 30. Comparison of Several Electron-deficient Heteroaryl Halides in a Coupling-aminovinylation Sequence

Interestingly, among several electron-deficient heterocycles, only the nitrothienyl-substituted alkyne **3a** was successfully transformed into the amino vinylated Michael adduct

5a. Neither the furyl aldehyde-substituted system **3d** nor pyridyl-substituted alkyne **3e** reacted in the sense of a Michael addition, even after prolonged heating. Obviously, the choice of the electron-deficient halide is crucial for the feasibility of a consecutive Michael addition.

As a consequence, the reaction of several (hetero)aromatic and aliphatic terminal alkynes **1** with 5-bromo 2-nitrothiophene (**2a**), 2-bromo 5-nitrothiazole (**2h**), and 2-bromo 5-nitropyridine (**2i**) under the conditions of Sonogashira coupling, followed by subsequent addition of various secondary amines **4**, furnished the acceptor-substituted enamines **5** in good yields as orange to red crystals (**5d** as deep red oil) with an intense metallic merocyanine luster (Scheme 31, Table 1).



5, 31-76 %

Scheme 31. Coupling-Aminovinylation Sequence to *β*-Amino Vinyl Heteroarenes 5

Table 1. Three-Component Coupling-Aminovinylation Sequence

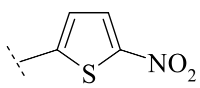
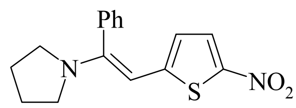
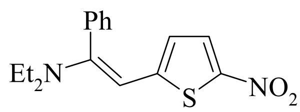
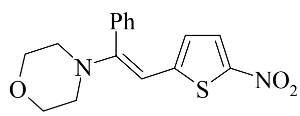
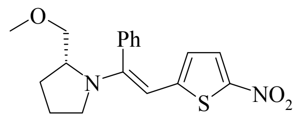
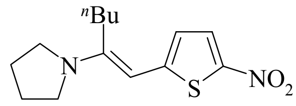
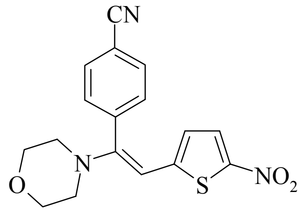
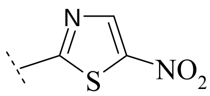
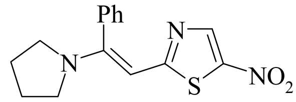
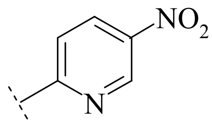
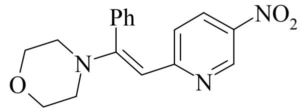
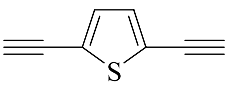
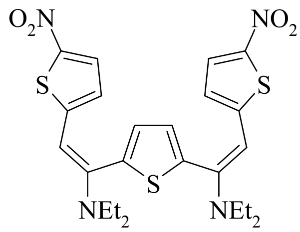
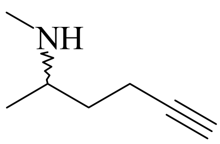
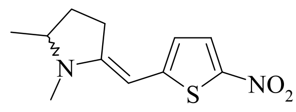
Entry	Alkyne **1**	Heteroaryl bromide **2**	Amine **4**	Enamine **5** (Yield %)
1	R^1 = Ph (**1a**)	π-Acc  (**2a**)	pyrrolidine (**4a**)	 **5a** (57 %)
2	**1a**	**2a**	$R^2 = R^3$ = Et (**4b**)	 **5b** (67 %)
3	**1a**	**2a**	morpholine (**4c**)	 **5c** (76 %)

Table 1. Continued

Entry	Alkyne **1**	Heteroaryl bromide **2**	Amine **4**	Enamine **5** (Yield %)
4	**1a**	**2a**	(2*R*)-methoxymethyl pyrrolidine (**4d**)	 **5d** (52 %)
5	$R^1 = {}^nBu$ (**1b**)	**2a**	**4a**	 **5e** (71 %)
6	$R^1 =$ *p*-C_6H_4CN (**1c**)	**2a**	**4c**	 **5f** (69 %)
7	**1a**	*π*-Acc  **2h**	**4a**	 **5g** (42 %)
8	**1a**	*π*-Acc  **2i**	**4c**	 **5h** (69 %)
9	 **1d**	**2a**	**4b**	 **5i** (67 %)
10	 **1e**	**2a**	–	 **5j** (67 %)

The one-pot sequence proceeds smoothly with a bisacetylene **1d** (entry 9) and also in an intramolecular fashion with a 5-amino alkyne **1e** (entry 10). The synthetic application of this novel one-pot coupling-aminovinylation sequence now opens straightforward access to push-pull chromophores **5** with a flexible substitution pattern.

Spectroscopic data

Characteristically, and as an indication for the successful aminovinylation, the singlets appearing between δ 5.36 and 5.96 in the proton NMR spectra of the enamines **5** can be assigned to the β-protons of the enamines. Expectedly, the magnetic anisotropy of the proximal (hetero)aryl substituents and steric biases around these protons by the alkylamino fragments affect the shifts of the signals. In the aromatic region two doublets of the nitrothienyl substituent appear at δ 6.42 (3-H) and 7.73 (4-H) with a coupling constant of J = 4.7 Hz (Fig. 5). The 4-H proton in the nitrothiazole substituent is found at δ 8.19 as a singlet. The nitropyridyl substituent was detected as two doublets at δ 6.10 (3-H) and 9.06 (6-H) with coupling constants J = 9.2 Hz and J = 2.6 Hz respectively, and a doublet of doublets (4-H) at δ 7.73 with ^3J = 9.2 Hz and ^4J = 2.6 Hz (Fig. 5).

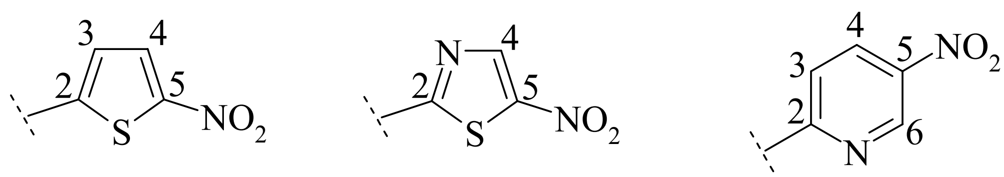


Fig. 5. The Numeration of Aromatic Substituents

All these data are in complete agreement with the usual downfield shift for EWG-containing aromatic compounds.[13]

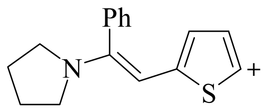
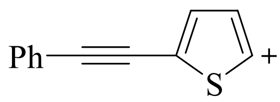
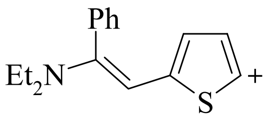
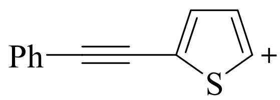
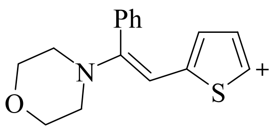
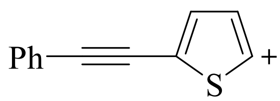
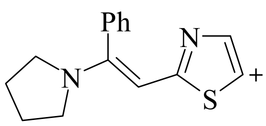
In the aliphatic region the α-protons of the pyrrolidine substituent (compounds **5a**, **5e**, **5g**) were detected as multiplets at δ 3.10-3.60 and the β-protons were identified as multiplets at δ 1.80-2.20 both with intensities for four protons. The morpholine protons (compounds **5c**, **5f**, **5h**) were detected as two triplets at δ 2.94-3.07 (α-protons) and δ 3.66-3.71 (β-protons) with coupling constants of J = 4.9 Hz. In turn, ^{1}H NMR of diethylamino group-containing compounds (**5b**, **5i)** showed the presence of triplets at δ 1.15-1.24 (β-protons) and quartets at δ 3.21-3.47 with coupling constants of J = 7.1 Hz.

In all cases the E-configured enamines **5** were formed with good to excellent stereoselectivity (ratio 4:1 to >99:<1). The E-configuration of the enamines was deduced from the appearance of strong cross-peaks in the two-dimensional NOESY experiments between the enamine *β*-protons and the *α*-protons of the amine substituents.

According to the ^{13}C NMR spectra, the sp^2-hybridized enamine *β*-methine carbon atoms can be easily identified at low field between *δ* 87.0 and 104.1 by intense cross-peaks in the HETCOR two-dimensional NMR experiments. In the aromatic region of nitrothienyl substituted compounds quaternary carbons $^5C_{quat}$ of thiophene ring that are appended to nitro group appear in a downfield between *δ* 153.7 and 157.6; for nitropyridyl substituted compound **5h** the resonance of $^5C_{quat}$ is shifted further to the downfield and is found at *δ* 164.5; for nitrothiazolyl substituted compound **5g** the resonance of $^5C_{quat}$ is detected at *δ* 174.7.

The mass spectra of the obtained compounds display the molecular peaks. The subsequent fragmentation leads usually to the loss of a nitro group and an alkyl amino chain (Table 2).

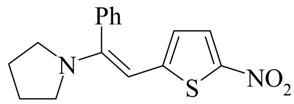
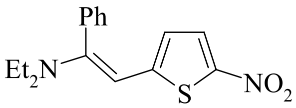
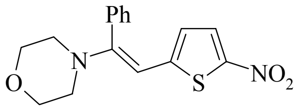
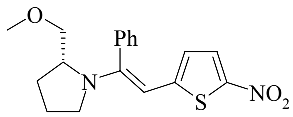
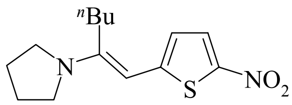
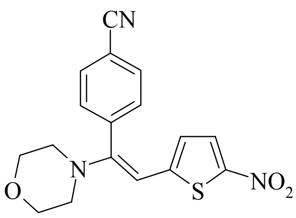
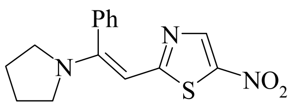
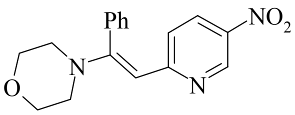
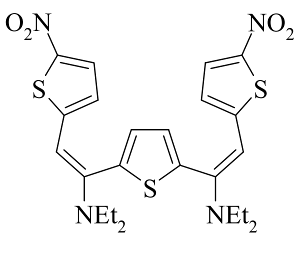
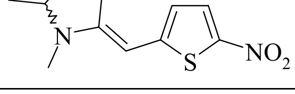
Table 2. The Fragmentation of Selected Enamines 5 (EI, 70 eV)

Compound	Fragment	*m/z* (M^+ - (*m/z*))	Fragment	*m/z* (M^+ - (*m/z*))
5a		254 (46)		184 (116)
5b		256 (46)		184 (118)
5c		270 (46)		184 (132)
5g		255 (46)		

The IR spectra show the presence of intense NO_2 bands between 1570 and 1553 cm^{-1}. The vibrations of CN group (**5f**) were detected at 2228 cm^{-1}.

The UV/vis spectra of the acceptor-substituted enamines **5** not only display remarkable solvochromicities ($\Delta\tilde{\nu}$(acetonitrile-diethyl ether) = 1300-2200 cm^{-1}) but also a wide range in the wavelength absorption maxima ($\Delta\lambda_{max}$= 404-499 nm (diethyl ether)).

Table 3. UV/vis Spectroscopic Data (Recorded in Diethyl Ether and Acetonitrile at 20 °C and Solvochromicity of Enamines 5

Push-pull chromophores **5**	λ_{max} [nm] (ε) in Et_2O	λ_{max} [nm] (ε) in CH_3CN	$\Delta\tilde{\nu}$ [cm^{-1}]
 **5a**	491 (32200)	537 (31100)	+1800
 **5b**	485 (27000)	553 (37100)	+2500
 **5c**	450 (20900)	498 (21700)	+2100
 **5d**	485 (21000)	528 (24300)	+1700
 **5e**	499 (20400)	545 (43700)	+1700
 **5f**	439 (18100)	486 (21000)	+2200
 **5g**	468 (14200)	500 (17500)	+1400
 **5h**	404 (23400)	426 (20400)	+1300
 **5i**	485 (21000)	518 (44100)	+1300
 **5j**	487 (29200)	532 (34300)	+1700

Additionally, the *E*-configurations of enamines **5** were unambiguously supported by an X-Ray structure analysis for compounds **5a**, **5b**, **5c** (Fig. 6, Fig. 7, Fig. 8).

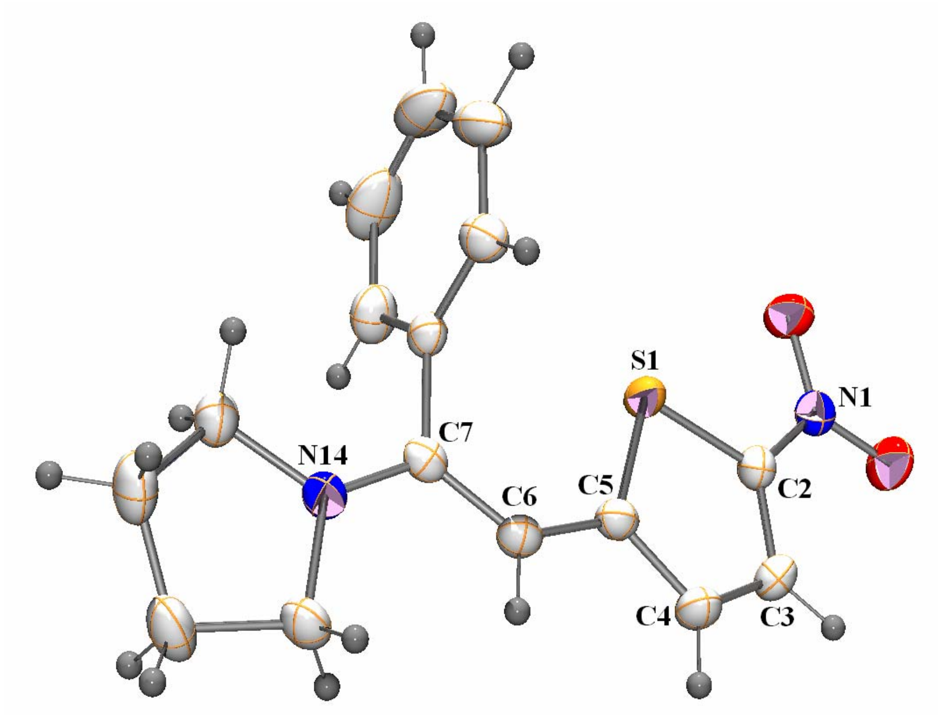


Fig. 6. ORTEP-presentation of (*E*)-1-[2-(5-Nitrothien-2-yl)-1-phenyl-vinyl] pyrrolidine (5a)

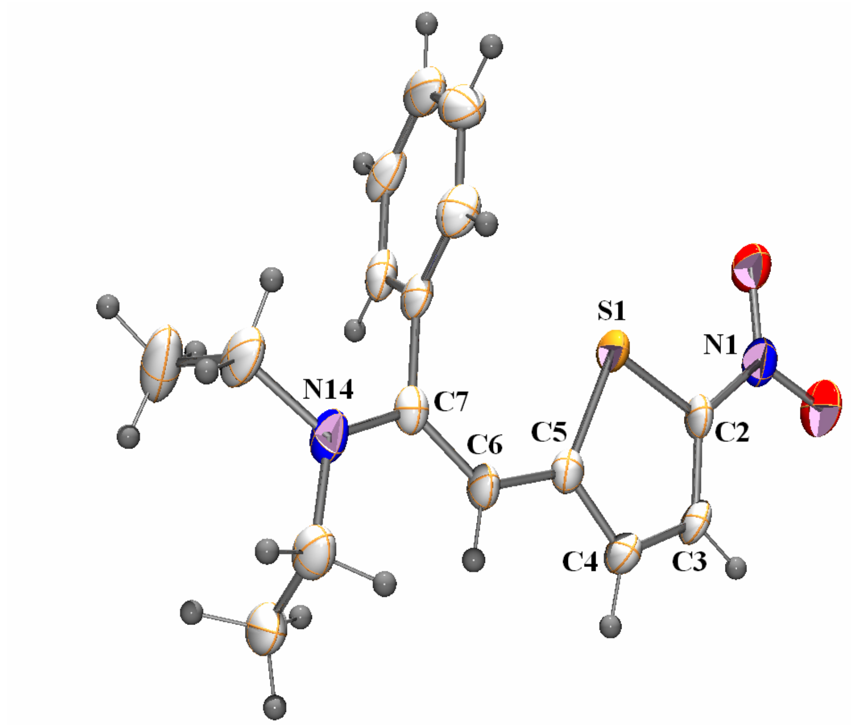


Fig. 7. ORTEP-presentation of (*E*)-Diethyl-[2-(5-nitrothien-2-yl)-1-phenyl-vinyl] amine (5b)

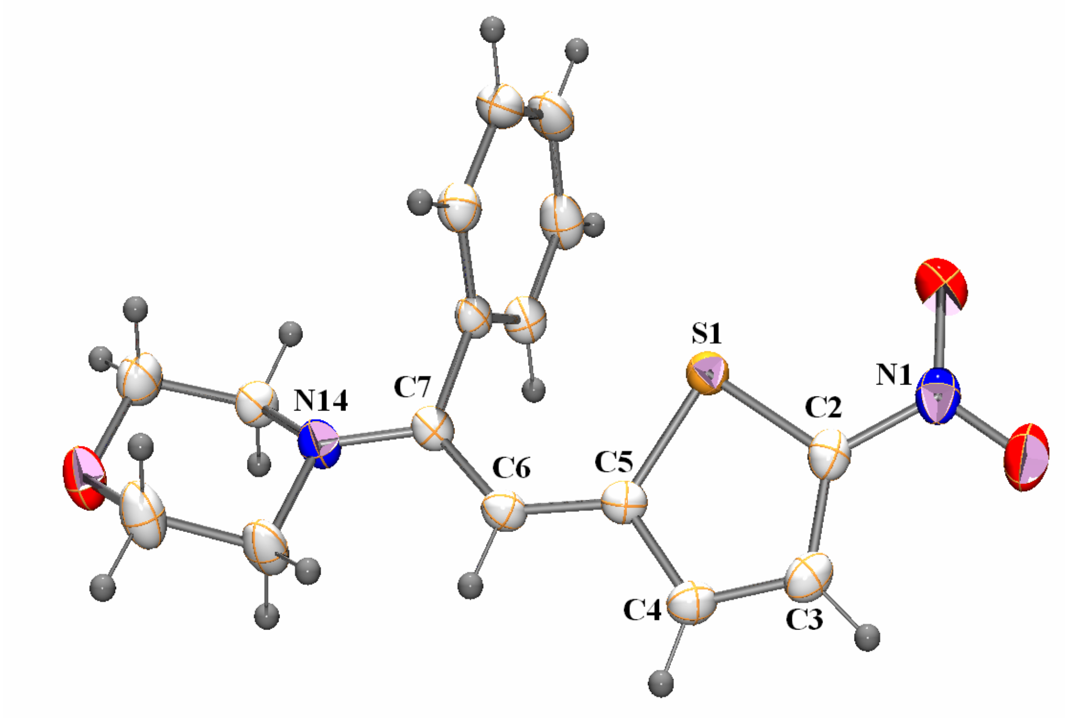


Fig. 8. ORTEP-presentation of (*E*)-4-[2-(5-Nitrothien-2-yl)-1-phenyl-vinyl] morpholine (5c)

A very favorable aspect for NLO applications can be deduced from intermediate bond length and angle alterations. Thus, the good coplanarity of the dialkylamino, vinylthiophene and nitro groups (the dihedral angle N14-C7-C6-C5 = 165.6-174.7°; the dihedral angle C7-C6-C5-S1 = 3.4-11.2°; the dihedral angle C5-S1-C2-N1 = -178.6-179.9°) would allow a facile charge-transfer from the amine electron donor to the nitro electron- acceptor. The C7-N14 bond lengths (1.35-1.39 Å) are fairly short and display a high C-N double-bond character, whereas, the C6-C7 bond lengths (1.36-1.39 Å) lie within the margin of highly delocalized aromatic π-electron systems (ethane C−C, 1.53 Å; ethylene C=C, 1.32 Å; butadiene C−C, 1.48 Å; butadiene C=C, 1.34 Å).[14] However, for second-order bulk effects ($\chi^{(2)}$) such as second harmonic generation (SHG) or electrooptical effects, it is necessary that the molecules crystallize in a noncentrosymmetric environment.[15] Unfortunately, all the enamines **5** were crystallized in centrosymmetric space groups ($P2_1/n$ for **5a**, $P2_1$ for **5b** and $P\bar{1}$ for **5c)**, thus leading to vanishing of $\chi^{(2)}$.

Enamine **5i** can be interesting for dipolar two-dimensional NLO-phores studies. X-Ray structure analysis for this compound (Fig. 9) shows the same trends as for the enamines **5a-5c**. The C6-N6 and C11-N11 bond lengths are 1.35 Å, the C5-C6 and C11-C12 bond lengths are 1.37 Å and 1.38 Å.

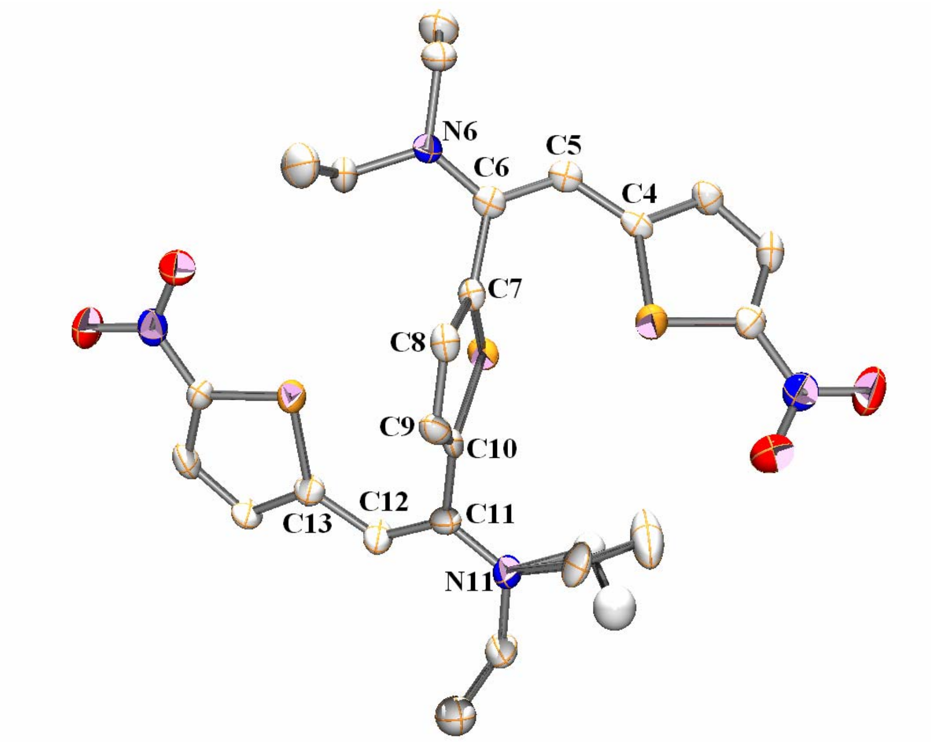


Fig. 9. ORTEP-presentation of (*E,E*)-2,5-Bis[2-(5-nitrothien-2-yl)-1-diethylamino-vinyl] thiophene (5i)

4.1.3 Computational Studies on the Michael Addition

As already mentioned in the previous part, the choice of the electron-deficient halide is crucial for the feasibility of a consecutive Michael addition. This observation prompted us to approach the nature of the electron-deficient alkynes **3** by taking a closer look at the ground-state electron distribution. The geometries of alkynes **3** were optimized using the 6-311G ++ (2d, 2p) basis set, at the DFT level of theory. The density functional that was chosen for this purpose was B3LYP, which is a hybrid functional made up of Becke's exchange functional, the Lee-Yang-Parr (LYP) correlation functional and a Hartree-Fock exchange term. These functionals were used as supplied in the Gaussian 03 suite of programs.[16] The analysis was focused on the calculated atomic charges, as reflected by the electrostatic potentials (ESP), the Mulliken natural bonding orbitals (NBO),[17] dipole moments and LUMO energies (Table 4).

Interestingly, neither the dipole moments are dominated by the polarity of the corresponding functional groups nor does the electrostatic potential at the alkyne carbon centers consistently correlate with the observed reactivity. For example, according to the electrostatic potential at the carbon centre C_β, the pyridyl derivative **3e** (ESP, C_β = -0.060) and the thiazolyl compound **3f** (ESP, C_β = -0.077) should readily react with secondary amines. Even the polarity of the triple bond reflected by the difference $|C_\beta - C_\alpha|$ (ESP and NBO) do not describe its reactivity towards Michael addition. For example, according to ESP, the nitro thiazolyl derivative **3h** (ESP, $|C_\beta - C_\alpha|$ = 0.046) should not react with amines and according to NBO, the formyl thienyl compound **3b** (NBO, $|C_\beta - C_\alpha|$ = 2.816) and cyano thienyl derivative **3c** (NBO, $|C_\beta - C_\alpha|$ = 2.822) should react with amines.

Table 4. Calculated (DFT B3LYP/6-311G ++ (2d, 2p)) Atomic Charges, Dipole Moments and LUMO Energies of Alkynes 3

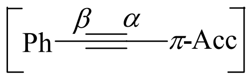
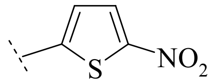
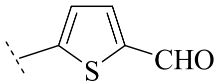
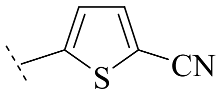
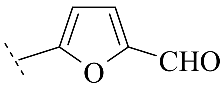
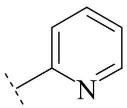
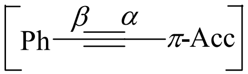
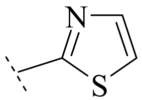
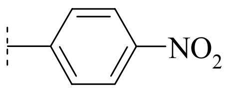
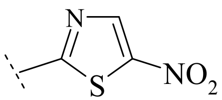
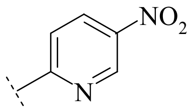
 **3** π-Acc	C_β			C_α			$\lvert C_\beta - C_\alpha \rvert$			Dipole moment, [D]	LUMO, [eV]	Reaction with amines
	ESP	NBO	^{13}C NMR	ESP	NBO	^{13}C NMR	ESP	NBO	^{13}C NMR			
 **3a**	-0.210	0.078	98.2	0.029	-0.043	81.1	0.239	0.121	17.1	6.63	-3.16	+
 **3b**	-0.188	1.853	97.9	-0.017	-0.963	82.0	0.171	2.816	15.9	4.82	-2.50	-
 **3c**	-0.198	1.857	96.8	0.009	-0.965	80.5	0.207	2.822	16.3	6.02	-2.34	-
 **3d**	-0.105	0.067	96.4	-0.163	-0.052	78.5	0.058	0.119	17.9	5.12	-2.31	-
 **3e**	-0.060	0.036	89.1	-0.272	0.001	88.4	0.212	0.035	0.7	1.86	-1.88	-

Table 4. Continued

 **3** π-Acc	C_β ESP	C_β NBO	C_β ^{13}C NMR	C_α ESP	C_α NBO	C_α ^{13}C NMR	$\lvert C_\beta - C_\alpha \rvert$ ESP	$\lvert C_\beta - C_\alpha \rvert$ NBO	$\lvert C_\beta - C_\alpha \rvert$ ^{13}C NMR	Dipole moment, [D]	LUMO, [eV]	Reaction with amines
 **3f**	-0.077	0.062	93.8	-0.179	-0.042	82.1	0.102	0.104	11.7	1.57	-1.66	-
 **3g**	-0.144	0.050	94.5	-0.162	-0.005	87.3	0.018	0.055	7.2	6.36	-3.02	-
 **3h**	-0.087	1.902	98.9	-0.984	-0.133	81.9	0.046	2.886	17.0	6.17	-3.37	+
 **3i**	-0.033	0.066	94.9	-0.276	-0.019	87.6	0.243	0.085	7.3	6.21	-3.24	+

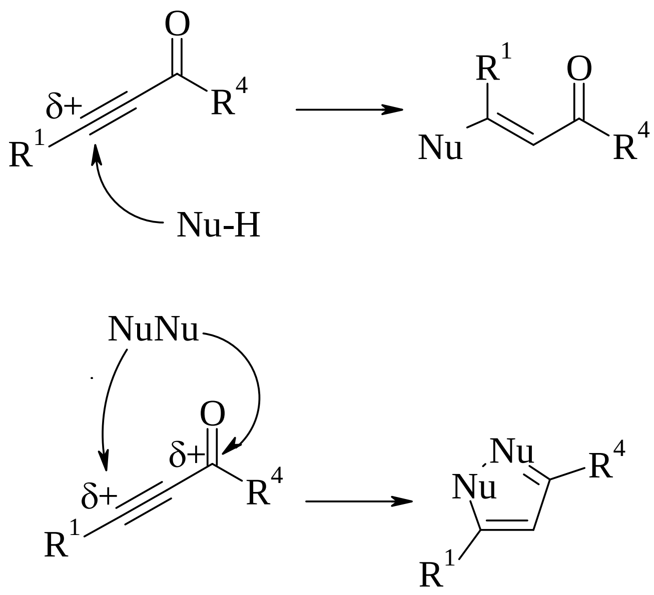
However, the relative LUMO energies that reflect the orbital coefficients and density distributions at the triple bonds reveal a satisfactorily qualitative picture and rationalize the observed reactivity. The lower the LUMO, the more likely the aminovinylation will proceed. According to the calculations, the rationale for the successful aminovinylation finds its borderline between the alkynes **3a** (LUMO = -3.16 eV) and **3g** (LUMO = -3.02 eV). This very small difference in the LUMO energies between **3a** and **3g** explains the lacking reactivity of *p*-nitrotolane **3g** under the applied conditions. Interestingly, a survey of the literature reveals that under drastic conditions in highly dipolar, aprotic solvents **3g** can be involved into Michael reaction.[18]

The ^{13}C NMR shifts of the C_α and C_β carbon centers as an experimental magnitude for the charge density[19] and as a measure for the propensity of **3** to participate in aminovinylations can only be interpreted here with caution. In the consanguine thiophene (**3a** (C_β = 98.2; $|C_\beta - C_\alpha|$ = 17.1), **3b** (C_β = 96.8; $|C_\beta - C_\alpha|$ = 16.3), **3c** (C_β = 97.9; $|C_\beta - C_\alpha|$ = 15.9)) and thiazole series (**3f** (C_β = 93.8; $|C_\beta - C_\alpha|$ = 11.8), **3h** (C_β = 98.9; $|C_\beta - C_\alpha|$ = 17.0)), the characteristic alkyne carbon resonances and their differences allow for an estimated prediction of aminovinylation reactivity.

4.2 One-Pot Reactions Initiated via Sonogashira Coupling of Acid Chlorides

4.2.1 Ynones – Literature Review

Ynones are organic compounds containing a triple bond and a carbonyl group in the same molecule. In this thesis only such ynones where a triple bond is directly appended to an electron-deficient carbonyl group are considered. These compounds possess two electrophilic centers; thus reactions with nucleophiles (Michael addition) and binucleophiles (cyclocondensation) are the most important transformations in the chemistry of ynones (Scheme 32).

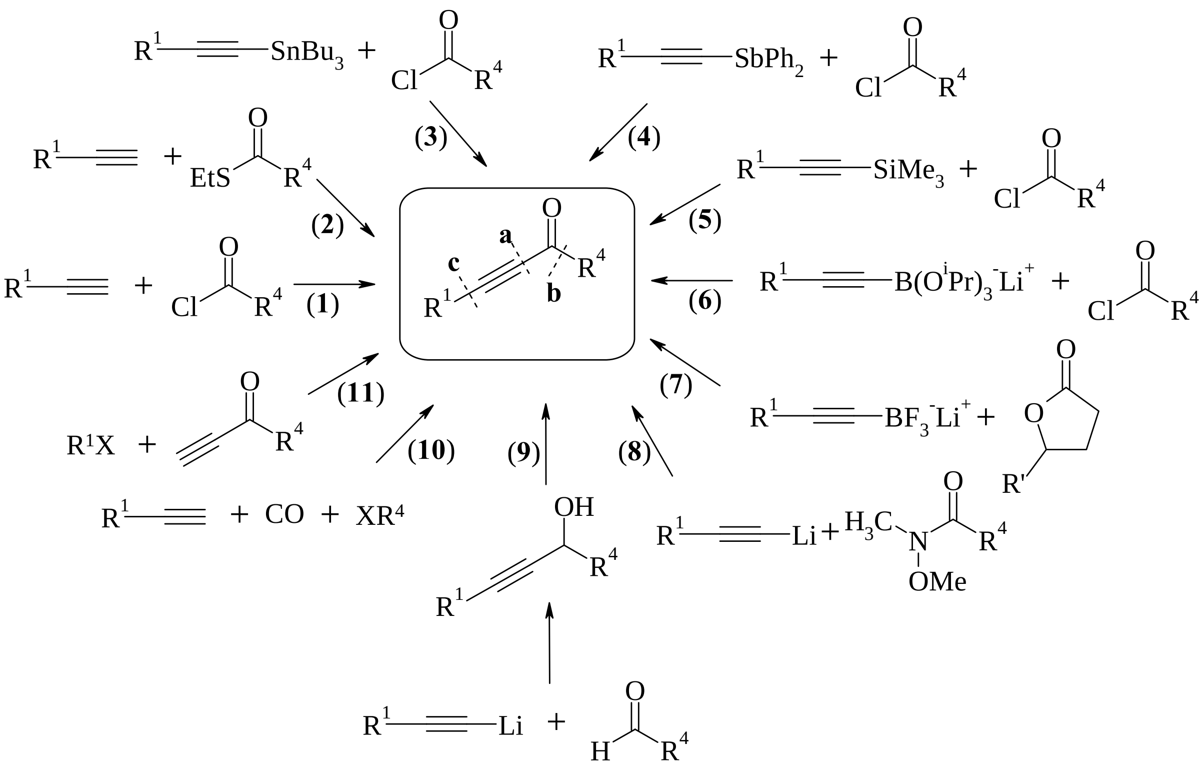


Scheme 32. Reactivity of Ynones

Due to the importance of ynones, synthetic chemists have made considerable efforts in the synthesis of these useful building blocks.

4.2.1.1 Synthesis of Ynones

The available methods for the preparation of ynones can be classified according to the retrosynthetic scissions (Scheme 33).



Scheme 33. Synthesis of Ynones

The most general retrosynthetic scission is the one that forms bond **a** (approaches 1-9). The first approach (**1**) is the most elegant and practical method of ynone formation. It is dated back to 1977 when Sonogashira et al. discovered that the mixture of triphenylphosphane-palladium dichloride and copper iodide catalyzes the coupling of alkynes and acid chlorides.[20] Interestingly, in the case of trimethylsilyl acetylene, this coupling failed and only the homo-coupling product of trimethylsilyl acetylene was isolated.[21] The conditions for this very attractive reaction were modified and improved. For example, this coupling can be performed even in water, using surfactant that prevents the molecules of acid chloride from hydrolysis.[22] It was shown that the use of palladacycle allows the reducing of the amount of Pd catalyst to only 0.2 mol % which is active without any copper additives (Fig. 10).[23] However, under these conditions, the desired products were isolated in significantly lower yields.

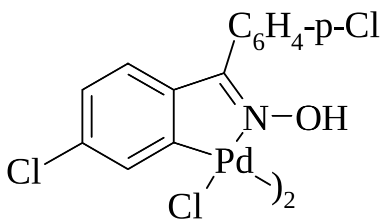


Fig. 10. Palladacycle Catalyst

It is also possible to perform this reaction using only Cu(I) salts without a Pd catalyst.[24,25]

In the second approach (**2**) thiol esters were used instead of acid chlorides.[26] Here the best catalytic system was found to be 5 mol % of Pd(dppf)Cl_2, 12.5 mol % of P(2-furyl)$_3$, and 1.7 equiv of CuI. The starting thiol esters in turn are readily available from the corresponding carboxylic acids by the mixed-anhydride method. This approach has the advantage that even OH groups can be tolerated and substrates derived from aliphatic, *α,β*-unsaturated, as well as aromatic carboxylic acids can be subjected to the reaction. Major drawbacks of this procedure are that more than the stoichiometric amount of CuI has to be used and EtSH is formed as a side product of the reaction. EtSH is not only very pungent and poisons the catalyst, but can lead also to side reactions, such as the addition of it to a conjugated triple bond. Additionally, the reaction using (TMS)-acetylene gave only recovered starting thiol ester.[26]

The third (**3**) and fourth (**4**) approaches are quite similar to the first (**1**). Here tin[27] or antimony[28] acetylides generated stoichiometrically from the appropriate alkynyllithium and chlorotributyl stannane or bromodiphenyl stibine were coupled with acid chlorides in the presence of triphenylphosphane-palladium dichloride as the catalyst. The greatest disadvantage of both these methods lies in the additional step of transforming acetylenes to tin or antimony derivatives.

In the fifth (**5**) approach alkynylsilanes were used as the starting compounds. The reaction can be catalyzed either by the use of Lewis acids such as $AlCl_3$[29,30,31] or simply by the use of iodine.[32]

In the sixth (**6**) and seventh (**7**) approaches alkynylborates and alkynyltrifluoroborates were transformed to conjugated ynones. It is interesting to mention that in the approach (**6**) Pd(0) or Pd(II) complexes and CuI successfully catalyzed the coupling.[33] However, in the approach (**7**) the reaction was carried out at -78 °C without any additives.[34] In both cases the starting alkynylboronate derivatives were prepared from the lithium acetylides and either triisopropoxyborate (**6**) or $BF_3{\cdot}OEt_2$ (**7**).

Alternatively, ynones can be prepared from the lithium acetylides and *N*-methoxy-*N*-methyl Weinreb amides (**8**).[35,36] Additionally, 2-pyridyl thiolate esters, dimethylpyrazolides, isoxazolides and tetrahydro-2*H*-1,2-oxazinides were used instead of amides.[37]

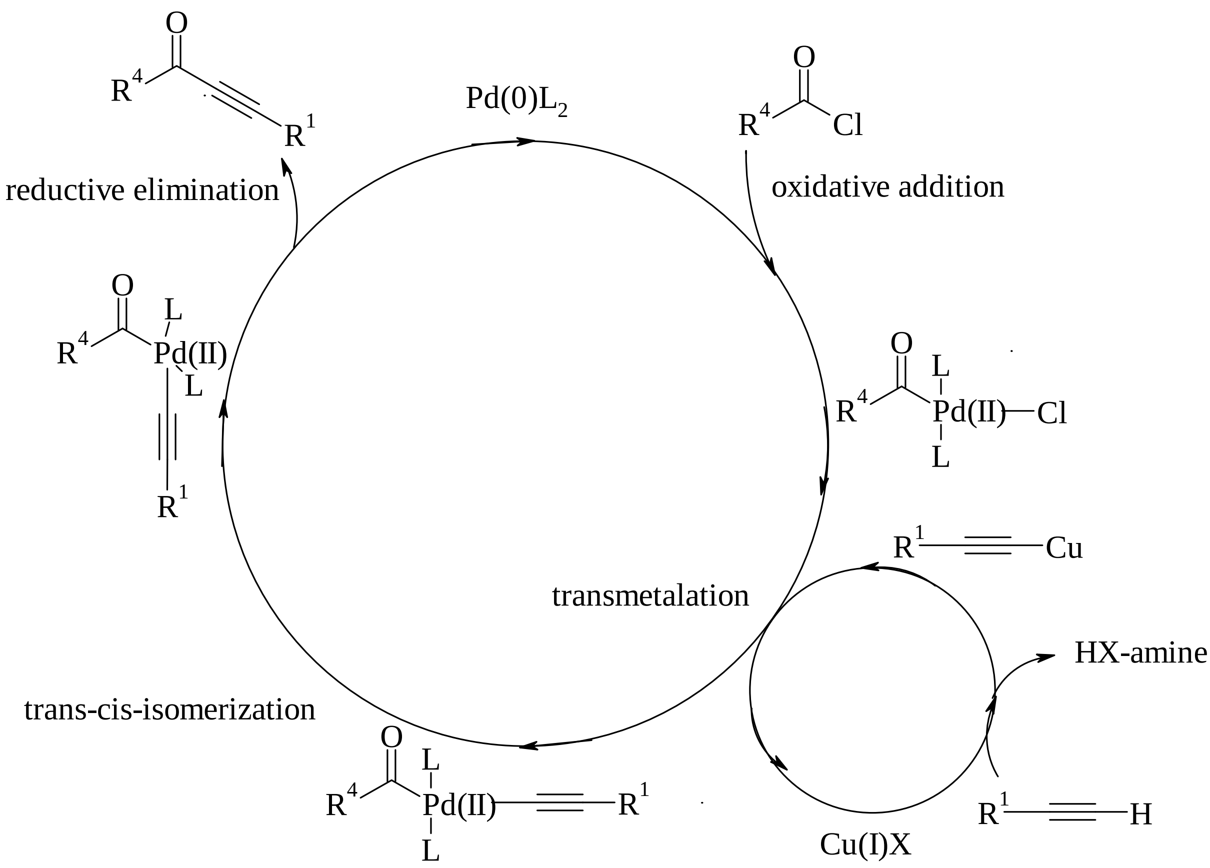
A two-step protocol via an oxidation of propargylic alcohols (**9**), which in turn were derived from the addition of lithium acetylides to aldehydes, provides an alternative route to ynones.[38]

The preparation of ynones via formation of bonds **a** and **b** (**10**) from the aryl iodides under CO pressure in the case of inaccessible acid chlorides can be sometimes preferable. It is worthwhile to mention that this carbonylative coupling has remained for a long time an unestablished methodology and high pressures of CO[39] were required for obtaining the ynones in reasonable yields. It was only in 1995, that an Italian group found that the reaction can be conducted under normal pressure of CO using THF as the solvent, 10 equiv of triethylamine and 1.2 equiv of Bu_4NF as the bases, and 5 mol % of $Pd(dppf)Cl_2$ as the catalyst.[40] These conditions, however, had a significant drawback: 2 equiv of aryl iodides were applied what can be inconvenient for expensive aryl iodides. However in 2003, a reasonable procedure for the carbonylative alkynylation under normal CO pressure using aqueous ammonia as the base was developed.[41]

Finally, the synthesis of ynones via the formation of bond **c** (**11**) is perhaps the least common. The usual Sonogashira coupling for alkynes containing EWG (directly attached to ethynyl carbons) leads to the desired products only in moderate yields. Therefore, iodonium salts should be applied instead of aryl iodides.[42]

As mentioned, the Sonogashira coupling (approach (**1**)) is the most elegant and practical approach to ynones.

Presumably, the reaction follows the usual mechanistic course similar to the proposed mechanism for the coupling of alkynes and aryl halogenides (Scheme 34).[43] Interestingly, although only 1 equiv of the base is required in this process according to the mechanism, triethylamine is the usual solvent for this reaction.[20]

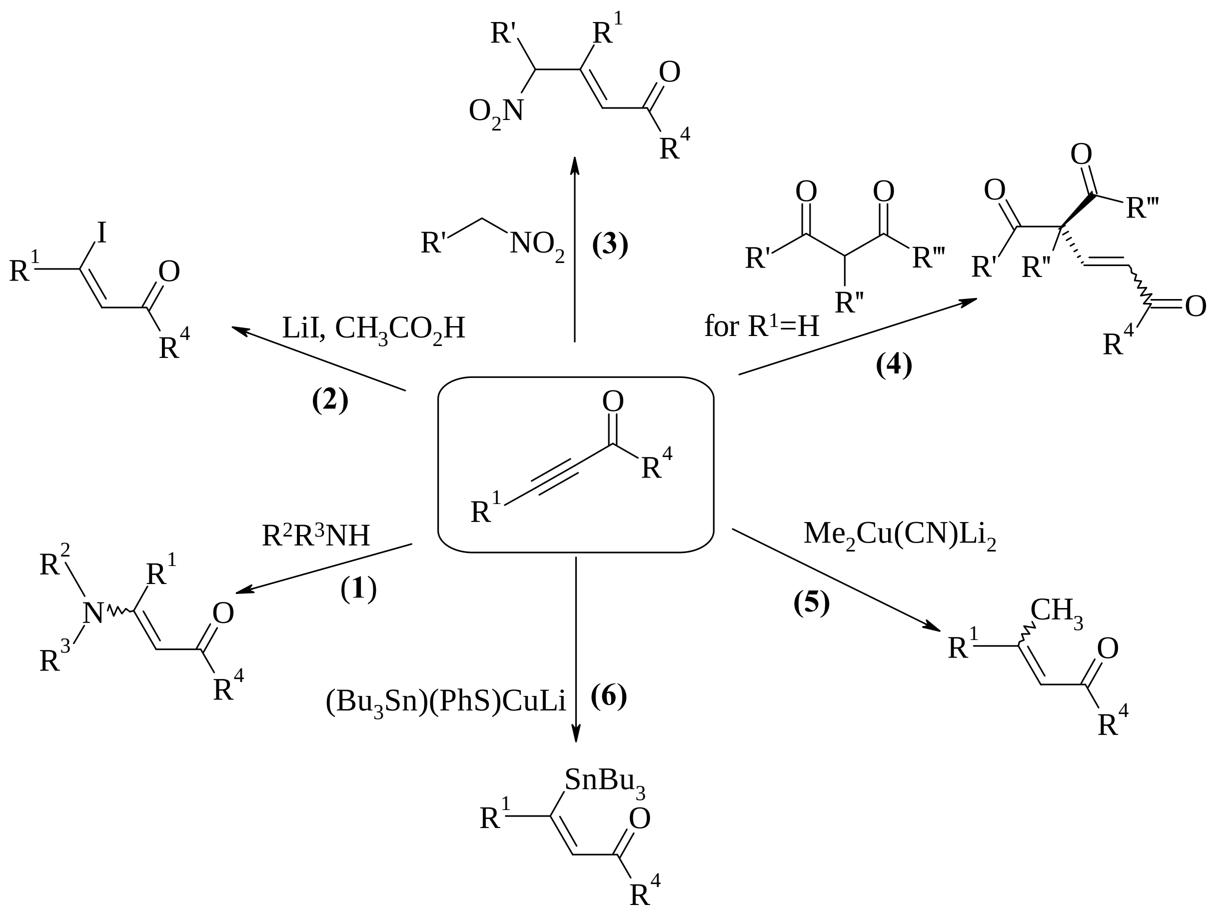


Scheme 34. Catalytic Cycle for Sonogashira Coupling of Alkynes and Acid Chlorides

4.2.1.2 Reactions of Ynones

Ethynyl ketones are useful intermediates in the organic chemistry.[44] Their reactions can be divided into three classes: Michael additions, cyclocondensations and cycloadditions.

Since Michael discovered of the addition of malonate to ynones,[19] numerous types of other nucleophiles have been applied to this reaction (Scheme 35).



Scheme 35. Michael Addition Reactions of Ynones

Nucleophiles can be divided into three main groups: heteronucleophiles, CH-acidic compounds and organometallic reagents.

The most well-known reaction is the addition of primary or secondary amines[45] **(1)**. It was shown that the addition proceeds readily at room temperature for primary and secondary aliphatic amines. The addition of aromatic amines requires heating for several hours.

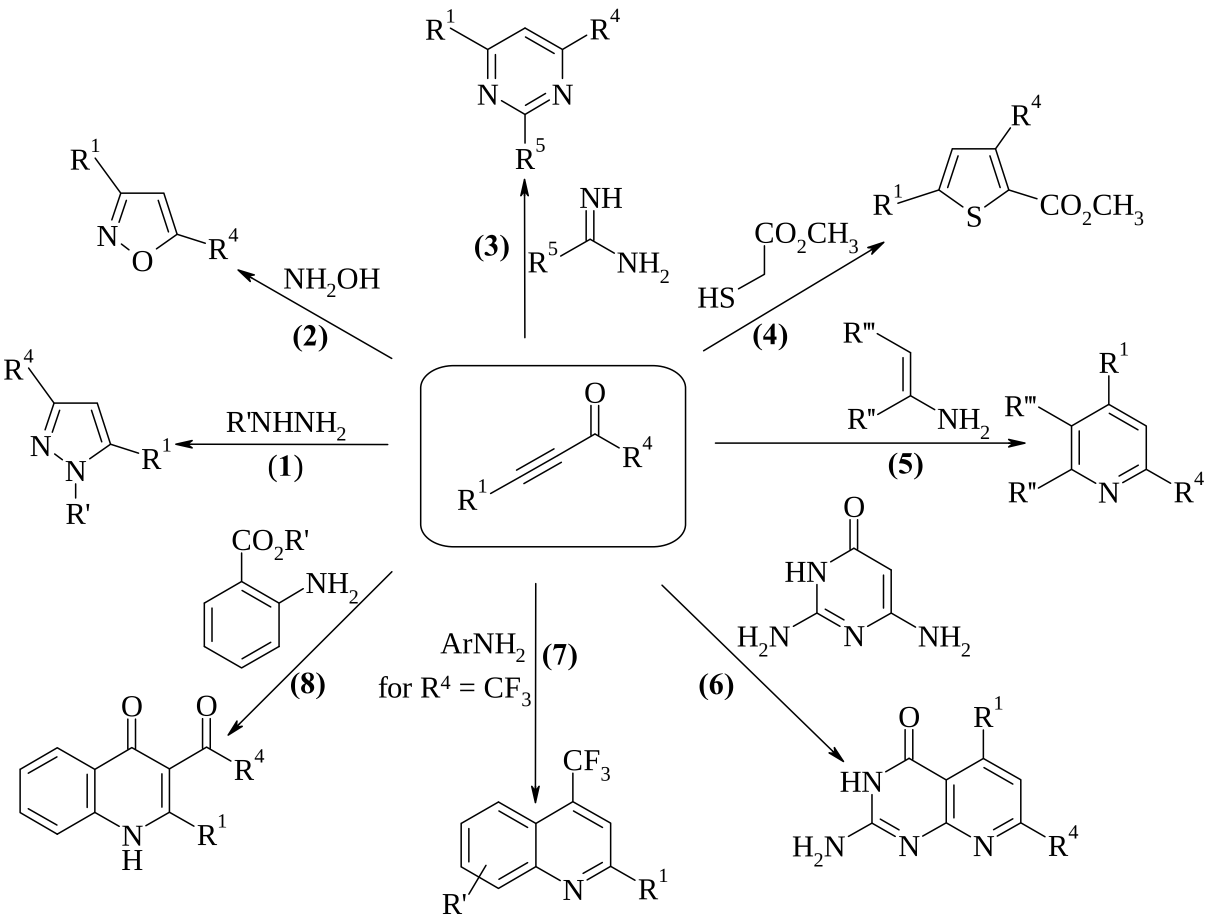
The addition of halides, as the second example of heteronucleophiles, for instance iodide, to the conjugated triple bond **(2)** can be performed either by using of LiI/AcOH or the mixture of TMSCl, NaI and 0.5 equiv of H_2O, giving excellent yield of the *Z*-isomer.[46]

As example of a reaction with CH-acidic compounds, addition of nitroalkanes **(3)** is represented here.[47] The addition of CH-acidic compounds can be achieved even in a stereoselective mode **(4)** catalyzed by cinchona alkaloids.[48] The products of this reaction are a mixture of *E*/*Z*-enones (1:1 – 2:1). The addition of 10 mol % of Bu_3P or I_2 isomerizes the *E*/*Z*-mixture to the more stable (*E*)-isomer.

The addition of cuprates[49] **(5)** or stannylcuprates[50] **(6)** was also demonstrated. Although it is somewhat difficult to control the stereoselectivity of the cuprate addition, it was shown that in the case of stannylcuprates, the *Z*-isomer can be obtained in over 95 % stereoselectivity.

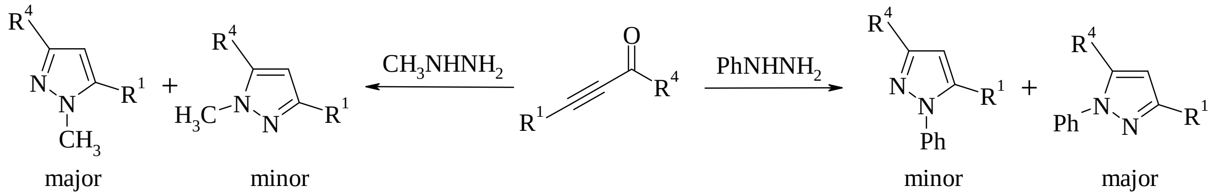
The second type of the ynone reactivity takes advantage of 1,3-electrophicility of these building blocks. The cyclization mode involves the intramolecular addition of a second functional group from the binucleophile molecule to a ketone group, with subsequent protonation of oxygen followed by loss of water.

As a consequence, cyclocondensation reactions of ynones were used in the preparation of a wide range of heterocycles (Scheme 36).



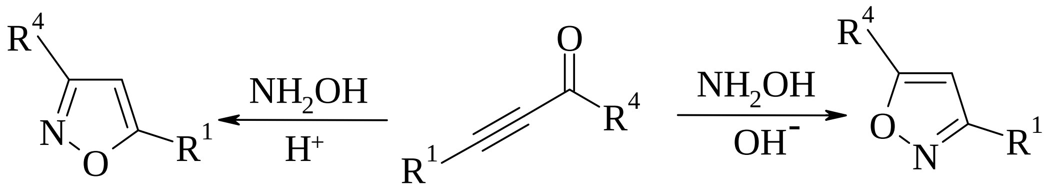
Scheme 36. Cyclocondensation Reactions of Ynones

The reaction of hydrazine derivatives with acetylenic ketones to give pyrazoles **(1)** was discovered a century ago.[51] It was further extended to the synthesis of highly functionalized pyrazoles with different substituents at C3 and C5,[52,53] including amino acid derivatives[54,55] and diacetylenic ketones.[56] The regioselectivity of this reaction in the case of substituted hydrazines was also investigated and it was shown that the ratio of pyrazole isomers can vary from 87:13 to 99:1 in the crude products and can be improved by recrystallization.[57] Interestingly, the structure of the major isomer is dependent on the nature of the hydrazine subjected to the reaction (Scheme 37).



Scheme 37. Regioselectivity of the Pyrazole Formation

Hydroxylamine as the second 1,2-binucleophile can be subjected to the reaction with ethynyl ketones **(2)** providing access to isoxazoles (Scheme 36).[58,59] In this case the regioselectivity of cyclocondensation is dependent on the reaction medium (Scheme 38).



Scheme 38. Regioselectivity of the Isoxazole Formation

This transformation was also extended to amino acids containing isoxazole derivatives.[54]

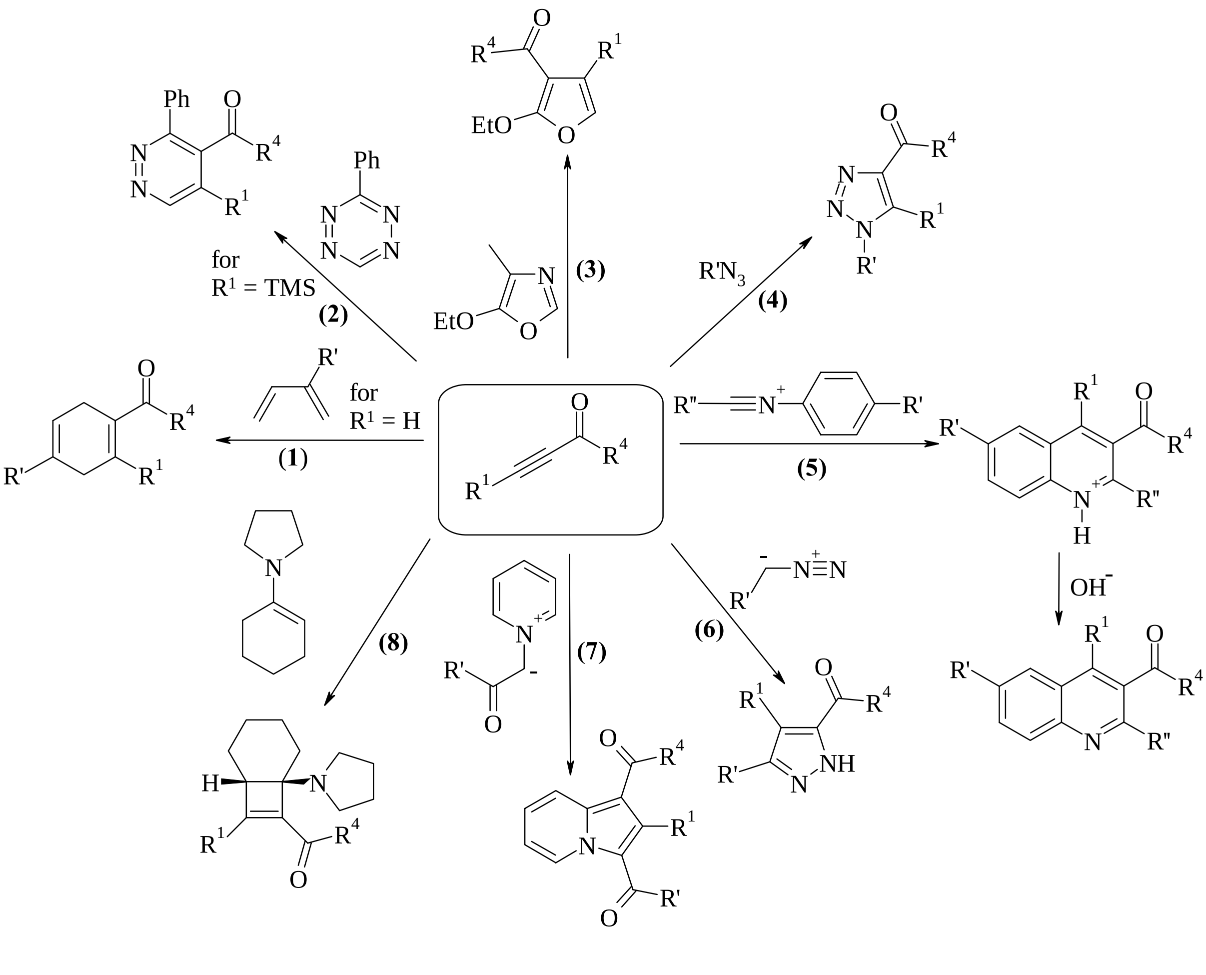
The reaction of ynones with amidinium salts **(3)** results to the formation of pyrimidines (Scheme 36).[58,60] It was further extended to amino acids containing pyrimidine derivatives.[61] This transformation was demonstrated under microwave-assisted conditions[62] or on solid support[63]. Even a one-pot synthesis of pyrimidines via oxidation of propargylic alcohols with subsequent ring closure was recently reported.[64]

A very elegant approach to 2,3,5-trisubstituted thiophenes via Michael addition of methylthioglycolate **(4)** with subsequent intramolecular Knoevenagel condensation was developed (Scheme 36).[65]

The synthesis of pyridines by Michael addition-cyclocondensation with *β*-enamines **(5)** was first reported by Bohlmann and Rahtz in 1957 (Scheme 36).[66] This method, which normally requires high (120-180 °C) temperatures, can be affected using either protic acids[67], Lewis acids[68], *N*-halosuccinimides[69] or under microwave-assisted conditions.[70] This approach was recently applied to the synthesis of amythiamicin cluster.[71] The methodology was further extended to the solid phase combinatorial synthesis.[72] The same procedure using 6-aminouracil as the enamine component leads to the formation of pyrido[2,3-d]pyrimidines **(6)**.[73]

Subjecting CF_3-substituted ynones to a reaction with anilines under acidic conditions **(7)** provides access to quinoline derivatives[74] and finally the reaction of ynones with *ortho*-substituted anilines **(8)** gives rise to quinolinones (Scheme 36).[75] Interestingly, in the latter case, the cyclization mode is different from other examples. Here, the condensation occurs between the anionic carbon alpha to the site of the initial Michael addition and the remaining functional group at the *ortho*-position.

The third mode of ynone reactivity is represented by cycloaddition reactions. Here, once again the reactivity of triple bond is enhanced via electron-withdrawing effect of a neighboring carbonyl group. A survey of the literature reveals that ynones were involved in the Diels-Alder reaction, 1,3-dipolar cycloaddition and even [2+2] cycloaddition (Scheme 39).



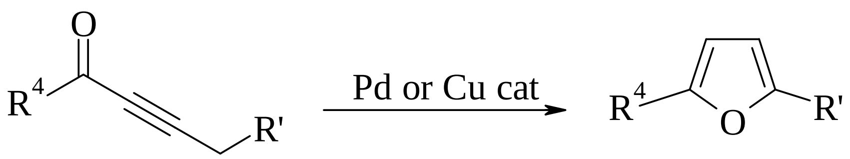
Scheme 39. Cycloaddition Reactions of Ynones

Although unsubstituted (R^1 = H) ynones are reactive **(1)** dienophiles,[76] the reactivity of disubstituted ethynyl ketones is somewhat lower.[77] Therefore, extremely reactive dienes should be applied for the successful [4+2] cycloaddition with ynones. Two tandem Diels-Alder and retro Diels-Alder processes were developed including reaction with 3-phenyl-1,2,4,5-tetrazin **(2)**, which provided access to pyridazines[78] (only for R^1 = TMS) and with 4-methyl-5-ethoxy oxazole **(3)** resulting in the formation of substituted furans, which were subsequently oxidized into butenolides.[79]

1,3-Dipolar cycloadditions proceed more smoothly. As a consequence, phenyl azide[54a] **(4)**, N-arylnitrilium salts[80] **(5)**, diazoalkanes[81] **(6)** and pyridinium salts[82] **(7)** as dipoles were subjected to a reaction with ynones.

As the example of [2+2] cycloaddition, one can only find a reaction with enamines **(8)** resulting in the formation of bicyclic cyclobutenes.[83]

The reactions which differ from these three modes of action are very rare. One of them is the transition metal-catalyzed rearrangement of acetylenic ketones to furans (Scheme 40).



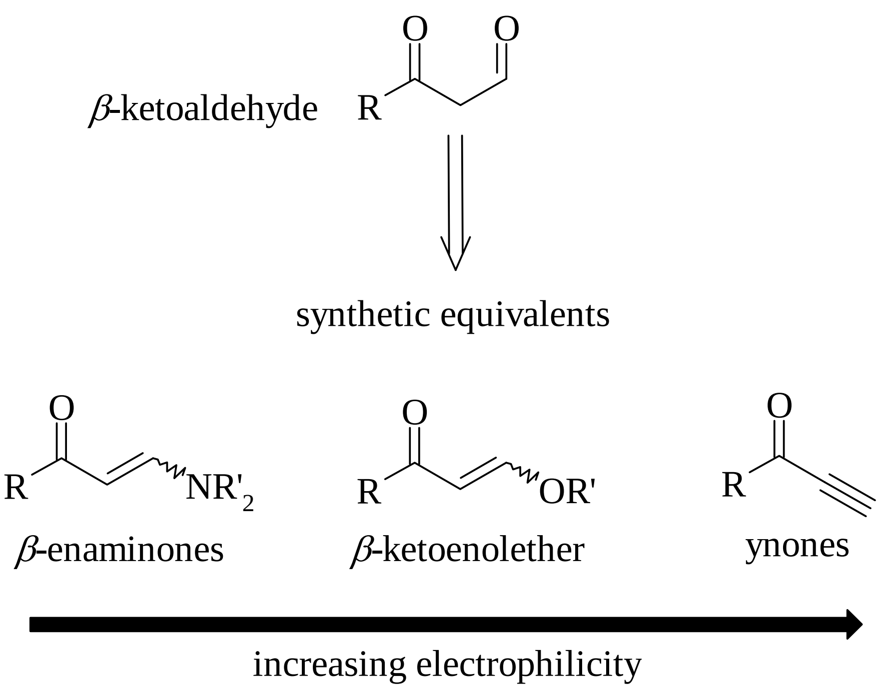
Scheme 40. Palladium-catalyzed Rearrangement of Ynones to Furans

It was shown that this isomerization can be successfully catalyzed by Pd-complexes[84] or simply in the presence of CuI.[85] In general, rather high temperatures (100-130 °C) were required for this transformation.

4.2.2 Synthesis of (TMS)-ynones via Sonogashira Coupling and Subsequent One-pot Transformations

On account of the enormous synthetic potential of ynones I decided to generate these compounds via Sonogashira coupling. This is the most elegant and atom-economical method of synthesis, and I subjected them directly, without isolation in a one-pot fashion to reactions with mono- and binucleophiles.

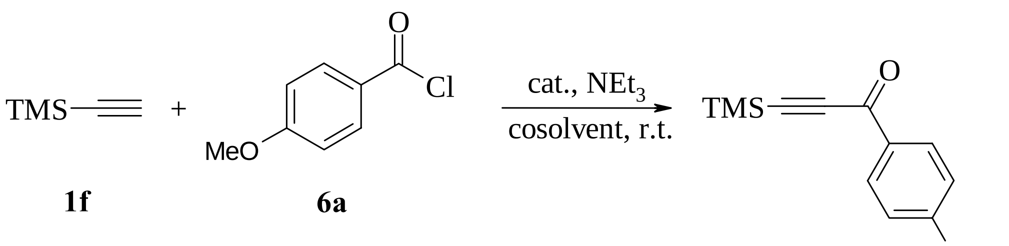
Before starting with one-pot transformations I needed to modify the original Sonogashira conditions, i.e. the use of triethylamine as the solvent.[20] Indeed these conditions have significant drawbacks. Triethylamine is definitely not the best solvent, for instance, if subsequent Brönsted or Lewis acid catalyzed reactions are considered. Additionally, these conditions do not tolerate the trimethylsilyl group. This restricts significantly the scope of the reaction, since (TMS)-ynones are very important synthetic equivalents of *β*-keto aldehydes,[86] which in their own turn are well-established three-carbon (C_3) building blocks in heterocyclic chemistry.[87] The other synthetic equivalents of *β*-keto aldehydes such as *β*-keto acetals, *β*-keto enolethers or *β*-enaminones provide a broader scope for regiocontrol in cyclocondensations. The common way to *β*-keto acetals, *β*-keto enolethers and *β*-enaminones is a Michael addition of alcohols or amines to ynones, which are even more electrophilic than all other synthetic equivalents of *β*-keto aldehydes (Scheme 41).



Scheme 41. Synthetic Equivalents of *β*-Ketoaldehydes

A limitation of unsubstituted ynones, however, is their high electrophilicity that makes them somewhat unstable. On the other hand, (TMS)-ynones are significantly more stable than the parent ynones. It was also desirable to extend Sonogashira coupling to the synthesis of this extremely important class of ynones.

First, I wanted to scout the conditions for the hitherto unknown coupling between acid chlorides and (TMS)-acetylene. I chose as model reaction partners *p*-methoxybenzoyl chloride (**6a**) and (TMS)-acetylene (**1f**) at room temperature with various catalyst combinations and amounts of triethylamine as a base (Scheme 42).



1f **6a** **7a**

Scheme 42. Coupling of *p*-Methoxybenzoyl chloride and (TMS)-acetylene

Neither the classical conditions (entry 1)[20] nor the copper-catalyzed variation (entry 2)[25], where triethylamine is applied as a solvent, gave rise to the isolation of the (TMS)-ynones **7a** (Table 5).

Table 5. Optimization of Conditions for the Coupling of *p*-Methoxybenzoyl chloride (6a) and (TMS)-acetylene (1f)[a]

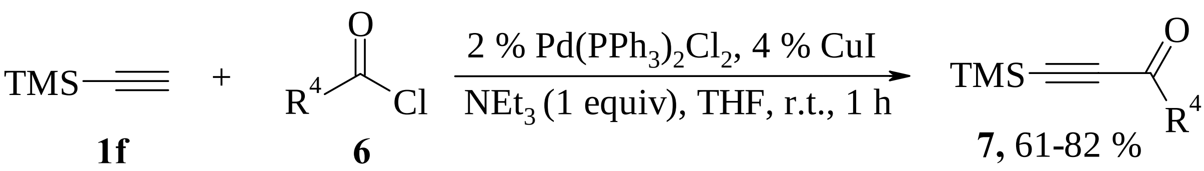
Entry	Catalyst[a]	Amount of NEt_3	Cosolvent	Time, h[b]	Yield of **7a**, %[c]
1	Pd/Cu	as a solvent	none	1	0
2	Cu	as a solvent	none	24	0
3	Pd/Cu	1.25 equiv	THF	48	22
4	Pd/Cu	1.00 equiv	THF	1	82
5	Pd	1.00 equiv	THF	48	79

[a] Reaction conditions: 1.0 equiv of *p*-methoxybenzoyl chloride (**6a**) and 1.0 equiv of (TMS)-acetylene (**1f**), 0.02 equiv of $(Ph_3P)_2PdCl_2$, and/or 0.04 equiv of CuI, various amount of NEt_3, and THF (5mL/mmol acid chloride).

[b] Consumption of (TMS)-acetylene (**1f**) was monitored by TLC, and the reaction was stopped after complete conversion. [c] Yields refer to isolated yields of compound (**7a**) after chromatography estimated to be >95% pure as determined by NMR spectroscopy.

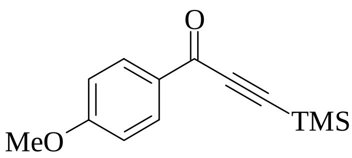
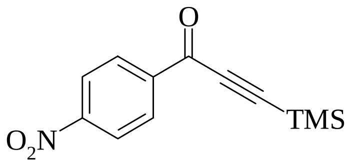
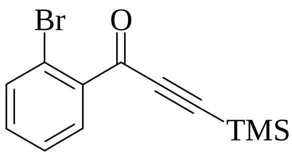
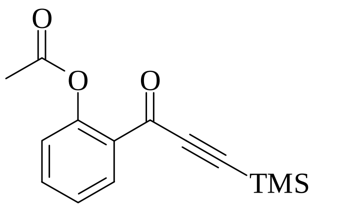
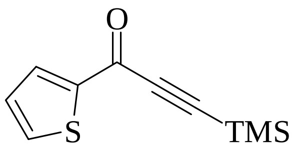
However, reducing the amount of triethylamine to one stoichiometrically necessary equivalent allowed the isolation of (TMS)-ynone **7a** in good yield. Surprisingly, the reaction proceeds so quickly that both starting materials are completely consumed after 1 h (entry 4) and prolonging the reaction time with only a slight excess of triethylamine causes a significant decrease in the yield (entry 3). The decrease in yield can be explained by feasibility of a cleavage of ethynyl-silicon bonds under basic conditions. An EWG (carbonyl group in our case) attached to a triple bond should even enhance the reactivity of this bond towards base. It was shown that the aryl (TMS)-ynones are cleaved by extremely weak bases such as dilute borax.[30] It means that in the presence of excess of triethylamine, the cleavage of TMS-group in (TMS)-ynone occurs facilitating numerous side reactions. Therefore, the key to the successful preparation of (TMS)-ynones **7** is the addition of only 1 equiv of triethylamine as the HCl-scavenging base. In accordance with Sonogashira couplings, the absence of the copper cocatalyst leads to the significant prolonging of the reaction time (entry 5).

Applying these peculiar conditions to a variety of (hetero)-aroyl chlorides **6**, the corresponding (TMS)-ynones **7** were obtained in moderate to good yields (Scheme 43, Table 6).



Scheme 43. Synthesis of (TMS)-ynones 7 by Sonogashira Coupling

Table 6. Synthesis of (TMS)-ynones by Sonogashira Coupling and Comparison with Literature Known Approaches

Entry	Acid chloride **6**	(TMS)-ynone **7** (Yield %)	Literature route (Yield %)
1	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	 **7a** (82 %)	Stille coupling[52] (70 %)[a]
2	R^4 = *p*-$NO_2C_6H_4$ (**6b**)	 **7b** (65 %)	Stille coupling[27] (51 %) $AlCl_3$-catalyzed acylation (43 %[29] or 93 %[30])
3	R^4 = *o*-BrC_6H_4 (**6c**)	 **7c** (61 %)	Stille coupling[21] (45 %)
4	R^4 = *o*-$CH_3C(O)OC_6H_4$ (**6d**)	 **7d** (61 %)	
5	R^4 = 2-thienyl (**6e**)	 **7e** (82 %)	

[a] After desilylation step.

It is noteworthy that the yields of this modified Sonogashira coupling are considerably higher than those of comparable Stille couplings (entries 1-3). Although the $AlCl_3$-catalyzed acylation of bis(trimethylsilyl) acetylene provides (TMS)-ynone in higher yield than by our approach in particular case (entry 2), it still remains unexplored for more heavily functionalized such as **6d** acid chlorides. In contrast to the Weinreb approach, sensitive or fragile functionalities such as nitro, bromo, or acetoxy substituents are tolerated.

Spectroscopic data

The structures of the (TMS)-ynones are unambiguously supported by the appearance of the characteristic singlets for the TMS-methyl proton resonances between δ 0.1 and 0.3 in the proton NMR spectra. In the aliphatic region in the case of *p*-methoxyphenyl substituted ynone **7a** a singlet with an intensity of three protons at δ 3.89 was assigned as the methoxy group. For the (TMS)-ynone **7d**, the methyl protons of acetoxy group appear at δ 2.36. The shifts of aromatic protons can be easily calculated according to the empirical increment rule ($\delta = 7.26 + \Sigma I$).[13] For example, for *p*-methoxyphenyl substituted ynone **7a** the increments of methoxy group I_{ortho} = -0.48 and I_{meta} = -0.09; the increments of carbonyl group I_{ortho} = 0.62 and I_{meta} = 0.14. The resonance of protons, calculated according to this rule, *ortho* to methoxy group δ 6.92 and *ortho* to carbonyl group δ 7.79. Indeed in ^{1}H NMR aromatic protons were detected as a couple of doublets at δ 6.96 and 8.12 with a coupling constant of J = 8.9 Hz. The thienyl core (compound **7e**) was identified as three doublets of doublets at δ 6.93 (4-H) with ^3J = 4.9 Hz and ^3J = 3.7 Hz; δ 7.48 (5-H) with ^3J = 4.9 Hz and ^4J = 1.2 Hz and δ 7.69 (3-H) with ^3J = 3.7 Hz and ^4J = 1.2 Hz (Fig. 11).

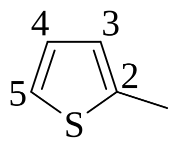
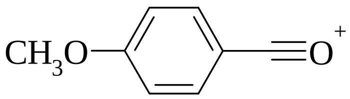
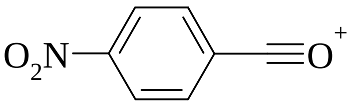
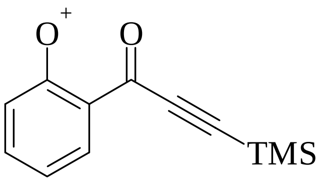
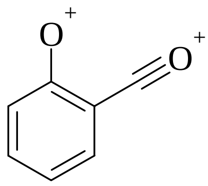


Fig. 11. The Numeration of the Thienyl Substituent

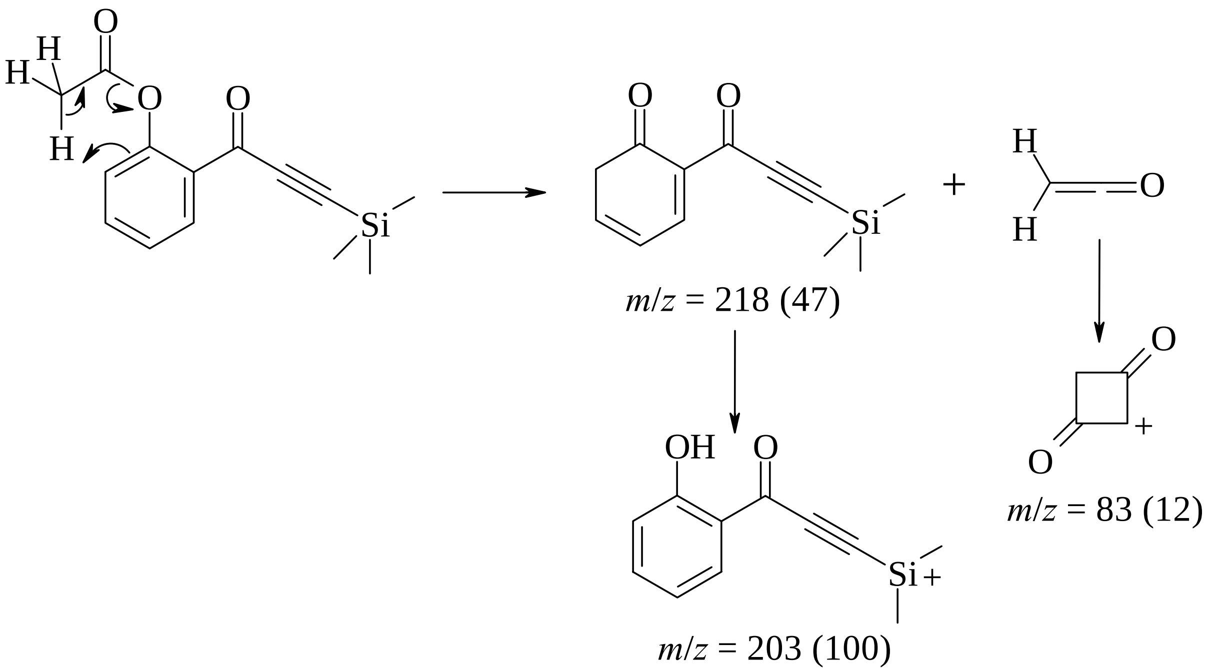
In the ^{13}C NMR spectra, the carbon resonances of the TMS-methyl group appear between δ -1.0 and -0.7, the signals of the quaternary carbon nuclei of the triple bonds were found at δ 98.8-101.5 (C_α) and δ 100.2-103.5 (C_β). The signals of the carbonyl groups lie between δ 169 and 177. For the (TMS)-ynone **7a** and **7d**, the methyl carbons of methoxy and acetoxy groups were detected at δ 55.5 and 20.8 respectively.

The mass spectra of all the obtained compounds show the molecular peaks, although often with a rather low intensity. A subsequent fragmentation leads usually to the loss of a methyl group at the Si atom. The fragment with m/z = 73 that corresponds to Me_3Si group can be also found in the mass spectra of almost all the (TMS)-ynones. Characteristically, for ketone derivatives is a α-fragmentation at the carbonyl group, leading to appearing of R^4CO^+ peaks in the mass spectra (Table 7).

Table 7. The Fragmentation of Selected (TMS)-ynones 7 (EI, 70 eV)

Compound	Fragment	*m/z* (%)	Fragment	*m/z* (%)
7a		135 (56)		
7b		150 (8)		
7d		217 (37)		120 (12)

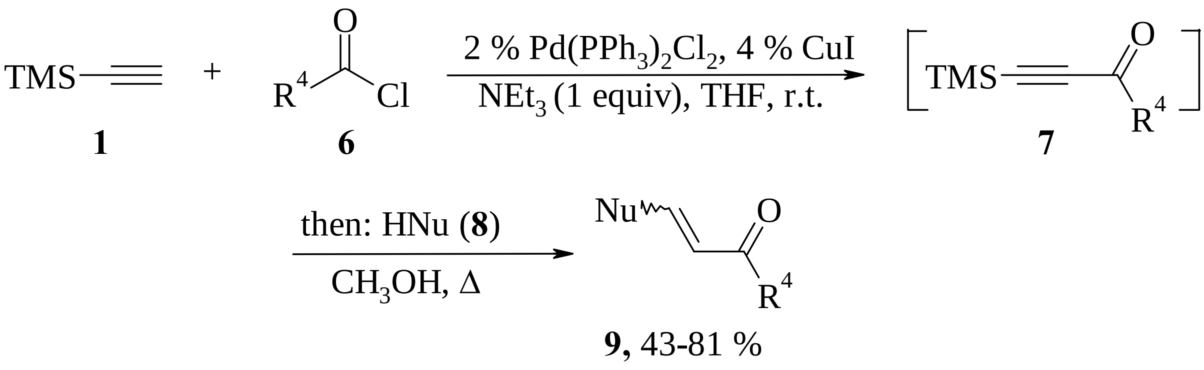
The fragmentation of ynone **7d** starts with the elimination of a ketene, which dimerizes to a diketene *m/z* = 83 (12). The second fragment of a ketene elimination is a phenol with *m/z* = 218 (47). The loss of one of a methyl group at Si results in the formation of a peak with the highest intensity *m/z* = 203 (100) (Scheme 44).



Scheme 44. Fragmentation Pathways of (TMS)-ynone 7d

Absorptions at 2153 cm^{-1}, 1772 cm^{-1} and 1646 cm^{-1} in the IR spectrum of the (TMS)-ynone **7d** clearly display the presence of a triple bond, an ester group and a keto group.

With this convenient catalytic access to (TMS)-ynones **7** in hand and reconsidering the mild reaction conditions, I next decided to test consecutive one-pot transformations of **7** into coupling-addition products **9** by a reaction with nucleophiles **8** (Scheme 45, Table 8).

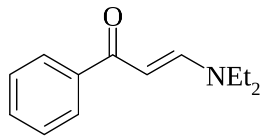
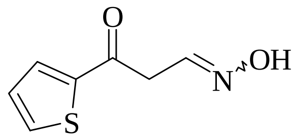
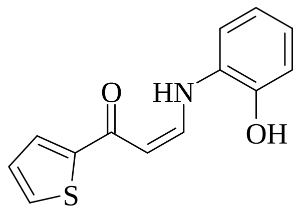
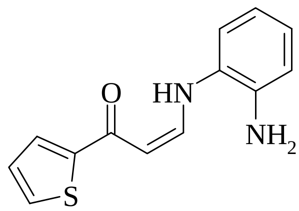
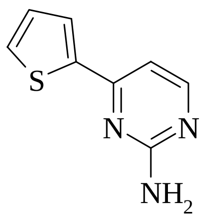


Scheme 45. One-pot Coupling-Addition Sequence

After the complete conversion of the acid chloride **6**, equimolar amounts of nitrogen mono- and bidentate nucleophiles (HNu) such as diethylamine, hydroxylamine hydrochloride/ sodium carbonate, *o*-amino phenol, *o*-phenylene diamine, or guanidine hydrochloride/ sodium carbonate were added in a small amount of methanol to the reaction mixture to furnish, after boiling for a short period of time, the *β*-enaminones **11a**, **9b**, **9c**, the *β*-ketoxime **9a** or pyrimidine **12a** in moderate to good yields.

As expected, these nucleophilic additions proceed with the concomitant loss of the trimethylsilyl group.[36] Although in the literature there is one report about the transformation of ynones to benzodiazepine and benzothiazepine in acetic acid,[88] under the chosen mild reaction conditions, no cyclocondensations occurred with the applied bidentate nucleophiles.[89] Interestingly, a survey of the literature reveals that the reaction of ynones with hydroxylamine to get an access to isoxazoles is also usually carried out under acidic conditions.[59] Under basic conditions, the desired isoxazole was isolated only in 13 % yield.[55] There was no report about the formation of a *β*-ketoxime in such a transformation (entry 2). Only upon addition of guanidinium salt (entry 5), as the bidentate nucleophile, with 2.5-3 equiv of sodium carbonate decahydrate to the (TMS)-ynone **7** in a one-pot process (entry 5), was the aminopyrimidine **12a** obtained in moderate yield.

Table 8. One-pot Coupling-Addition Sequence

Entry	Acid chloride **6**	Nucleophile	Product (Yield %)
1	R^4 = Ph (**6f**)	diethylamine (**4b**)	 **11a** (74 %)
2	R^4 = 2-thienyl (**6e**)	hydroxylamine hydrochloride (**8a**) and $Na_2CO_3 \cdot 10H_2O$	 **9a** (80 %, *E*/*Z* = 1:6)
3	**6e**	*o*-amino phenol (**8b**)	 **9b** (61 %)
4	**6e**	*o*-phenylene diamine (**8c**)	 **9c** (43 %, 2:1 ratio of tautomers)
5	**6e**	guanidine hydrochloride (**10a**) and $Na_2CO_3 \cdot 10H_2O$	 **12a** (51 %)

Spectroscopic data

The structure of the *β*-enaminone **11a** is unambiguously supported by the appearance of two characteristic doublets in the olefinic region at *δ* 5.74 and 7.79 in the proton NMR spectrum. The *trans*-stereochemistry of the double bond follows from the coupling constant J = 12.5 Hz as well as from the NOESY experiment. The structures of *β*-enaminones **9b** and **9c** are unambiguously supported by the appearance of two characteristic doublets in the olefinic region at *δ* 6.00 and 7.38 (for **9b**) and at *δ* 6.01 (for **9c**, the resonance of the second doublet was overlapped with protons of the aromatic ring) in the proton NMR spectrum. The *cis*-stereochemistry of the double bond follows from the coupling constants J = 7.7 Hz (for **9b**) and J = 7.9 Hz (for **9c**) as well as from the NOESY experiments. The formation of the *cis*-isomers can be explained by intramolecular hydrogen bonding. The ^{1}H NMR spectrum of **9b**, showed after D_2O exchange that resonances at *δ* 10.04 and 11.80 completely disappeared allowing their assignment as OH and NH groups. The ^{1}H NMR spectrum of **9c**, revealed after D_2O exchange that signals at *δ* 4.82 (with an intensity of two protons) and 11.62 completely disappeared that allows their assignment as NH_2 and NH groups. The structure of the *β*-ketoxime **9a** is unambiguously supported by the appearance of the characteristic A_2X pattern in the ^{1}H NMR spectrum as a triplet and a doublet at *δ* 4.00 (the protons of a CH_2 group, an intensity of two protons) and 6.98 (the proton of a CH group in the oxime) with a coupling constant of J = 5.3 Hz. The D_2O exchange displayed a disappearance of a singlet at *δ* 11.20 which can be assigned as the OH group. The predominant formation of the *E*-isomer clearly follows from the 2D-NOESY experiment, which shows the cross-peak between protons of OH and CH groups for the minor isomer (Fig. 12).

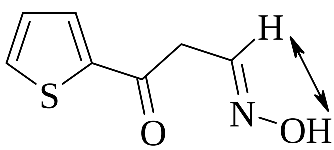


Fig. 12. The Confirmation of the Structure for the Minor Isomer of 9a by 2D NOESY

Interestingly, for all the compounds (**9a-9c**) the downfield shift of the signals of OH group (*δ* 11.20, **9a**) or NH groups (*δ* 11.80 for **9b** and *δ* 11.62 **9c**) was detected. This fact strongly points to the formation of an intramolecular hydrogen bond, which is characteristic for the *cis* configuration of a double bond (compounds **9b** and **9c**).

The formation of pyrimidyl core in **12a** is strongly supported by the appearance of the characteristic AX-spin patterns in the ^1H NMR spectrum at δ 7.07 (5-H) and 8.25 (6-H) with a coupling constant of J = 5.2 Hz (Fig. 13).

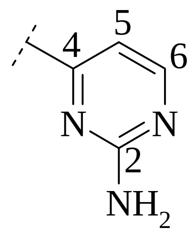


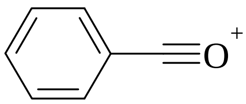
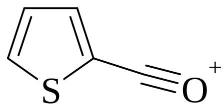
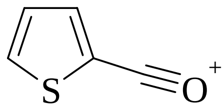
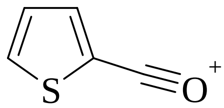
Fig. 13. The Numeration of the Pyrimidyl Substituent

The amino group was detected as a singlet at δ 6.67 with an intensity of two protons. The thienyl core (compound **12a**) was assigned as three doublets of doublets at δ 7.19 (4-H) with coupling constants ^3J = 4.9 Hz and ^3J = 3.7 Hz; δ 7.73 (5-H) with coupling constants ^3J = 4.9 Hz and ^4J = 1.2 Hz and δ 7.89 (3-H) with coupling constants ^3J = 3.7 Hz and ^4J = 1.2 Hz.

In the ^{13}C NMR spectra of compounds **11a** and **9a-9c**, the carbon resonances of the carbonyl groups lie between δ 182 and 189. The sp^2-hybridized enamine β-methine carbon atoms (**11a**, **9b** and **9c**) can be easily identified at low field between δ 93.0 and 96.1. The ^{13}C NMR spectrum of the β-ketoxime **9a** shows the presence of the CH_2 group at δ 35.4.

The mass spectra of all the obtained compounds display the molecular peaks. Characteristically for ketone derivatives is the α-fragmentation at the carbonyl group, leading to appearing of R^4CO^+ peaks in the mass spectra (Table 9).

Table 9. The Fragmentation of Selected Coupling-addition Products (EI, 70 eV)

Compound	Fragment	*m/z* (%)
11a		105 (100)
9a		111 (100)
9b		111 (33)
9c		111 (17)

The vibrations of carbonyl groups (compounds **11a**, **9a**-**9c**) appear in a wide region of 1654-1622 cm^{-1} in the IR spectra. The absorption of a highly polarized double bond in the IR spectra of aminovinyl ketone **11a** was identified at 1582 cm^{-1}. Additionally, absorptions at 3420-2861 cm^{-1} (**9c**); 3423 cm^{-1} (**9b**); 3390 and 3339 cm^{-1} (**9c**), indicate the presence of amino and hydroxy groups. Due to the mixture of possible isomers and tautomers, inter- and intramolecular hydrogen bondings it is rather difficult to assign them unambiguously.

4.2.3 One-pot Synthesis of *β*-Enaminones and Pyrimidines by Coupling-Addition-Cyclocondensation Sequences

In the previous chapters it was shown that Sonogashira coupling is the most elegant and atom-economic way of transforming acid chlorides into ynones. In turn, the resulting ynones are highly reactive Michael acceptors that readily react with all kinds of mono- and bidentate nucleophiles. We discovered that adding only one equivalent of triethylamine as the hydrochloric acid scavenging base, proves to be most favourable, in particular, for the successful coupling of TMSA. The intermediate (TMS)-ynones were subjected directly without isolation in a one-pot sense to the reaction with amines and guanidine providing access to *β*-enaminones and pyrimidines. It was obvious to extend the one-pot coupling-addition-cyclocondensation concept to other alkynes and to explore the scope and limitations of this approach.

4.2.3.1 *β*-Enaminones – Literature Review

β-Enaminones are polyfunctional compounds possessing both electrophilic and nucleophilic properties.[90] Typical electrophilic positions are C-3 (alkylamino methylene group) and C-1 (the carbonyl group). Due to this type of the reactivity they are well-established, three-carbon building blocks in heterocyclic chemistry.[91] In this sense *β*-enaminones are C_3 synthons of 1,3-dicarbonyl compounds. Since ynones represent the other type of C_3 synthons, and their reactivity in cyclocondensation reactions was already discussed in the previous chapters (Scheme 36) only additional transformations that are typical exclusively for *β*-enaminones will be illustrated here. Secondly, *β*-enaminones exhibit enamine character towards electrophiles, with a nucleophilic position at C-2 (Fig. 14).

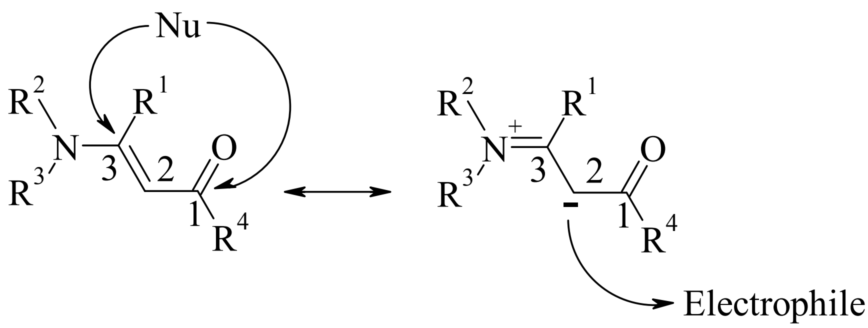
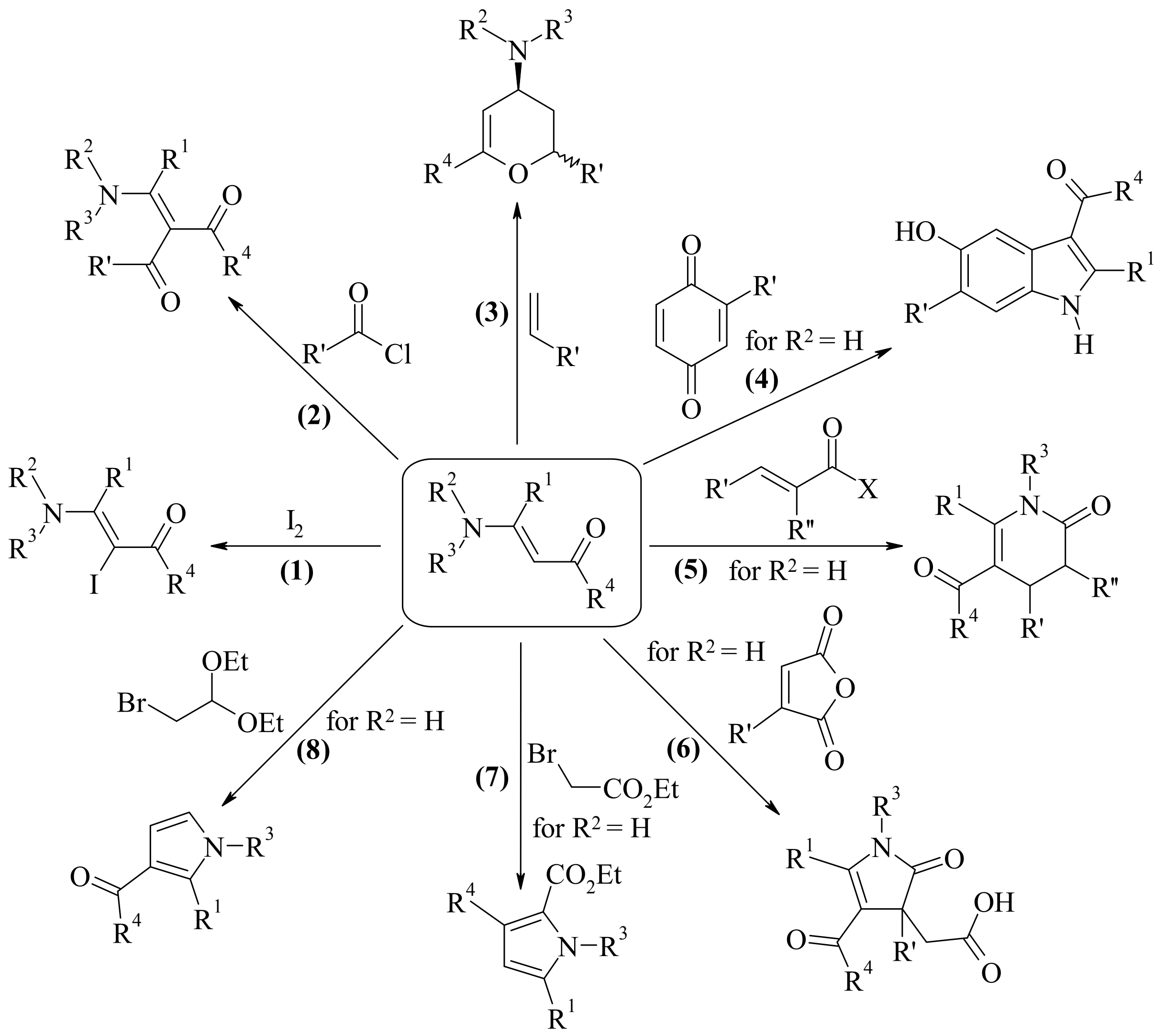


Fig. 14. Reactivity of *β*-Enaminones

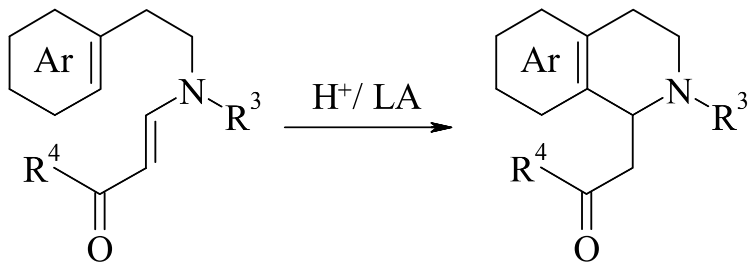
Some of the interesting synthetic transformations of β-enaminones are delineated at Scheme 46.



Scheme 46. Synthetic Transformations of *β*-Enaminones

It is clearly seen from this scheme, that the most of the applications of β-enaminones were developed for the β-enaminones derived from the primary amines (R^2 = H). Except for iodination **(1)**[92], reactions with acid chlorides **(2)**[93] and hetero Diels-Alder reactions **(3)**[94] in all cases the monosubstituted nitrogen is required for the successful consecutive transformations. The reaction **(4)** between β-enaminones and *p*-benzoquinones is known in the literature as the Nenitzescu synthesis of 5-hydroxyindoles.[95] It has generally been thought to proceed via Michael addition of enaminones, followed by several steps including an internal oxidation-reduction.[96] The treatment of β-enaminones with α,β-unsaturated acid derivatives provides access to a lactam system **(5)**. This type of transformation, which is believed to proceed via initial Michael addition of the enamine to an *α,β*-unsaturated acid derivative followed by an intramolecular *N*-acylation is known as the aza-annulation reaction.[97,98,99,100] In a similar way, the reaction of *β*-enaminones proceeds with maleic or citraconic anhydride **(6)**.[101] The [3+2] cyclocondensation with 1,2-electrophilic species, such as ethyl bromoacetate **(7)** or bromoacetaldehyde diethylacetal **(8)** leads to pyrrol derivatives.[101]

Finally, functionalized 1,2,3,4-tetrahydro-*β*-carbolines[102] and 1,2,3,4-tetrahydroisoquinolines[103] can be synthesized via a Pictet-Spengler reaction starting from the *β*-enaminones containing (hetero)arylethyl substituents tethered to the nitrogen (Scheme 47).



Scheme 47. Pictet-Spengler Reaction of *β*-Enaminones

Apart from their enormous synthetic potential, *β*-enaminones in their own right are highly pharmacologically active and reveal a pronounced anticonvulsant activity.[104] It was shown that these compounds cause their anticonvulsant properties by binding to the voltage-dependent sodium channel. Two, among 103 tested *β*-enaminones, showed the biological activity in the µM range (Fig. 15).

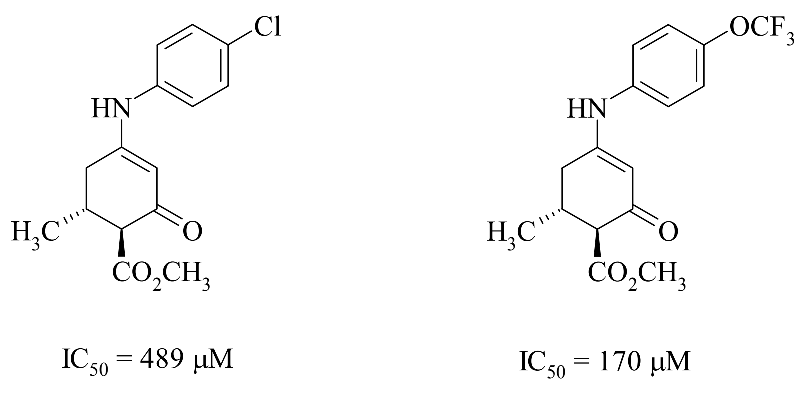
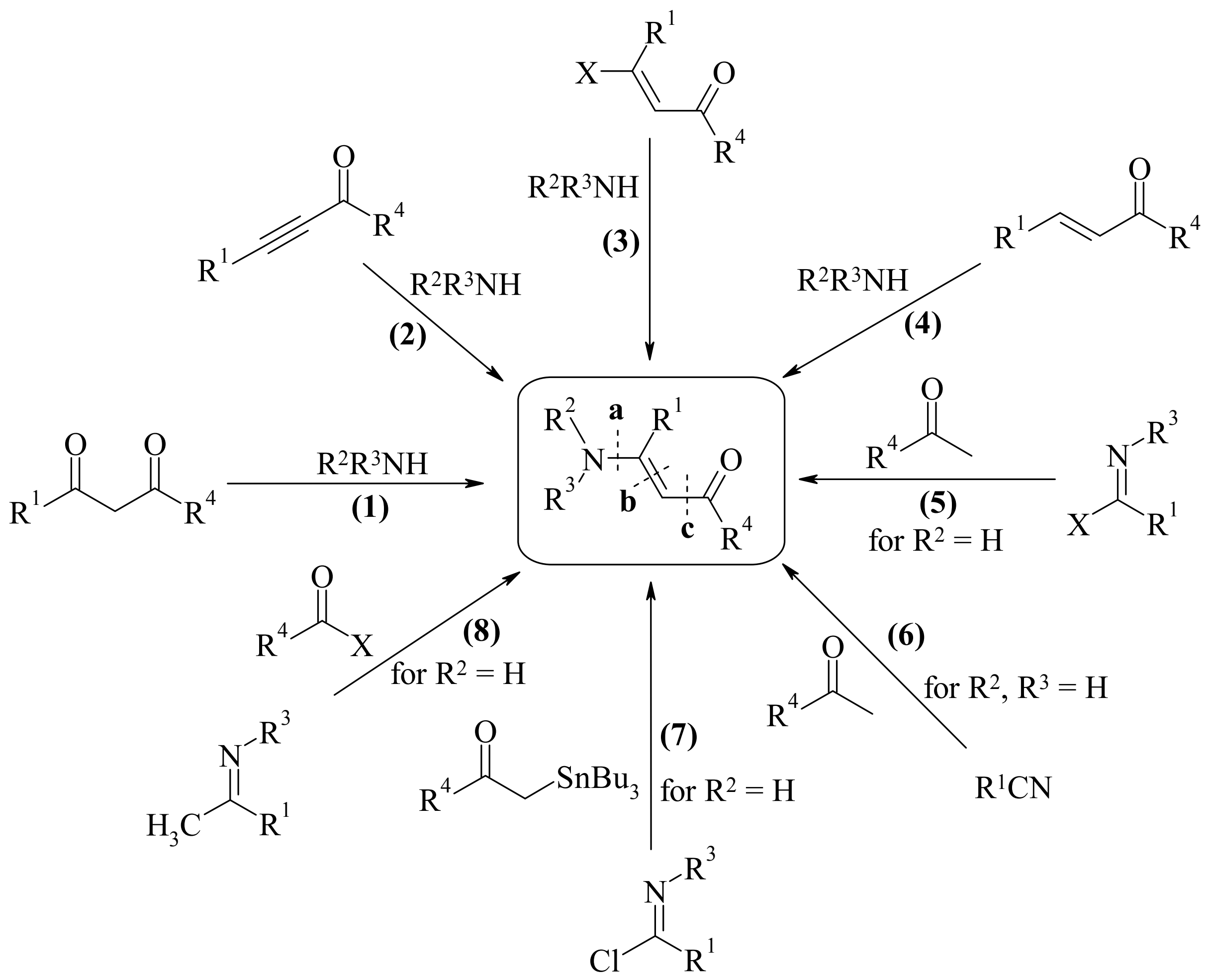


Fig. 15. Selected Potential Anticonvulsants

The literature methods for the synthesis of β-enaminones can be classified according to the bond which was formed (Scheme 48).[105]

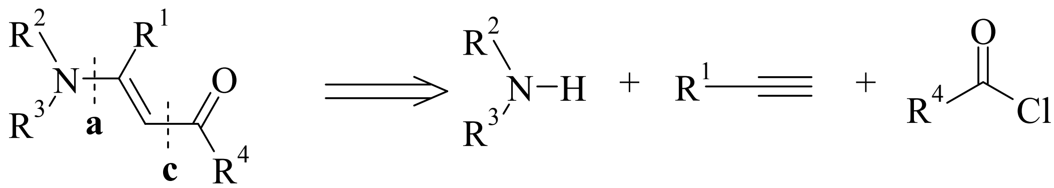


Scheme 48. Synthesis of β-Enaminones

Four approaches were used to form bond **a**: condensation of 1,3-diketones with amines in the presence of catalysts, such as $Zn(ClO_4)_2 \cdot 6\ H_2O$[106] or $CeCl_3 \cdot 7\ H_2O$/TBAB[107] **(1)**; addition of amines to ynones[45] **(2)**; substitution of β-functional group, such as alkylthio,[108] imidazolyl[109] or methoxy[110] **(3)**; and Pd-catalyzed amination of α,β-unsaturated ketones[111] **(4)**. For the synthesis of β-enaminones via bond **b** there are three approaches: the reaction of imidoyl chlorides[112] or imidoylbenzotriazoles[105] with enolates **(5)**; the reaction of nitriles with ketones[113] **(6)**; the reaction of imidoyl chlorides with acetonyltributyltin[114] **(7)** and the only route to the formation of β-enaminones via bond **c**: the reaction between imine anions and esters[115] or acylbenzotriazoles[116] **(8)**. The comparison of advantages and disadvantages for these methods was described in detail and it was mentioned that “formation of β-enaminones via bond **a** shows limited convergence since the enaminones carbon skeleton is part of the starting material".[105] On the other hand it is worth emphasizing that all the other approaches are only designed for the synthesis of enaminones derived from the primary amines (R^2 = H).

4.2.3.2 Synthesis of *β*-Enaminones via Coupling-Addition Sequence

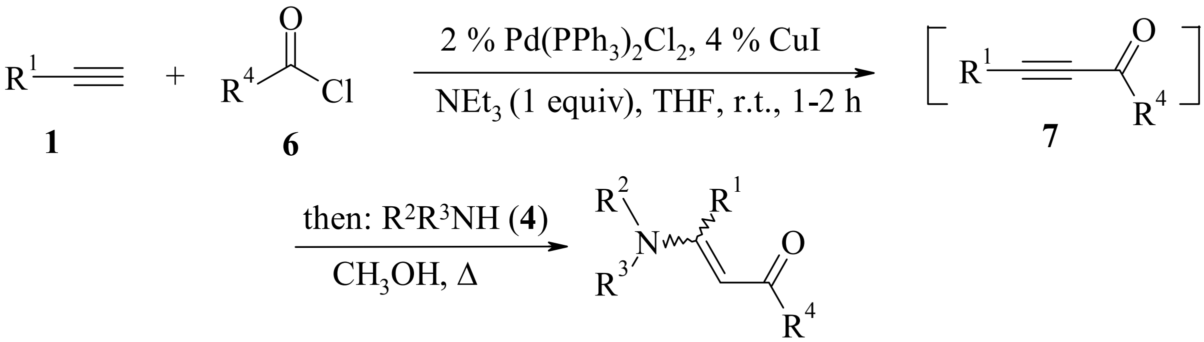
The addition of primary and secondary amines to ynones, giving rise to *β*-enaminones is a well-established reaction.[45] On the other hand this method has scarcely been used for the targeted synthesis of these compounds mostly due to the lack of a reasonable protocol for the synthesis of the starting materials. The situation changed when Sonogashira found that acid chlorides can be coupled with alkynes in the presence of Pd and Cu salts as catalysts.[20] I discovered extremely mild conditions for Sonogashira coupling, applying only one equivalent of triethylamine as a base, and found that intermediate ynones can be subjected directly without isolation in a one-pot fashion to the reaction with different nucleophiles. The retrosynthetic scheme for the synthesis of *β*-enaminones via a coupling-addition sequence provides acid chlorides, alkynes and amines as the readily available starting materials (Scheme 49).



Scheme 49. Retrosynthetic Analysis of *β*-Enaminones

This approach represents a diverse synthetic method of *β*-enaminones by cutting two bonds at the same time. I reasoned that this route can be useful for the preparation of unsymmetrical *β*-enaminones with a highly flexible substitution pattern.

Therefore, in the sense of a consecutive three-component one-pot reaction, after reacting various terminal alkynes **1** with acid chlorides **6** under modified Sonogashira conditions for 1-2 h at r.t. to produce the expected ynones **7**, methanolic solutions of primary and secondary amines **4** were subsequently added. The heating of the resulting mixture for several hours furnished *β*-enaminones **11** in good to excellent yields and depending on the amines (primary amines gave rise to *Z*-isomer (R^2 = H) and secondary amines resulted in formation of *E*-isomer ($R^2 \neq$ H)) in good *E*/*Z*-selectivity (Scheme 50, Table 10).



11, 69-99 %

Scheme 50. Three-component One-pot Synthesis of *β*-Enaminones 11

Table 10. Three-component One-pot Synthesis of *β*-Enaminones 11

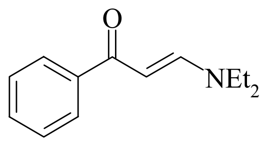
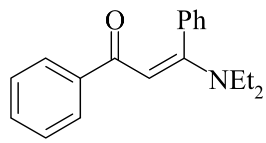
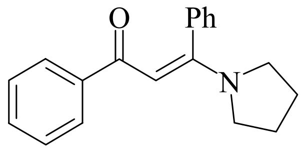
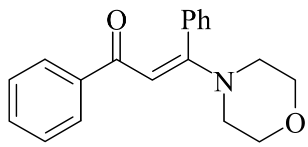
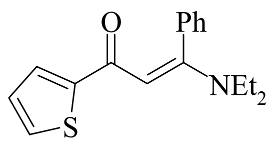
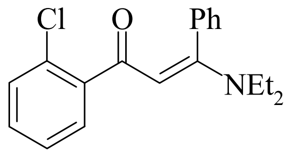
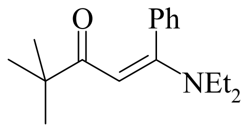
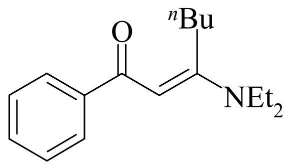
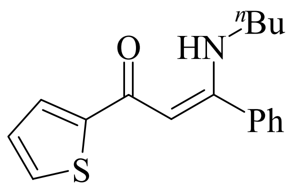
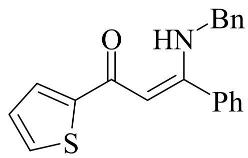
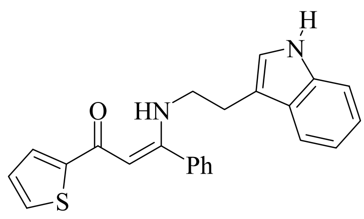
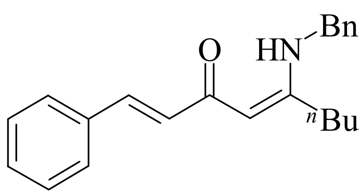
Entry	Alkyne **1**	Acid chloride **6**	Amine **4**	Product (Yield %)
1	R^1 = TMS (**1f**)	R^4 = Ph (**6f**)	R^2 = R^3 = Et (**4b**)	 **11a** (74 %)
2	R^1 = Ph (**1a**)	**6f**	**4b**	 **11b** (97 %, *E*/*Z* = 30:1)
3	**1a**	**6f**	pyrrolidine (**4a**)	 **11c** (95 %, *E*/*Z* = 5:1)
4	**1a**	**6f**	morpholine (**4c**)	 **11d** (99 %, *E*/*Z* = 4:1)
5	**1a**	R^4 = 2-thienyl (**6e**)	**4b**	 **11e** (95 %, *E*/*Z* = 14:1)

Table 10. Continued

Entry	Alkyne **1**	Acid chloride **6**	Amine **4**	Product (Yield %)
6	**1a**	$R^4 = o\text{-}ClC_6H_4$ (**6g**)	**4b**	 **11f** (96 %)
7	**1a**	$R^4 =$ *tert*-Bu (**6h**)	**4b**	 **11g** (76 %)
8	$R^1 = {}^n\text{Bu}$ (**1b**)	**6f**	**4b**	 **11h** (97 %)
9	**1a**	**6e**	R^2 = H, $R^3 = {}^n\text{Bu}$ (**4e**)	 **11i** (95 %)
10	**1a**	**6e**	R^2 = H, R^3 = Bn (**4f**)	 **11j** (97 %)
11	**1a**	**6e**	R^2 = H, R^3 = CH_2CH_2-3-indolyl (**4g**)	 **11k** (78 %)
12	**1b**	$R^4 = C_6H_5CH{=}CH$ (**6i**)	**4f**	 **11l** (69 %)

The applicability of this approach is fairly broad and occurs under mild conditions and with excellent chemoselectivity. Therefore, tryptamine (**4g**, entry 11) needs neither to be protected at the indol nitrogen nor can any enamine reactivity at C^2 or C^3 be detected. A striking advantage over existing two step protocols lies in the fact that the highly electrophilic, and therefore base sensitive ynones, do not need to be isolated. The time of the second Michael addition step is varied from 3 h at the room temperature for secondary amines, to 24 h at reflux for primary amines. The role of methanol as the solvent can be regarded as a proton donor through a six-membered transition state.[117] Interestingly, the Michael addition to the triple bond can be performed regioselectively in the presence of an activated double bond (entry 12) even upon application of a 5-fold excess of benzylamine.

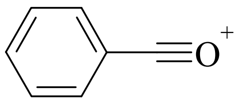
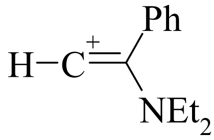
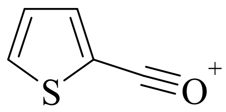
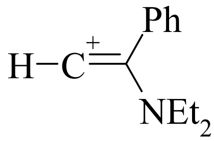
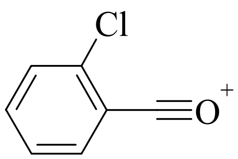
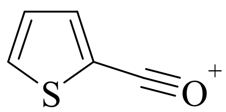
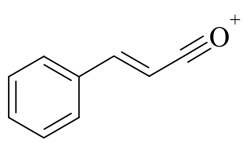
Spectroscopic data

The structure of the *β*-enaminones **11** was unambiguously assigned by ^{1}H, ^{13}C and NOESY NMR experiments. Most characteristically, in the ^{1}H NMR spectra the *α*-methine proton resonances appear as distinct singlets between δ 5.46 and 6.26. The formation of **5a** is accompanied by a protodesilylation at C-*β*, and therefore, the *α*,*β*-disubstituted olefin displays a doublet with a coupling constant of J = 12.5 Hz for the *α*-methine proton resonance indicating that a *trans*-configured push-pull alkene has been formed. In addition, the *E*-configuration of the *β*-enaminones **11a-h**, resulting from the Michael addition of the secondary amines **4a-c** to the intermediate ynones **7**, is strongly supported by the appearance of the characteristic cross-peaks (between the *α*-CH and the *α*-amino methylene resonances of the amines at C-*β*) in the 2D NOESY spectra. Likewise, the *Z*-configuration of the *β*-enaminones **11i-l** can be deduced in accordance with the characteristic appearance of cross-peaks (α-CH and the aliphatic or aromatic proton resonances of the substituents at C-*β*) in the NOESY spectra. In the case of the *β*-enaminones **11i-l**, derived from the addition of primary amines, the broad singlets between δ 11.00 and 11.36 were assigned to the NH protons. These downfield shifts of the NH resonances suggest a six-membered intramolecular hydrogen bonding. For **11a** and **11h**, triplets at δ 0.95-1.19 and quartets at δ 3.30-3.33 with coupling constants J = 7.1-7.2 Hz were assigned to *β*- and *α*-amino methylene resonances of diethylamino substituents. For **11b**, **11e**, **11f**, **11g**, this diethylamino substituents were detected as sets of multiplets in the ranges of δ 0.95-1.29 (with an intensity of 6 protons) and δ 2.98-3.54 (with an intensity of 4 protons). Two triplets at δ 3.21 and 3.72 with a coupling constant of J = 2.9 Hz for **11d** were assigned to aliphatic protons of morpholine. For **11k** the set of signals in the range of δ 2.98-3.51 was assigned as the CH_2 groups of the tryptamine substituents. The stereochemistry of the second double bond (**11l**) in the cinnamyl substituent retained the same as in the starting acid chloride. One of its doublets is found at δ 6.70 with a coupling constant of J = 15.8 Hz, that is characteristic for the *E*-configured double bond.

In the ^{13}C NMR spectra the α-CH resonances can be detected between δ 90.7-99.0 and the resonances of the *β*-C nuclei appear between δ 161.4-168.9 (quaternary signals) and at δ 152.3 for the *β*-methine nucleus of compound **11a**. The shifts of ketone carbonyl resonances are strongly dependent on the substitution pattern and are found in a range of δ 178.9-201.2 as quaternary signals. The quaternary carbons of phenyl groups that are directly appended to the carbonyl group are also somewhat downfield shifted and detected at δ 141.0-143.3. The quaternary carbons of thienyl groups that are directly appended to the carbonyl group are identified at δ 147.0-149.4. As well as for **11f** the carbon resonance attached to Cl is downfield shifted to δ 135.7. In turn, for electron rich indolyl substituent the set of signals δ 111.1-122.5 can be assigned as the indolyl carbons. The *β*- and *α*-amino methylene (or methyl) carbons appear between δ 13.2-25.2 and δ 44.0-49.8, respectively. Only for a morpholine containing compound **11d** the *β*- and *α*-amino methylene carbons are found at δ 66.5 and δ 48.2.

The mass spectra of all the obtained compounds display the molecular peaks. The fragmentation mode leads to the loss of the OH and C_2H_5 groups. Characteristically for ketone derivatives is the *α*-fragmentation at the carbonyl group, leading to appearing of R^4CO^+ peaks in the mass spectra (Table 11).

Table 11. The Fragmentation of Selected *β*-Enaminones 11 (EI, 70 eV)

Compound	Fragment	*m/z* (%)	Fragment	*m/z* (%)
11b		105 (44)		174 (37)
11e		111 (42)		174 (22)
11f		139 (40)		
11i		111 (63)		
11l		131 (35)		

For compounds **11j** and **11l** the fragmentation of Bn group leads to the peak with a mass of 91 (C_7H_7) with a very high intensity that can be explained by its rearrangement into a very stable tropylium cation.

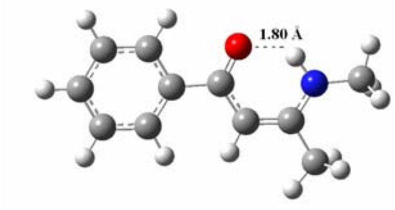
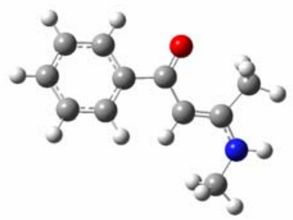
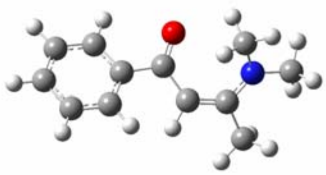
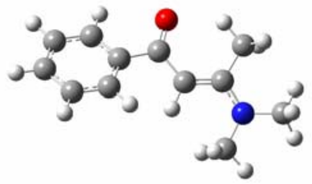
The vibrations of carbonyl groups for *E* isomers (**11a-11h**) appear in a wide region of 1639-1609 cm^{-1} in the IR spectra. The IR frequencies of carbonyl groups for *Z* isomers (**11i-11l**) are shifted towards lower frequencies 1591-1590 cm^{-1}, due to the presence of the intramolecular hydrogen bonding. In addition, the absorptions of highly polarized double bonds in the IR spectra of *β*-enaminones **11** are detected at 1589-1568 cm^{-1}.

4.2.3.3 Computational Studies on the Stereochemistry of *β*-Enaminone Formation

As it has already been mentioned in the previous part when secondary amines **4** were subjected to the reaction with ynones **7**, (*E*)-isomers of *β*-enaminones **11** were predominantly formed in a ratio E/Z = 4-30:1. In the case of primary amines **4** only the (*Z*)-isomer was detected by the ^{1}H NMR spectra (Z/E >99:<1). In order to rationalize this selectivity, the geometries for β-enaminones were optimized using the 6-311G ++ (2d, 2p) basis set, at the DFT level of theory. The density functional that was chosen for this purpose was B3LYP, that is a hybrid functional made up of Becke's exchange functional, the Lee-Yang-Parr (LYP) correlation functional and a Hartree-Fock exchange term. These functionals were used as implemented in the Gaussian 03 suite of programs.[16]

For these studies methyl and dimethyl amines were selected as the model primary and secondary amines (Table 12).

Table 12. Geometries and Energies for (*Z*)- and (*E*)- Isomers of *β*-Enaminones

	(*Z*)-Isomer $\mathbf{E_1}$	(*E*)-Isomer $\mathbf{E_2}$	ΔE (kcal/mol) = $\mathbf{E_2 - E_1}$
Addition of methylamine	 E = -557.153398 (a.u.)	 E = -557.144559 (a.u.)	5.55
Addition of dimethylamine	 E = -596.451200 (a.u.)	 E = -596.455091 (a.u.)	-2.44

The obtained results confirmed the observed selectivity. Indeed, in the case of the addition of a primary amine, the (*Z*)-isomer was by 5.55 kcal/mol more stable than (*E*)-isomer, corresponding to a ratio $Z/E = \sim 5000{:}1$ at 330 K. On the contrary, during the addition of a secondary amine, the (*E*)-isomer is favored by 2.44 kcal/mol over (*Z*)-isomer, i. e. the ratio $E/Z = \sim 40{:}1$ at 330K.

Interestingly, only in the case of the (*Z*)-isomer derived from the addition of a primary amine, can the additional stabilization through the intramolecular hydrogen bonding occur, since only in this case, the favorable six-membered ring (counting the hydrogen as one of the six) can be formed. Indeed, the distance between the hydrogen of an amino group and the carbonyl oxygen is equal according to the calculations to 1.80 Å.[118] On the other hand, the sum of Van der Waals radii for H and O is equal to 2.6 Å, which corresponds to the closest approach. The actual separation is about 0.8 Å less. This can only be explained by the existance of hydrogen bonding. The length of 1.80 Å is intermediate between the sum of Van der Waals radii and a usual O-H covalent bond of 0.96 Å and consistent with a typical hydrogen bonding distance.[119]

4.2.3.4 Pyrimidines – Literature Review

Pyrimidines represent an important class of heterocycles and their structural framework is a key constituent of nucleic bases[120] and numerous pharmacophores with antibacterial, antimicrobial, antifungal, antimycotic, antiviral, and antitumor activity. Glivec is one of the most interesting examples of the pyrimidine-containing drugs (Fig. 16).[121]

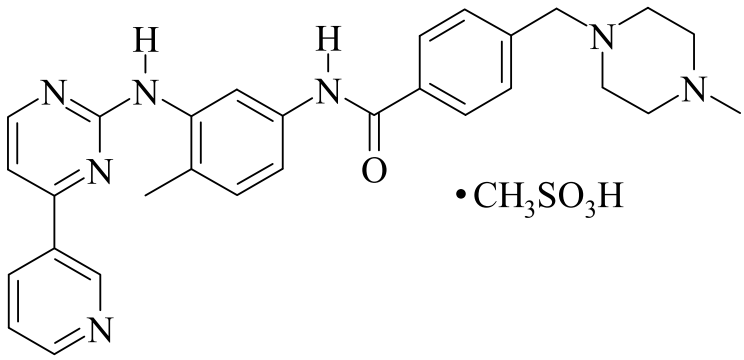
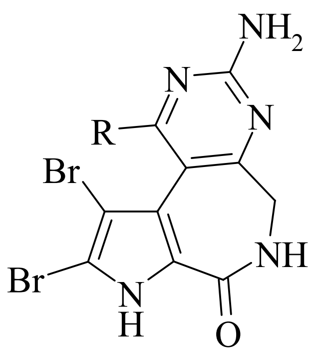


Fig. 16. The Structure of Glivec

It was shown that the presence of the phenylamino-pyrimidine core is necessary for the inhibition of protein kinase C, thus leading to the antitumor activity.

Two natural products Latonduines A and B containing a pyrimidine ring were recently isolated from the marine sponge Stylissa carteri (Fig. 17).[122]



Latonduine A R = H
Latonduine B R = CO_2H

Fig. 17. The Structure of Latonduines

These compounds belong to oroidin alkaloids and have been shown to inhibit the protein kinases and modulate the proinflammatory transcription.

Additionally pyrimidines are also known as a central unit in grid-forming ligands for supramolecular scaffolds (Fig. 18).[123]

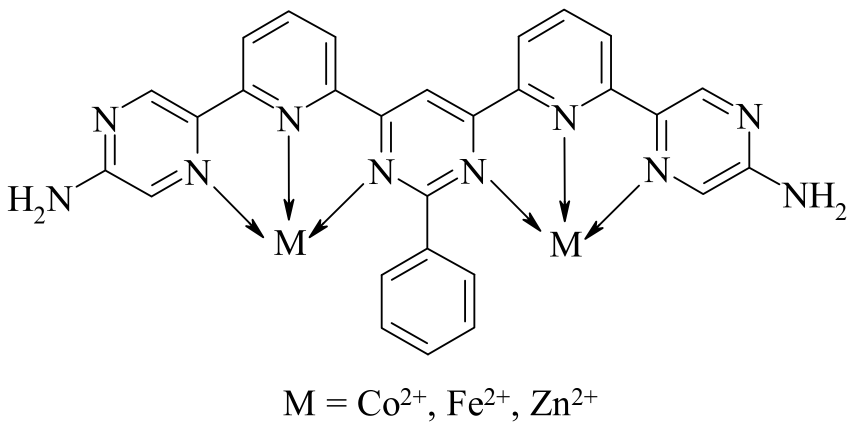
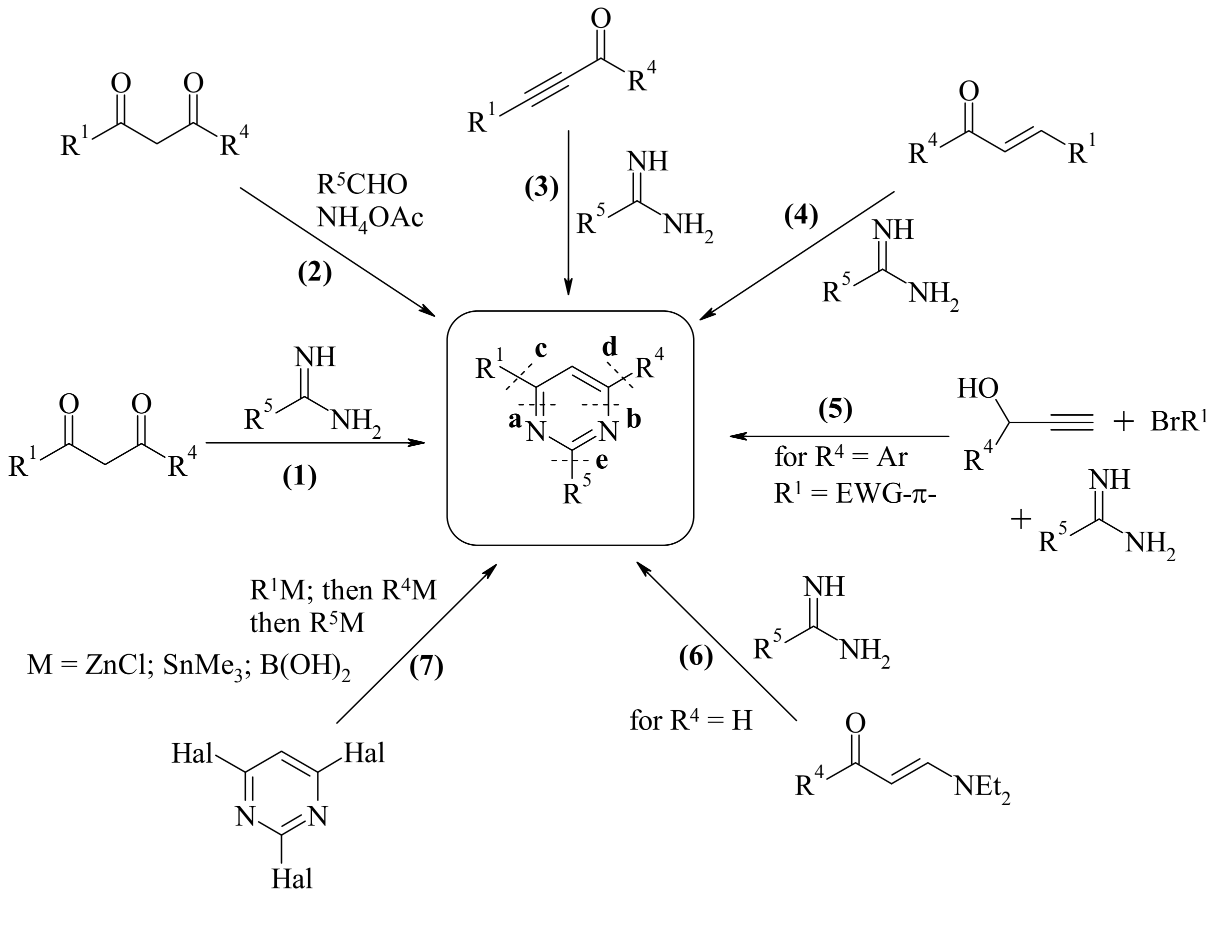


Fig. 18. The Pyrimidine Ligands Suitable for Self-assembly

As a consequence, many pyrimidine syntheses are known (Scheme 51).

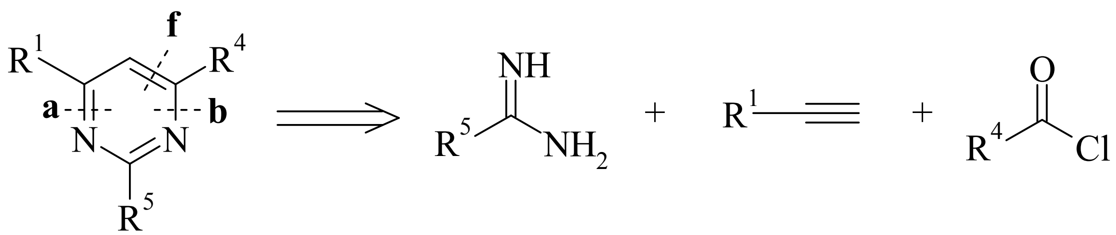


Scheme 51. Synthesis of 2,4,6-Trisubstituted Pyrimidines

The most efficient of these methods apply cyclocondensations of 1,3-dicarbonyl compounds or their synthetic equivalents with amidines as a key step. The processes which form bonds **a** and **b**, for example, the cyclocondensation of 1,3-dicarbonyl compounds with amidinium salts (Pinner reaction)[124] **(1)** or aldehydes and ammonia under oxidative conditions[125] **(2)**, lead to the formation of trisubstituted pyrimidines. The reaction of ynones **(3)**[58,60,61,62] or chalcones[126] **(4)** and amidinium salts provide the alternative syntheses of this type of heterocycles. The latter approach was further extended to a three-component coupling-isomerization-cyclocondensation sequence **(5)**, producing additionally the bond **c**.[127] The reaction of enaminones with amidinium salts[128] (Bredereck synthesis) **(6)** provides access to pyrimidines via bonds **a** and **b**. This route is suitable however, only for twosubstituted (R^4 = H) pyrimidines. Finally, step-wise protocols including consecutive cross-coupling reactions of trihalosubstituted pyrimidines and boronic acids,[129,130] tin[123,131] or zinc[132] derivatives **(7)** give rise to 2,4,6-trisubstituted pyrimidines via bonds **c**, **d** and **e**. Interestingly, the chloro pyrimidines have proven to be the better coupling partners than the highly reactive iodo or bromo substrates and it was shown that the 4- and the 6- positions are more reactive than the position 2.[129]

4.2.3.5 Synthesis of Pyrimidines via Coupling-Cyclocondensation Sequence

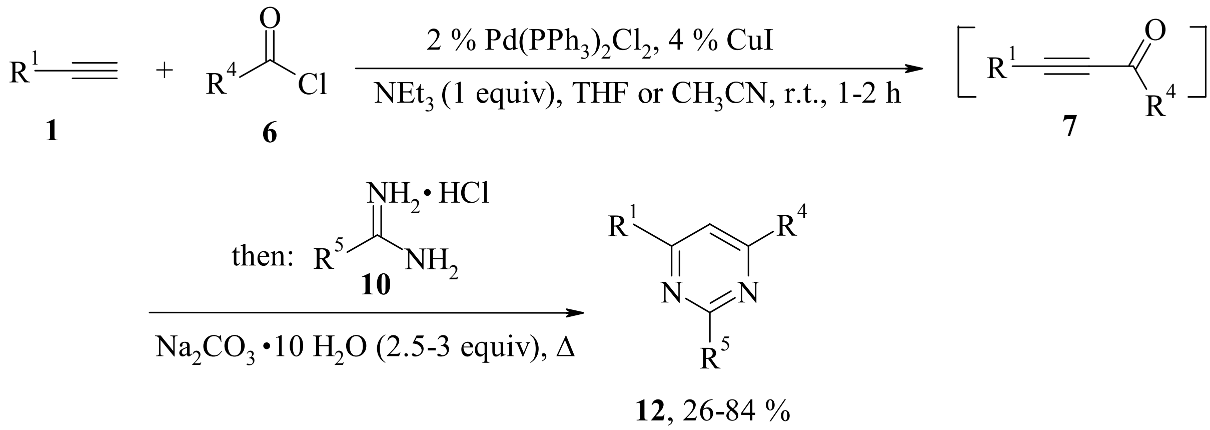
Among these approaches, the reaction of ynones and amidinium salts represents an intriguing entry to pyrimidines, in particular, since ynones can readily be formed in catalytic way by a Sonogashira coupling of an acid chloride with a terminal alkyne.[20] The retrosynthetic scheme for the synthesis of pyrimidines via coupling-cyclocondensation sequence produces acid chlorides, alkynes and amidinium salts as the readily available starting compounds (Scheme 52).



Scheme 52. Retrosynthetic Analysis of Pyrimidines

Interestingly, besides the usual formation of bonds **a** and **b**, this process allows the formation of the additional bond **f**. The retrosynthetic scission of the pyrimidine core at this bond was unexplored until present.

After performing the ynones synthesis under modified Sonogashira conditions from terminal alkynes **1** and acid chlorides **6**, the amidinium or guanidinium salts **10** together with 2.5-3 equiv of sodium carbonate decahydrate were successively added and after heating for 12-14 h the pyrimidines **12** were obtained as light yellow oils (**12b**, **12e**, **12i**, **12j**) or crystalline solids (**12a**, **12c**, **12d**, **12f-h**, **12k-12o**) in modest to good yields (Scheme 53, Table 13).



Scheme 53. Three-component One-pot Synthesis of Pyrimidines 12

Table 13. Coupling-Cyclocondensation Synthesis of Pyrimidines 12

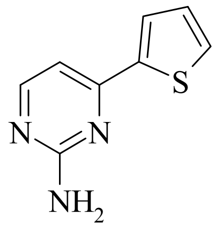
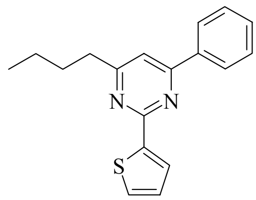
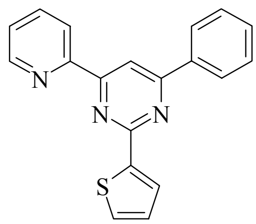
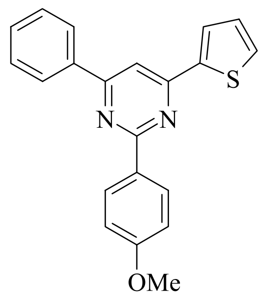
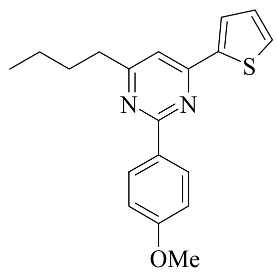
Entry	Alkyne **1**	Acid chloride **6**	Amidine **10**	Product (Yield %)
1	R^1 = TMS (**1f**)	R^4 = 2-thienyl (**6e**)	guanidine hydrochloride (**10a**)	 **12a** (51 %)
2	R^1 = ^{n}Bu (**1b**)	R^4 = Ph (**6f**)	R^5 = 2-thienyl (**10b**)	 **12b** (70 %)
3	R^1 = 2-pyridyl (**1g**)	**6f**	**10b**	 **12c** (43 %)
4	R^1 = Ph (**1a**)	**6e**	R^5 = *p*-$CH_3OC_6H_4$ (**10c**)	 **12d** (49 %)
5	**1b**	**6e**	**10c**	 **12e** (49 %)

Table 13. Continued

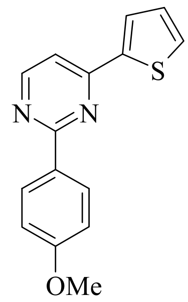
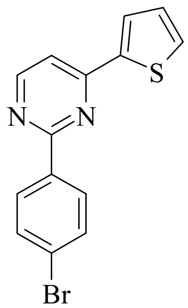
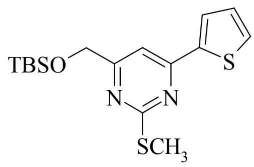
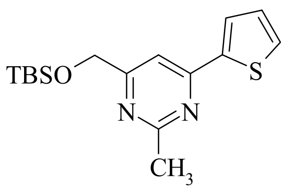
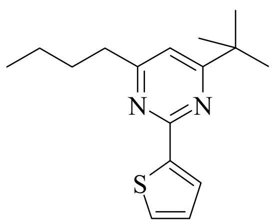
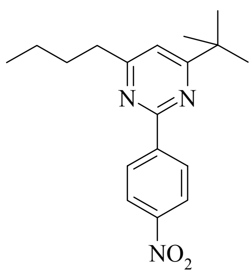
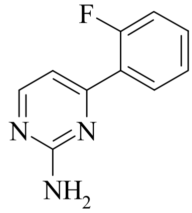
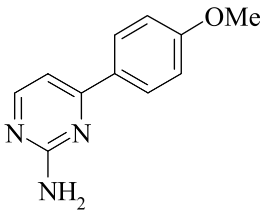
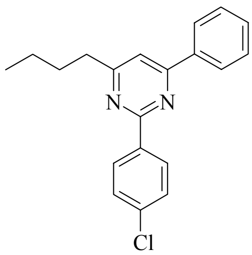
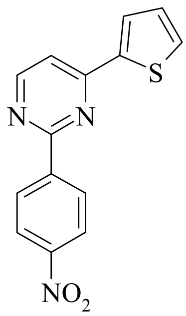
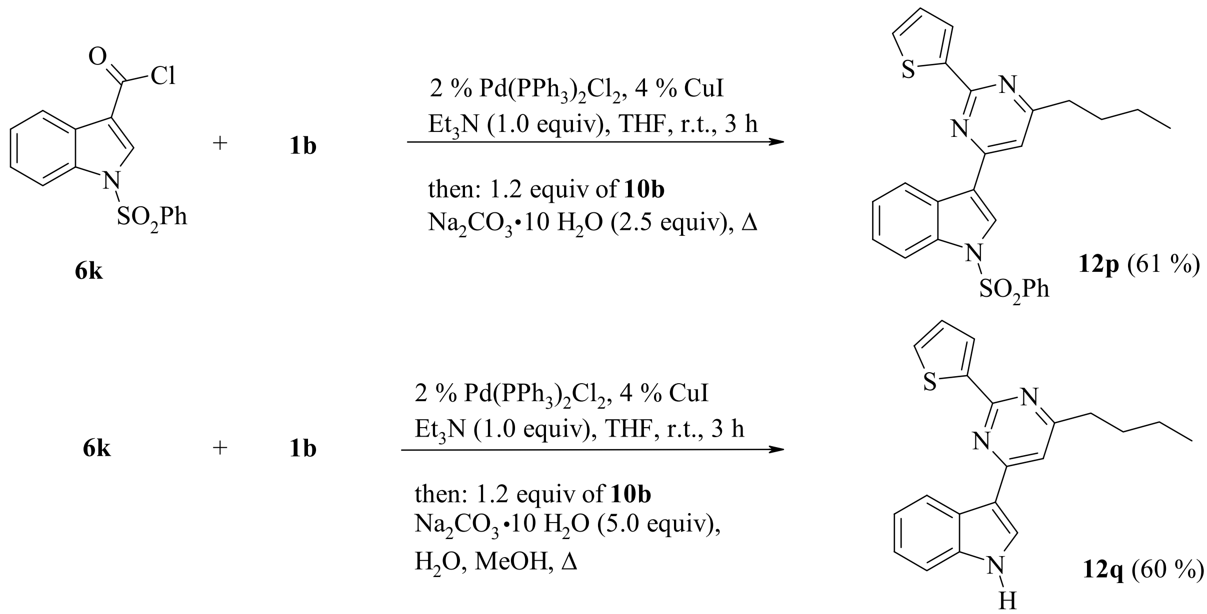
Entry	Alkyne **1**	Acid chloride **6**	Amidine **10**	Product (Yield %)
6	**1f**	**6e**	**10c**	 **12f** (81 %)
7	**1f**	**6e**	R^5 = *p*-BrC_6H_4 (**10d**)	 **12g** (38 %)
8	R^1 = CH_2OTBS (**1h**)	**6e**	R^5 = SMe (**10e**)	 **12h** (56 %)
9	**1h**	**6e**	R^5 = Me (**10f**)	 **12i** (35 %)
10	**1b**	R^4 = *tert*-Bu (**6h**)	**10b**	 **12j** (26 %)
11	**1b**	**6h**	R^5 = *p*-$NO_2C_6H_4$ (**10g**)	 **12k** (33 %)

Table 13. Continued

Entry	Alkyne **1**	Acid chloride **6**	Amidine **10**	Product (Yield %)
12	**1f**	R^4 = *o*-FC_6H_4 (**6j**)	**10a**	 **12l** (44 %)
13	**1f**	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	**10a**	 **12m** (49 %)
14	**1b**	**6f**	R^5 = *p*-ClC_6H_4 (**10h**)	 **12n** (60 %)
15	**1f**	**6e**	**10g**	 **12o** (30 %)

As a consequence of the mild ynone formation by a palladium-copper catalyzed cross-coupling reaction, and the subsequent transformation to the pyrimidines, the substitution pattern on the pyrimidine ring is highly flexible. All kinds of aromatic, heteroaromatic and aliphatic substituents are tolerated, even haloarenes (entries 7, 12, 14). *tert*-Alkyl fragments can be introduced by the acid chloride (entries 10 and 11) and TBDMS protected alcohols are carried through the sequence (entries 8 and 9), now giving rise to starting materials for sophisticated pyrimidine transformations. Even 2-aminopyrimidines (entries 1, 12 and 13) are readily accessible by this novel, one-pot coupling-cyclocondensation pyrimidine synthesis.

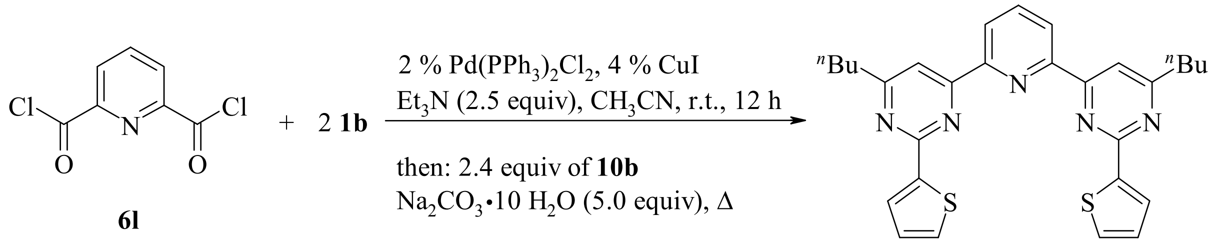
Extending this three-component pyrimidine synthesis to N-phenylsulfonyl indole 3-carbonylchloride **6k**, reveals a remarkable effect of the amount of applied sodium carbonate hydrate on a stability of a base sensitive protecting group. Surprisingly, the phenylsulfonylamide stays unaffected when only a slight excess of sodium carbonate is applied and the three-component reaction produces the N-phenylsulfonyl protected indolyl pyrimidine derivative in good yield **12p** (Scheme 54).



Scheme 54. Influence of the Basicity on the Tolerance of Functional Groups in the Cyclocondensation Step

However, if an excess of sodium carbonate, methanol and water as cosolvents are added in the final cyclocondensation step, the deprotected indolyl pyrimidine **12q** is formed in comparable yield. This observation is particularly interesting since the basicity of the reaction medium in the cyclocondensation can not only be fine tuned, but also allows a control of the functional group tolerance. This peculiar aspect will be addressed in detail in more sophisticated pyrimidine syntheses.

Finally, we wanted to probe the applicability of our novel one-pot coupling-cyclocondensation pyrimidine synthesis to the construction of more complex systems such as ligands. In a preliminary experiment we found that the pyridine-2,6-dicarbonyl dichloride (**6l**) reacts with 2 equiv of **1b** and 2.4 equiv of **10b** in a one-pot coupling-cyclocondensation sequence to furnish the dipyrimidyl pyridine (DIPYRIMPY) derivative **12r** in 17 % yield (Scheme 55).



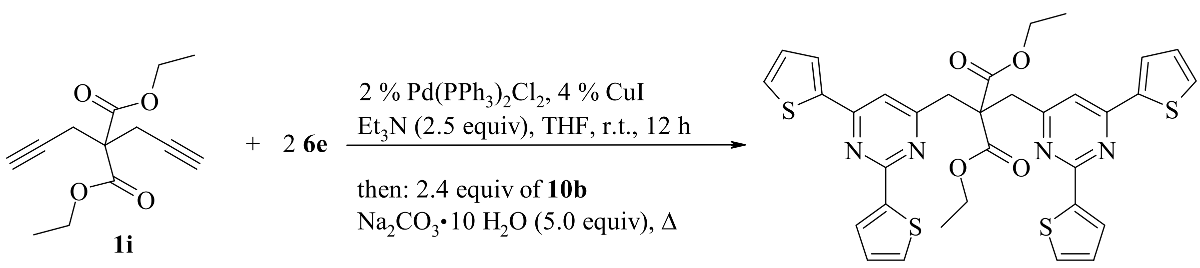
6l

12r (17 %)

Scheme 55. One-pot Coupling-Cyclocondensation Synthesis of a DIPYRIMPY Ligand

At first sight, the yield does not seem to be too breathtaking, however, if one considers that 6 C-C and C-N bonds are formed in this consecutive process, it becomes apparent that the average yield for each bond forming step is 74 %. In a multistep synthesis by Lehn the overall yield of a ligand with comparable complexity was 15 %.[123]

Accordingly, 2 equiv of **6e** and the diyne component **1i** react with 2.4 equiv of **10b** in a one-pot coupling-cyclocondensation sequence to give the bispyrimidine system **12s** in 21 % yield (Scheme 56).



1i

12s (21 %)

Scheme 56. One-pot Coupling-Cyclocondensation Synthesis of a DIPYRIM Ligand

Spectroscopic data

The formation of the pyrimidyl core is unambiguously supported by the spectroscopic and analytical data. In the ^{1}H NMR spectra of the 2,4-disubstituted pyrimidines (**12a**, **12f-g**, **12l-m, 12o**) the pyrimidyl methine protons can be readily assigned by the appearance of the characteristic AX-spin patterns at δ 7.05-7.54 (C^{5}H) and δ 8.25-8.80 (C^{6}H) with coupling constants of 5.2-5.4 Hz. For the 2,4,6-trisubstituted pyrimidines (**12b-e**, **12h-k, 12n, 12p-12s**) the pyrimidyl methine resonance is found in a wide range of δ 6.80-8.20 (C^{5}H) as a distinct singlet (Fig. 19).

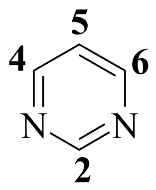


Fig. 19. The Numeration of the Pyrimidyl Substituent

For **12a-j, 12p-s** thienyl substituents appear as three doublets of doublets in the ranges of δ 6.98-7.12 (with coupling constants of 5.1 and 3.7 Hz); δ 7.33-7.48 (with coupling constants of 5.1 and 1.1 Hz) and δ 7.62-7.94 (with coupling constants of 3.7 and 1.1 Hz). Relatively downfield shifted resonances at δ 8.28-8.70 for **12c** can be interpreted as the protons of the pyridyl substituents. For **12b**, **12e**, **12j**, **12k**, **12n, 12p**, **12q,** and **12r** butyl substituents are identified as the sets of signals in the ranges of δ 0.84-0.89 (triplets with coupling constants 7.2-7.4 Hz and an intensity of 3 protons (6 protons for **12r**)); δ 1.26-1.75 (two multiplets with intensities of 2 protons (4 protons for **12r**)) and δ 2.65-2.74 (triplets with coupling constants 7.4-7.7 Hz and an intensity of 2 protons (4 protons for **12r**)). For **12j** and **12k** *tert*-butyl substituents are found as singlets in the range of δ 1.28-1.34 (with an intensity of 9 protons). $TBSOCH_2$ fragments for **12h** and **12i** are detected as the sets of signals in the highfield shifted ranges of δ 0.00-0.01 (singlets with an intensity of 6 protons); δ 0.82-0.84 (singlets with an intensity of 9 protons) and in the lowfield shifted ranges of δ 4.59-4.61 (singlets with an intensity of 2 protons). For **12h** a thiomethyl group is identified as a singlet at δ 2.61 (with an intensity of 3 protons). For **12i** a methyl group appears as a singlet at δ 2.55 (with an intensity of 3 protons). For **12d-f** and **12m** methoxy groups are detected as singlets at δ 3.70-3.83 (with an intensity of 3 protons). NH_2 groups of pyrimidines **12a**, **12l** and **12m** are found as singlets in the range of δ 6.58-6.75 (with an intensity of 2 protons). For **12q** a lowfield shifted singlet at δ 11.88 can be assigned as the N-H proton of the unprotected indole. For **12r** the resonances of pyridyl protons are found as a triplet at δ 8.11 and doublet at δ 8.79 (with an intensity of two protons) with a coupling constant of 8.0 Hz. For **12r** ethyl groups were detected as triplets at δ 1.25 and quartets at δ 4.31 with coupling constants of 7.2 Hz.

Accordingly, in the ^{13}C NMR spectra of the 2,4-disubstituted pyrimidines (**12a**, **12f-g**, **12l-m, 12o**) the four pyrimidyl carbon nuclei are detected at δ 163.5-169.7 (C^2_{quat}), δ 159.2-163.1 (C^4_{quat}), δ 105.0-113.0 (C^5H), and δ 157.1-158.7 (C^6H). The carbon resonances of pyrimidyl systems of the 2,4,6-trisubstituted pyrimidines (**12b-e**, **12h-k, 12n, 12p-12s**) can be unambiguously assigned at δ 165.0-177.2 for the quaternary C^2, at δ 163.4-171.0 for the quaternary C^4, at δ 106.2-112.8 for the methine C^5, and at δ 159.4-161.6 for the quaternary C^6. The methyl groups of a $TBSOCH_2$ fragment which attached directly to a Si atom for **12h** and **12i** appear in the highfield at δ -5.4.

In the presence of F atom it is possible to determine the C-F coupling constants (Table 14).

Table 14. Fluorine-Carbon Coupling Constants for 12l

^1J(C, F)	^2J(C, F)	^3J(C, F)	^4J(C, F)
248 Hz	22 Hz	9 Hz	3 Hz

The mass spectra of all the obtained compounds display the molecular peaks. The fragmentation mode for butyl substituted pyrimidines leads to the loss of the C_3H_7 group.

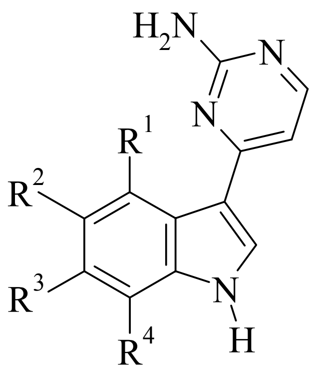
The IR spectra of **12a** and **12l-m** reveal bands in a region of 3344-3342 cm^{-1} for the NH_2 group.

4.3 Multi-component Reactions Based upon Carbonylative Coupling

In the previous chapters it was shown that the coupling of acid chlorides with terminal alkynes under Sonogashira conditions, followed by the subsequent addition of amidinium salts to the intermediate ynones, represents a straightforward one-pot three component access to pyrimidines under mild conditions, producing excellent yields. Since the pyrimidine core is a structural motif of numerous natural products, it was obvious to extend this one-pot coupling-cyclocondensation concept to the more sophisticated natural pyrimidines.

4.3.1 Meridianins – Literature Overview

Numerous biologically active indole alkaloids have been isolated from the marine environment over the past few years. From these, in particular 3-substituted indoles represent an emerging structural class of marine alkaloids based upon their high degree of biological activity. The substituent at the 3-position of the indole core is often an additional heterocyclic ring. New indole alkaloids, meridianins A-G were recently isolated from *Aplidium meridianum*, an Ascidian collected in the South Atlantic (Fig. 20).[133]



A: R^1 = OH, R^2 = H, R^3 = H, R^4 = H
B: R^1 = OH, R^2 = H, R^3 = Br, R^4 = H
C: R^1 = H, R^2 = Br, R^3 = H, R^4 = H
D: R^1 = H, R^2 = H, R^3 = Br, R^4 = H
E: R^1 = OH, R^2 = H, R^3 = H, R^4 = Br
F: R^1 = H, R^2 = Br, R^3 = Br, R^4 = H
G: R^1 = H, R^2 = H, R^3 = H, R^4 = H

Fig. 20. Meridianins

These alkaloids, have a brominated and/or hydroxylated indole nucleus with a pyrimidine ring as substituent at the 3-position.

Later it was shown that meridianins, with the exception of unsubstituted meridianin G, inhibit a range of protein kinases (Table 15).[134]

Table 15. IC_{50} Values of Meridianins, [µM]

Protein kinase	Meridianins A	B	C	D	E	F	G
CDK 1/ cyclin B	2.50	1.50	3.00	13.00	0.18	20.00	150.00
CDK 5/p25	3.00	1.00	6.00	5.50	0.15	20.00	140.00
PKA	11.00	0.21	0.70	1.00	0.09	3.20	120.00
PKG	200.00	1.00	0.40	0.80	0.60	0.60	400.00
GSK 3-*β*	1.30	0.50	2.00	2.50	2.50	2.00	350.00
CK 1	-	1.00	30.00	100.00	0.40	-	-

This table indicates clearly that meridianins B and E are the most potent inhibitors.

Interestingly, meridianins show a structural similarity to the alkaloids variolins isolated from the Antarctic sponge *Kirkpatricka varialosa*.[135] All of the variolins contain a fused pyrido[3´,2´:4,5]pyrrolo[1,2-c]pyrimidine core with an aminopyrimidine ring (as oxidized for variolin A or reduced for the *N*-(3')-methyltetrahydrovariolin B form) or an ester group for variolin D (Fig. 21).

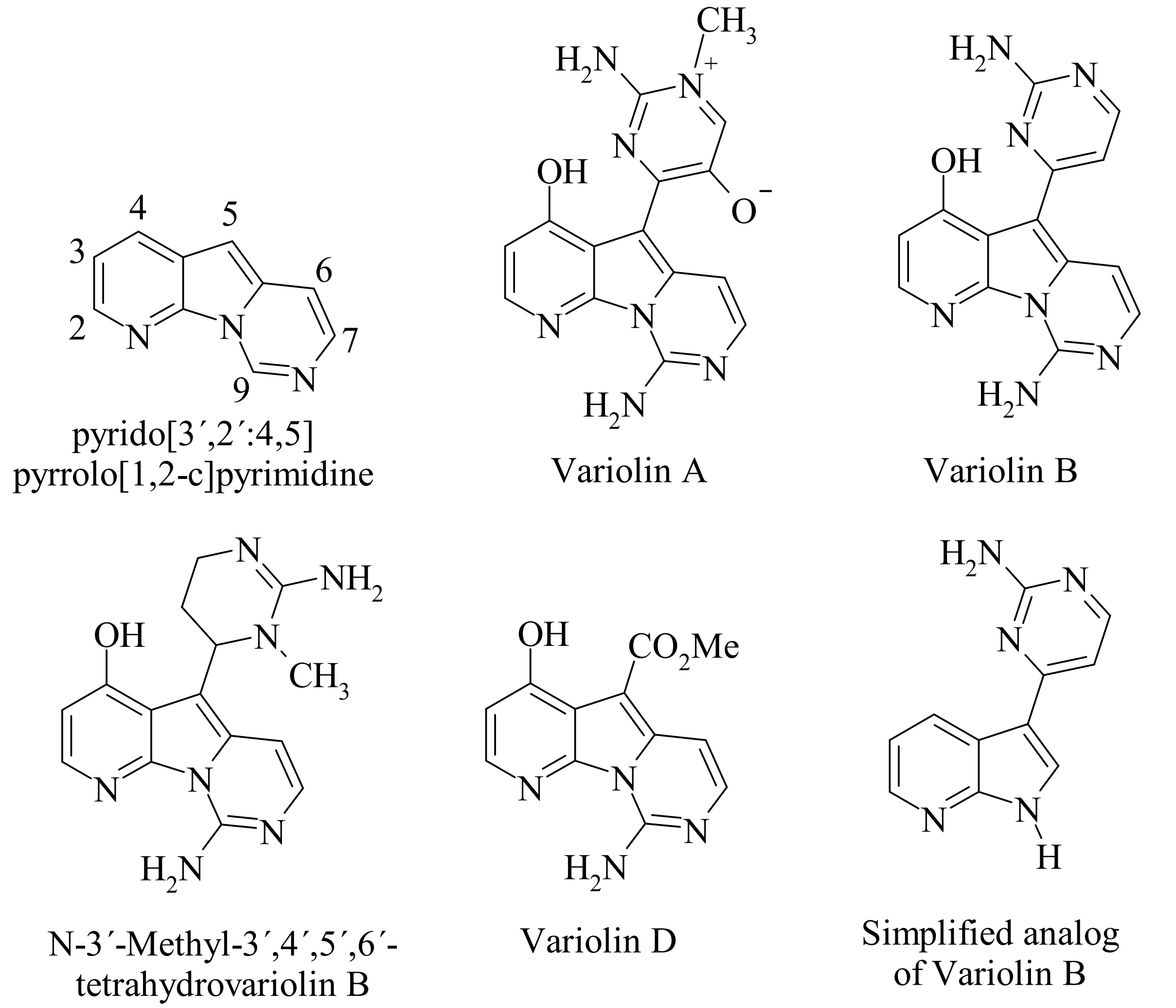
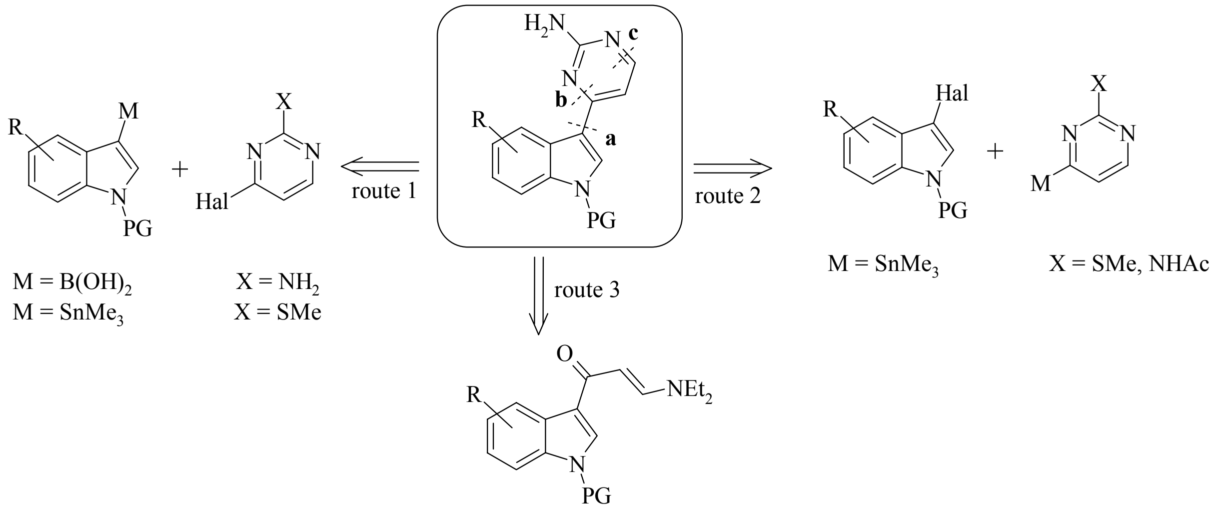


Fig. 21. Variolins

Among these alkaloids, variolin B is the most biologically active compound. It shows the inhibition of the growth of the P388 tumor cell line and is also active against *Herpes Simplex* and the polio virus. In contrast, Variolin D was completely inactive which emphasizes the importance of the aminopyrimidine substituent at the fifth position.[135]

There are three approaches to meridianins and variolins which are known in the literature. The first two routes involve the retrosynthetic scission of bond **a** furnishing tin[136] or boron[130] derivatives of indole and halopyrimidine (route 1) or haloindoles and tin derivatives of pyrimidine[137] (route 2) as the precursors for cross-coupling reactions.

Either 2-amino-4-chloropyrimidine (the compound is not readily available, the purification via recrystallization is required for its synthesis) was applied directly or a thiomethyl derivative (a thiomethyl group can be converted to an amino group via an oxidation-nucleophilic substitution sequence) was used as the halopyrimidine component (Scheme 57).

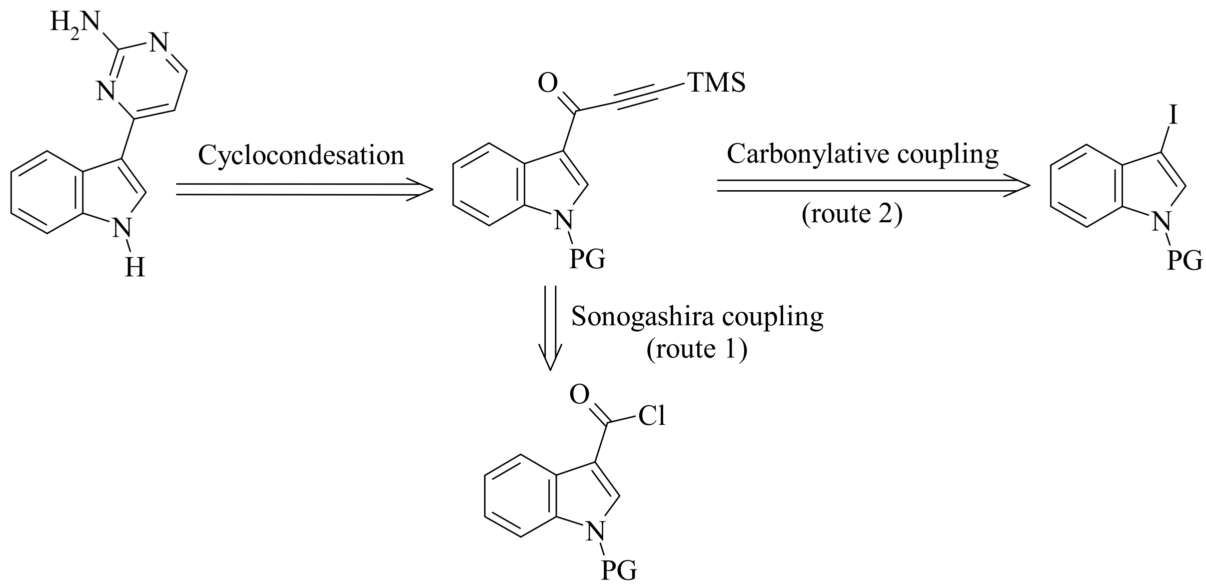


Scheme 57. Literature Approaches to Merdianins and Variolins

In the third approach, the aminopyrimidine ring is installed via *β*-enaminones as the precursors (bonds **b** and **c**) using Bredereck's protocol.[138,139]

4.3.2 Synthesis of Meridianins

In our approach to the meridianin alkaloids, I decided to use (TMS)-ynones as the versatile synthetic equivalents of *β*-ketoaldehydes for the construction of an aminopyrimidine ring. The usual Sonogashira coupling as the route to (TMS)-ynones requires the protected indolyl acid chlorides as the starting materials (route 1, Scheme 58). Unfortunately, all attempts to accomplish the formation of protected indolyl acid chlorides via the standard Friedel-Crafts acylation procedure were met with significant resistance. Only the phenylsulfonyl group survived under these relatively drastic, extremely acidic conditions, but was not appropriate for the subsequent steps. Therefore, in this case I decided to switch to the carbonylative coupling of iodo substituted indoles and TMSA (route 2, Scheme 58).

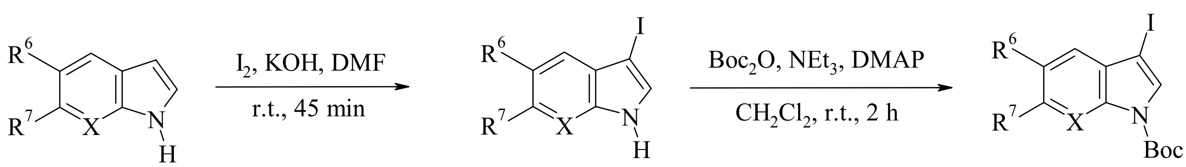


Scheme 58. Retrosynthetic Analysis of Meridianins

Although to the best of my knowledge, there has been no report on the synthesis of (TMS)-ynones via carbonylative coupling in the literature, bearing in mind that the amount of the base could be crucial for the successive coupling of TMSA, I decided to apply our modified conditions to the carbonylative coupling.

With this general retrosynthetic scheme in our hands it was only a question of selection a suitable protecting group for the indole nitrogen. I choose the *tert*-butoxycarbonyl group (Boc), which is one of the most frequently used nitrogen protecting groups in organic synthesis, and is extremely resistant towards basic and nucleophilic reagents. It additionally possesses electron-withdrawing character and should therefore facilitate subsequent cross-coupling reactions.

The synthesis of meridianins began with iodination of indoles and subsequent protection of the indole nitrogen with the Boc group (Scheme 59).[140]



13a R^6 = H, R^7 = H, X = CH
13b R^6 = Br, R^7 = H, X = CH
13c R^6 = H, R^7 = Br, X = CH
13d R^6 = H, R^7 = H, X = N

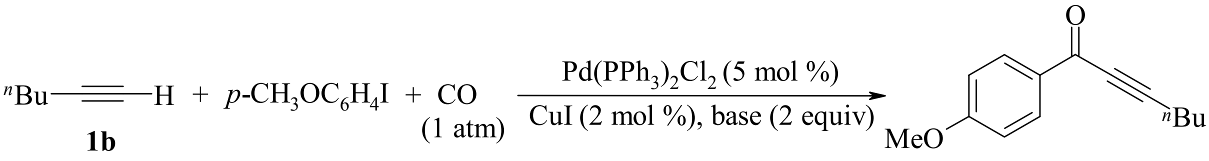
14a 79 %
14b 96 %
14c 99 %
14d 94 %

15a 80 %
15b 86 %
15c 77 %
15d 72 %

Scheme 59. Synthesis of Boc-protected 3-iodoindoles 15

Before pressing forward with the carbonylative coupling of Boc-protected iodo-indoles **15** I performed the model studies on *p*-iodoanisole which has the electronic properties similar to our substrate.

First of all, I tried to reproduce the conditions described in the literature[41], using 2 equiv of aqueous ammonia as the base (Scheme 60, Table 16).



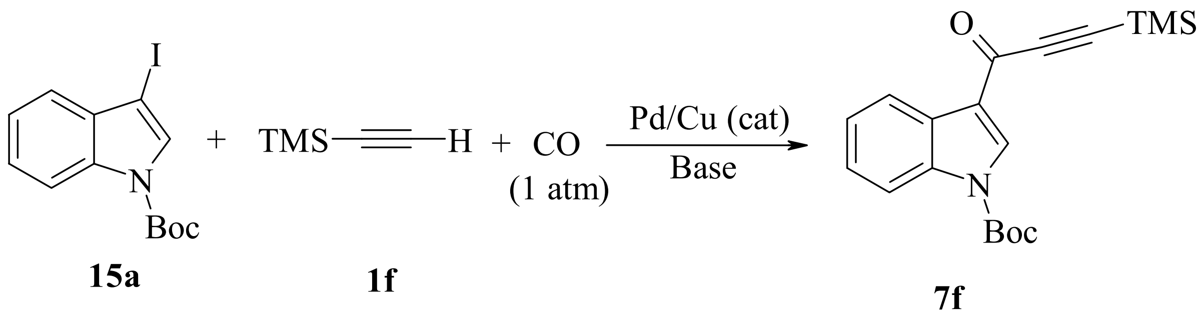
Scheme 60. Model Studies on Carbonylative Coupling

Table 16. Carbonylative Coupling (Model Studies)

Entry	Solvent	Base	Conditions	Alkynone (Yield %)
1	THF	NH_3	4 days, r.t.	No product
2	THF	NEt_3	24 h, r.t.	82

Interestingly, the use of 2 equiv of aqueous ammonia (entry 1) as the base was not successful. Instead, the carbonylative coupling of *p*-iodoanisole proceeded smoothly using 2 equiv of triethylamine (entry 2).

Inspired by the success at this initial stage, we continued the optimization of carbonylative coupling conditions, this time for the model unsubstituted Boc-protected iodo-indole **15a** and TMSA (**1f**) (Scheme 61, Table 17).

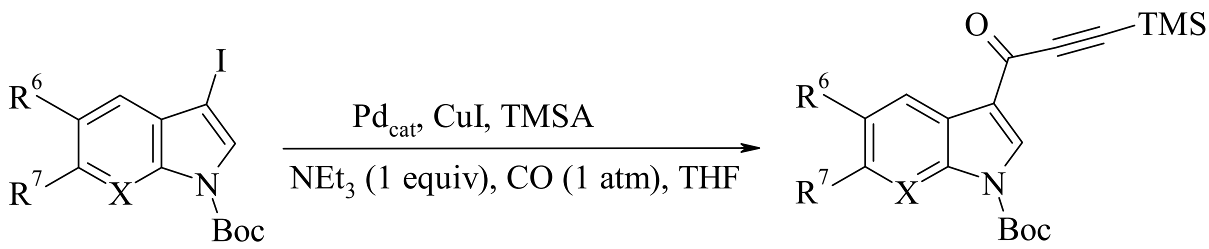


Scheme 61. Optimization of Conditions for Carbonylative Coupling of the Model BOC-protected Iodoindole (15a)

Table 17. Optimization of Conditions for Carbonylative Coupling of the Model Boc-protected Iodoindole (15a)

Entry	Amount of TMSA (**1f**)	Solvent	Catalysts	Amount of NEt_3	Reaction time	Product (Yield %)
1	1.1 equiv	THF	5 mol % of $Pd(PPh_3)_2Cl_2$ and 2 mol % of CuI	1.0 equiv	48 h	50
2	1.1 equiv	THF	5 mol % of $Pd(PPh_3)_2Cl_2$ and 2 mol % of CuI	1.5 equiv	48 h	no
3	1.5 equiv	THF	5 mol % of $Pd(PPh_3)_2Cl_2$, 1 mol % of $Pd(dppf)Cl_2$ and 2 mol % of CuI	1.0 equiv	48 h	68
4	1.5 equiv	CH_3CN	5 mol % of $Pd(PPh_3)_2Cl_2$, 1 mol % of $Pd(dppf)Cl_2$ and 2 mol % of CuI	1.0 equiv	48 h	44
5	1.5 equiv	THF	5 mol % of $Pd(PPh_3)_2Cl_2$, 1 mol % of $Pd(dppf)Cl_2$	1.0 equiv	48 h	46% of **7f** and 11% of **15a**
6	1.5 equiv	THF	5 mol % of $Pd(dppf)Cl_2$ and 2 mol % of CuI	1.0 equiv	48 h	25 % of **7f** and 56 % of alkynylindole
7	1.5 equiv	THF	5 mol % of $Pd(PPh_3)_2Cl_2$ 1 mol % of dppf 2 mol % of CuI	1.0 equiv	48 h	26

The best result for the carbonylative coupling was obtained in THF as the solvent using 1.5 equiv of TMSA, 1.0 equiv of NEt_3, and 5 mol % of $Pd(PPh_3)_2Cl_2$, 1 mol % of $Pd(dppf)Cl_2$, and 2 mol % of CuI as a catalytic system (entry 3). The excess of the base led to the significant decrease in the yield (entry 2), as well as the use of only $Pd(PPh_3)_2Cl_2$ as the catalyst without the additional amount of $Pd(dppf)Cl_2$ (entry 1) or the application of CH_3CN as the solvent (entry 4). Interestingly, the use of 5 mol% of $Pd(dppf)Cl_2$ led to the desired carbonylative product (25 %) and to the product of Sonogashira coupling without an insertion of CO (56%) (entry 6). This occurrence can be explained by significant acceleration of the reaction rates, and a reduced selectivity in the reaction pathway. Accordingly, the use of Pd catalysts without CuI led to the slight decrease in the yield (entry 5). The beneficial effect of 1 mol % of $Pd(dppf)Cl_2$ as the catalytic additive remains unclear, furthermore the use of the dppf ligand in the same amount instead of $Pd(dppf)Cl_2$ leads to decrease in the yield (entry 7). However, under these superior conditions all the desired (TMS)-ynones were obtained in good yields (Scheme 62). It was only for the iodo-aza-indole **15d** that the carbonylative coupling proceeded better without additional amount of $Pd(dppf)Cl_2$. In this electronically poorer case its addition even led to the mixture of carbonylative and noncarbonylative products. It seems that for aryl iodides bearing EWG the additive of $Pd(dppf)Cl_2$ leads to a lower chemoselectivity.

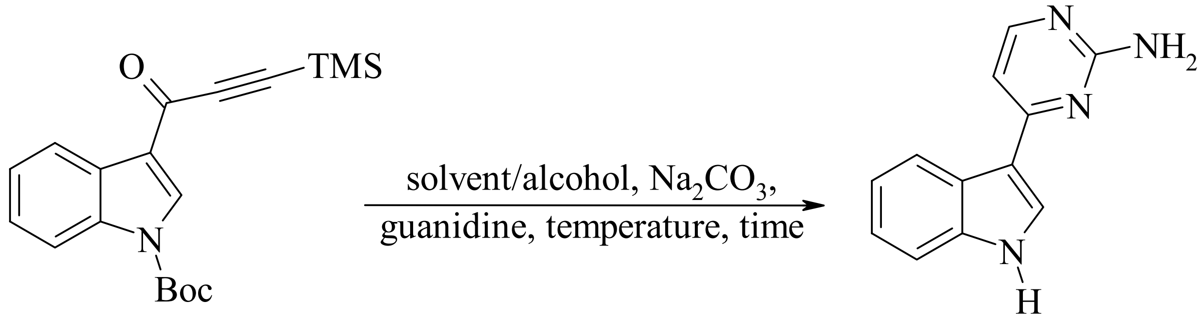


15a R^6 = H, R^7 = H, X = CH	**7f** 68 %
15b R^6 = Br, R^7 = H, X = CH	**7g** 68 %
15c R^6 = H, R^7 = Br, X = CH	**7h** 64 %
15d R^6 = H, R^7 = H, X = N	**7i** 63 %

Scheme 62. Synthesis of (TMS)-ynones 7f-i via Carbonylative Coupling

To summarize our investigations on the carbonylative coupling, fine tuning of the catalytic system is required, depending on the electronic nature of the substrate. On the other hand, the carbonylative coupling can be performed chemoselectively on iodoindole in the presence of bromine functionality that opens additional perspectives for the applicability of this approach.

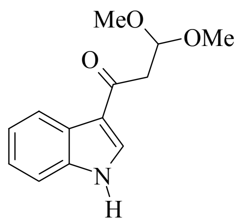
Finally, the conditions for the last cyclocondensation step were optimized (Scheme 63, Table 18).



7f **16a**

Scheme 63. Cyclization to the Model Meridianin G

Table 18. Cyclization to the Model Meridianin G

Entry	Solvent (desilylating reagent)	Reaction temperature	Reaction time	Product (Yield %)
1	CH_3CN/MeOH[a] 1:1	80 °C	12 h	17 % and 55 % of 
2	CH_3CN/MeOH[b] 1:1	80 °C	46 h	57
3	THF/MeOH[b] 1:1	80 °C	40 h	No product
4	CH_3CN[b] (1.2 equiv of TBAF)	80 °C	40 h	No product
5	THF (1.2 equiv of TBAF)	70 °C	40 h	No product
6	CH_3CN/*tert*-BuOH[b] 1:1	80 °C	40 h	66
7	THF/*tert*-BuOH[b] 1:1	70 °C	40 h	40

[a] 3.5 equiv of $Na_2CO_3 \cdot 10H_2O$ and 2.5 equiv of guanidine hydrochloride were added to the reaction mixture; [b] 1.0 equiv of Na_2CO_3 and 2.5 equiv of 5M water solution of guanidine (prepared by neutralizing of guanidine hydrochloride with equimolar amount of NaOH just before using) were added to the reaction mixture

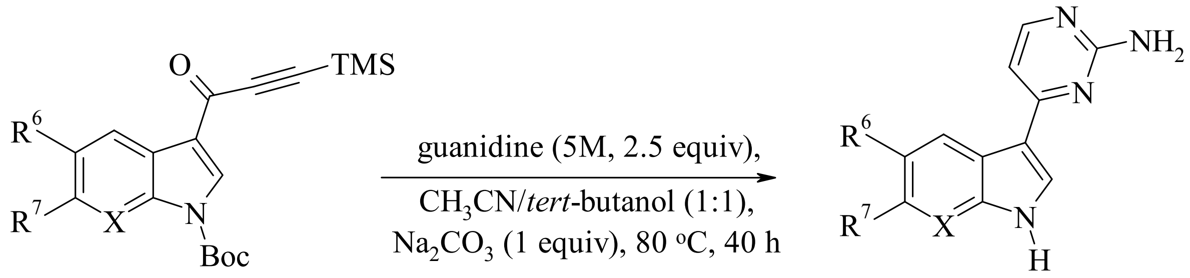
Interestingly, the Boc-protecting group was cleaved under our reaction conditions, so that no further deprotection step was necessary. The use of CH_3CN/MeOH as the solvent mixture led to the predominant formation of the product which arised from the double Michael addition of MeOH to the (TMS)-ynone (entry 1). Since only 17 % of the product was isolated, we decided to use guanidine as a free base and not as the hydrochloride in order to enhance its reactivity. In CH_3CN /MeOH as the solvent mixture, 57 % of the desired product was obtained after 40 h of heating (entry 2). In contrast to these results, for the solvent system THF/MeOH no product was isolated (entry 3).

Next, I tried to accelerate the addition of guanidine either by using TBAF as the TMS-cleaving agent or by hampering the addition of alcohol on the (TMS)-ynone using non-nucleophilic *tert*-butanol instead of methanol. Although the use of TBAF was disappointing (entries 4,5), the application of *tert*-butanol was successful in increasing the yield of the model meridianin **16a** to 66 % (entry 6).

In comparison, the reported literature yield for the similar transformation of (TMS)-ynones to 4-substituted 2-aminopyrimidines is only 28 %,[61] therefore, the authors preferred the cyclocondensation with 2-methyl-2-thiopseudourea with subsequent conversion of the thiomethyl group to an amino group through an oxidation-nucleophilic substitution sequence. Only very recently the aminopyrimidine formation starting from a (TMS)-ynone under microwave conditions was reported for the single example to proceed with a 90 % yield.[62]

Our conditions for the direct conversion of (TMS)-ynone to a 4-substituted 2-aminopyrimidine with a cleavage of a Boc-group in a one-pot fashion seem to be comparably in the efficient.

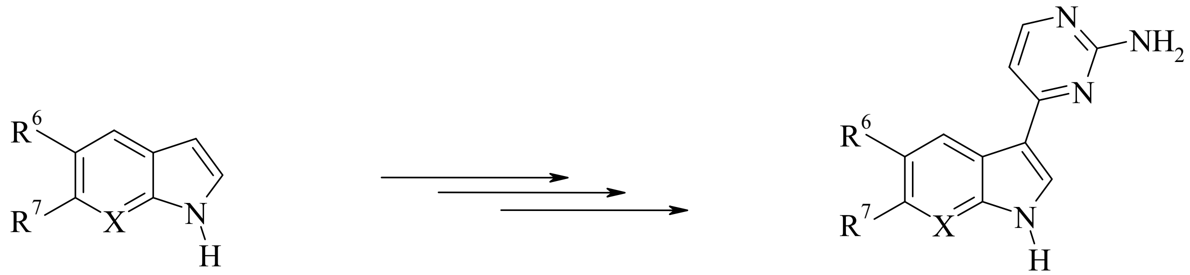
Using the same protocol, the meridianins C (**16b**) and D (**16c**) were synthesized in 73 % and 78 % yield and a simplified variolin B analog (**16d**) was obtained in 59 % yield (Scheme 64).



7f $R^6 = H$, $R^7 = H$, X = CH	**16a** 66 %
7g $R^6 = Br$, $R^7 = H$, X = CH	**16b** 73 %
7h $R^6 = H$, $R^7 = Br$, X = CH	**16c** 78 %
7i $R^6 = H$, $R^7 = H$, X = N	**16d** 59 %

Scheme 64. Cyclocondensation of (TMS)-ynones to Meridianins

This method of meridianin synthesis seems to be general, additionally allowing the introduction of substituents into the 6 position of a pyrimidine ring (using other alkynes instead of TMSA). The overall yields, achieved by our four step approach, lie in the range of 25-41 % (Scheme 65).



13a $R^6 = H$, $R^7 = H$, X = CH	Meridianin G (**16a**) 28 %
13b $R^6 = Br$, $R^7 = H$, X = CH	Meridianin C (**16b**) 41 %
13c $R^6 = H$, $R^7 = Br$, X = CH	Meridianin D (**16c**) 38 %
13d $R^6 = H$, $R^7 = H$, X = N	Variolin analog (**16d**) 25 %

Scheme 65. Overall Yields of the Meridianin Syntheses

The synthesized compounds displayed the inhibition of hitherto untested protein kinases at the low micromolar range (Fig. 22, Table 19).[141] Among these kinases, hSGK1 (human serum- and glucocorticoid-dependant kinase 1) is a kinase, which plays a key role in the “metabolic syndrome” process. The other kinases are of particular interest for oncology. For example, Tie-2 is a kinase, which is responsible for a production of blood vessels in tumour tissues. The inhibition of protein kinases was measured using a 1µM solution of natural products. The results of kinase assays are presented as a kinase activity as a percentage of that in control incubations. This means, the lower is the activity of a kinase at Fig. 22, the more potent is an inhibitor (meridianin).

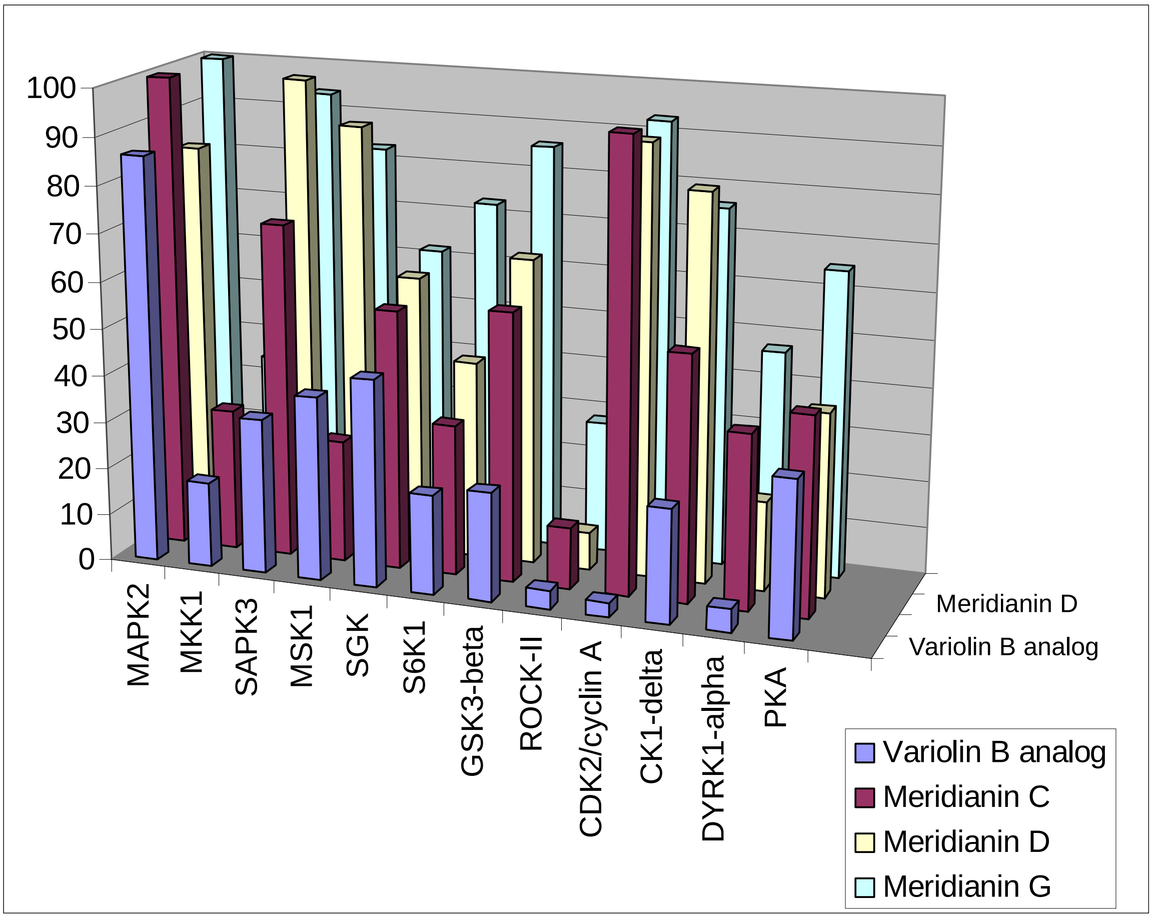


Fig. 22. Inhibition of Protein Kinases by Meridianins (The inhibitor concentration = 1µM. Results are presented as kinase activity as a percentage of that in control incubations.)

IC_{50} values were determined for the protein kinases that were inhibited most strongly (Table 19).

Table 19. IC_{50} Values of Meridianins, [µM]

Protein kinase	Meridianins			
	Meridianin G **(16a)**	Meridianin C **(16b)**	Meridianin D **(16c)**	Variolin analog **(16d)**
hSGK1	>10	2.0	4.5	2.4
Tie-2	>1	0.75	1.6	1
Meck-EE kinase	>10	10>IC_{50}>1	10	>10

These results show that meridianin G is a very weak inhibitor of several kinases, meridianins C and D inhibit more kinases than meridianin G with a mediocre activity and variolin B analog inhibits a range of kinases also with a mediocre activity. These natural products represent a class of unselective inhibitors. Therefore, further modifications of these compounds revealing a complete structure-activity profile are needed to be performed for a discovery of a pharmaceutically interesting derivative.

Spectroscopic data

The structures of iodoindoles **14b-d** were clearly assigned by ^{1}H NMR and ^{13}C NMR spectroscopy. In ^{1}H NMR distinct singlets appear at δ 7.52 and 7.71 which were assigned as 2-H protons of indole rings for **14b** and **14d** respectively. Broad singlets at low field between δ 10.81-12.1 were assigned to the NH groups of indoles. In addition, for **14b** and **14d** it was possible to assign all the rest of indole signals. For 5-bromo substituted indole **14b** 6-H was detected as a doublet of doublets at δ 7.25 with coupling constants of 8.6 Hz and 2.1 Hz; 7-H was found as a doublet at δ 7.39 with a coupling constant of 8.6 Hz and 4-H appears as a doublet at δ 7.45 with a coupling constant of 2.1 Hz (Fig. 23).

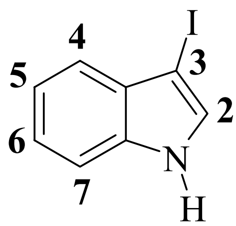


Fig. 23. The Numeration of the Indole Core

For 7-aza indole derivative **14d** 5-H appears as a doublet of doublets at δ 7.16 with coupling constants 7.9 Hz and 4.8 Hz; 4-H was detected as a doublet of doublets at δ 7.68 with coupling constants 7.9 Hz and 1.5 Hz and 6-H was found as a doublet of doublets in a low field (characteristically for pyridine derivatives) at δ 8.25 with coupling constants 4.8 Hz and 1.5 Hz. In ^{13}C NMR spectra of **14b-14d** C^{3}_{quat} resonances are shifted to a rather high field between δ 55.2-54.2, as a consequence of heavy atom effect.[142] The mass spectra of all obtained compounds show the molecular peaks. For bromo substituted compounds two signals (^{81}Br) and (^{79}Br) with intensities 50:49 confirm the presence of a bromine atom. The fragmentation leads to the loss of Br or I.

For **15b-d** a singlet appearing at δ 7.86-7.99 was assigned as 2-H protons of an ndole ring (shifted to the low field due to the electron-withdrawing effect of the Boc group). Instead of the broad singlets of NH groups at δ 10.81-12.1, singlets with the intensity of nine protons of the Boc groups were identified at δ 1.67-1.69. In the ^{13}C NMR spectra the set of signals belonging to Boc groups was detected at δ 28.0-28.1 (CH_3), 84.8-85.9 (C_{quat}) and 147.8-148.9 (C_{quat} of carbonyl groups). The resonances of C^3_{quat} are found again at high field between δ 61.9-64.9 due to the heavy element effect.[142]

The mass spectra of all obtained compounds show the molecular peaks. For bromo substituted compounds two peaks (^{81}Br) and (^{79}Br) with intensities 50:49 confirm the presence of a bromine atom. The further fragmentation leads to the loss of the Boc group. The presence of *tert*-Bu^+ peak was detected in the mass spectra of all compounds.

The structures of TMS-alkynones **7f-i** were clearly assigned by ^{1}H NMR and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra the trimethylsilyl groups give rise to singlets in the regions of δ 0.32-0.35, the Boc groups to singlets at δ 1.70-1.74 and 2-H of indole rings appear as distinct singlets in the regions of δ 8.36-8.44 (shifted one more time to the low field due to the presence of a carbonyl group in the third position). In the ^{13}C NMR spectra the TMS-methyl carbon resonances are identified between δ -0.7 and -0.8, the resonances of the carbonyl groups of TMS-ynones are found between δ 171.5 and 171.9, the signals of α-carbons of the triple bond are detected at δ 96.0-97.3, and those of β-carbons at δ 100.8-102.0. The Boc groups give rise to three signals: δ 27.9-28.0 (CH_3), 85.8-86.4 (C_{quat}) and 148.4-149.3 (C_{quat} of carbonyl groups).

For the compound **7i** the structure was unambiguously supported by X-Ray structure analysis (Fig. 24).

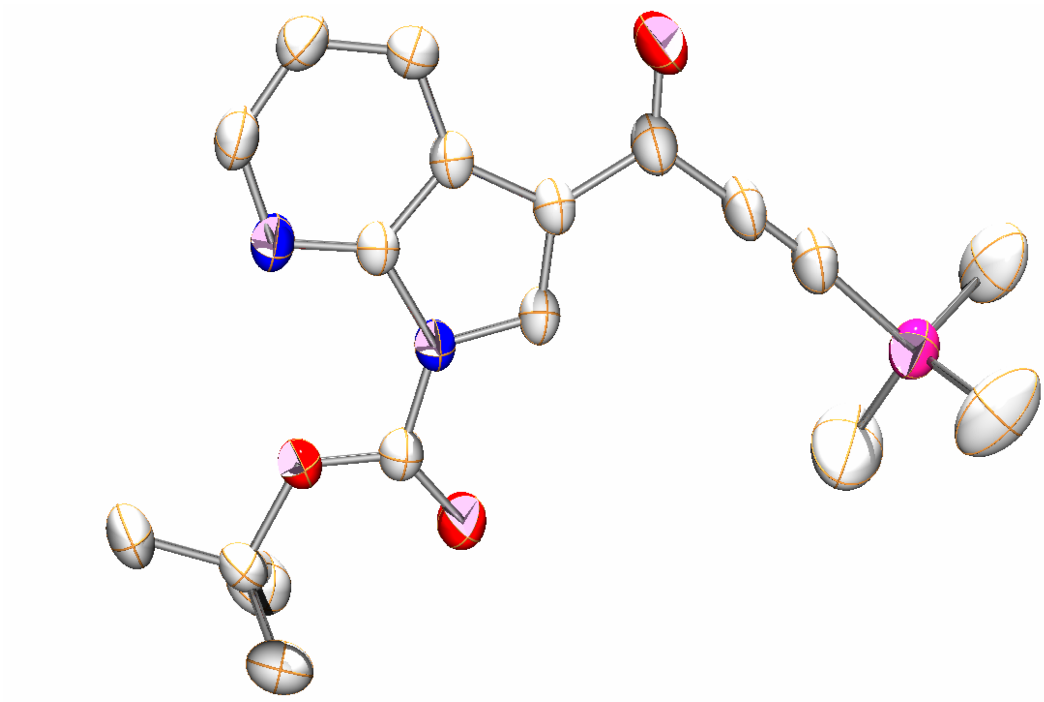
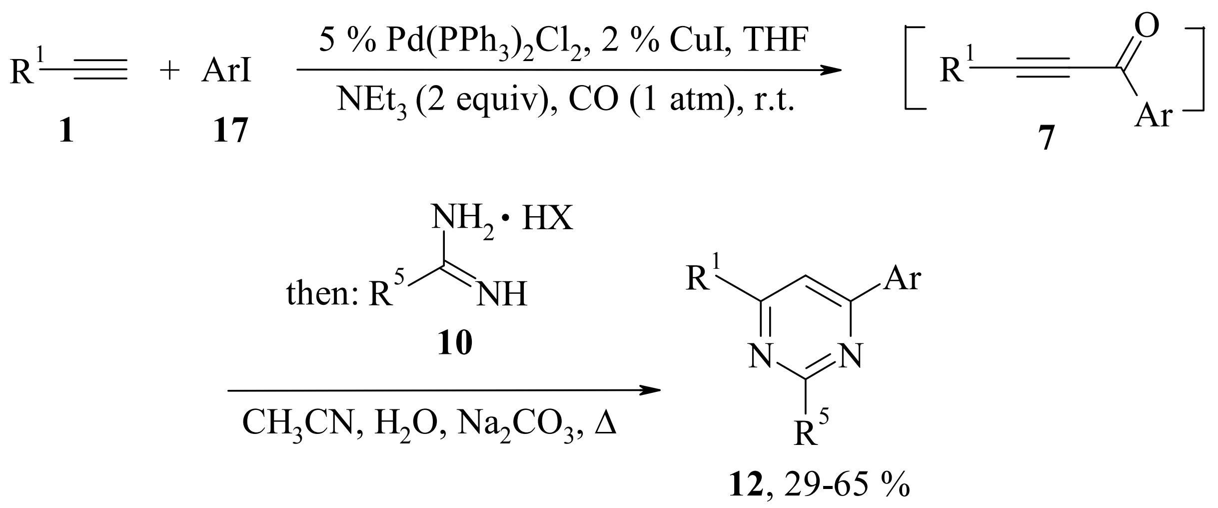


Fig. 24. ORTEP Presentation of 3-(3-Trimethylsilanyl-propynoyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid *tert*-butyl ester (7i)

The structures of meridianins **16a-d** were supported by ^{1}H NMR and ^{13}C NMR spectra, which were consistent with those described in the literature.[130,139] In the ^{1}H NMR spectra the resonances of the pyrimidine amino groups are identified as broad singlets at δ 6.42-6.52, H-5´ and H-6´ of 2,4-disubstituted pyrimidine were detected as characteristic doublets with a coupling constant of 5.1 Hz at δ 7.00-7.06 and 8.10-8.14 respectively. The resonances of H-2 of indole rings appear as distinct singlets in the region of δ 8.19-8.34. The indole NH groups give rise to broad singlets in the region of δ 11.67-12.20.

4.3.3 One-pot Four-component Carbonylative Coupling-Cyclocondensation Synthesis of Pyrimidines

The last problem that remained unsolved was to conduct the carbonylative coupling-cyclocondensation sequence in a one-pot fashion. The attempts to carry out this sequence in a one-pot fashion led to the inseparable mixture of products. However, for the other aryl iodides **17** without complex functionalization, this approach was extended to a one-pot four-component carbonylative coupling-cyclocondensation synthesis (Scheme 66, Table 20).

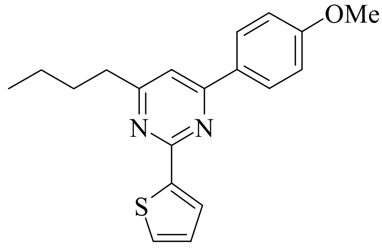
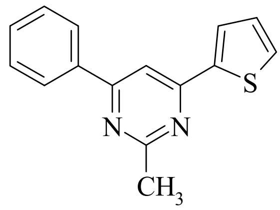
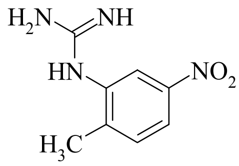
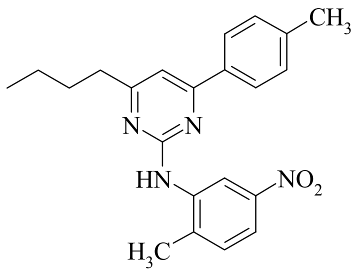
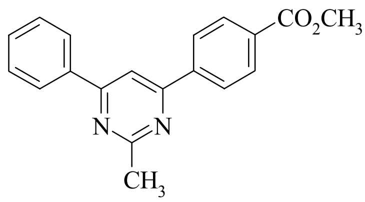
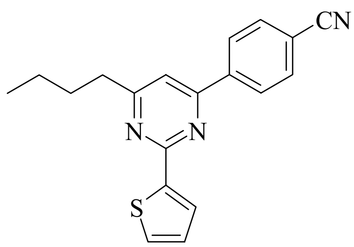


Scheme 66. One-Pot Four-Component Carbonylative Coupling-Cyclocondensation Synthesis of Pyrimidines 12

It is noteworthy that this four-component carbonylative coupling-cyclocondensation works efficiently only for electron rich or neutral aryl iodides **17**. Upon subjection of aryl iodides bearing EWG, the mixture of carbonylative and non-carbonylative products was isolated in the ratio 1:2. On the other hand, attempts to replace the aryl iodides with aryl bromides, in order to increase the selectivity, led to the complete loss of reactivity and only starting substrates were recovered. Finally, after considerable experimentation, it was found that stirring of aryl iodides for 5 days with only 1 mol % of $Pd(PPh_3)_2Cl_2$ as a catalyst in the absence of CuI as cocatalyst leads predominantly to the formation of carbonylative product, that was subjected to the cyclocondensation, giving rise to the desired pyrimidine in 28 % yield (entry 5).

The scope of the alkyne **1** and the amidinium component **10** is similar as in the pyrimidine synthesis via acid chlorides and was, therefore, not exhaustively screened here.

Table 20. One-Pot Four-Component Carbonylative Coupling-Cyclocondensation Synthesis of Pyrimidines 12

Entry	Alkyne **1**	Aryl iodide **17**	Amidine **10**	Product (Yield %)
1	$R^1 = {}^n$Bu (**1b**)	*p*-$CH_3OC_6H_4I$ (**17a**)	R^5 = 2-thienyl (**10b**)	 **12t** (51 %)
2	R^1 = Ph (**1a**)	2-iod thiophene (**17b**)	R^5 = Me (**10f**)	 **12u** (56 %)
3	**1b**	*p*-$CH_3C_6H_4I$ (**17c**)	 (as nitrate) **10i**	 **12v** (29 %)
4	**1a**	*p*-$CH_3O_2CC_6H_4I$ (**17d**)	**10f**	 **12w** (43 %)
5	**1b**	*p*-CNC_6H_4I (**17e**)	**10b**	 **12x** (28 %)

Generally, this carbonylative pyrimidine synthesis proceeds in lower yields in comparison to the synthesis starting from acid chlorides; however, it can be considered as complementary since acid sensitive functionality can be tolerated here. Potentially, it is possible to avoid the protection of hydroxy and amino groups. Further studies are currently under investigation.

Spectroscopic data

The formation of the pyrimidyl core is unambiguously supported by the spectroscopic and analytical data. In the ^{1}H NMR spectra of the 2,4,6-trisubstituted pyrimidines the pyrimidyl methine resonance is found in a wide range of δ 7.12-7.91 (C^5H) as a distinct singlet. For **12t, 12u** and **12x** thienyl substituents are detected as three doublets of doublets at δ 7.14-7.18 (with coupling constants of 5.1 and 3.7 Hz); δ 7.45-7.49 (with coupling constants of 5.1 and 1.1 Hz) and δ 7.84-8.10 (with coupling constants of 3.7 and 1.1 Hz). For **12t**, **12v** and **12x** butyl substituents are identified as the sets of signals at δ 0.97-0.98 (triplet with a coupling constant of 7.0-7.4 Hz and an intensity of 3 protons); δ 1.38-1.86 (two multiplets with intensities of 2 protons) and δ 2.72-2.85 (triplet with a coupling constant of 7.7-7.9 Hz and an intensity of 2 protons). For **12u-12w** methyl groups on pyrimidine or aromatic ring give rise to singlets at δ 2.42-2.87 (with an intensity of 3 protons). For **12t** and **12m** methoxy groups appear as singlets at δ 3.87 (with an intensity of 3 protons). For **12v** proton resonances of methyl-nitro-aniline substituents are found in a relatively low shifted field in the range of δ 7.79 (a doublet of doublets with coupling constants of 8.2 Hz and 2.4 Hz) and 9.71 (a doublet with a coupling constant of 2.4 Hz).

Accordingly, in the ^{13}C NMR spectra the carbon resonances of pyrimidyl systems of the 2,4,6-trisubstituted pyrimidines can be unambiguously assigned at δ 168.4-172.8 for the quaternary C^2, at δ 163.1-165.2 for the quaternary C^4, at δ 107.9-113.2 for the methine C^5, and at δ 159.3-163.6 for the quaternary C^6. For **12v** one of the carbon resonances for the quaternary carbon of nitro-substituted benzene ring is found in a low field at δ 147.1 that can be explained by electron-withdrawing effect of the nitro group. The quaternary carbon of the ester group for compound **12w** is identified in a low field at δ 166.6. In turn, the quaternary carbon of the nitrile group for the compound **12x** appears in a relatively high field at δ 101.5.

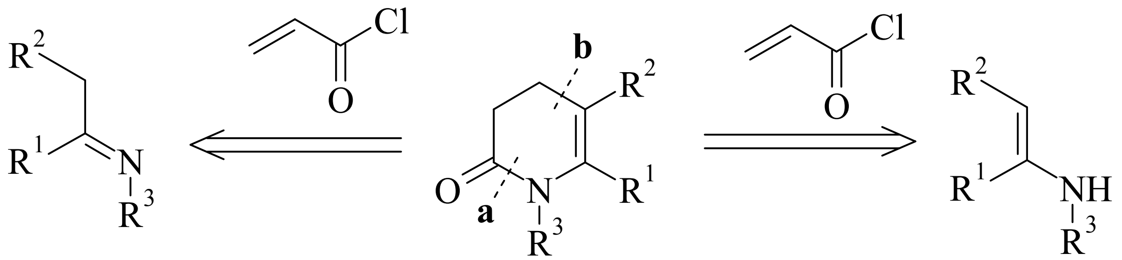
The mass spectra of all obtained compounds show the molecular peaks. The usual fragmentation mode for butyl substituted pyrimidines leads to the loss of methyl, ethyl and allyl fragments. For **12w** the loss of methoxy and carbomethoxy groups was detected.

The vibrations of CN group (**12x**) were identified at 2229 cm^{-1} in the IR spectra.

4.4 A Four-Component Coupling-Amination-Aza-Annulation-Pictet-Spengler (CAAPS) Sequence as a Novel Access to Tetrahydro-β-carbolines

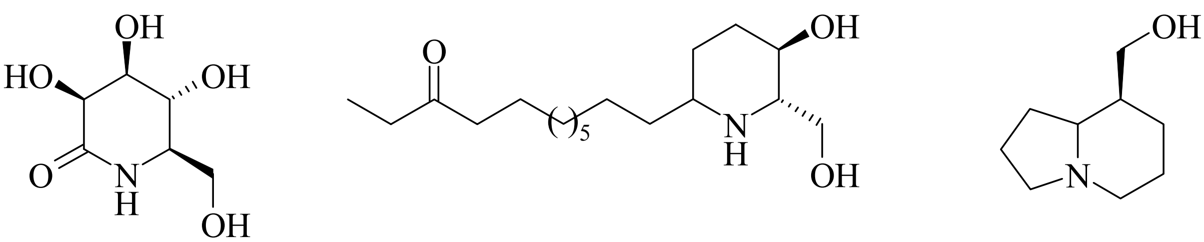
4.4.1 Aza-Annulation and Pictet-Spengler Reactions Literature Review

The aza-annulation reaction is one of the most efficient synthetic routes to prepare nitrogen heterocycles, using imines or enamines and *α,β*-unsaturated chlorides as the starting compounds (Scheme 67).[97]



Scheme 67. Aza-annulation Reaction

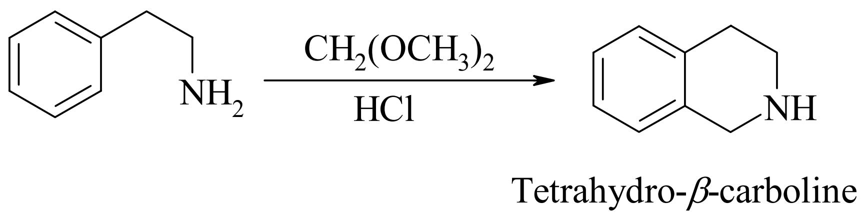
The aza-annulation reaction is believed to proceed via initial Michael addition of the enamine to an *α,β*-unsaturated acid derivative followed by an intramolecular *N*-acylation.[100] In this approach, a carbon-carbon (**b**) and a carbon-nitrogen (**a**) bonds are formed in a two-step, one-pot procedure. The resultant *δ*-lactam (dihydro pyridone) core was used as a valuable building block in the synthesis of numerous alkaloids, such as D-mannolactam,[98] prosopinine[98] and tashiromine[99] (Fig. 25).



D-Mannolactam Prosopinine Tashiromine

Fig. 25. Selected Alkaloids Synthesized via Aza-annulation Reaction

The Pictet-Spengler condensation was discovered in 1911 by Amé Pictet and Theodor Spengler[143,144] and provides a straightforward route to tetrahydro-*β*-carboline (THBC) core, a very popular template for drug discovery (Scheme 68).

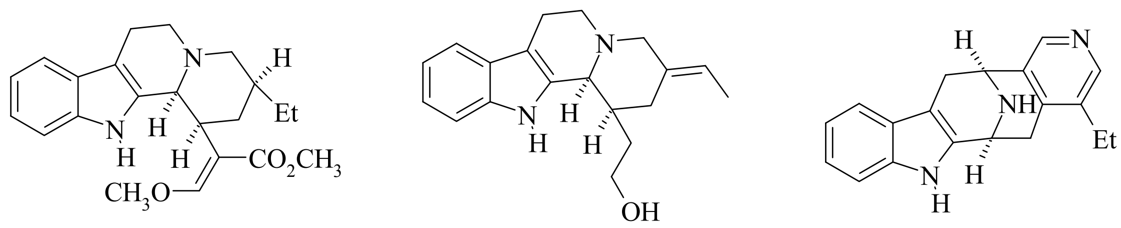


Scheme 68. Pictet-Spengler Cyclocondensation

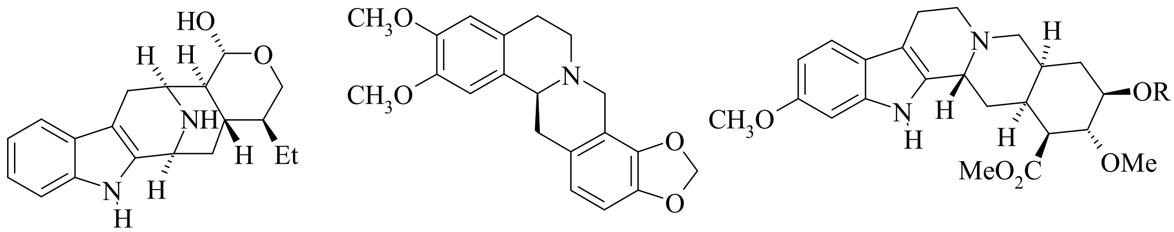
The reaction proceeds through an iminium cation, that has been derived either from a condensation of amines with carbonyl compounds[145] or from an addition of amines to an activated triple bond.[146] It was shown that the reaction can proceed in nonacidic aprotic media as well as under the conditions of acid or superacid catalysis.[147] The use of superacids is particularly interesting, since even inactivated 2-phenethylamines are involved into the PS condensation.

Lewis-acid catalyzed PS reactions were achieved in short reaction times with the assistance of microwave irradiation.[148]

The numerous types of alkaloids have been synthesized using PS reaction, such as (-)-corynantheidine, (-)-corynantheidol, (-)-geissoschizol and (+)-geissoschizine;[149] (+)-ajmaline, alkaloid G, norsuaveoline and sarpagine;[150] (+)-majvinine, (+)-10-methoxyaffinisine and macralstonidine;[151] (-)-reserpine;[152] (S)-tetrahydropalmatine, (S)-canadine, (S)-sinactine, (S)-corypalmine, (S)-isocorypalmine[153] and (-)-raumacline (Fig. 26).[154]



(-)-Corynantheidine (-)-Geissoschizol Norsuaveoline



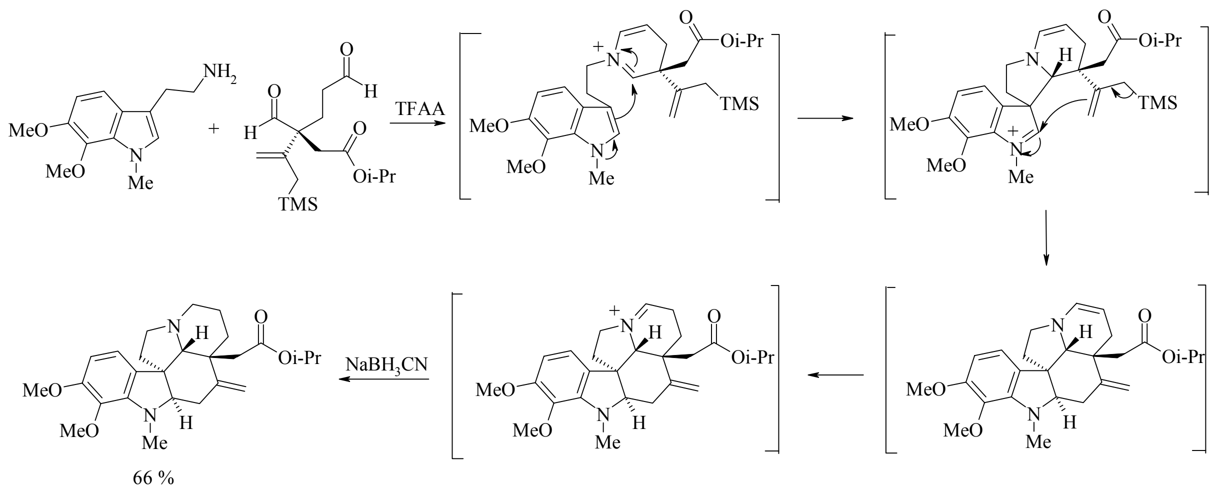
(-)-Raumacline (*S*)-Sinactine (-)-Reserpine

Fig. 26. Selected Examples of Alkaloids Synthesized via PS Reaction

However, the most impressive transformations that involve the PS reaction are cascade reactions, which allow the fashioning of diverse molecular architectures of alkaloids rapidly through efficient and atom-economical processes.

An elegant and concise route to the corynanthein-type alkaloids was achieved by combining the PS reaction with the subsequent ene-reaction.[155]

The highly efficient total synthesis of aspidophytine developed by Corey, demonstrates a high level of power that can be achieved by cascade reactions.[156] The main operation of this total synthesis is drawn on Scheme 69.



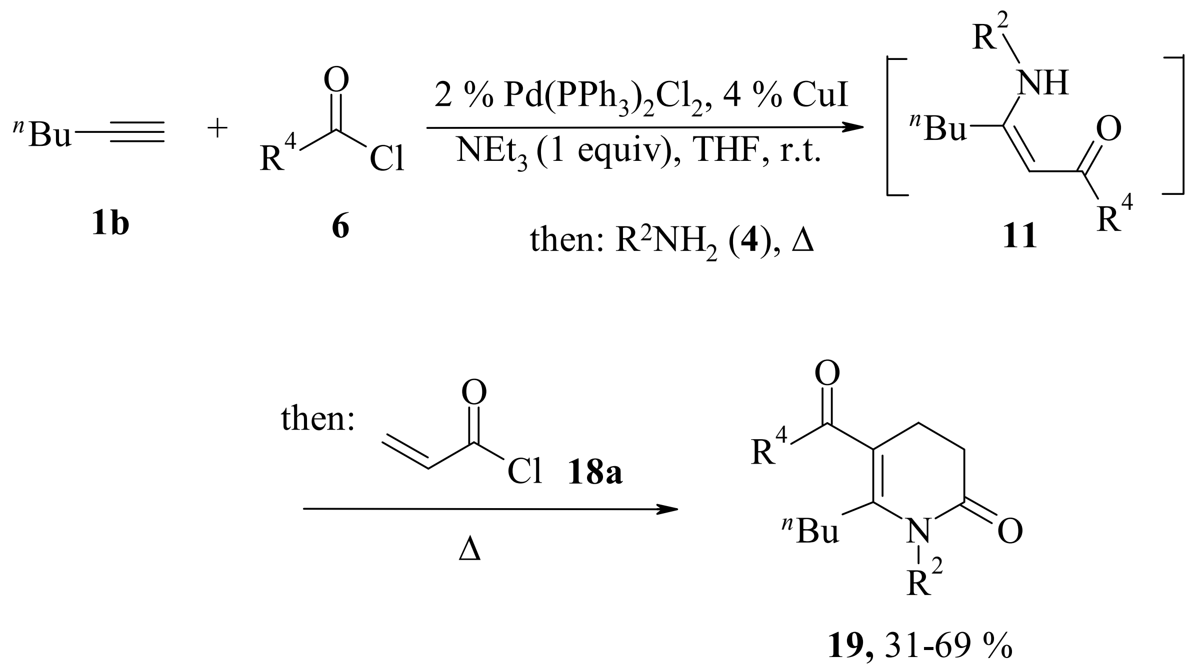
Scheme 69. The Cascade Sequence Leading to Aspidophytine Core

4.4.2 One-pot Four-component Coupling-Amination-Aza-Annulation (CAA) Sequence

In the previous chapters it was shown that ynones generated via Sonogashira coupling can be used as versatile intermediates and subjected directly, without isolation into the subsequent transformations. For instance, the reaction with amines gave rise to *β*-enaminones that are in their own right extremely valuable intermediates in organic chemistry.

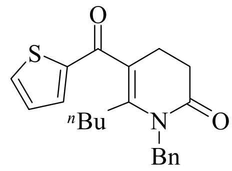
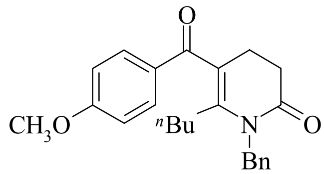
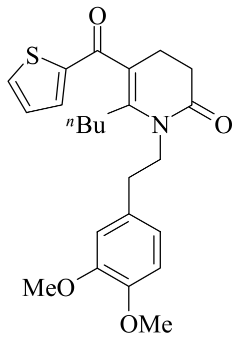
This time I decided to utilise the enormous synthetic potential of *β*-enaminones. However, since in cyclocondensation reactions they are synthons of ynones, it does not make sense to apply them to heterocycle synthesis. It seems to be more useful to take advantage of their unique reactivity and to try to keep all the atoms including nitrogen in the final products. Since under our modified Sonogashira conditions, we have essentially neutral reaction medium after the first cross-coupling step, I decided to involve *α,β*-unsaturated chlorides as a fourth component of our assembly, thus probing the compatibility of an aza-annulation reaction with the conditions of coupling-amination (CA) sequence.

Hence, after performing the CA reaction with hexyne (**1b**), *p*-methoxy benzoyl or thienoyl chloride (**6a** or **6e**), and benzyl amine (**4f**) or homoveratryl amine (**4h**); acryloyl chloride (**18a**) was added, and after gentle heating, the intermediate *β*-enaminones were smoothly converted into 5-acyl dihydropyrid-2-ones (**19**) that were subsequently isolated in moderate to good yields as yellow or colorless oils (Scheme 70, Table 21).



Scheme 70. One-pot Four-component CAA Sequence

Table 21. CAA Sequence

Entry	Alkyne **1**	Acid chloride **6**	Amine **4**	Product (Yield %)
1	R^1 = ^{n}Bu (**1b**)	R^4 = 2-thienyl (**6e**)	R^2 = Bn (**4f**)	 **19a**, 31 %[a]
2	**1b**	R^4 = p-$CH_3OC_6H_4$ (**6a**)	**4f**	 **19b**, 63 %[b]
3	**1b**	**6e**	R^2 = 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (**4h**)	 **19c**, 69 %[c]

[a] 1.2 equiv of benzyl amine **4f** and 1.2 equiv of acryloyl chloride **18a** were used; [b] 1.2 equiv of benzyl amine **4f** and 1.5 equiv of acryloyl chloride **18a** were used; [c] 1.2 equiv of homoveratryl amine **4g** and 2.1 equiv of acryloyl chloride **18a** were used

Interestingly, the use of an excess of acryloyl chloride **19a** leads to the significant increase of the yield (compare entry 1 and entries 2, 3).

Spectroscopic data

The formation of the dihydropyrid-2-one core is unambiguously supported by the spectroscopic and analytical data. In the ^{1}H NMR spectra the resonances of two CH_2 groups are found at δ 2.39-2.69 either as distinct singlets (for **19a** and **19c** with an intensity of four protons) or as two multiplets (for **19b** with intensities of two protons). For **19a** and **19c** thienyl substituents are identified as three doublets of doublets at δ 7.00-7.18 (with coupling constants of 4.9 and 3.8 Hz); δ 7.20-7.49 (with coupling constants of 3.8 and 1.2 Hz) and δ

7.51-7.54 (with coupling constants of 4.9 and 1.2 Hz). For **19a-19c** butyl substituents are found as a set of signals in the ranges of δ 0.73-0.84 (triplets with a coupling constant of 7.1-7.4 Hz and an intensity of 3 protons), δ 1.05-2.18 (two multiplets with intensities of 2 protons) and δ 2.15 (triplets with a coupling constant of 7.7 Hz and an intensity of 2 protons). The resonances of benzyl CH_2 protons of **19a** and **19b** give rise to distinct singlets in a range of δ 4.89-4.98 (with an intensity of two protons).

Accordingly, in the ^{13}C NMR spectra of the carbon resonances of dihydropyrid-2-one systems can be unambiguously assigned at δ 30.3-32.0 for the two CH_2 groups (C^3 and C^4), at δ 118.2-119.5 for C^5 and δ 144.5-145.0 for C^6 for two olefinic quaternary carbons and at δ 170.6-171.1 for the amide quaternary carbon C^2 (Fig. 27).

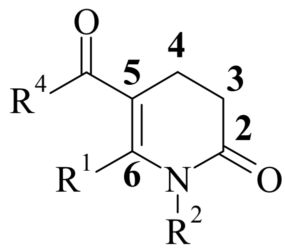
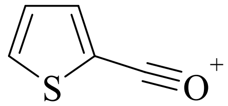
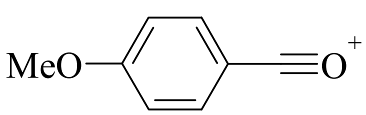


Fig. 27. The Numeration of Dihydro-1H-pyridin-2-one

The second carbonyl groups are found at δ 188.0-195.5 as the quaternary carbons.

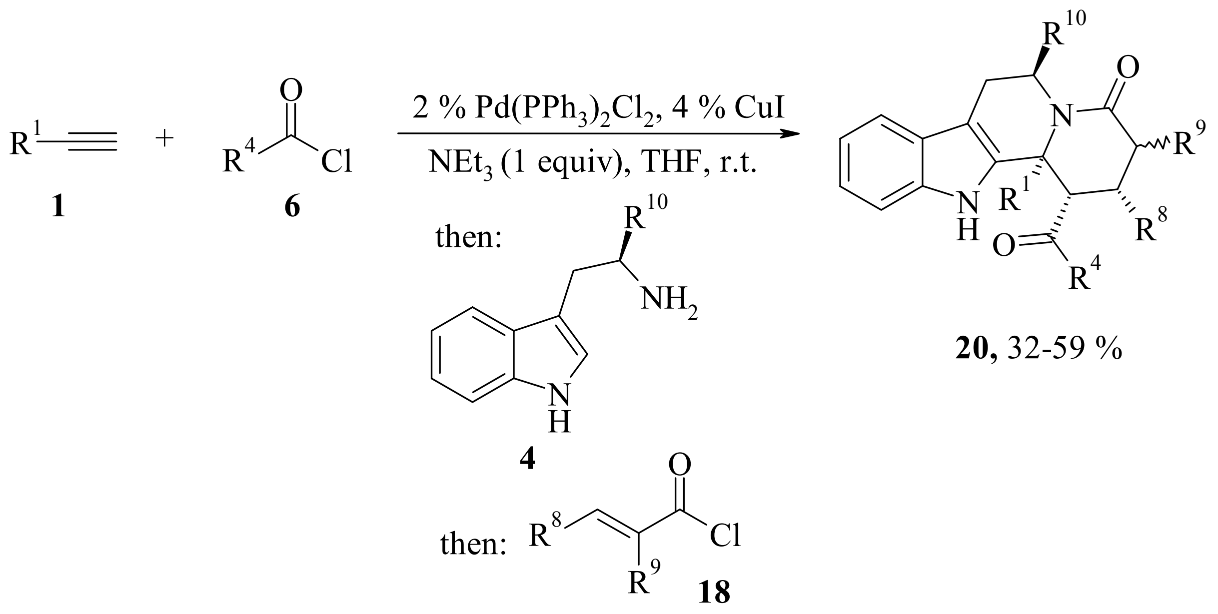
The mass spectra of all the obtained compounds show the molecular peaks. Characteristically for ketone derivatives is the α-fragmentation at the carbonyl group, leading to appearing of R^4CO^+ peaks in the mass spectra (Table 22).

Table 22. The Fragmentation of Selected Lactams 19 (EI, 70 eV)

Compound	Fragment	*m/z* (%)
19a		111 (32)
19b		135 (100)

4.4.3 One-pot Four-component Coupling-Amination-Aza-Annulation-Pictet-Spengler (CAAPS) Sequence

Interestingly, upon the application of tryptamine (**4g**) or (S)-(**–**)-tryptophane methyl ester (**4i**) as primary amines in the CAA sequence, lactams **19** were not the final products, but as a result of a subsequent Pictet-Spengler reaction, only the indolo[2,3-a]quinolizin-4-ones **20** were isolated in moderate to good yields (Scheme 71, Table 23).



Scheme 71. CAAPS Sequence

Table 23. CAAPS Sequence

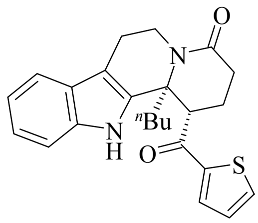
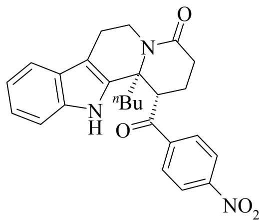
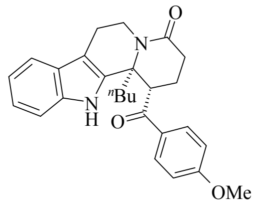
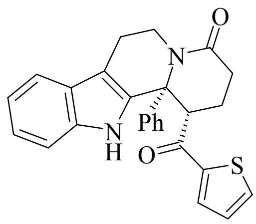
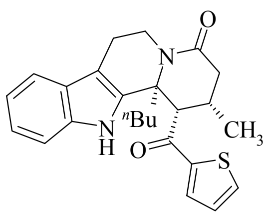
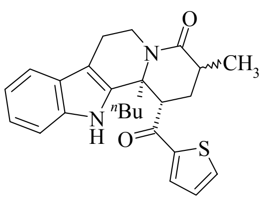
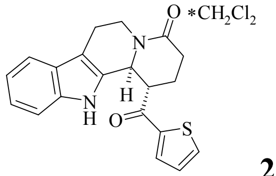
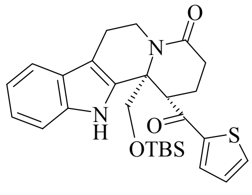
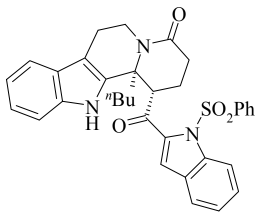
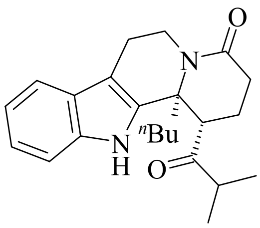
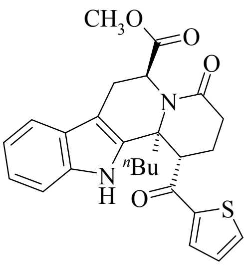
Entry	Alkyne **1**	Acid chloride **6**	Tryptamine **4**	α,β-Unsaturated acid chloride **18**	Product (Yield %)
1 [a]	R^1 = ^{n}Bu (**1b**)	R^4 = 2-thienyl (**6e**)	R^{10} = H (**4g**)	R^8 = H, R^9 = H (**18a**)	 **20a**, 52 %
2 [a]	**1b**	R^4 = *p*-$NO_2C_6H_4$ (**6b**)	**4g**	**18a**	 **20b**, 43 %
3 [a]	**1b**	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	**4g**	**18a**	 **20c**, 59 %
4 [a]	R^1 = Ph (**1a**)	**6e**	**4g**	**18a**	 **20d**, 41 %
5 [a]	**1b**	**6e**	**4g**	R^8 = CH_3, R^9 = H (**18b**)	 **20e**, 50 %
6 [a]	**1b**	**6e**	**4g**	R^8 = H, R^9 = CH_3 (**18c**)	 **20f**, 54 % (*syn-syn*/*syn-anti* = 4.5:1) [e]

Table 23. Continued

Entry	Alkyne **1**	Acid chloride **6**	Tryptamine **4**	α,β-Unsaturated acid chloride **18**	Product (Yield %)
7 [a]	R^1 = TMS (**1f**)	**6e**	**4g** [c]	**18a**	 **20g**, 32 %
8 [a]	R^1 = CH_2OTBS (**1h**)	**6e**	**4g**	**18a**	 **20h**, 30 %
9 [a]	**1b**	R^4 = *N*-(Phenyl-sulfonyl)-3-indolyl (**6k**)	**4g**	**18a**	 **20i**, 36 %
10 [a]	**1b**	R^4 = *iso*-Propyl (**6m**)	**4g**	**18a**	 **20j**, 36 %
11 [b]	**1b**	**6e**	R^{10} = CO_2CH_3 (**4i**) [d]	**18a**	 **20k**, 45 %

[a] the reaction was carried out in THF as a solvent; [b] the reaction was carried out in toluene as a solvent; [c] *n*-Bu_4NF (1 mL, 1 *M* solution in THF) was added after the coupling step and the reaction mixture was stirred for 5 min before amine **4g** was added; [d] Amine **4i** (as a hydrochloride) was added with additional amounts of triethylamine (0.28 mL, 2.00 mmol); [e] The mixture of diastereomers was separated by column chromatography.

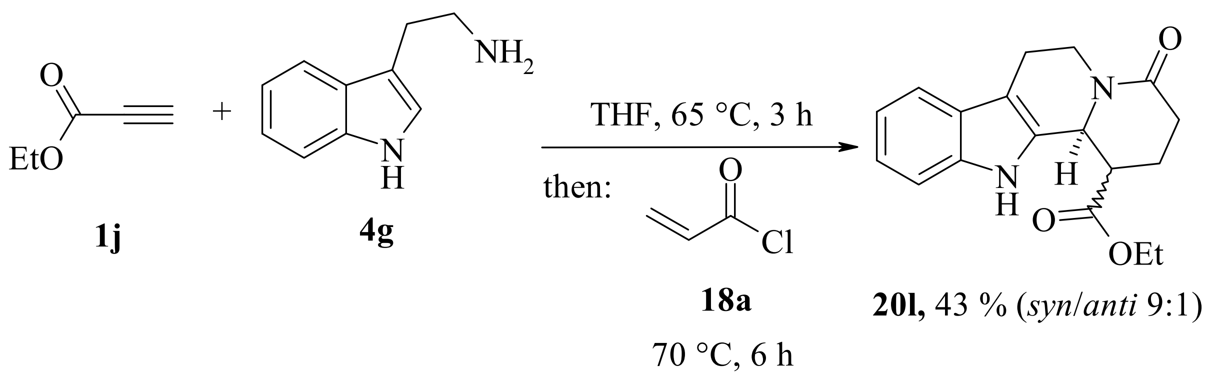
The results show that the CAAPS sequence proceeds with good yields for acid chlorides with electron rich substituent **6a** (entry 3) and electron withdrawing substituent **6b** (entry 2). Aliphatic **1a, 2h,** aromatic **1a** alkynes and TMSA **1f** can be involved into this four-component synthesis. In the case of phenylacetylene **1a** (entry 4), the prolongation of heating is required to complete the reaction. For example, 3 h of reflux afforded the target product **20d** in only 27 % yield, and 32 % of the uncyclized aza-annulation product was isolated (overall yield 59 %). After 24 h of reflux, the desired product **20d** was obtained in 41 % yield, and no traces of the aza-annulation product was observed. This occurence can be explained by the steric hindrance of the bulky phenyl substituent, which led to the prolongation of the reaction time.

The reaction proceeded smoothly for acryloyl **18a** (entries 1-4, 7-11), crotonyl **18b** (entry 5) and methacryloyl **18c** (entry 6) chlorides.

This generating of iminium salts via an aza-annulation reaction with subsequent trapping through the Pictet-Spengler cyclocondensation remained unexplored.[157]

Interestingly, for the complete conversion of ynone to *β*-enaminone, 2 equiv of the amine **4g** was required (entries 1-8). It can be explained by its conversion to the hydrochloride form, because tryptamine is more basic than triethylamine. However, this amount can be reduced to 1.1 equiv, by adding 1.0 equiv of DBU as the strong, non-nucleophilic base to the reaction mixture on the second step (entries 9, 10).

I found that this sequence can be performed starting directly with an alkyne bearing EWG, without a first cross-coupling step in a three-component fashion (Scheme 72).

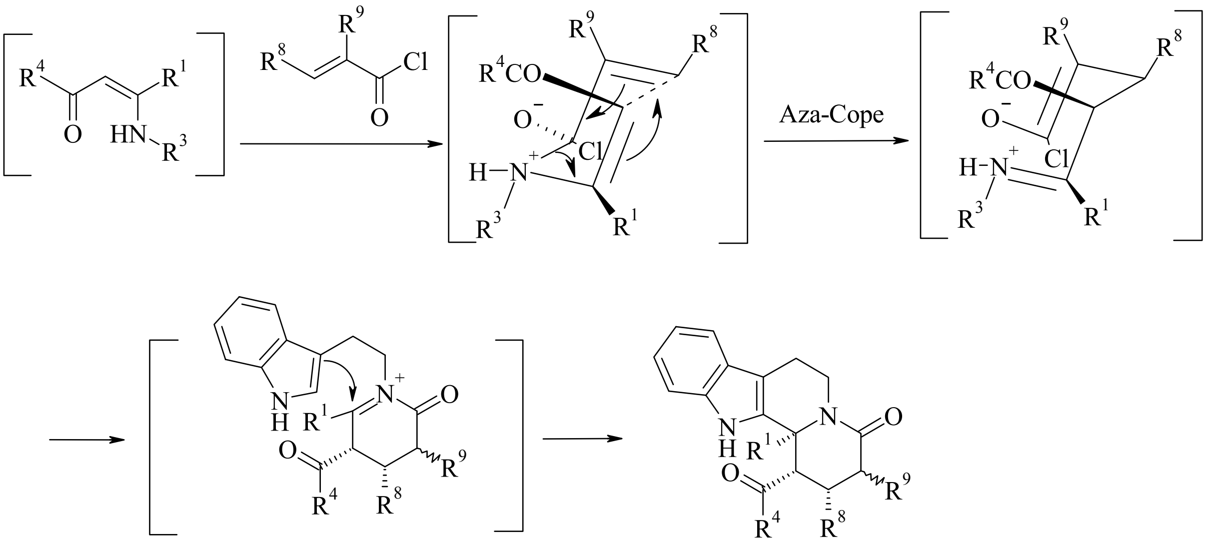


Scheme 72. One-pot Three-component Amination-Aza-annulation-Pictet-Spengler Sequence

This time, since no triethylammmonium hydrochloride is present in the reaction mixture, only 1.0 equiv of tryptamine **4g** is sufficient to complete the *β*-enaminone formation.

This one-pot three-component amination-aza-annulation-Pictet-Spengler sequence provides the additional flexibility in a tetrahydro-*β*-carboline substitution pattern.

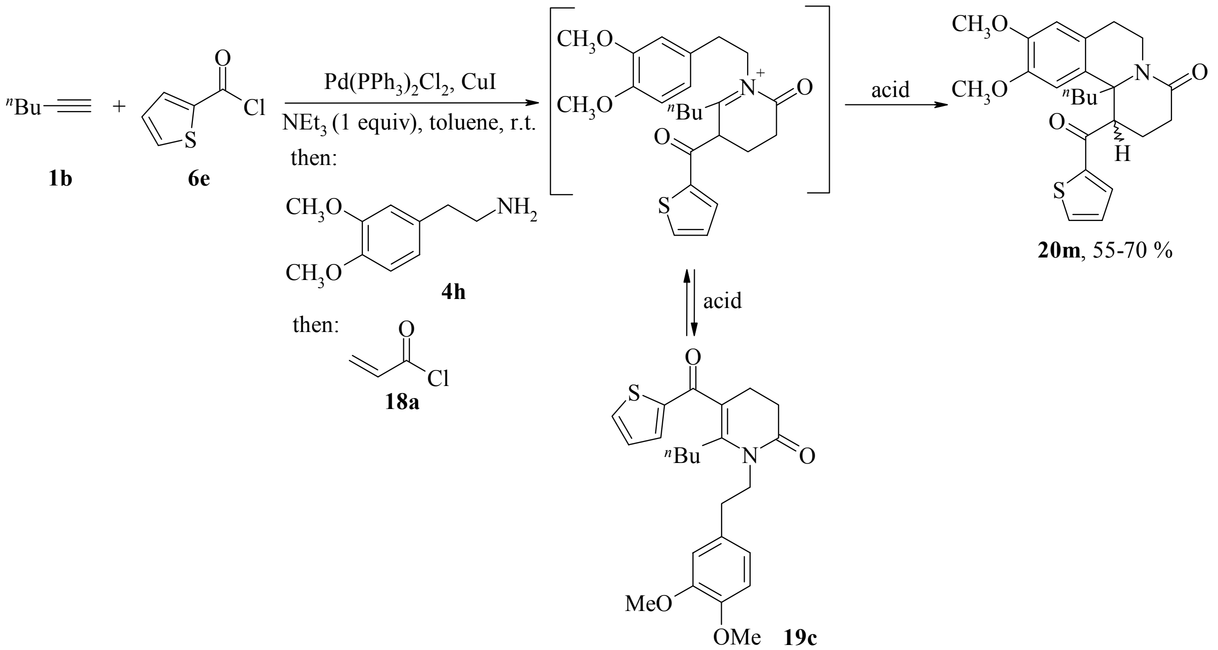
The most intriguing feature of our sequence, however, was the exclusive diastereoselectivity (excepting **20f** and **20l** where two diastereomers were formed, most probably via epimirization). This result can be attributed to the mechanism of the aza-annulation-PS steps (Scheme 73).



Scheme 73. The Proposed Mechanism of CAAPS

First, the reaction of ynones with tryptamine (**4g**) results in the formation of the (*Z*)-isomer of *β*-enaminone. The reaction of *β*-enaminone with *α*,*β*-unsaturated acid chlorides produces the zwitterionic intermediate that now undergoes a cationic aza-Cope-type rearrangement, so that R^8 and carbonyl substituents are oriented *cis* to each other. In the next step, Pictet-Spengler cyclocondensation proceeds via a spiroindolenine intermediate. This is not important for us with regard to diastereoselectivity. Important, however, is that in the resulting iminium species,[158] nucleophilic attack by indolyl position would be expected to occur predominantly on the opposite side of the more bulky carbonyl group, leading mainly to the *cis* diastereomer. Furthermore, the subjecting of the chiral tryptophane ester (**4i**) gave rise to only one enantiomer. This means that four stereocenters can be installed stereoselectively.

Next, we turned our attention to the case of the homoveratryamine **4h** that gave rise to the aza-annulation product **19c**. We reasoned that the aromatic ring of the homoveratryl amine carries the activating substituents and should provide the electronic character for annulation to occur. It seems reasonable to assume, that the intermediate iminium salt in this case is less reactive (comparatively to tryptamine species). Therefore, we decided to try a range of Lewis and protic acids, in order to enhance the reactivity of the acyliminiumsalt and to induce the Pictet-Spengler cyclocondensation. Since it is well known that THF undergoes the ring-opening under acidic conditions, we performed the sequence in toluene as the solvent (Scheme 74).

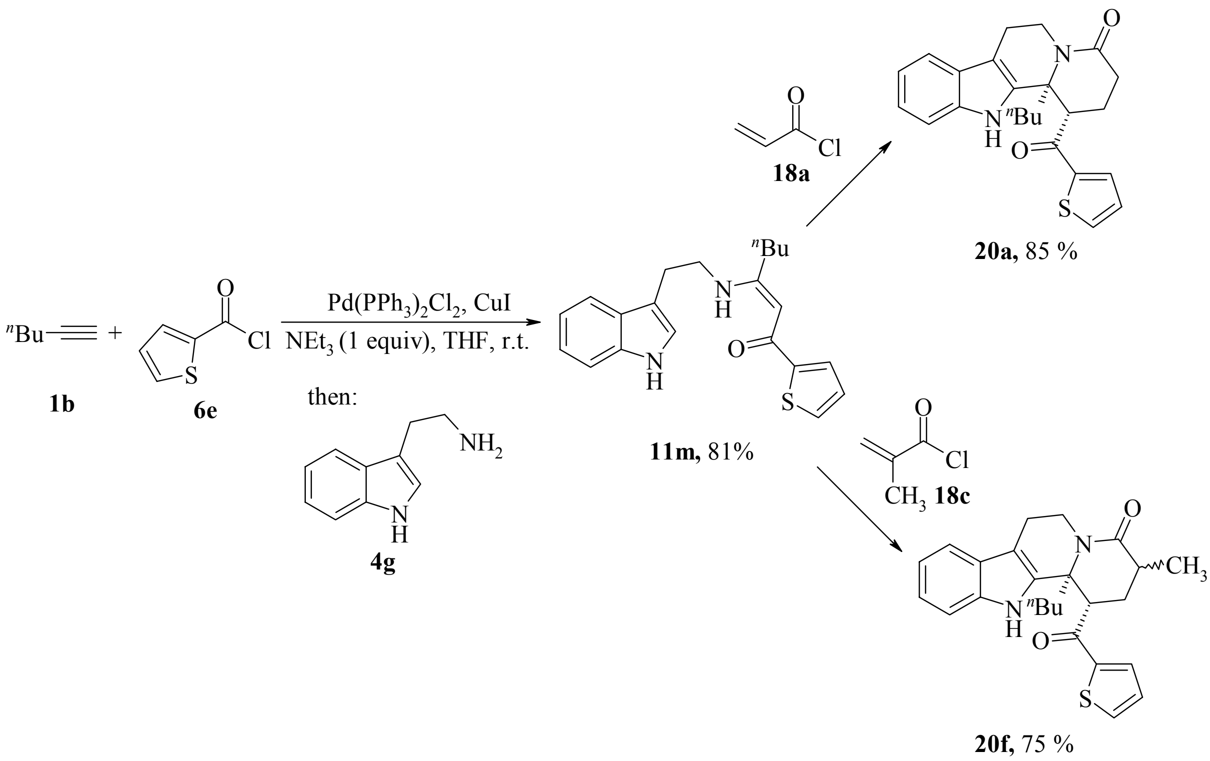


Scheme 74. CAAPS Sequence for Homoveratryl Amine (4h)

The Sonogashira coupling of acid chloride **6e** with alkyne **1b** (1:1.05 ratio) proceeded at r.t. for 3 h. Addition of 3,4-dimethoxyphenylethylamine **4h** (1.2 equiv) with a subsequent heating at 100 °C for 8 h led to the formation of a *β*-enaminone. Subsequent treatment with acryloyl chloride **18a** (2 equiv) to produce the aza-annulation product **19c** was effected by heating at 70 °C over the course of 3 h. Then an acid (4 equiv) was added and the reaction mixture was heated until consumption of the aza-annulation product.

By applying strong protic acids such as CH_3SO_3H, CF_3SO_3H or CF_3CO_2H the desired product **20m** was obtained in 55, 66, and 70 % yields respectively, but unfortunately as the mixture of diastereomers with *dr* of 1-1.4:1. After addition of weak Lewis acids such as BF_3, TFAA or TMSCl, only the aza-annulation product **19c** was detected by TLC. The application of strong Lewis acids such as $TiCl_4$, $SnCl_4$ and $POCl_3$ led to the formation of a black tar. Finally, TMSOTf was the superior Lewis acid resulting to the formation of **20m** in 65 % with *dr* 1.6:1.

In order to compare our consecutive approach to the stepwise splitting protocol, I synthesized the *β*-enaminone **11m** in 81 % yield via our coupling-amination sequence and subjected it to the aza-annulation-PS sequence with acryloyl **18a** and methacryloyl **18c** chlorides (Scheme 75).



Scheme 75. CAAPS Sequence in Splitting Protocol

Indolo[2,3-a]quinolizin-4-ones **20a** and **20f** were obtained in 85 % and 75 % yields correspondingly. The overall yield for this splitting protocol lies in the same range as our CAAPS sequence. However, avoiding the isolation and purification of the intermediate *β*-enaminone favors the application of the direct CAAPS approach.

Spectroscopic data

The formation of the indolo[2,3-a]quinolizin-4-one core is unambiguously supported by the spectroscopic and analytical data. In the ^{1}H NMR spectra of **20a-k** there were no distinct singlets of the indole-2-H. A set of signals corresponding to the 1,2,3,6,7-H protons of quinolizin-4-one is found in a range of δ 1.96-5.52 (Fig. 28).

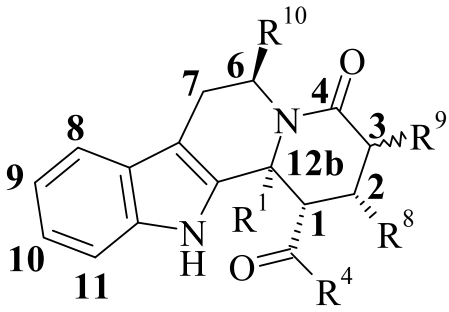


Fig. 28. Numeration of Quinolizinone Core

These signals are sometimes overlapped with resonances of butyl protons. However several general peaks can be distinguished (Table 24).

Table 24. Selected Proton Resonances of Quinolizin-4-one Core (500MHz spectra were recorded in $CDCl_3$ at 300K)

Compound	1-H	2-H	3-H	6-H	7-H
20a	δ 3.73 (dd, ^3J = 13.4, ^3J = 5.0 Hz, 1H)	δ 2.35-2.44 (m, 1H) not distinguished	Not distinguished	δ 5.22 (ddd, ^2J = 12.8, ^3J = 4.8, ^3J = 1.5 Hz, 1H) δ 2.98 (dt, ^2J = 12.4, ^3J = 3.8 Hz, 1H)	Not distinguished
20b	δ 3.92 (dd, ^3J = 13.4, ^3J = 5.0 Hz, 1H)	Not distinguished	Not distinguished	δ 5.24 (ddd, ^2J = 12.7, ^3J = 4.7, ^3J = 1.3 Hz, 1H) δ 2.98 (dt, ^2J = 12.4, ^3J = 3.4 Hz, 1H)	Not distinguished
20c	δ 3.93 (dd, ^3J = 13.3, ^3J = 5.0 Hz, 1H)	Not distinguished	Not distinguished	δ 5.27 (ddd, ^2J = 12.8, ^3J = 4.8, ^3J = 1.5 Hz, 1H) δ 2.98 (dt, ^2J = 12.0, ^3J = 4.0 Hz, 1H)	Not distinguished
20d[a]	δ 4.81 (t, ^3J = 3.6 Hz, 1H)	δ 1.80-1.90 (m, 1H) δ 1.92-1.99 (m, 1H)	δ 2.26 (dd, ^2J = 17.7, ^3J = 5.4 Hz, 1H) δ 2.78 (ddd, ^2J = 17.7, ^3J = 12.9, ^3J = 6.8 Hz, 1H)	δ 4.66 (dd, ^2J = 12.7, ^3J = 5.6 Hz, 1H) 2.99 (dt, ^2J = 12.1 Hz, ^3J = 4.4 Hz, 1 H)	δ 2.91 (dt, ^2J = 15.1 Hz, ^3J = 5.6 Hz, 1 H) δ 2.41 (dd, ^2J = 14.9 Hz, ^3J = 4.2 Hz, 1 H)

Table 24. Continued

Compound	1-H	2-H	3-H	6-H	7-H
20e[a]	δ 4.66 (d, ^3J = 3.7 Hz, 1H)	δ 1.88-1.96 (m, 1 H)	Not distinguished	δ 4.76 (dd, ^2J = 13.7, ^3J = 6.9 Hz, 1H) 3.41 (dt, ^2J = 12.8 Hz, ^3J = 5.0 Hz, 1 H)	δ 2.80 (ddd, ^2J = 15.6 Hz, ^3J = 11.5 Hz, ^3J = 6.9 Hz, 1 H) δ 2.55 (dd, ^2J = 15.6 Hz, ^3J = 5.0 Hz, 1 H)
20f	δ 3.75 (dd, ^3J = 13.1, ^3J = 6.0 Hz, 1H)	δ 1.84 (ddd, ^2J = 14.1, ^3J = 5.7, ^3J = 4.4, Hz, 1H) δ 2.62 (dt, ^2J = 13.7, ^3J = 9.8, Hz, 1H)	δ 2.81-2.86 (m, 2 H) overlapped with 7-H	δ 5.23 (ddd, ^2J = 12.8, ^3J = 4.8, ^3J = 1.6 Hz, 1H) δ 2.96 (dt, ^2J = 12.4, ^3J = 3.7 Hz, 1H)	δ 2.81-2.86 (m, 2 H) overlapped with 3-H δ 2.68-2.78 (m, 2 H) overlapped with ^{n}Bu
20h	δ 3.80-3.80 (m, 1H)	δ 2.65-2.87 (m, 5 H) overlapped with 3-H and 7-H δ 2.00-2.10 (m, 1H)	δ 2.65-2.87 (m, 5 H) overlapped with 2-H and 7-H	δ 5.17 (dd, ^2J = 12.8, ^3J = 3.3 Hz, 1H) δ 2.95 (dt, ^2J = 12.0 Hz, ^3J = 4.2 Hz, 1 H)	δ 2.65-2.87 (m, 5 H) overlapped with 2-H and 3-H
20i	δ 3.67 (dd, ^3J = 13.4, ^3J = 5.4 Hz, 1H)	δ 2.37-2.47 (m, 1H) δ 2.06-2.14 (m, 1H)	δ 2.71-2.93 (m, 5H) overlapped with 7-H and ^{n}Bu	δ 5.25 (ddd, ^2J = 12.7, ^3J = 4.6, ^3J = 1.8 Hz, 1H) δ 2.99 (dt, ^2J = 12.0, ^3J = 4.0 Hz, 1H)	δ 2.71-2.93 (m, 5H) overlapped with 3-H and ^{n}Bu
20j	δ 3.16 (dd, ^3J = 13.5, ^3J = 5.0 Hz, 1H)	δ 1.96 (ddd, ^2J = 18.1, ^3J = 9.0, ^3J = 4.7, Hz, 1H) δ 2.13-2.21 (m, 1H)	δ 2.66-2.76 (m, 3H) overlapped with 7-H	δ 5.16 (ddd, ^2J = 12.7, ^3J = 4.8, ^3J = 1.5 Hz, 1H) δ 2.91 (dt, ^2J = 12.4, ^3J = 3.7 Hz, 1H)	δ 2.83 (ddd, ^2J = 15.4, ^3J = 3.4, ^3J = 1.6, Hz, 1H) δ 2.66-2.76 (m, 3H) overlapped with 3-H
20k	δ 4.90 (t, J = 9.9 Hz, 1H)	δ 2.31-2.37 (m, 2H)	δ 2.82-2.86 (m, 2H)	δ 5.52 (dd, ^3J = 6.8, ^3J = 2.7 Hz, 1H)	δ 3.45 (dd, ^2J = 15.8, ^3J = 2.7 Hz, 1H) δ 3.10 (dd, ^2J = 15.8, ^3J = 6.9 Hz, 1H)

[a] spectra were recorded in DMSO-d_6

First, the equatorial proton 6-Hα appearing at δ 4.76-5.25 can be unambiguously assigned due to its characteristic downfield shift explained by the deshielding of the amide carbonyl. Usually it appears as a doublet of doublets of doublets with coupling constants of 12.7-12.8 (geminal), 4.6-4.8 (equatorial-axial, dihedral angle from X-Ray of 43-54 °) and 1.3-1.8 Hz (equatorial-equatorial, dihedral angle from X-Ray of 65-75 °). For compound **20k** where the ester group takes the equatorial position the resonance at δ 5.52 can be assigned as 6-Hβ and gives rise to a doublet of doublets with coupling constants of 6.8 (axial-axial) and 2.7 (axial-equatorial) Hz. From NOESY and COSY experiments the rest of 6-H and 7-H signals can be assigned. The resonances of 6-H*β* are detected at δ 2.91-3.41 as a doublet of triplets with coupling constants of 12.0-12.7 (geminal) and 3.4-4.7 Hz. The resonances of 7-H are identified in the region of δ 2.66-2.93 and are overlapped with butyl protons, but for **20d** they are found as a doublet of triplets with coupling constants of 15.1 (geminal) and 5.6 Hz and a doublet of doublets with coupling constants of 14.9 (geminal) and 4.2 Hz. For **20e** the resonances of 7-H give rise to a doublet of doublets of doublets at δ 2.80 with coupling constants of 15.6 (geminal), 11.5 (axial-axial) and 6.9 Hz (axial-equatorial) and a doublet of doublets at δ 2.55 with coupling constants of 15.6 (geminal), 5.0 (equatorial-axial). Accordingly, the resonance of 1-H, which usually takes the axial position, at δ 3.16-4.90 appearing as the doublet of doublets with coupling constants of 13.1-13.5 (axial-axial, dihedral angle from X-Ray of 170-173 °) and 5.0-6.0 (axial-equatorial, dihedral angle from X-Ray of 52-54 °) Hz can be unambiguously assigned from the cross-peak of $^{1}\underline{C}H$ carbon and 1-H proton in HMBC spectra, since usually only one CH group is present in compounds. Finally, 2-H resonances can be found at δ 1.88-2.62 and then 3-H resonances are detected at δ 2.31-2.93 and can be assigned from the COSY experiments.

For compounds **20g** the most interesting information comes from the coupling constant of 1-H and 12b-H resonances. The resonance of 12b-H gives rise to a doublet at δ 5.44 with a coupling constant of 10.0 Hz (axial-axial coupling, confirms *trans*-stereochemistry), the resonance of 1-H appears as the doublet at δ 3.60 with coupling constants of 12.0 (axial-axial), 10.0 (axial-axial coupling, confirms *trans*- stereochemistry) and 3.2 Hz (axial-equatorial) coupling.

In addition, to these core system peaks, the signals of side chains can be assigned. For instance, for **20j** the isopropyl group is identified as two doublets at δ 0.69 and 0.94; and septet at δ 2.28 with a coupling constant of 7.0 Hz.

The resonances of methyl protons for **20e** are found as doublets at δ 0.77 with a coupling constant of 6.9 Hz. For **20f** and **20f'** the methyl groups are detected at δ 0.77 and 1.42 with coupling constants 6.9 and 6.0 Hz, respectively. For **20j**, **20l** the resonances of indole protons appear in the low field as two doublets at δ 7.26-7.31 (8-H) and 7.49 (11-H) (with coupling constants 8.0 Hz) and two doublets of triplets at δ 7.11 (9-H) and 7.16-7.18 (10-H) (with coupling constants ^3J = 8.0 Hz and ^4J = 1.0 Hz). For **20l** the ethoxy group appears as a triplet and quartet at δ 1.34 and 4.39 with coupling constant of 7.1 Hz. The NH signals for **20a-c** and **20f-l** are identified at δ 7.70-8.50 as distinct singlets (in $CDCl_3$). The NH signal for **20d** and **20e** are detected at δ 11.16-11.76 as distinct singlets (in DMSO-d_6).

In the ^{13}C NMR spectra for **20a-d** and **20h-j** the set of signals corresponding to the 1,2,3,6,7-C carbons of quinolizin-4-one is found in a range of δ 20.9-21.0 ($^7CH_2$), δ 20.4-21.7 ($^2CH_2$), δ 29.4-29.6 ($^3CH_2$), δ 36.7-42.4 ($^6CH_2$), δ 47.2-56.8 (^{1}CH). For **20k** the set of signals corresponding to the 1,2,3,6,7-C carbons of quinolizin-4-one is found in a range of δ 22.7 ($^7CH_2$), δ 23.0 ($^2CH_2$), δ 30.0 ($^3CH_2$), δ 54.8 (^{6}CH), δ 52.0 (^{1}CH). The resonances of quaternary carbon $^{12b}C_{quat}$ for **20a-f**, **20h-k** and **20m** appear at δ 61.4-66.7. Instead of that the compounds **20g** and **20l** with H as the substituent R^1 contain the additional resonance of ^{12b}CH carbon at δ 46.1-50.7. In the ^{13}C NMR spectra of **20a-k** and **20m** two quaternary signals at δ 168.3-173.0 and 192.1-201.8 were assigned as an amide and a carbonyl group, respectively. In the ^{13}C NMR spectrum of **20l** two quaternary signals at δ 168.5 and 174.8 were assigned as an amide and an ester groups.

The mass spectra (FAB) of all the obtained compounds display the molecular peaks. Characteristically for quinolizin-4-one derivatives is the fragmentation at the quaternary carbon $^{12b}C_{quat}$, leading to the loss of R^1 fragment. The use of the EI mode leads to the α-fragmentation at the carbonyl group and appearing of R^4CO^+ peaks in the mass spectra.

The IR spectra of CAAPS products reveal bands in a region of 1651-1611 cm^{-1} typical for the carbonyl and lactam groups.

Additionally, the configurations of diastereomers and enantiomers were unambiguously supported by an X-Ray structure analysis for compounds **20a**, **20b**, **20c, 20e, 20f, 20l, 20m** (Fig. 29, Fig. 30, Fig. 31, Fig. 32, Fig. 33, Fig. 34, Fig. 35).

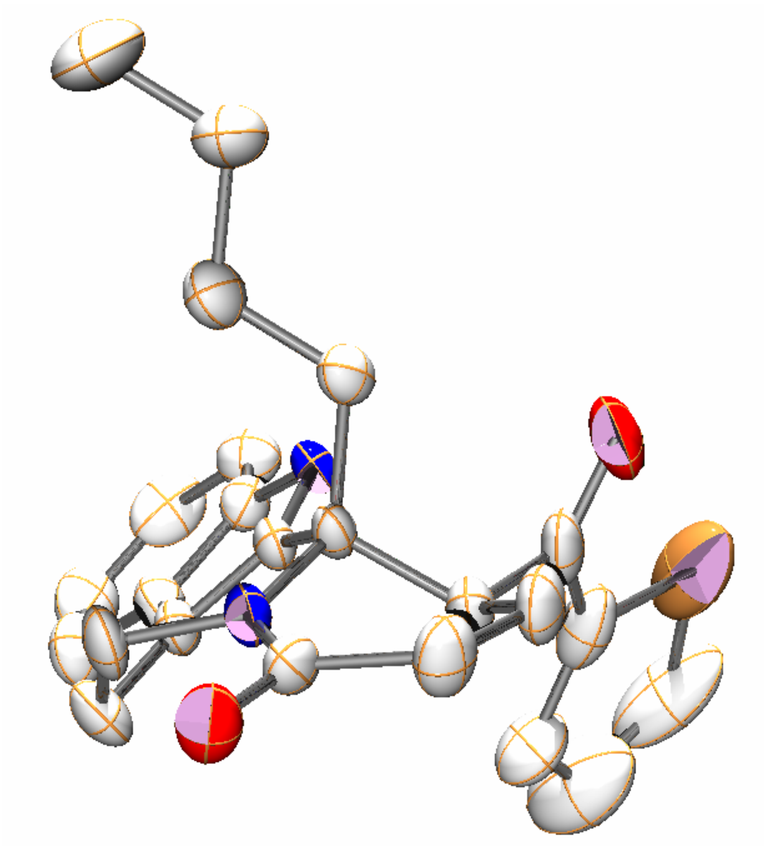


Fig. 29. ORTEP Presentation of 12b-Butyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (20a)

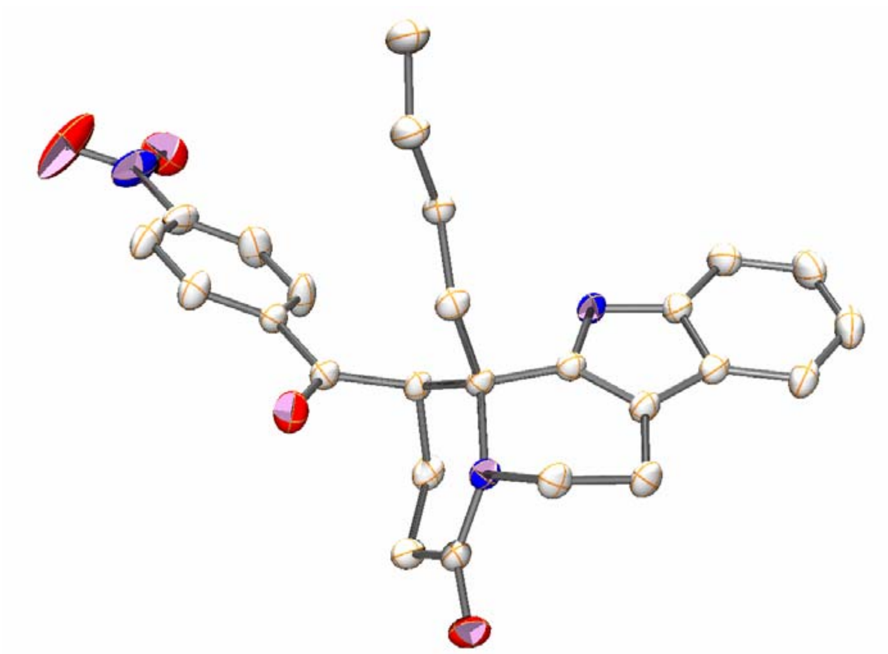


Fig. 30. ORTEP Presentation of 12b-Butyl-1-(4-nitrophenyl-1-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (20b)

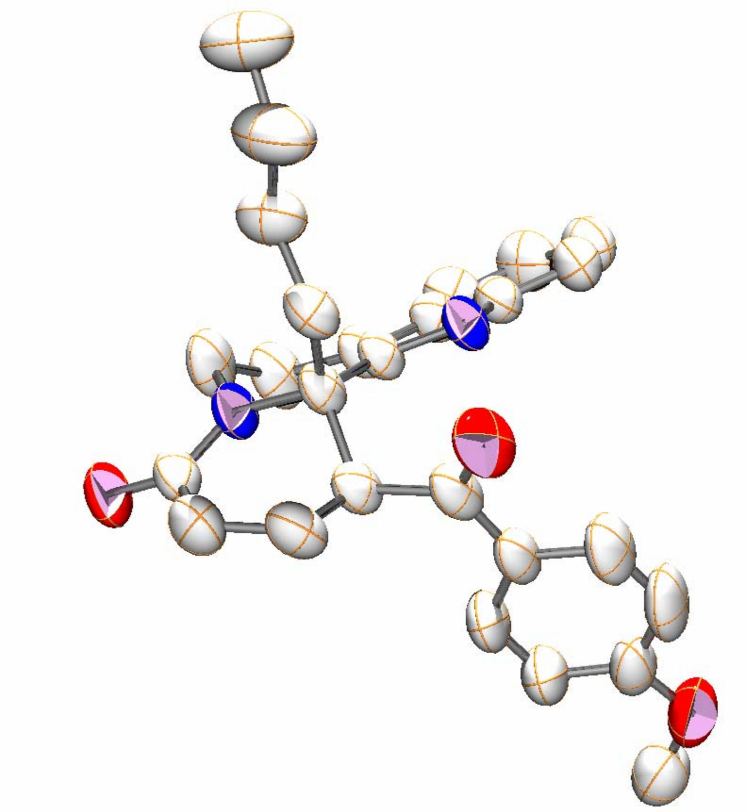


Fig. 31. ORTEP Presentation of 12b-Butyl-1-(4-methoxyphenyl-1-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (20c)

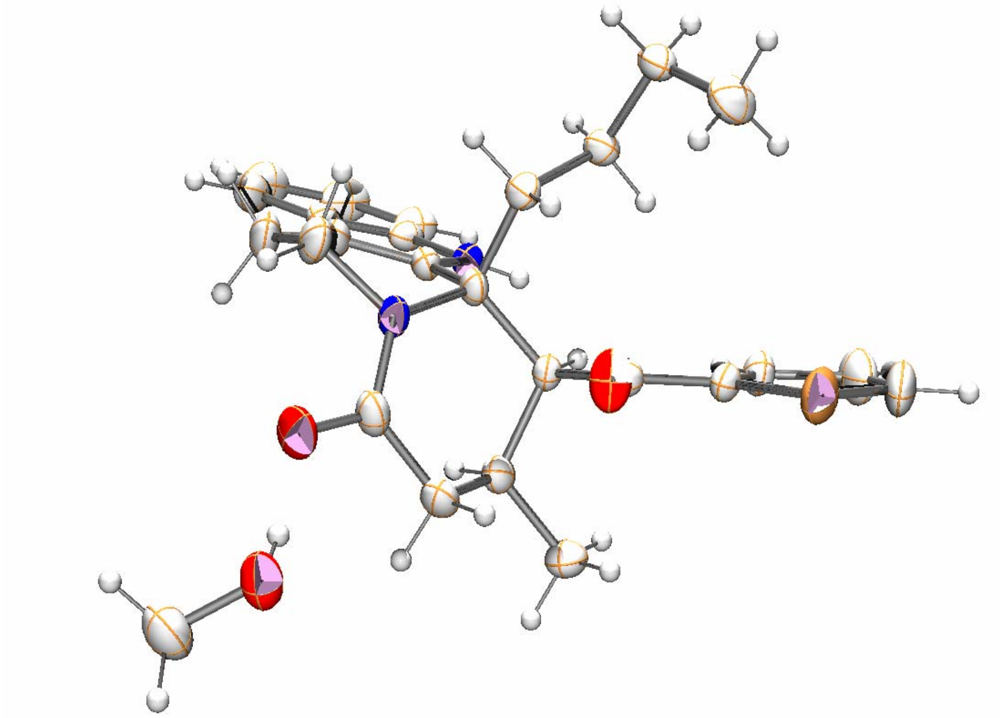


Fig. 32. ORTEP Presentation of 12b-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (20e)

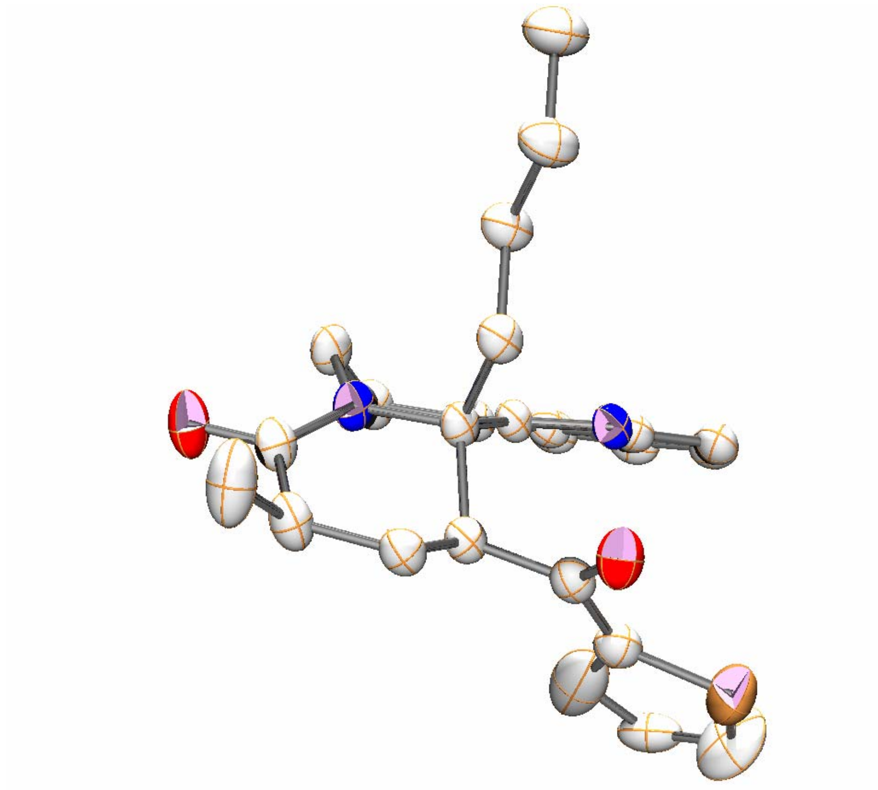


Fig. 33. ORTEP Presentation of 12b-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (20f) (major diastereomer)

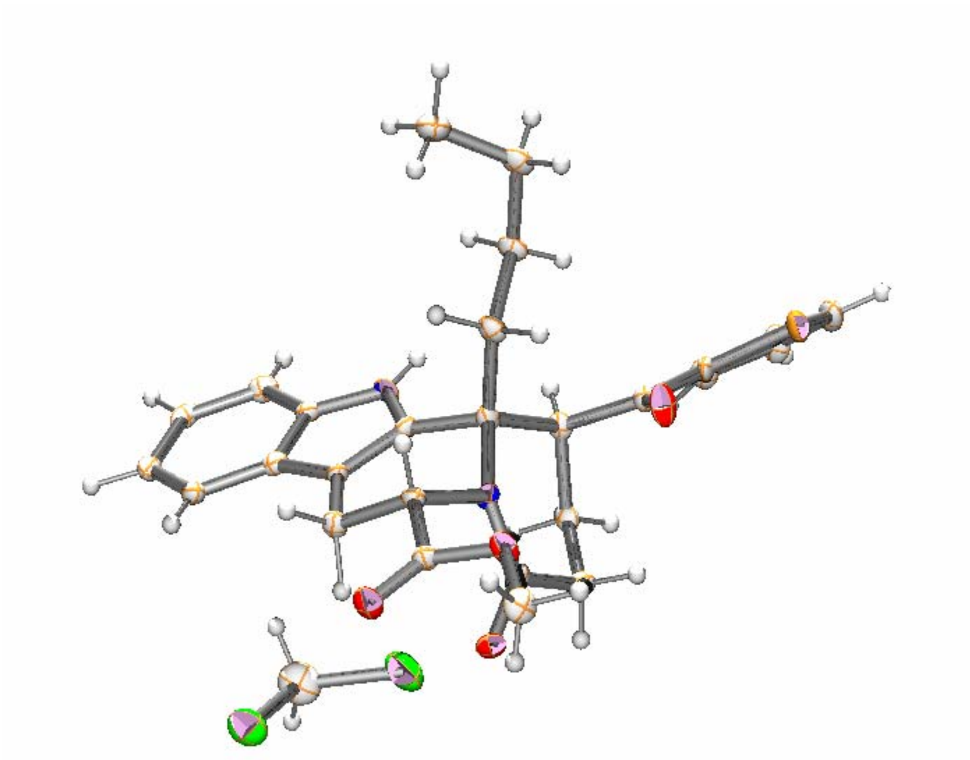


Fig. 34. ORTEP Presentation of (6*S,* 4*S,* 12b*S,*)-12b-Butyl-4-oxo-1-(thiophene-2-carbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-6-carboxylic acid methyl ester (20k)

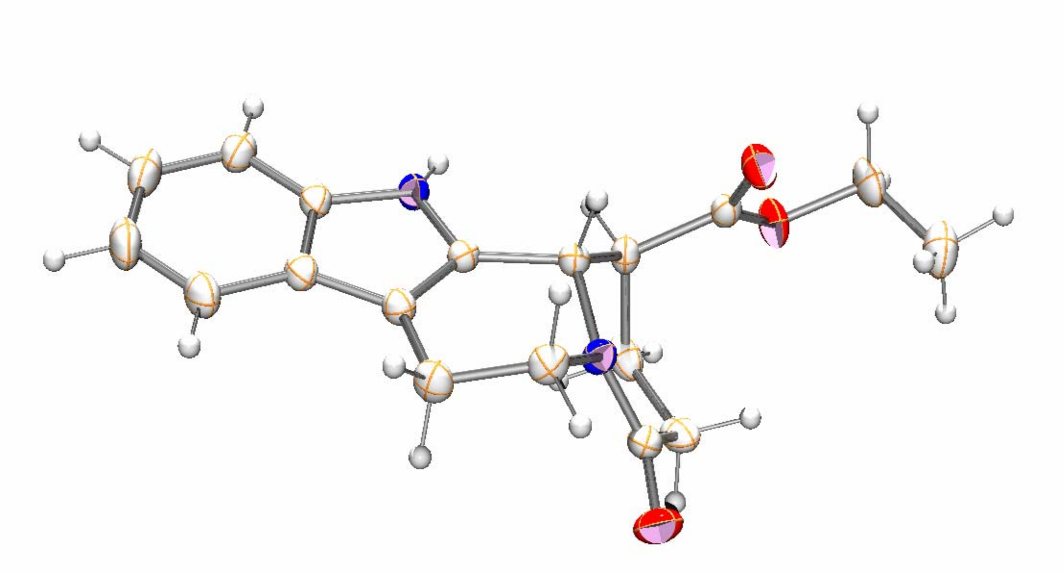


Fig. 35. ORTEP Presentation of 4-oxo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine-1-carboxylic acid ethyl ester (20l) (major diastereomer)

4.5 One-pot Three-component Synthesis of β-Halofurans

4.5.1 *β*-Halofurans Literature Overview

Furans are of considerable interest since their core is a subunit of numerous natural products. Examples include furanosteroids viridin and wortmannin,[159] which have a therapeutic potential in the treatment of neoplasms; manzamine alkaloid (-)-nakadomarin A,[160] which shows the inhibition of CDK4 and antimicrobial activity; furocarbazole alkaloid furostifoline,[161] flavors, fragrances (for example, rosefuran),[162] pharmaceuticals,[163] and even optoelectronics (Fig. 36).[164]

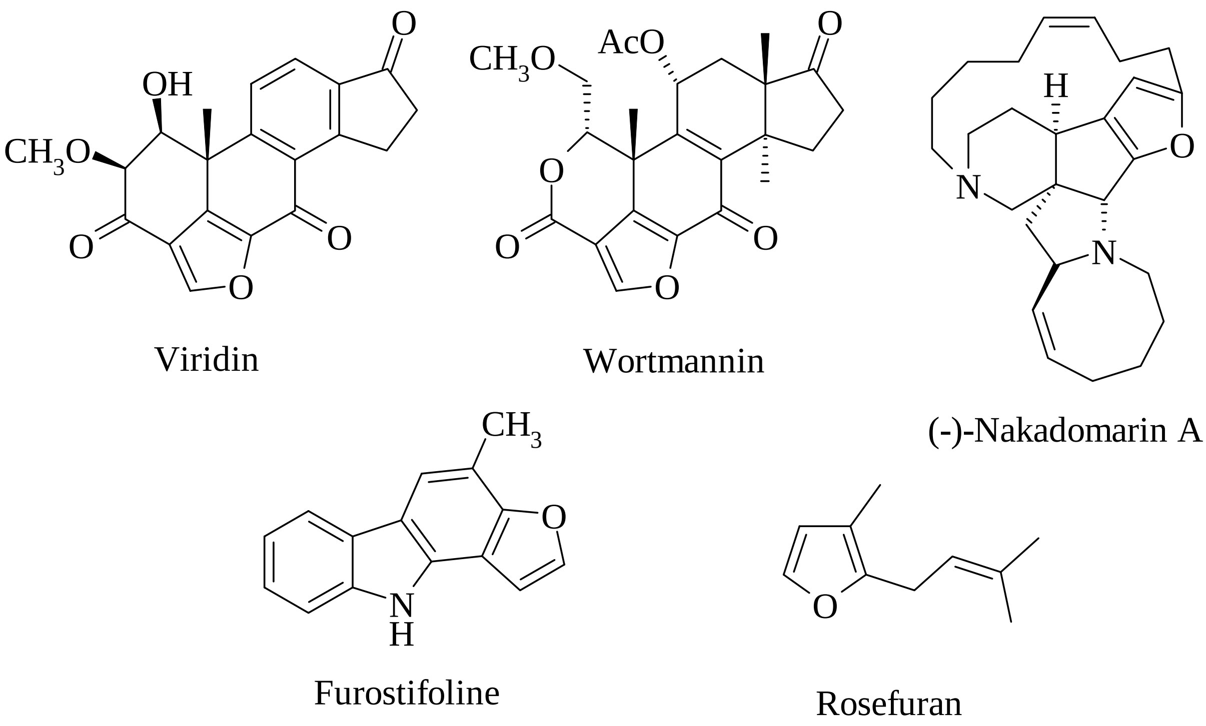
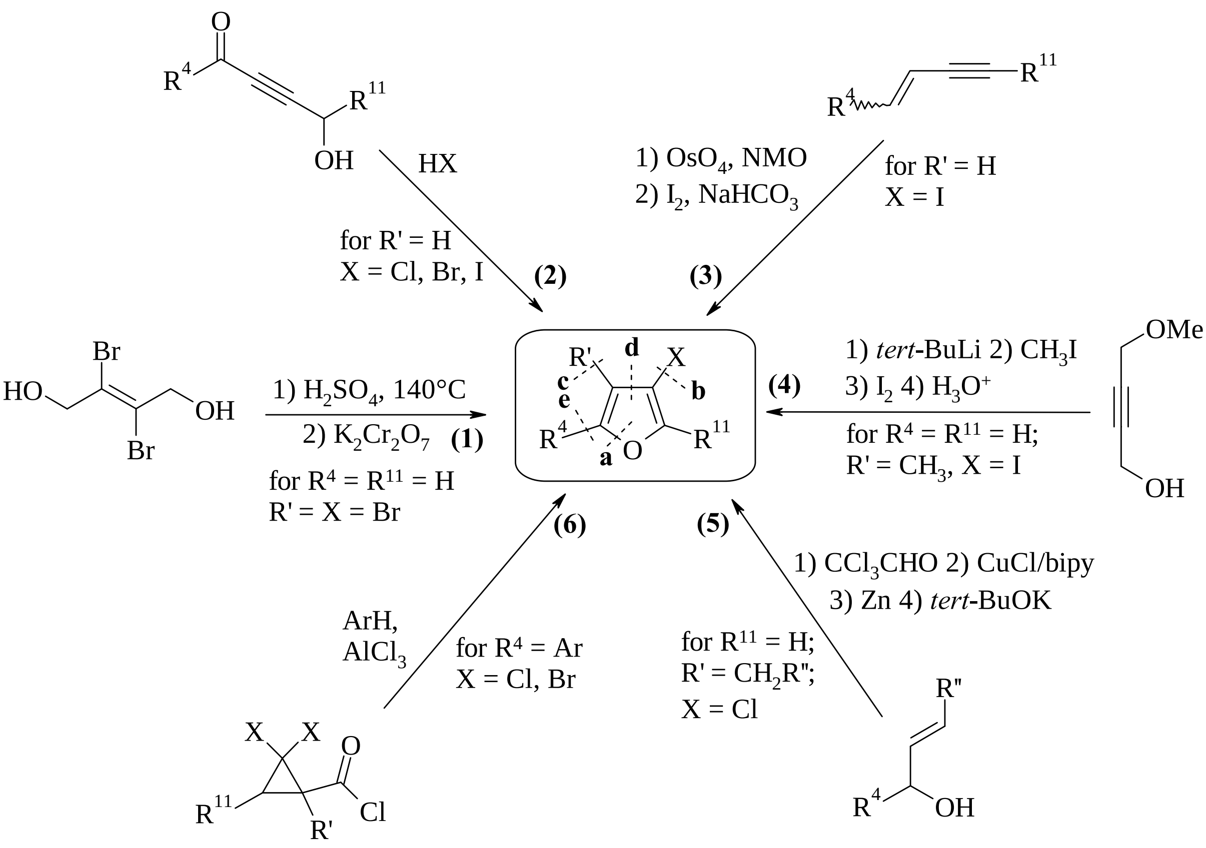


Fig. 36. Furan-containing Natural Products

There are two main approaches to furans.[165] The first route is based upon the construction of the furan ring starting from the acyclic intermediate.[166] The application of this approach to the specific target is dependent on the accessibility of the initial acyclic compound, therefore, the development of modular approaches where these intermediates can be generated *in-situ* from simple starting materials and cyclized to furans in a one-pot fashion are of significant interest.

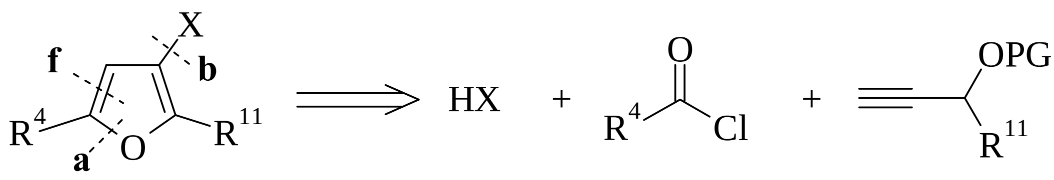
The second route involves substitution reactions. In turn, in the synthetic approaches to furan-containing compounds through substitution reactions, halofurans are used as the main building blocks. This is because a halogen atom can be easily transformed to more sophisticated derivatives via halogen-metal exchange and subsequent trapping with electrophiles[167,168] or through different cross-coupling reactions.[169,170] However, 3- and 4-substituted halofurans are quite challenging systems (Scheme 76).



Scheme 76. Synthesis of *β*-Halofurans

The retrosynthetic scission of bond **a** produces 2,3-dibromo-2-buten-1,4-diol as the starting compound **(1)**. Two approaches were used to directly fashion two bonds **a** and **b** resulting in ynones[171] **(2)** and enynes[172] **(3)** as precursors. Even three bonds **a**, **b** and **c** can be formed via one-pot procedure **(4)** which was described, however, only for a single example.[173] An interesting route to *β*-chlorofurans using allylic alcohols and chloral as the starting materials **(5)** with Cu(I)-catalyzed cyclization as the key step allows to create bonds **a** and **d**.[174] 2,5-Diaryl-3-halofurans can be prepared via regioselective dihalocyclopropane carbonyl chlorides ring-cleavage **(6)** forming bonds **a** and **e**.[175]

A straightforward route to 3-halofurans based upon the cyclization of acetylenic ketones is particularly interesting, since the starting compounds can be synthesized via Sonogashira-coupling and subjected directly to the reaction with hydrohalogenic acid in a one-pot sense. Therefore, I decided to extend our methodology to a one-pot synthesis of *β*-halofurans (Scheme 77).

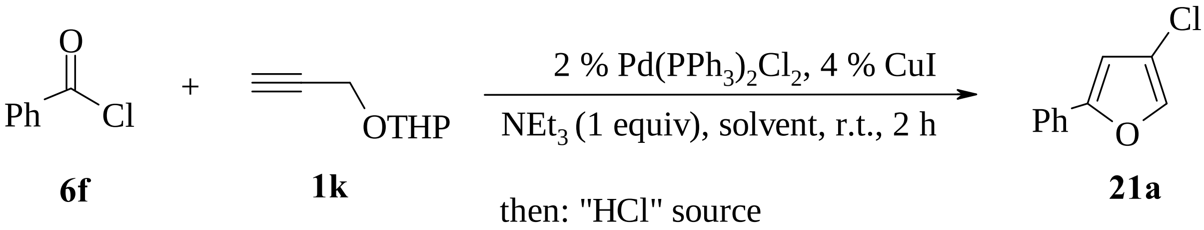


Scheme 77. Retrosynthetic Analysis of *β*-Halofurans

However, an important issue is that only 1 equiv of the base is necessary for the successful cross-coupling under our modified conditions, therefore, the reaction medium after the scavenging of HCl is essentially neutral. As a consequence a hydrohalogenic acid can be added in a one-pot fashion.

4.5.2 One-pot Three-component Synthesis of *β*-Halofurans

First, we tested the cross-coupling reaction of acid chlorides with propargylic alcohols. Unfortunately, a mixture of products was isolated. It was reasonable to assume that a protection of the free alcohol group needed to be performed. Thinking of the subsequent one-pot transformation, I chose a protecting group that would be stable under basic and could be cleaved under acidic conditions. Fortunately, there are many appropriate protecting groups and we conceded that tetrahydropyranyl (THP) group is the one of choice. Indeed the subjecting of the THP-protected propargylic alcohol (**1k**) to the Sonogashira coupling with benzoyl chloride (**6f**) under our modified conditions upon sequential treatment with the solution of “HCl” source gave rise to the expected 2-substituted-4-chlorofuran (**21a**) (Scheme 78, Table 25).



Scheme 78. Optimization of Conditions for the One-pot Synthesis of *β*-Chlorofuran

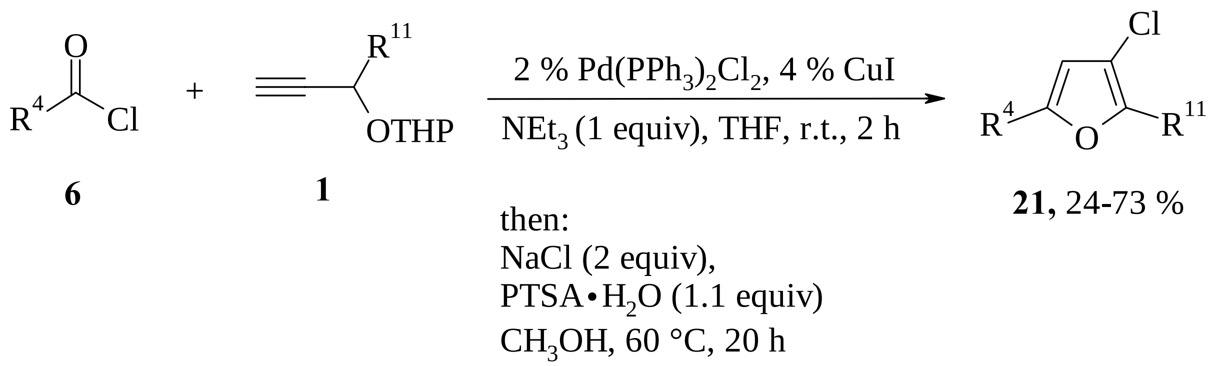
Table 25. Optimization of Conditions for the One-pot Synthesis of *β*-Chlorofuran

Entry	"HCl" source	Solvent	Temperature, time (2 step)	Yield, %
1	HCl (2 M) 2 equiv	THF	60 °C, 10 h	53
2	HCl (2 M) 2 equiv	THF	60 °C, 40 h	64
3	HCl (2 M) 2 equiv	CH_3CN	60 °C, 40 h	0
4	HCl (2 M) 2 equiv	Toluene	60 °C, 40 h	28
5	PTSA·H_2O (1.1 equiv)	THF/CH_3OH[a]	60 °C, 40 h	47
6	PTSA·H_2O (1.1 equiv), NaCl (2.0 equiv)	THF/CH_3OH[a]	60 °C, 20 h	63

[a] Methanol was added at the second step

The results show that the reaction proceeds in good yield. THF was the best solvent (entries 1-4) using an aqueous solution of HCl as the "HCl" source, but the heating for 40 h at 60 °C was required to complete the conversion (entry 2). The reaction time can be decreased if the mixture of NaCl and PTSA·H_2O is used as the "HCl" source (entry 6). It would be more elegant to use the acid chloride itself as the chloride source (entry 5), but the small concentration of chloride, which is a relatively weak nucleophile, was not sufficient to obtain the desired product in comparable yield.

Using the best conditions, the scope and limitations of this one-pot synthesis were investigated (Scheme 79, Table 26).



6 **1** **21,** 24-73 %

Scheme 79. One-pot Synthesis of *β*-Chlorofurans 21

Table 26. One-pot Synthesis of *β*-Chlorofurans 21

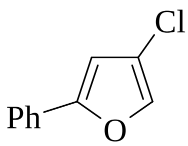
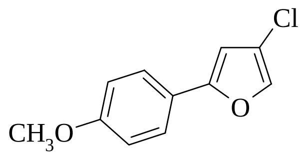
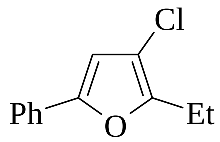
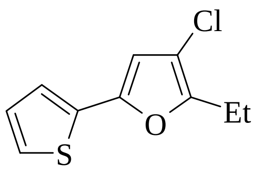
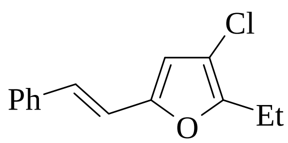
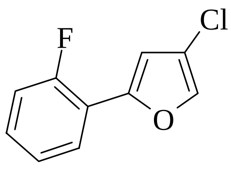
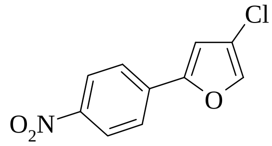
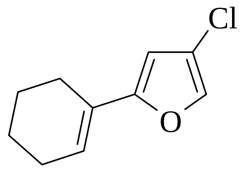
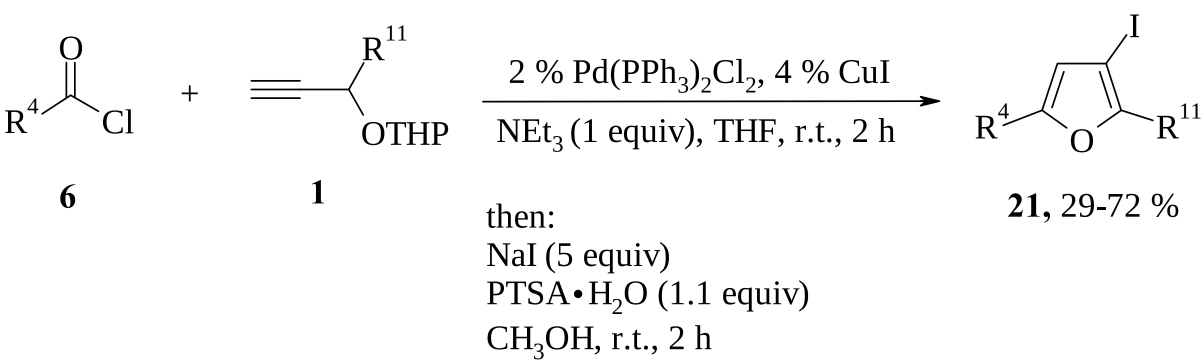
Entry	Acid chloride **6**	Alkyne **1**	Product (Yield, %)
1	R^4 = Ph (**6f**)	R^{11} = H (**1k**)	 **21a**, 63 %
2	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	**1k**	 **21b**, 71 %
3	**6f**	R^{11} = Et (**1l**)	 **21c**, 70 %
4	R^4 = 2-thienyl (**6e**)	**1l**	 **21d**, 59 %
5	R^4 = C_6H_5CH=CH (**6i**)	**1l**	 **21e**, 73 %
6	R^4 = *o*-FC_6H_4 (**6j**)	**1k**	 **21f**, 47 %

Table 26. Continued

Entry	Acid chloride **6**	Alkyne **1**	Product (Yield, %)
7	R^4 = *p*-$NO_2C_6H_4$ (**6b**)	**1k**	 **21g**, 24 %
8	R^4 = 1-cyclohexenyl (**6n**)	**1k**	 **21h**, 64 %

The results show that the one-pot *β*-chlorofuran synthesis proceeds in good yields for acid chlorides bearing electron rich (entry 2), electron withdrawing (entry 6) and electron neutral substituents (entries 1, 3, 5). For the nitrosubstituted acid chloride **6b**, the obtained yield is somewhat lower (entry 7). Even *α,β*-unsaturated acid chlorides **6i** and **6n** reacted smoothly giving rise to desired *β*-chlorofurans. Unsubstituted **1k** and alkylsubstituted **1l** THP-protected propargylic alcohols can be involved in this sequence.

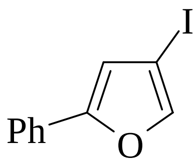
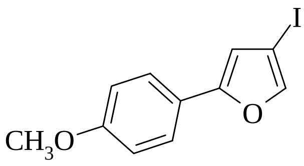
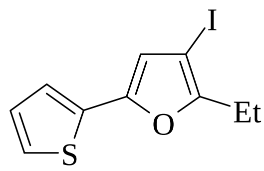
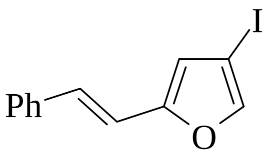
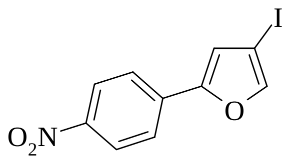
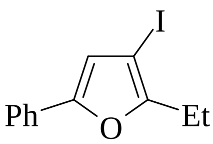
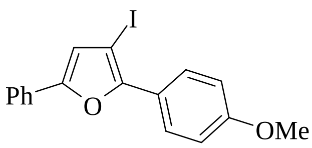
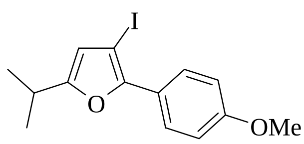
Next, I decided to test the applicability of this approach in the synthesis of *β*-iodofurans. *β*-Iodofurans are more attractive substrates since iodine can be exchanged with organometallic reagents and the resulting organometallic species can be trapped with various electrophiles. Additionally, they can serve as an aryl iodide component in numerous cross-coupling reactions. The exhaustive screening of conditions showed that the second cyclocondensation step required only 2 h stirring at the room temperature. It was expected since iodide is a much stronger nucleophile in comparison to the chloride, but only THF resulted in the formation of completely pure compounds. In all the other solvents, small amounts of *β*-chlorofurans were detected by GCMS (Scheme 80, Table 27).



6 **1** **21,** 29-72 %

Scheme 80. One-pot Synthesis of *β*-Iodofurans 21

Table 27. One-pot Synthesis of *β*-Iodofurans 21

Entry	Acid chloride **6**	Alkyne **1**	Product (Yield, %)
1	R^4 = Ph (**6f**)	R^{11} = H (**1k**)	 **21i**, 63 %
2	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	**1k**	 **21j**, 63 %
3	R^4 = 2-thienyl (**6e**)	R^{11} = Et (**1l**)	 **21k**, 49 %
4	R^4 = $C_6H_5CH{=}CH$ (**6i**)	**1k**	 **21l**, 61 %
5	R^4 = *p*-$NO_2C_6H_4$ (**6b**)	**1k**	 **21m**, 40 %
6	**6f**	**1l**	 **21n**, 72 %
7	**6f**	R^{11} = *p*-$CH_3OC_6H_4$ (**1m**)	 **21o**, 39 %
8	R^4 = *iso*-Propyl (**6m**)	**1m**	 **21p**, 29 %

The β-iodofurans **21** were synthesized in moderate to good yields where R^4 can be an electron rich (entry 2), an electron neutral (entries 1,3,6,7) and an electron-withdrawing aryl substituent (entry 5), an alkenyl (entry 4) and even an alkyl substituent containing an α-H atom (entry 8). The unsubstituted **1k**, alkyl- **1l** and aryl-substituted **1m** propargylic alcohols can be successively involved into the sequence. It is worth to mention that the deprotection step of the THP-protected propargylic alcohols and immediate cyclization to the desired products has to be performed in 2 h, since a prolongation of the reaction time leads to a significant decrease of yields, which can be explained by the high acid sensitivity of β-iodofurans. The obtained products are oils or crystalline compounds, which should be rapidly isolated on neutral aluminium oxide (the column chromatography on silica gel causes red coloring), and can be stored at low temperatures (0 °C) and under nitrogen without traces of decomposition.

The method seems to be quite general, since the acid that is used for the deprotection and cyclization is a mild one and a plethora of acid chlorides with different functional groups can be involved in the sequence. Only the choice of R^{11} is somewhat limited since it has to be compatible with Grignard reagents. This requirement follows from the fact that the corresponding propargylic alcohols (**1k-1m**) were synthesized by the addition of ethynyl magnesium bromide to aldehydes.

Although β-bromofurans do not have any additional advantages, I tried to apply our approach to their synthesis. Unfortunately, under conditions screened so far, only mixtures of bromo- and chlorofurans were obtained.

Spectroscopic data

The formation of the halofuran core is unambiguously supported by the spectroscopic and analytical data. For 2-substituted-4-halofurans **21a-b**, **21g-j**, **21l-m** in the ^{1}H NMR spectra two doublets in the region of δ 6.34-7.35 and δ 7.49-7.90 with ^4J coupling constants of 0-1.1 Hz were assigned as 3-H and 5-H furan protons respectively (Fig. 37).

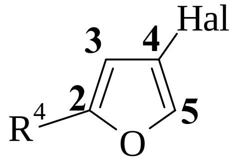


Fig. 37. The Numeration of 2-Substituted 4-Halofurans

For a fluoro containing compound **21f** the resonance of 3-H gives rise to a doublet at δ 6.84 with a coupling constant ^5J (H, F) of 3.8 Hz. In turn the resonance of 5-H appears as a distinct singlet at δ 7.52.

In the ^{13}C NMR spectra for 2-substituted-4-halofurans the resonances of ^{3}C carbon are identified as CH signals in the high field between δ 105.2-116.8; the resonances of ^{5}C carbon are detected as CH signals in the low field between δ 137.8-148.4; the resonances of ^{4}C quaternary carbon for 4-chlorofurans **21a-b**, **21g-**h are found at δ 117.3-118.6 and for 4-iodofurans **21i-j**, **21l-m** the resonances of ^{4}C quaternary carbon are shifted to a rather high field between δ 66.3-67.1, due to heavy element effect.[142] The resonance of ^{2}C quaternary carbon appears in the low field region of δ 146.4-156.7.

Accordingly, for 2,5-disubstituted-3-halofurans **21c-f**, **21k**, **21n-p** in the ^{1}H NMR spectra distinct singlets at δ 6.27-7.11 were assigned as 4-H furan protons (Fig. 38).

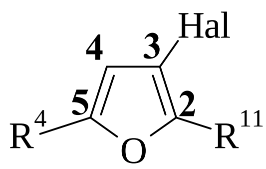


Fig. 38. The Numeration of 2,5-Disubstituted 3-Halofurans

Interestingly, for R^4 = *iso*-Pr (**21p**) the resonance of 4-H gives rise to a doublet at δ 6.27 with a coupling constant ^4J of 1.1 Hz. Accordingly, the proton of *iso*-Pr group appears as the doublet of septets with coupling constants of ^3J = 7.0 Hz and ^4J = 1.1 Hz.

In the ^{13}C NMR spectra for 2,5-disubstituted-3-halofurans the resonances of ^{4}C carbon are identified as CH signals in the high field between δ 106.7-114.9; the resonances of ^{2}C and ^{5}C are found as quaternary carbons in the low field between δ 147.4-160.3; the resonance of ^{3}C quaternary carbons for 3-chlorofurans **21c-f** are detected at δ 112.0-112.2; for 3-iodofurans **21k**, **21n-p** the resonance of ^{3}C quaternary carbons appear at δ 60.2-63.9, that corresponds to the expecting shifting to the high field of a carbon attached to a heavy element.

In addition to the core peaks, the signals of side chains can be assigned. For example, for **21d** and **21k** thienyl substituents are identified in the ^{1}H NMR spectra as three doublets of doublets at δ 7.03-7.09 (with coupling constants of 5.1 and 3.7 Hz); δ 7.22-7.33 (with coupling constants of 3.7 and 1.1 Hz) and δ 7.25-7.44 (with coupling constants of 5.1 and 1.1 Hz). The *p*-methoxyphenyl substituents for **21b**, **21j**, **21o-p** give rise to two doublets at δ

6.92-7.08 (with a coupling constant of 8.8-9.2 Hz, with intensity of two protons); δ 7.55-8.04 (with coupling constant of 8.8-9.2 Hz, with an intensity of two protons) and distinct singlets at δ 3.81-3.87 (with an intensity of three protons). For **21c-e, 21k**, and **21n** ethyl substituents are found as triplets at δ 1.23-1.29 and quartets between δ 2.65-2.74 (with coupling constants of 7.5-7.7 Hz). The double bonds of the cinnamyl substituent for **21e** and **21l** are detected in the expected olefinic region as two doublets at δ 6.79-7.05 and δ 6.99-7.12 with a coupling constant of 16.5 Hz that confirms its *trans*-configuration. The 1-cyclohexenyl substituent for **21h** gives rise to a set of signals in the range of δ 1.58-2.28 (multiplets with an intensity of 8 protons) and δ 6.27-6.31 (the multiplet with an intensity of one proton).

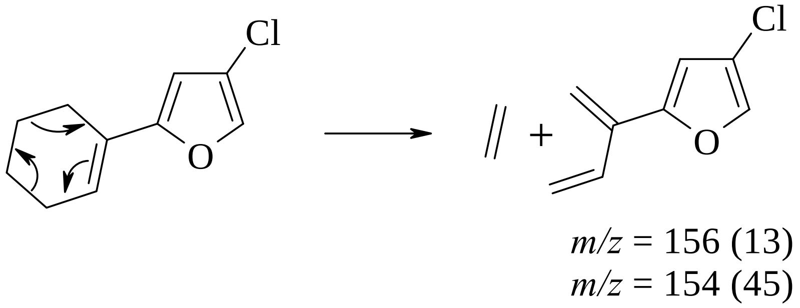
In the presence of a F atom for **21f** it is possible to assign the C-F coupling constants in the ^{13}C NMR spectrum (Table 28).

Table 28. Fluorine-Carbon Coupling Constants for 21f

^1J(C, F)	^2J(C, F)	^3J(C, F)	^4J(C, F)
251 Hz	21.5 Hz	11.9 Hz	2.8-3.4 Hz

The mass spectra of all obtained compounds show the molecular peaks. For the chlorofurans **21a-h** the presence of chlorine is confirmed by the isotope pattern of ^{37}Cl and ^{35}Cl (with intensities 1:3). The usual fragmentation mode leads to the loss of halogen atoms or of the methyl group for ethyl-substituted halofurans. The loss of the CHO fragment is characteristic for 2-substituted 4-chlorofurans **21a**, **21b** and the loss of the COHal fragment is characteristic for 2-substituted 4-halofurans **21a**, **21b, 21i**.

Interestingly, in the mass spectrum of **21h** the retro Diels-Alder reaction occurs under the ionization leading to appearing of butadiene derivative (Scheme 81).



Scheme 81. Retro Diels-Alder Reaction of 21h

In addition, the regiochemistry of “HHal” addition was unambiguously supported by an X-Ray structure analysis for 4-iodo-2-(4-nitro-phenyl)-furan **21m** (Fig. 39).

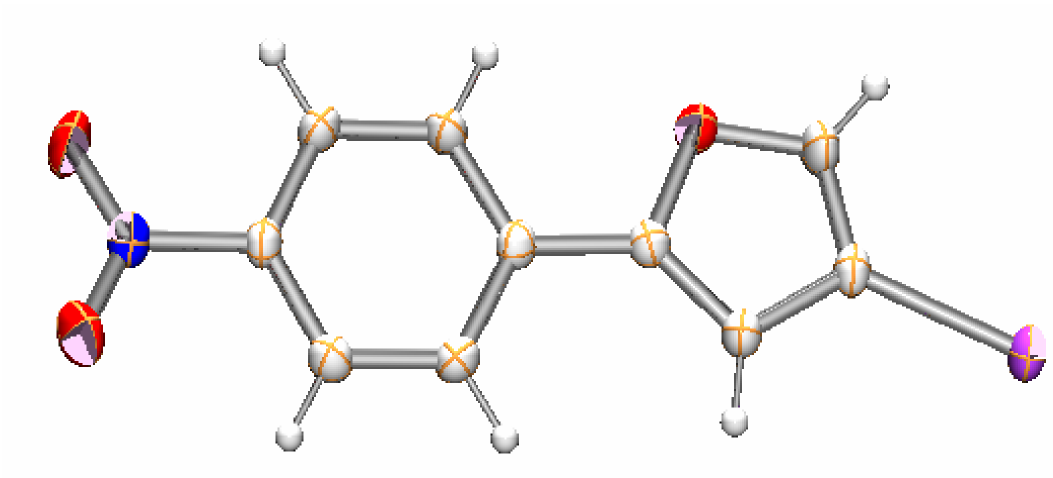


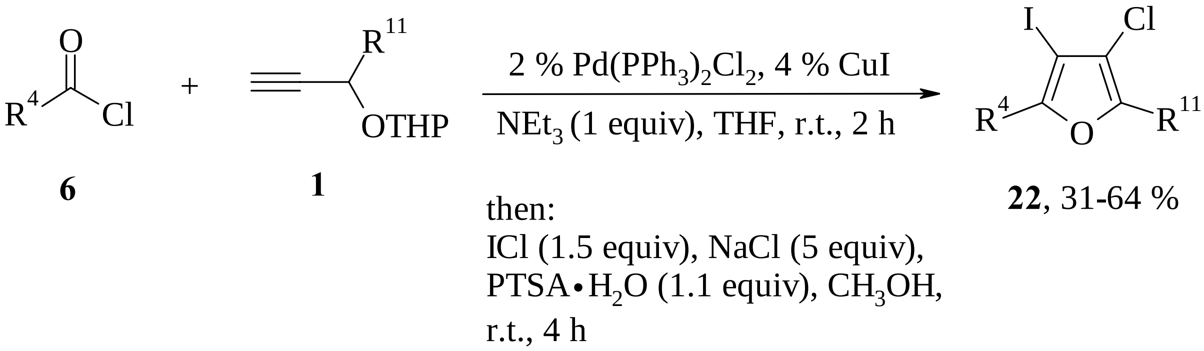
Fig. 39. ORTEP Presentation of 4-Iodo-2-(4-nitro-phenyl)-furan (21m)

4.5.3 One-pot Three-component Synthesis of *β*-Dihalofurans

Next, we wanted to screen the applicability of our approach to the synthesis of 3,4-dihalosubstituted furans adding ICl to the reaction mixture with the subsequent cyclization in one-pot. Interestingly, although the addition of ICl to ynones has been reported,[176] there have been no attempts to cyclize the intermediate vinyl iodochloro ketones. Furthermore, to the best of our knowledge the products of cyclization 3-chloro-4-iodosubstituted furans represent a hitherto unknown class of organic compounds.

The optimization of conditions revealed that THF was the best solvent, 1.5-2.5 equiv of iodine monochloride with 5.0 equiv of NaCl resulted in the formation of the desired products in reasonable yields. When the amount of ICl was increased to 5.0 equiv, side products, presumably the products of the electrophilic substitution on the furan ring, were observed.

The optimized reaction conditions were applied to various substrates to show the scope and limitations of this approach (Scheme 82, Table 29).



6 **1** **22**, 31-64 %

Scheme 82. One-pot Synthesis of 3-Chloro-4-iodofurans 22

Table 29. One-pot Synthesis of 3-Chloro-4-iodofurans 22

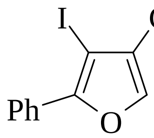
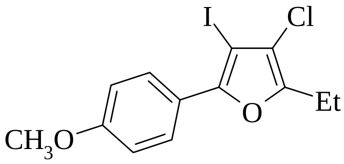
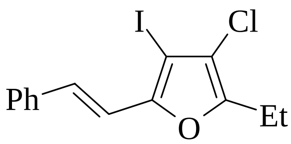
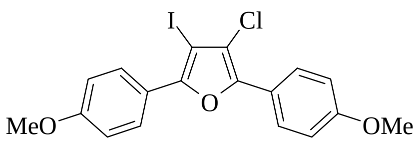
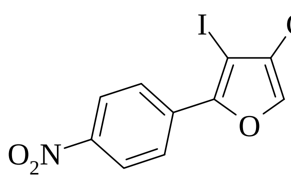
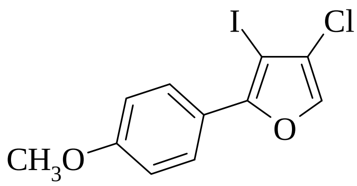
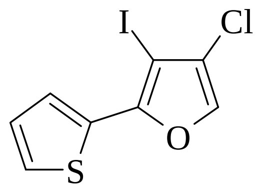
Entry	Acid chloride **6**	Alkyne **1**	Product (Yield, %)
1	R^4 = Ph (**6f**)	R^{11} = H (**1k**)	 **22a**, 52 %
2	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	R^{11} = Et (**1l**)	 **22b**, 64 %
3	R^4 = C_6H_5CH=CH (**6i**)	**1l**	 **22c**, 57 %
4	**6a**	R^{11} = *p*-$CH_3OC_6H_4$ (**1m**)	 **22d**, 51 %
5	R^4 = *p*-$NO_2C_6H_4$ (**6b**)	**1k**	 **22e**, 31 %

Table 29. Continued

Entry	Acid chloride **6**	Alkyne **1**	Product (Yield, %)
6	**6a**	**1k**	 **22f**, 42 %
7	R^4 = 2-thienyl (**6e**)	**1k**	 **22g**, 31 %

The 3-chloro-4-iodo-furans **22** were synthesized in reasonable yields similar to that of iodo-furans. The obtained products are oils or crystalline compounds which should be rapidly isolated on neutral aluminium oxide (the column chromatography on silica gel causes red coloring) and can be stored at low temperatures (0 °C) and under nitrogen without traces of decomposition.

No addition to the double bond occurred in the case of cinnamoyl chloride **6i** (entry 3) and only the desired product **22c** was isolated. Although we tested only few acid chlorides in our study, all the usual range of acid chlorides can be applied. Compound **22d** was synthesized in 51 % with 11 % of 3,4-diiodo-2,5-(4-methoxy-phenyl)-furan, when the reaction mixture was stirred after addition of ICl and NaCl for 2 h before the PTSA·H_2O and methanol were added. This result emphasizes the importance of addition of all the reagents at the same time.

Spectroscopic data

The formation of the dihalofuran core is unambiguously supported by the spectroscopic and analytical data. In the ^1H NMR spectra for monosubstituted 4-chloro-3-iodofuran **22a** and **22e-g** the resonances of 5-H give rise to distinct singlets at δ 7.56-8.12 (Fig. 40).

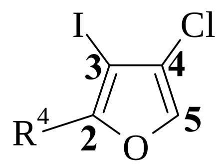


Fig. 40. The Numeration of Monosubstituted 4-Chloro-3-iodofurans

In the ^{13}C NMR spectra ^{5}C appears as CH signal at δ 137.6-141.2, the resonances of ^{2}C, ^{3}C and ^{4}C quaternary carbons are identified as C_{quat} signals in the region between δ 148.1-153.5, δ 66.3-71.9 (that corresponds to the expecting shift to rather high field of a carbon attached to a heavy atom)[142] and δ 123.2-124.5, respectively. For unsubstituted-3-chloro-4-iodofurans **22b-d** in the ^{13}C NMR spectra the resonances of ^{3}C and ^{4}C furan carbons are found as C_{quat} signals in the high field between δ 116.9-117.6 and δ 66.2-72.2 (that corresponds to the expecting shift to rather high field of a carbon attached to a heavy atom). The resonances of ^{2}C and ^{5}C are identified as C_{quat} signals in the high field at δ 147.4-153.3 (Fig. 41).

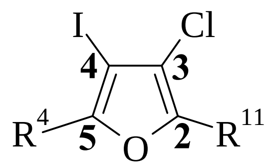


Fig. 41. The Numeration of Unsubstituted 3-Chloro-4-iodofurans

The mass spectra of all obtained compounds show the molecular peaks. The presence of chlorine is confirmed by the isotope pattern of ^{37}Cl and ^{35}Cl (with intensities 1:3). The usual fragmentation mode leads to the loss of the halogen atoms.

Additionally, the regiochemistry of ICl addition was unambiguously supported by an X-Ray structure analysis (Fig. 42).

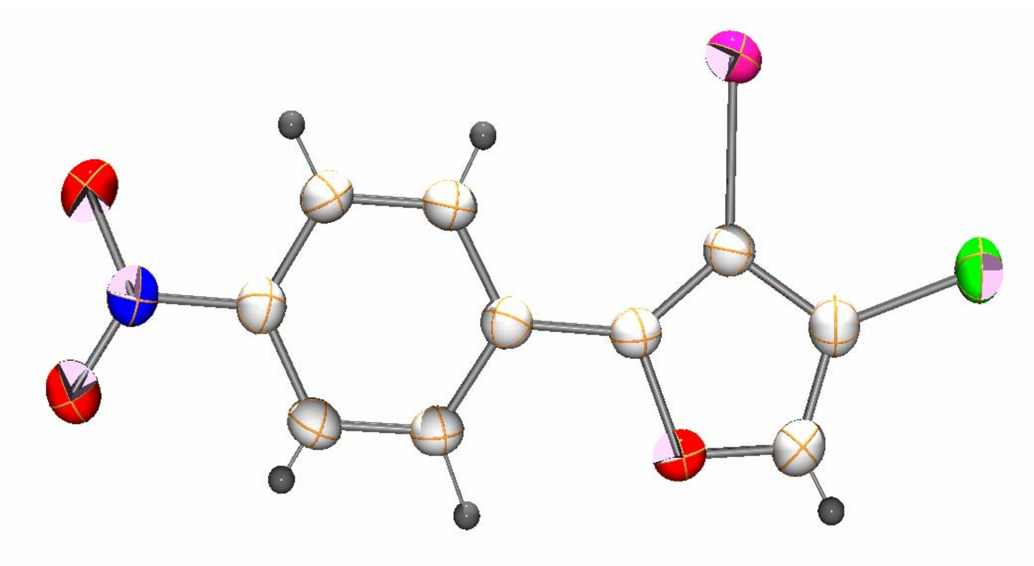
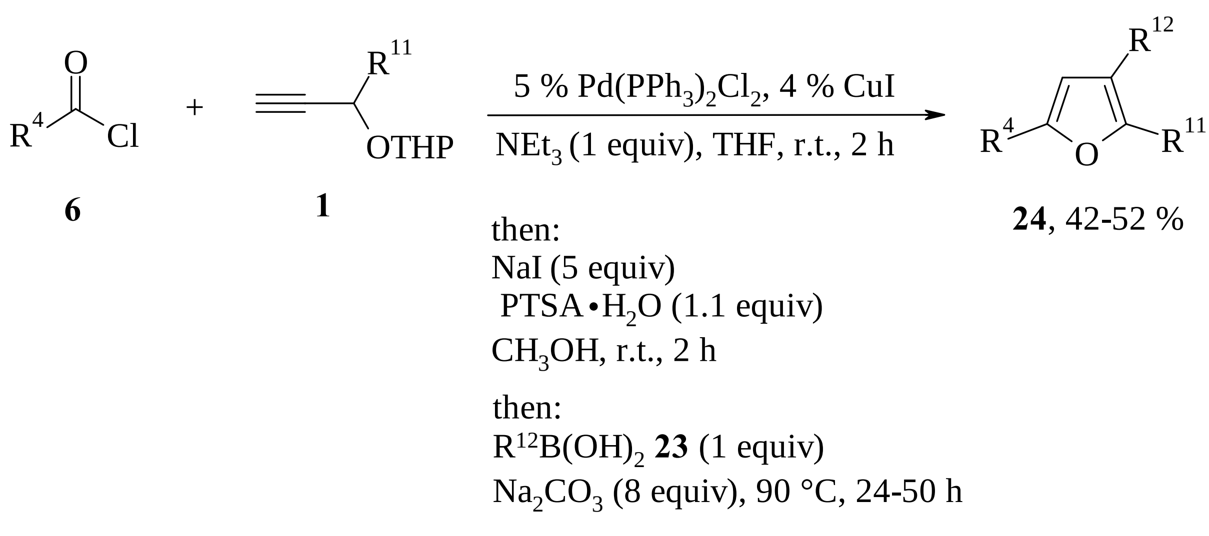


Fig. 42. ORTEP Presentation of 4-Chloro-3-iodo-2-(4-nitro-phenyl)-furan (22e)

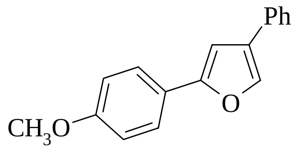
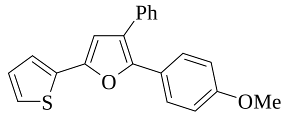
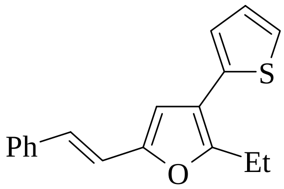
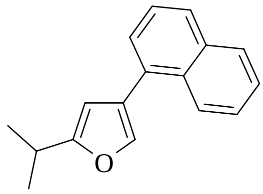
4.5.4 One-pot Three-component Synthesis of 2,3,5-Trisubstituted Furans

I reasoned that the halogen atom can be used for the subsequent transformation preferentially in a one-pot fashion. Additionally, I decided to utilize the Pd catalyst which is still present in the reaction mixture and can initiate a consecutive cross-coupling. I chose Suzuki coupling for the final step, since it can be carried out in all possible solvent mixtures including THF/CH_3OH, which I used for our sequence. Therefore, after the formation of *β*-iodofurans via coupling-addition-deprotection-cyclization sequence, the boronic acids **23** with excess of sodium carbonate were added to the reaction mixture, providing after heating, a one-pot three-component access to 2,3,5-trisubstituted furans **24** (Scheme 83, Table 30).



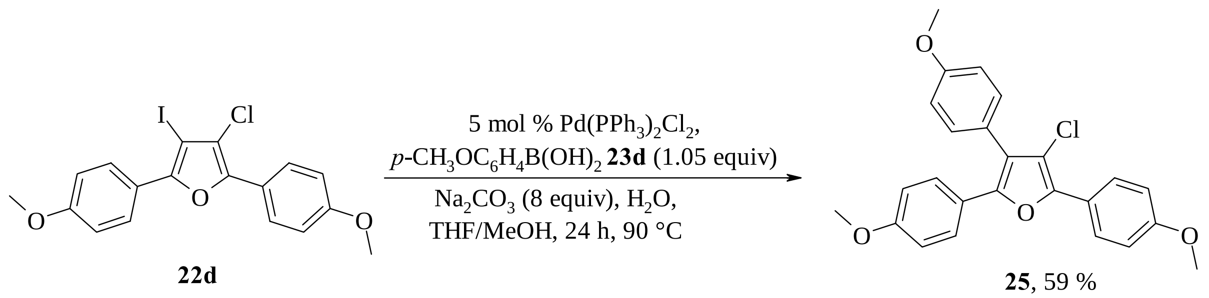
Scheme 83. One-pot Three-component Synthesis of 2,3,5-Trisubstituted Furans 24

Table 30. One-pot Three-component Synthesis of 2,3,5-Trisubstituted Furans 24

Entry	Acid chloride **6**	Alkyne **1**	Boronic acid **23**	Product (Yield, %)
1	R^4 = *p*-$CH_3OC_6H_4$ (**6a**)	R^{11} = H (**1k**)	R^{12} = Ph (**23a**)	 **24a**, 50 %
2	R^4 = 2-thienyl (**6e**)	R^{11} = *p*-$CH_3OC_6H_4$ (**1m**)	**23a**	 **24b**, 52 %
3	R^4 = C_6H_5CH=CH (**6i**)	R^{11} = Et (**1l**)	R^{12} = 2-thienyl (**23b**)	 **24c**, 42 %
4	R^4 = *iso*-Propyl (**6m**)	**1k**	R^{12} = 1-naphthyl (**23c**)	 **24d**, 52 %

The reaction proceeds with reasonable yields of 42-52 % using 5 mol % of $Pd(PPh_3)_2Cl_2$ as a catalyst. At the first glance, the yields do not seem to be very impressive, but if one considers that two new C-C bonds and one C-O bond were formed during a five-step sequence then it becomes evident that every new bond was formed in an 80 % average yield. The reaction represents a very simple access to 2,3,5-trisubstituted furans **24** with a highly flexible substituent pattern. It is noteworthy that the overall yield over a two-step protocol via isolation of β-iodofurans and subsequent separated Suzuki coupling leads to the desired products with the same or lower yields. The additional advantage of this one-pot sequence lies in the fact that even highly volatile β-iodofurans can be successively treated with boronic acid and isolated as the more heavily functionalized derivatives (entry 4). Interestingly, it was not possible to subject iodo-chlorofurans **22** to the cross-coupling in a one-pot sense. However, the reaction sequence can be performed separately.

For example iodochlorofuran **22d** was transformed to the trisubstituted chlorofuran **25** (Scheme 84).



Scheme 84. Synthesis of Trisubstituted Chlorofuran

As expected, the substitution occurs selectively and only the iodine atom was substituted.

Spectroscopic data

The formation of the 2,3,5-trisubstituted furan core is unambiguously supported by the spectroscopic and analytical data. For 2,4-disubstituted furans (R^{11} = H) **24a** and **24d** in the ^{1}H NMR spectra two doublets in the region of δ 6.32-7.16 and δ 7.55-8.02 with ^4J coupling constants of 1.1 Hz were assigned as 3-H and 5-H furan protons respectively. Accordnigly, for 2,3,5-trisubstituted furans **24b-c** in the ^{1}H NMR spectra distinct singlets in the region of δ 6.50-6.68 were assigned as 4-H furan protons.

In the ^{13}C NMR spectra for 2,4-disubstituted furans (R^{11} = H) **24a** and **24d** the resonances of ^{3}C carbon give rise to CH signals in the high field between δ 103.3-105.5; the resonances of ^{5}C carbons are identified as CH signals in the downfield at δ 138.2-138.6; the resonances of ^{4}C quaternary carbon are found at δ 124.5-124.9 and the resonances of ^{2}C quaternary carbon appear in the low field at δ 133.4-133.7. Accordingly, for 2,3,5-trisubstituted furans **24b-c** in the ^{13}C NMR spectra the resonances of ^{4}C carbon give rise to CH signals in the high field at δ 109.0-109.6; the resonances of ^{2}C and ^{5}C appear as quaternary carbons in the downfield between δ 147.5-152.8; the resonances of ^{3}C quaternary carbon are detected in the region of δ 116.1-122.8.

The mass spectra of all obtained compounds show the molecular peaks. For the 2,4-disubstituted furan **24a** the fragmentation leads to the loss of the CHO fragment.

5 Conclusions and Outlook

It was shown that arylbromides bearing electron-withdrawing groups in appropriate positions can be subjected to Sonogashira coupling with terminal alkynes, producing internal alkynes that can now undergo a Michael addition with suitable secondary amines. This coupling-aminovinylation sequence can be performed in a one-pot fashion, providing a straightforward access to push-pull chromophores.

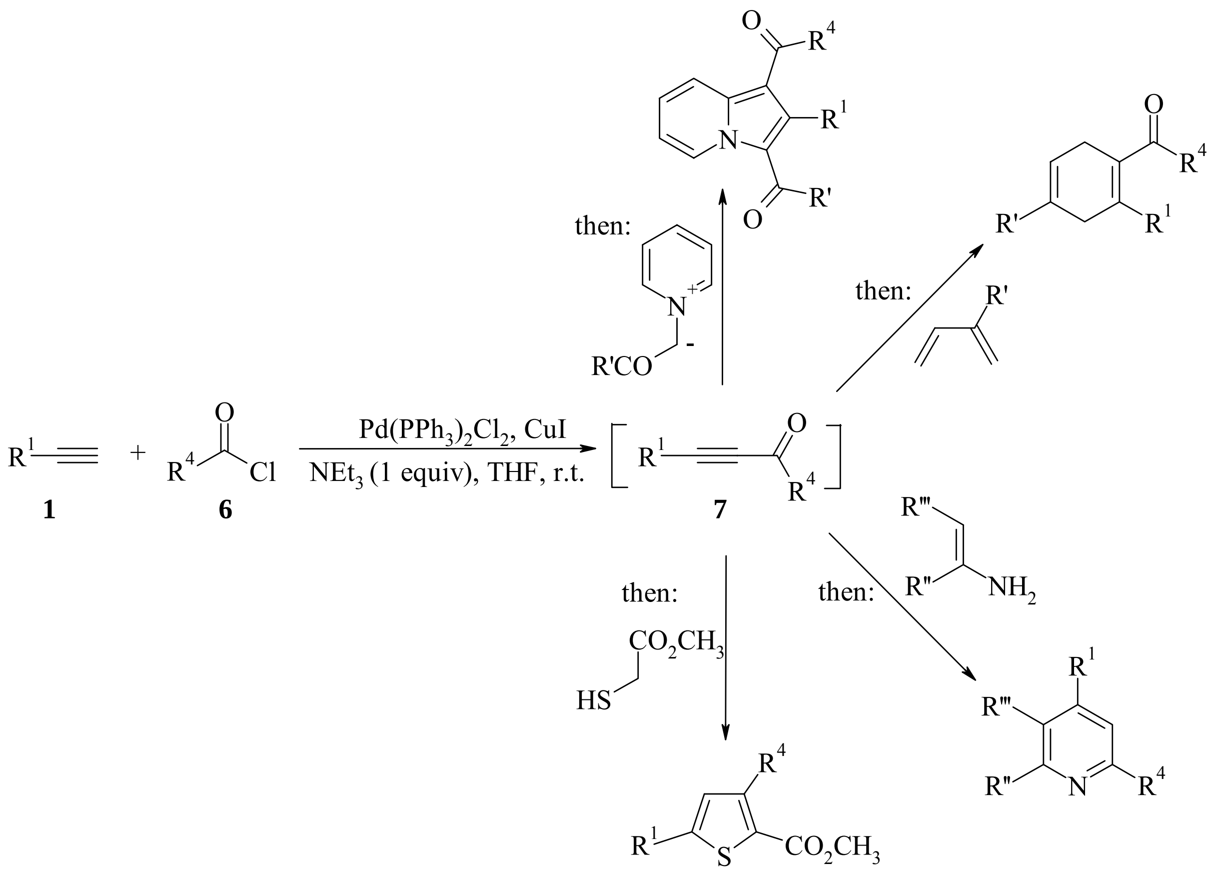
It was discovered that the polarizability of the π-electron system that conjugates the acetylene fragment with the acceptor moiety, plays a key role for opening of this additional Michael type reactivity. Computational studies showed that the relative LUMO energies reveal a satisfactory picture and rationalize the observed reactivity. The lower the LUMO, the more likely the aminovinylation will proceed.

By aapplying acid chlorides instead of arylbromides, it was possible to synthesize ynones that are highly reactive and valuable intermediates. Furthermore, we succeeded in directly converting these building blocks into β-enaminones, pyrimidines and halofurans in a one-pot three-component fashion. The conditions of the first cross-coupling step were successfully altered and only one equivalent of the base was applied. Even (TMS)-acetylene can be involved into the sequence under these extremely mild conditions.

In the case of inaccessible acid chlorides, carbonylative coupling of alkynes and aryl iodides represents a complementary approach to ynones, which in turn can be transformed in a one-pot four-component fashion to pyrimidines. Based upon this methodology, natural products like meridianins were synthesized starting from the readily available indoles via a four-step protocol with overall yields of 24-41 %.

The potential of ynones as the reactive intermediates is not only limited to the reactions described in this thesis. It can be assumed that other consecutive transformations are also compatible with our modified conditions used in the first step.

For example, pyridinium salts, dienes, β-enamines or methylthioglycolate can be subjected to the reaction mixture, creating novel and complex molecular architectures (Scheme 85).



Scheme 85. Further Possible One-pot Syntheses

Furthermore, the obtained addition products need not be isolated. For instance, *β*-enaminones are in their own right reactive intermediates and can be subjected to the subsequent aza-annulation reaction with *α*,*β*-unsaturated chlorides providing a one-pot four-component access to lactams. By aapplying tryptamine or (*S*)-(−)-tryptophane methyl ester as primary amines in the same sequence, a Pictet-Spengler reaction completed the reaction resulting in the formation of indolo[2,3-a]quinolizin-4-ones.

Without a doubt, the synthetic potential of this new *in-situ* alkyne activation concept can be extended to further transformations. In addition, this novel combinatorial strategy can be used for the synthesis of kinase inhibitors with an aminopyrimidine ring as a structural motif in medicinal chemistry.

6 Experimental Part

6.1 General conditions

All reactions involving water-sensitive compounds were carried out in oven-dried Schlenk glassware under nitrogen atmosphere unless stated otherwise. Nitrogen gas was dried by passage through phosphorus pentoxide and silica gel. THF, NEt_3, benzene, toluene and diethyl ether were distilled from a deep blue sodium benzophenone; CH_2Cl_2 and CH_3CN were distilled from CaH_2 prior to use. All the other solvents were dried according to standard procedures[177] and were distilled prior to use. $Pd(PPh_3)_2Cl_2$, CuI, alkynes **1**, heteroaryl bromides **2**, amines **4**, acid chlorides **6**, guanidine hydrochloride (**10a**), 2-methyl-2-thiopseudourea sulfate (**10e**), indole (**13a**), 5-bromoindole (**13b**), 7-azaindole (**13d**), aryl iodides (**17**), *α*,*β*-unsaturated acid chlorides (**18**), boronic acids (**23**) and iodine monochloride, were purchased from ACROS, Aldrich, Fluka, Merck, ABCR or Lancaster and used without further purification. 2-Bromo-5-nitrothiophene (**2a**),[178] 2-bromo-5-cyanothiophene (**2c**),[179] 2-bromo-5-furfural (**2d**),[180] 2,5-diethynyl thiophene (**1d**),[181] amidinium salts **10**,[182] 1-(phenylsulfonyl)indole-3-yl carbonyl chloride (**6j**),[183,184] pyridine-2,6-dicarbonyl dichloride (**6k**)[185] and 2,2-di-prop-2-ynyl-malonic acid diethyl ester (**1i**),[186] 6-bromoindole (**13c**),[187] 2-methyl-5-nitrophenyl guanidinium nitrate (**10i**),[188] homoveratryl amine (**4h**), (*S*)-(**—**)-tryptophane methyl ester (**4i**), THP-protected alcohols (**1k-m**)[189] were synthesized according to literature procedures. *p*-Cyanophenylacetylene (**1c**)[43] and 2-ethynylpyridine (**1g**)[190] were prepared by Sonogashira coupling of the corresponding bromo derivative and TMSA and subsequent alkaline desilylation in excellent yields. *N*-Methyl-1-methyl-4-pentylamine (**1e**) was prepared in analogy to published procedure.[191]

The column chromatography was performed on silica gel 60 M (mesh 230-400) Macherey-Nagel or aluminium oxide 90 active neutral (mesh 70-230) Merck. Thin layer chromatography (TLC): silica gel layered aluminium foil (60 F_{254} Merck, Darmstadt).

^{1}H-, ^{13}C-, DEPT-, NOESY-, COSY-, HMQC-, and HMBC- spectra were recorded on Bruker ARX 250, Bruker DRX 300, Varian VXR 400S or Bruker DRX 500 spectrometers by using acetone-d_6, CD_2Cl_2, $CDCl_3$ or DMSO-d_6 as solvents unless otherwise stated. The signals positions (δ values) were measured relative to the signals for $CHCl_3$ (7.27) and $CDCl_3$ (77.0), respectively. The assignments of quaternary C, CH, CH_2 and CH_3 were made on the basis of DEPT spectra. IR spectra were obtained for thin films on KBr-plates on a Bruker Vector 22 FT-IR spectrophotometer. UV/Vis spectra were recorded on Hewlett Packard HP8452 A spectrometer. Mass spectra were recorded on Jeol JMS-700 und Finnigan TSQ 700 spectrometers. The melting points (uncorrected) were measured on Reichert-Jung Thermovar and Büchi Melting Point B-540 apparatus. Elemental analyses were carried out in the microanalitycal laboratory of the Organisch-Chemisches-Institut der Universität Heidelberg or in the microanalitycal laboratory of the Department Chemie der Ludwig-Maximilians-Universität München.

6.2 General Procedure for the Coupling-Aminovinylation Sequence

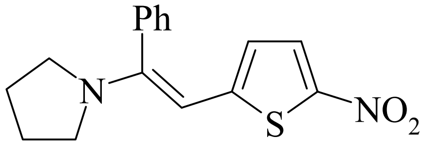
To a stirred mixture of the heteroaryl bromide **2** (1 mmol), 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 7 mg (0.04 mmol) of CuI in a mixture of 5 mL of THF and 1 mL of NEt_3 under nitrogen was added dropwise over 10 min a solution of acetylene **1** (1.1 mmol) in 5 mL of THF. The reaction mixture was stirred at room temperatur for 6 h until the complete consumption of **2** (monitored by TLC or GCMS). Then a solution of the amine **4** (2 mmol) in 5 mL of methanol was added, and the reaction mixture was heated to reflux temperatures for 3-6 h until the complete conversion of the intermediate alkyne **3** (monitored by TLC or GCMS). The solvents were evaporated in vacuo, and the residue was chromatographed over a short pad of aluminium oxide eluting with dichloromethane to furnish after recrystallization from hexane/chloroform the analytically pure enamines **5** as crystalline solids (see Table 31 for experimental details).

Table 31. Experimental Details of the One-pot Coupling-aminovinylation Reaction to the Enamines 5 or Alkynes 3, respectively

Entry	Alkyne **1**	Heteroaryl halide **2**	Amine **4**	Alkyne **3**/Enamine **5** (Yield %)
1	0.12 mL (1.10 mmol) of **1a**	208 mg (1.00 mmol) of **2a**	0.17 ml (2.00 mmol) of **4a**	170 mg (57 %) of **5a**
2	0.12 mL (1.10 mmol) of **1a**	190 mg (1.00 mmol) of **2b**	0.17 ml (2.00 mmol) of **4a**	**3b**[a]
3	0.12 mL (1.10 mmol) of **1a**	188 mg (1.00 mmol) of **2c**	0.17 ml (2.00 mmol) of **4a**	**3c**[a]
4	0.12 mL (1.10 mmol) of **1a**	159 mg (1.00 mmol) of **2d**	0.17 ml (2.00 mmol) of **4a**	171 mg (87 %) of **3d**
5	0.12 mL (1.10 mmol) of **1a**	158 mg (1.00 mmol) of **2e**	0.17 ml (2.00 mmol) of **4a**	**3e**[a]
6	0.12 mL (1.10 mmol) of **1a**	0.09 ml (1.00 mmol) of **2f**	0.17 ml (2.00 mmol) of **4a**	**3f**[a]
7	0.12 mL (1.10 mmol) of **1a**	158 mg (1.00 mmol) of **2g**	0.17 ml (2.00 mmol) of **4a**	**3g**[a]
7	0.12 mL (1.10 mmol) of **1a**	208 mg (1.00 mmol) of **2a**	0.21 ml (2.00 mmol) of **4b**	202 mg (67 %) of **5b**
8	0.12 mL (1.10 mmol) of **1a**	208 mg (1.00 mmol) of **2a**	0.17 ml (2.00 mmol) of **4c**	240 mg (76 %) of **5c**
9	0.12 mL (1.10 mmol) of **1a**	208 mg (1.00 mmol) of **2a**	0.25 ml (2.00 mmol) of **4d**	175 mg (52 %) of **5d**
10	0.13 mL (1.10 mmol) of **1b**	208 mg (1.00 mmol) of **2a**	0.17 ml (2.00 mmol) of **4a**	200 mg (71 %) of **5e**
11	140 mg (1.10 mmol) of **1c**	208 mg (1.00 mmol) of **2a**	0.17 ml (2.00 mmol) of **4c**	235 mg (69 %) of **5f**
12	0.12 mL (1.10 mmol) of **1a**	209 mg (1.00 mmol) of **2h**	0.17 ml (2.00 mmol) of **4a**	125 mg (42 %) of **5g**
13	0.12 mL (1.10 mmol) of **1a**	203 mg (1.00 mmol) of **2i**	0.17 ml (2.00 mmol) of **4c**	202 mg (69 %) of **5h**
14	132 mg (1.00 mmol) of **1d**	416 mg (2.00 mmol) of **2a**	0.42 ml (4.00 mmol) of **4b**	356 mg (67 %) of **5i**
15	122 mg (1.10 mmol) of (**1e**)	208 mg (1.00 mmol) of **2a**	-	74 mg (31 %) of **5j**

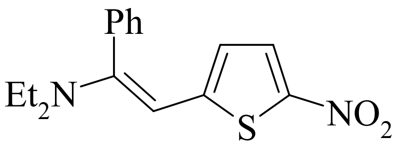
[a] The alkyne **3** was identified by GC/MS analysis (100 % conversion of the halide) and was not isolated.

(*E*)-1-[2-(5-Nitrothien-2-yl)-1-phenyl-vinyl] pyrrolidine (5a)



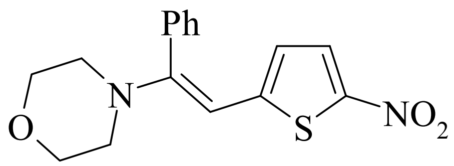
E/Z = 60:1 (^{1}H NMR, minor diastereomer not listed). Crystals with a green metallic luster, Mp. 169-170 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90-1.98 (m, 4 H), 3.18-3.26 (m, 4 H), 5.51 (s, 1 H), 6.20 (d, J = 4.6 Hz, 1 H), 7.25-7.29 (m, 2 H), 7.51-7.57 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.3 (CH_2), 49.0 (CH_2), 92.8 (CH), 120.5 (CH), 126.5 ($C_{quat.}$), 128.4 (CH), 130.2 (CH), 130.3 (CH), 130.3 (CH), 135.5 ($C_{quat.}$), 153.7 ($C_{quat.}$), 157.0 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 300 (M^+, 100), 254 (M^+ - NO_2, 21). 184 (M^+ - NO_2, - $N(C_2H_4)_2$, 22). IR (KBr): $\tilde{\nu}$ 1557, 1437, 1273, 1166, 1114, 1040 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 537 nm (37100). UV/Vis (ether): λ_{max} (ε) 491 nm (32200). Anal. calcd. for $C_{16}H_{16}N_2O_2S$ (300.38): C 63.98, H 5.37, N 9.33, S 10.67. Found: C 63.92, H 5.31, N 9.19, S 10.95.

(*E*)-Diethyl-[2-(5-nitrothien-2-yl)-1-phenyl-vinyl] amine (5b)



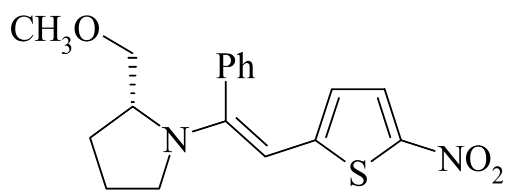
E/Z = 20:1 (^{1}H NMR, minor diastereomer not listed). Red brown crystals with a metallic luster, Mp. 157-158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, J = 7.1 Hz, 6 H), 3.21 (q, J = 7.1 Hz, 4 H), 5.63 (s, 1 H), 6.21 (d, J = 4.6 Hz, 1 H), 7.22-7.26 (m, 2 H), 7.52-7.58 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.2 (CH_3), 44.1 (CH_2), 93.1 (CH), 120.7 (CH), 129.00 (CH), 129.1 ($C_{quat.}$), 129.9 (CH), 130.3 (CH), 130.3 (CH), 134.6 ($C_{quat.}$), 154.4 ($C_{quat.}$), 156.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 302 (M^+, 100), 273 (M^+ - C_2H_5, 12), 256 (M^+ - NO_2, 66). 184 (M^+ - NO_2, - $N(C_2H_5)_2$, 27). IR (KBr): $\tilde{\nu}$ 1553, 1430, 1288, 1267, 1243, 1122, 1096, 1042 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 533 nm (37100). UV/Vis (ether): λ_{max} (ε) 485 nm (27000). Anal. calcd. for $C_{16}H_{18}N_2O_2S$ (302.40): C 63.55, H 6.00, N 9.26, S 10.60. Found: C 63.20, H 5.91, N 9.16, S 10.64.

(*E*)-4-[2-(5-Nitrothien-2-yl)-1-phenyl-vinyl] morpholine (5c)



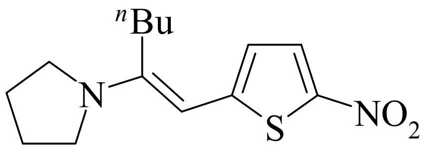
E/Z = 60:1 (^{1}H NMR, minor diastereomer not listed). Crystals with a green metallic luster, Mp. 147-148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.07 (t, J = 4.9 Hz, 4 H), 3.71 (t, J = 4.9 Hz, 4 H), 5.73 (s, 1 H), 6.33 (d, J = 4.6 Hz, 1 H), 7.25-7.30 (m, 2 H), 7.48-7.56 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.1 (CH_2), 66.5 (CH_2), 96.6 (CH), 122.6 (CH), 128.4 ($C_{quat.}$), 129.3 (CH), 129.6 (CH), 130.1 (CH), 130.5 (CH), 134.3 ($C_{quat.}$), 153.8 ($C_{quat.}$), 155.1 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 316 (M^+, 100), 270 (M^+ - NO_2, 28), 184 (M^+ - NO_2, - C_4H_8NO, 44). IR (KBr): $\tilde{\nu}$ 1570, 1431, 1298, 1232, 1137, 1111, 1040, 1018 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 498 nm (21700). UV/Vis (ether): λ_{max} (ε) 450 nm (20900). Anal. calcd. for $C_{16}H_{16}N_2O_3S$ (316.38): C 60.74, H 5.10, N 8.85, S 10.13. Found: C 60.38, H 5.07, N 8.67, S 10.54.

(*E*)-1-[2-(5-Nitrothien-2-yl)-1-phenyl-vinyl]-(2*R*)-methoxymethyl pyrrolidine (5d)



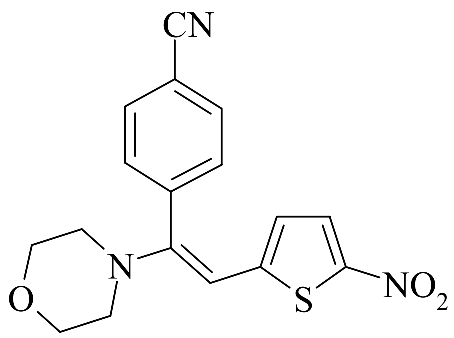
Only *E* (^{1}H NMR). Deep red oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.84-1.98 (m, 4 H), 3.07-3.26 (m, 7 H), 3.70-3.76 (m, 1 H), 5.53 (s, 1 H), 6.16 (d, J = 4.6 Hz, 1 H), 7.14-7.26 (m, 2 H), 7.45-7.50 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0 (CH_2), 27.4 (CH_2), 48.5 (CH_2), 57.3 (CH), 58.0 (CH_3), 72.1 (CH_2), 93.0 (CH), 119.9 (CH), 127.4 (CH), 128.3 (CH), 129.0 (CH), 129.2 (CH), 131.1 ($C_{quat.}$), 133.9 ($C_{quat.}$), 152.1 ($C_{quat.}$), 155.4 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 344 (M^+, 19), 299 (M^+ - CH_2OCH_3, 86), 267 (M^+ - OCH_3, - NO_2, 100). IR (KBr): $\tilde{\nu}$ 1559, 1435, 1276, 1170, 1120, 1036 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 528 nm (24300). UV/Vis (ether): λ_{max} (ε) 485 nm (21000). HRMS calcd. for $C_{18}H_{20}N_2O_3S$, 344.1190; found 344.1205.

(*E*)-1-[2-(5-Nitrothien-2-yl)-1-butyl-vinyl] pyrrolidine (5e)



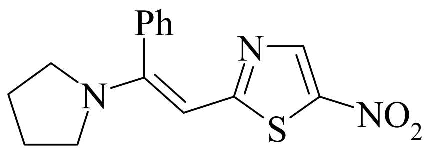
Only *E* (^{1}H NMR). Crystals with a blue metallic luster, Mp. 100-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, J = 7.0 Hz, 3 H), 1.50-1.64 (m, 4 H), 1.96-2.02 (m, 4 H), 2.62-2.67 (m, 2 H), 3.36-3.46 (m, 4 H), 5.36 (s, 1 H), 6.42 (d, J = 4.7 Hz, 1 H), 7.73 (d, J = 4.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8 (CH_3), 23.0 (CH_2), 25.2 (CH_2), 29.0 (CH_2), 31.2 (CH_2), 48.3 (CH_2), 92.6 (CH), 120.3 (CH), 131.1 (CH), 128.2 ($C_{quat.}$), 155.6 ($C_{quat.}$), 156.2 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 280 (M^+, 6), 217 (M^+ - NO_2, - CH_3, - 2H, 100). IR (KBr): $\tilde{\nu}$ 1557, 1442, 1286, 1162, 1126, 1092, 1042 cm^{-1} UV/Vis (CH_3CN): λ_{max} (ε) 545 nm (43700). UV/Vis (ether): λ_{max} (ε) 499 nm (20400). Anal. calcd. for $C_{14}H_{20}N_2O_2S$ (280.39): C 59.97, H 7.19, N 9.99, S 11.44. Found: C 59.80, H 7.08, N 9.96, S 11.57.

(*E*)-4-{2-[5-Nitrothien-2-yl]-1-(4-cyano)phenyl-vinyl} morpholine (5f)



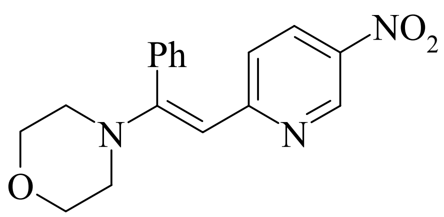
E/Z = 9:1 (^{1}H NMR). Red crystals, Mp. 222-223 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.94 (t, J = 4.9 Hz, 4 H), 3.66 (t, J = 4.9 Hz, 4 H), 5.70 (s, 1 H), 6.28 (d, J = 4.6 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 4.6 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 2 H); additional signals for the minor isomer: δ 3.18 (t, J = 4.8 Hz, 2 H), 3.22 (t, J = 4.9 Hz, 2 H), 3.74 (t, J = 4.9 Hz, 4 H), 5.70 (s, 1 H), 6.28 (d, J = 4.6 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 4.6 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.4 (CH_2), 66.4 (CH_2), 98.0 (CH), 114.3 ($C_{quat.}$), 118.0 ($C_{quat.}$), 123.5 (CH), 129.2 (CH), 130.9 (CH), 133.6 (CH), 139.4 ($C_{quat.}$), 151.4 ($C_{quat.}$), 152.6 ($C_{quat.}$); additional signals for the minor isomer: 43.2 (CH_2), 49.1 (CH_2), 63.8 (CH_2), 65.7 (CH_2), 102.9 (CH), 128.8 (CH), 132.8 (CH). EI MS (70 eV, *m/z* (%)): 341 (M^+, 100), 295 (M^+ - NO_2, 17), 209 (M^+ - NO_2, - C_4H_8NO, 27), 102 (4-CN-Ph, 11). IR (KBr): $\tilde{\nu}$ 2228, 1579, 1429, 1303, 1227, 1170, 1110, 1023, 892 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 486 nm (21000). UV/Vis (ether): λ_{max} (ε) 439 nm (18100). Anal. calcd. for $C_{17}H_{15}N_3O_3S$ (341.39): C 59.81, H 4.43, N 12.31, S 9.39. Found: C 59.56, H 4.38, N 12.17, S 9.43.

(*E*)-1-[2-(5-Nitrothiazol-2-yl)-1-phenyl-vinyl] pyrrolidine (5g)



Only *E* (^{1}H NMR). Red crystals, Mp. 132-133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.80-2.20 (m, 4 H), 3.10-3.60 (m, 4 H), 5.96 (s, 1 H), 7.27-7.30 (m, 2 H), 7.59-7.63 (m, 3 H), 8.19 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.2 (CH_2), 49.4 (CH_2), 95.0 (CH), 127.7 (CH), 130.96 (CH), 130.99 (CH), 134.3 ($C_{quat.}$), 141.2 ($C_{quat.}$), 143.7 (CH), 158.5 ($C_{quat.}$), 174.7 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 301 (M^+, 40), 255 (M^+ - NO_2, 100), 232 (M^+ - $N(C_2H_4)_2$, 14). IR (KBr): $\tilde{\nu}$ 1548, 1456, 1264, 1207, 1175, 1108 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 500 nm (17500). UV/Vis (ether): λ_{max} (ε) 468 nm (14200). Anal. calcd. for $C_{15}H_{15}N_3O_2S$ (301.37): C 59.78, H 5.02, N 13.94, S 10.64. Found: C 59.89, H 5.16, N 13.55.

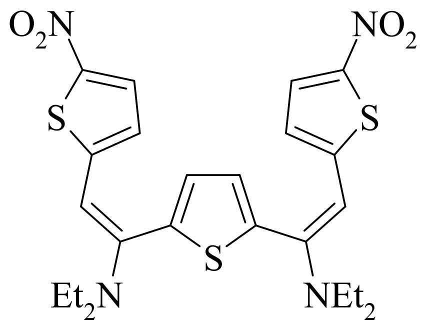
(*E*)-4-[2-(5-Nitropyrid-2-yl)-1-phenyl-vinyl] morpholine (5h)



E/Z = 15:1 (^{1}H NMR). Orange crystals, Mp. 109-110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.06 (t, *J* = 4.8 Hz, 4 H), 3.68 (t, *J* = 4.9 Hz, 4 H), 5.80 (s, 1 H), 6.10 (d, *J* = 9.2 Hz, 1 H), 7.21-7.25 (m, 2 H), 7.32-7.41 (m, 3 H), 7.73 (dd, *J* = 2.6 Hz, *J* = 9.2 Hz, 1 H), 9.06 (d, *J* = 2.6 Hz, 1 H); additional signals for the minor isomer: δ 3.14 (t, *J* = 4.9 Hz, 4 H), 3.95 (t, *J* = 4.9 Hz, 4 H), 5.41 (s, 1 H), 6.19 (d, *J* = 4.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 46.7 (CH_2), 66.6

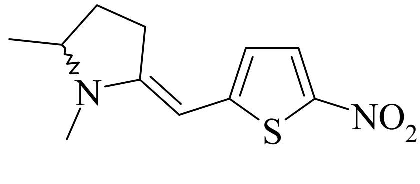
(CH_2), 104.1 (CH), 120.3 (CH), 128.6 ($C_{quat.}$), 129.5 (CH), 129.6 (CH), 129.7 (CH), 129.9 (CH), 135.3 ($C_{quat.}$), 145.1 (CH), 158.4 ($C_{quat.}$), 164.5 ($C_{quat.}$); additional signals for the minor isomer: δ 43.3 (CH_2), 63.9 (CH_2), 94.2 (CH), 126.1 (CH), 128.6 (CH), 130.8 (CH). EI MS (70 eV, *m/z* (%)): 311 (M^+, 55), 265 (M^+ - NO_2, 16), 225 (M^+ - C_4H_8NO, 100), 179 (M^+ - NO_2, - C_4H_8NO, 62). IR (KBr): $\tilde{\nu}$ 1581, 1558, 1508, 1337, 1280, 1244, 1198, 1107, 1022 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 426 nm (20400). UV/Vis (ether): λ_{max} (ε) 404 nm (23400). Anal. calcd. for $C_{17}H_{17}N_3O_3$ (311.34): C 65.58, H 5.50, N 13.50. Found: C 65.64, H 5.63, N 13.00.

(*E,E*)-2,5-Bis[2-(5-nitrothien-2-yl)-1-diethylamino-vinyl] thiophene (5i)



E,E/E/Z = 8:1 (^{1}H NMR, minor diastereomer not entered). Violet crystals, Mp. 206-207 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, J = 7.0 Hz, 12 H), 3.47 (q, J = 7.0 Hz, 8 H), 5.78 (s, 2 H), 6.51 (d, J = 4.5 Hz, 2 H), 7.24 (s, 2 H), 7.64 (d, J = 4.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.3 (CH_3), 44.6 (CH_2), 96.0 (CH), 121.9 (CH), 129.6 (CH), 131.9 (CH), 138.7 ($C_{quat.}$), 144.0 ($C_{quat.}$), 145.0 ($C_{quat.}$), 154.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 532 (M^+, 100), 486 (M^+ - NO_2, 39). IR (KBr): $\tilde{\nu}$ 1568, 1430, 1290, 1240, 1166, 1195, 1037 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 518 nm (44100). UV/Vis (ether): λ_{max} (ε) 485 nm (21000). Anal. calcd. for $C_{24}H_{28}N_4O_4S_3$ (532.71): C 54.11, H 5.30, N 10.52, S 18.06. Found: C 53.90, H 5.12, N 10.18, S 17.95.

***rac*-2-(5-Nitrothien-2-ylidene)-1,5-dimethylpyrrolidine (5j)**



Only *E* (^{1}H NMR). Violet crystals, Mp. 127-128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (d, *J* = 6.4 Hz, 3 H), 1.67-1.76 (m, 1 H), 2.24-2.34 (m, 1 H), 2.79-2.95 (m, 5 H), 3.64-3.72 (m, 1 H), 5.37 (s, 1 H), 6.44 (d, *J* = 4.8 Hz, 1 H), 7.76 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (CH_3), 29.2 (CH_2), 31.1 (CH_2), 31.3 (CH_3), 60.8 (CH), 87.0 (CH), 119.1 (CH), 131.4 (CH), 141.7 ($C_{quat.}$), 157.6 ($C_{quat.}$), 157.8 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 238 (M^+, 100), 223 (M^+ - CH_3, 62), 208 (M^+ - 2CH_3, 27), 192 (M^+ - NO_2, 21), 150 (M^+ - 2CH_3, - NO_2, 19). IR (KBr): $\tilde{\nu}$ 1585, 1447, 1325, 1299, 1251, 1168, 1131, 1034 cm^{-1}. UV/Vis (CH_3CN): λ_{max} (ε) 532 nm (34300). UV/Vis (ether): λ_{max} (ε) 487 nm (29200). Anal. calcd. for $C_{11}H_{14}N_2O_2S$ (238.31): C 55.44, H 5.92, N 11.76, S 13.45. Found: C 55.13, H 5.84, N 11.72, S 13.58.

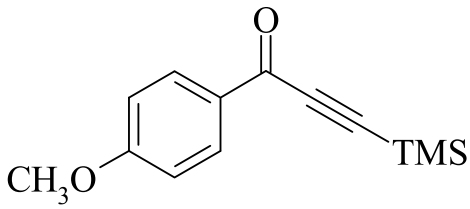
6.3 General Procedure for the Synthesis of (TMS)-ynones

A stirred mixture of 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF was stirred and degassed with nitrogen before 0.14 mL (1.00 mmol) of NEt_3, 1 mmol of acid chloride **6**, and 0.14 mL (1.05 mmol) of (TMS)-acetylene **1f** were successively added. The reaction mixture was then stirred at room temperature for 1 h until the complete consumption of alkyne (monitored by TLC). The solvents were evaporated in vacuo, and the residue was chromatographed on silica gel eluting with diethyl ether/pentane 1:9 (R_f ~ 0.3) to furnish analytically pure **7** as oils or solids (see Table 32 for experimental details).

Table 32. Experimental Details of the Synthesis of (TMS)-ynones 7

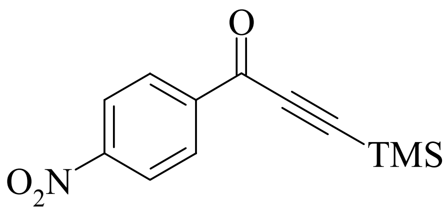
Entry	Acid chloride **6**	(TMS)-ynone **7** (Yield %)
1	171 mg (1.00 mmol) of **6a**	191 mg (82 %) of **7a**
2	186 mg (1.00 mmol) of **6b**	162 mg (65 %) of **7b**
3	185 mg (1.00 mmol) of **6c**	169 mg (61 %) of **7c**
4	199 mg (1.00 mmol) of **6d**	190 mg (73 %) of **7d**
5	147 mg (1.00 mmol) of **6e**	170 mg (82 %) of **7e**

1-(4-Methoxy-phenyl)-3-trimethylsilanyl-propynone (7a)



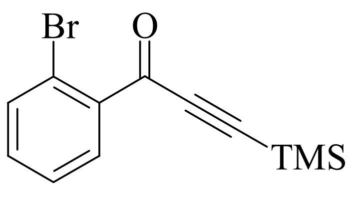
Colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.32 (s, 9 H), 3.89 (s, 3 H), 6.96 (d, J = 8.9 Hz, 2 H), 8.12 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.7 (CH_3), 55.5 (CH_3), 99.4 ($C_{quat.}$), 101.0 ($C_{quat.}$), 113.8 (CH), 129.9 ($C_{quat.}$), 132.0 (CH), 164.5 ($C_{quat.}$), 176.2 ($C_{quat.}$). EI +Q1MS (*m/z* (%)): 232 (M^+, 55), 217 (M^+ - CH_3, 100), 135 ((MeOPhCO)$^+$, 56).

1-(4-Nitro-phenyl)-3-trimethylsilanyl-propynone (7b)



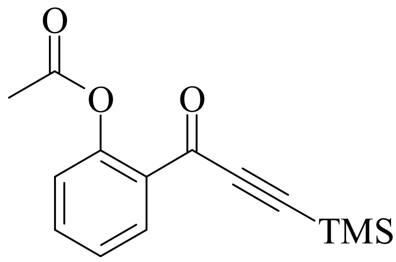
Colorless crystals, Mp. 107-108 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.12 (s, 9 H), 8.04-8.15 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.8 (CH_3), 100.1 ($C_{quat.}$), 103.5 ($C_{quat.}$), 123.8 (CH), 130.6 (CH), 140.6 ($C_{quat.}$), 150.9 ($C_{quat.}$), 175.6 ($C_{quat.}$). EI +Q1MS (*m/z* (%)): 247 (M^+, 5), 232 (M^+ - CH_3, 100). Anal. calcd. for $C_{12}H_{13}NO_3Si$ (247.33): C 58.28, H 5.30, N 5.66. Found: C 58.51, H 5.47, N 5.81.

1-(2-Bromo-phenyl)-3-trimethylsilanyl-propynone (7c)



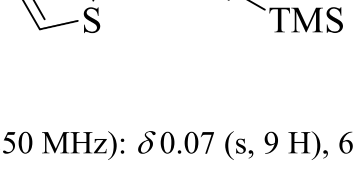
Yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.32 (s, 9 H), 7.35-7.50 (m, 2 H), 7.67-7.73 (m, 1 H), 8.04-8.09 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.8 (CH_3), 101.5 ($C_{quat.}$), 101.6 ($C_{quat.}$), 121.3 ($C_{quat.}$), 127.3 (CH), 133.1 (CH), 133.4 (CH), 135.0 (CH), 136.9 ($C_{quat.}$), 176.9 ($C_{quat.}$).

Acetic acid 2-(3-trimethylsilanyl-propynoyl)-phenyl ester (7d)



Yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.30 (s, 9 H), 2.36 (s, 3 H), 7.11 (d, J = 7.9 Hz, 1 H), 7.38 (t, J = 7.9 Hz, 1 H), 7.60 (t, J = 7.9 Hz, 1 H), 8.22 (d, J = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.9 (CH_3), 20.8 (CH_3), 99.9 ($C_{quat.}$), 101.2 ($C_{quat.}$), 123.9 (CH), 126.0 (CH), 128.7 ($C_{quat.}$), 133.4 (CH), 135.7 (CH), 150.0 ($C_{quat.}$), 169.2 ($C_{quat.}$), 175.4 ($C_{quat.}$). EI +Q1MS (m/z (%)): 260 (M^+, 2), 245 (M^+ - CH_3, 42), 218 (M^+ - CH_2CO, 47), 217 (M^+ - CH_3CO, 37), 203 (M^+ - CH_3 - CH_2CO, 100), 83 ($(CH_2CO)_2^+$, 12), 73 (Me_3Si^+, 9). IR (film): $\tilde{\nu}$ 2902, 2153, 2095, 1772, 1646, 1604, 1481, 1368, 1239, 1019, 849, 764 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 248 nm (8800), 266 nm (11700). HRMS calcd. for $C_{14}H_{16}O_3Si$, 260.0864; found 260.0881.

1-Thiophene-2-yl-3-trimethylsilanyl-propynone (7e)



Colorless oil. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.07 (s, 9 H), 6.93 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.48 (dd, J = 4.9 Hz, J = 1.2 Hz, 1 H), 7.69 (dd, J = 3.7 Hz, J = 1.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -1.0 (CH_3), 98.8 ($C_{quat.}$), 100.2 ($C_{quat.}$), 128.6 (CH), 135.3 (CH), 135.4 (CH), 144.4 ($C_{quat.}$), 169.1 ($C_{quat.}$).

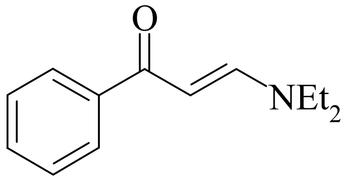
6.4 General Procedure for the Coupling-addition Sequence

A stirred mixture of 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF was stirred and degassed with nitrogen before 0.14 mL (1.00 mmol) of NEt_3, 1 mmol of acid chloride **6**, and 0.14 mL (1.05 mmol) of (TMS)-acetylene **1f** were successively added. The reaction mixture was then stirred at room temperature for 1 h until the complete consumption of alkyne (monitored by TLC). Then HNu **8** in 5 mL of methanol was added. The reaction mixture was heated to reflux temperature until conversion was complete (monitored by TLC). The solvents were evaporated in vacuo, and the residue was chromatographed on silica gel (**9a**, **9b**, **9c** and **12a**) or neutral aluminium oxide (**11a**) eluting with diethyl hexane/ethylacetate 4:1 to furnish analytically pure **9** as oils or solids (see Table 33 for experimental details).

Table 33. Experimental Details of the Coupling-addition Sequence

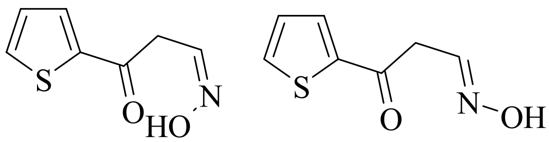
Entry	Acid chloride **6**	Nucleophile **8** (reaction time for the second step)	Product (Yield %)	Eluent
1	141 mg (1.00 mmol) of **6f**	1.00 mL (10.0 mmol) of **4b** (3h)	150 mg (74 %) of **11a**	HE:EA 4:1
2	147 mg (1.00 mmol) of **6e**	140 mg (2.00 mmol) of **8a** and 687 mg (2.40 mmol) of $Na_2CO_3 \cdot 10H_2O$ (2h)	135 mg (80 %) of **9a**	HE:EA 4:1
3	147 mg (1.00 mmol) of **6e**	131 mg (1.20 mmol) of **8b** (2h)	150 mg (61 %) of **9b**	HE:EA 2:1
4	147 mg (1.00 mmol) of **6e**	130 mg (1.20 mmol) of **8c** (2h)	105 mg (43 %) of **9c**	HE:EA 2:1
5	147 mg (1.00 mmol) of **6e**	240 mg (2.50 mmol) of **10a** and 1.00 g (3.50 mmol) of $Na_2CO_3 \cdot 10H_2O$ (14h)	90 mg (51 %) of **12a**	EA

(*E*)-3-Diethylamino-1-phenyl-propenone (11a)



Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19 (t, J = 7.2 Hz, 6 H), 3.30 (q, J = 7.2 Hz, 4 H), 5.74 (d, J = 12.5 Hz, 1 H), 7.37-7.42 (m, 3 H), 7.79 (d, J = 12.5 Hz, 1 H), 7.84-7.88 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.6 (CH_3), 14.7 (CH_3), 42.7 (CH_2), 50.4 (CH_2), 91.6 (CH), 127.4 (CH), 128.3 (CH), 130.6 (CH), 140.7 ($C_{quat.}$), 152.3 (CH), 188.6 ($C_{quat.}$). EI +Q1MS (*m/z* (%)): 203 (M^+, 46), 186 (M^+ - OH, 30), 105 ($PhCO^+$, 100). IR (Film): $\tilde{\nu}$ 2975, 2934, 1639, 1582, 1365, 1219, 1051, 707 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 246 nm (11200), 340 nm (19400). HRMS calcd. for $C_{13}H_{17}NO$, 203.1306; found 203.1314.

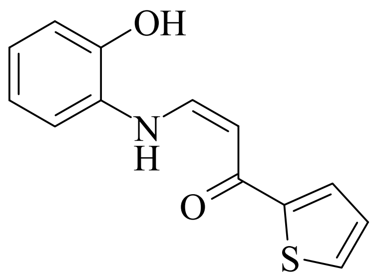
3-Oxo-3-thiophene-2-yl-propionaldehyde oxime (9a)



ratio 6:1

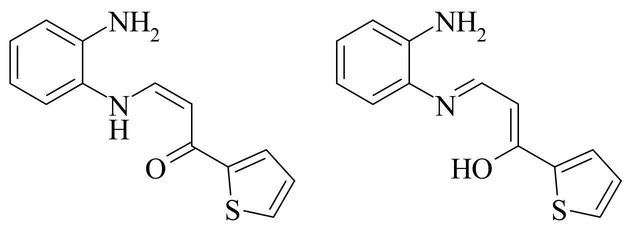
Yellow crystals, Mp. 113-114 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.00 (d, J = 5.3 Hz, 2 H), 6.98 (t, J = 5.3 Hz, 1 H), 7.21-7.28 (m, 1 H), 7.98-8.04 (m, 2 H), 11.20 (s, 1 H, disappears upon addition of D_2O). Additional signals for the minor isomer: δ 3.90 (d, J = 6.0 Hz, 2 H), 7.21-7.28 (m, 1 H), 7.45 (t, J = 6.0 Hz, 1 H), 7.98-8.04 (m, 2 H), 10.80 (s, 1 H, disappears upon addition of D_2O). In the 2D-NOESY a cross-peak between protons of OH and CH groups for minor isomer appears. Therefore, the minor isomer is *E*-configured. ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.4 (CH_2), 128.8 (CH), 133.9 (CH), 135.3 (CH), 142.9 (CH), 143.2 (C_{quat}), 188.7 (C_{quat}). Additional signals for the minor isomer: δ 39.5 (CH_2), 128.8 (CH), 134.2 (CH), 135.3 (CH), 144.4 (CH), 189.6 (C_{quat}). EI +Q1MS (*m/z* (%)): 169 (M^+, 4), 111 (2-$ThCO^+$, 100). IR (KBr): $\tilde{\nu}$ 3206, 3102, 2861, 1654, 1515, 1414, 1213, 1083, 911, 827, 741 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 264 nm (8400), 286 nm (6900). Anal. calcd. for $C_7H_7NO_2S$ (169.20): C 49.69, H 4.17, N 8.28. Found: C 49.44, H 4.13, N 8.28.

3-(2-Hydroxyphenyl-1-amino)-1-(2-thienyl)-propenone (9b)



Yellow crystals, Mp. 217-218 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.00 (d, J = 7.7 Hz, 1 H), 6.80-6.96 (m, 3 H), 7.18 (dd, J = 4.8 Hz, J = 3.7 Hz, 1 H), 7.38 (d, J = 7.7 Hz, 1 H), 7.78-7.88 (m, 3 H), 10.04 (s, 1 H, disappears upon addition of D_2O), 11.80 (d, J = 13.2 Hz, 1 H, disappears upon addition of D_2O). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 93.1 (CH), 113.6 (CH), 115.3 (CH), 119.7 (CH), 123.4 (CH), 128.4 (CH), 128.9 (C_{quat}), 129.4 (CH), 132.3 (CH), 144.1 (CH), 145.7 (C_{quat}), 146.3 (C_{quat}), 182.3 (C_{quat}). EI +Q1MS (m/z (%)): 246 (M^+ + 1, 18), 245 (M^+, 100), 244 (M^+ - 1, 64), 111 (2-ThCO$^+$, 33). IR (KBr): $\tilde{\nu}$ 1631, 1300, 1255, 780, 743 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 264 nm (9800), 288 nm (6700), 388 nm (24300). Anal. calcd. for $C_{13}H_{11}NO_2S$ (245.30): C 63.65, H 4.52, N 5.71. Found: C 63.68, H 4.60, N 5.72.

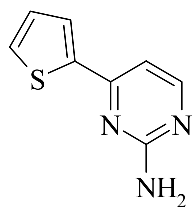
3-(2-Aminophenyl-1-amino)-1-(2-thienyl)-propenone (9c)



ratio 2:1

Red crystals, Mp. 174-175 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.84 (s, 2 H, disappears upon addition of D_2O), 6.01 (d, J = 7.9 Hz, 1 H), 6.80-6.90 (m, 3 H), 7.14-7.22 (m, 3 H), 7.75 (dd, J = 12.4 Hz, J = 7.9 Hz, 1 H), 7.80-7.82 (m, 1 H), 11.62 (d, J = 12.4 Hz, 1 H, disappears upon addition of D_2O). Additional signals for the minor isomer: δ 5.02 (s, 2 H, disappears upon addition of D_2O), 6.24 and 9.17 (2 br s, together 1 H, disappear upon addition of D_2O), 6.57-6.64 (m, 1 H), 7.02 (d, J = 7.5 Hz, 1 H), 7.61-7.64 (m, 1 H), 7.82-7.95 (m, 6 H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 93.0 (CH), 116.2 (CH), 117.3 (CH), 118.4 (CH), 124.4 (CH), 128.1 (C_{quat}), 128.5 (CH), 129.2 (CH), 132.3 (CH), 138.2 (C_{quat}), 146.5 (CH), 147.1 (C_{quat}), 182.2 (C_{quat}). Minor isomer: δ 115.8 (CH), 128.3 (CH), 128.9 (CH), 131.7 (CH), 132.2 (CH), 179.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 246 (M^+ + 2, 5), 245 (M^+ + 1, 17), 244 (M^+, 100), 243 (M^+ - 1, 54), 111 (2-ThCO$^+$, 17). IR (KBr): $\tilde{\nu}$ 3390, 3339, 1622, 1517, 1478, 1296, 1060, 982 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 262 nm (10800), 284 nm (8800), 393 nm (20200). Anal. calcd. for $C_{13}H_{12}N_2OS$ (244.32): C 63.91, H 4.95, N 11.47. Found: C 63.76, H 4.97, N 11.38.

4-Thiophen-2-yl-pyrimidin-2-ylamine (12a)



Colorless crystals, Mp. 189-190 °C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.67 (s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.19 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.73 (dd, J = 5.2 Hz, J = 1.2 Hz, 1 H), 7.89 (dd, J = 3.7 Hz, J = 1.2 Hz, 1 H), 8.25 (d, J = 5.2 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 104.3 (CH), 127.5 (CH), 128.4 (CH), 129.8 (CH), 142.8 (C_{quat}), 158.7 (CH), 158.9 (C_{quat}), 163.5 (C_{quat}). EI MS (*m/z* (%)): 177 (M, 100), 176 (M^+ – H, 44), 135 (M^+ - H_2NCN, 23.5). IR (KBr): $\tilde{\nu}$ 3344, 3186, 1643, 1557, 1461 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 248 (14379). Anal. calcd. for $C_8H_7N_3S$ (177.23): C 54.22, H 3.98, N 23.71. Found: C 54.03, H 4.02, N 23.58.

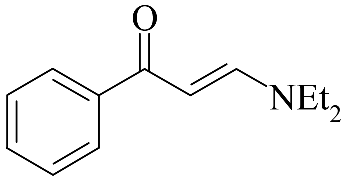
6.5 General Procedure for the Synthesis of β-Enaminones

A stirred mixture of 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF was stirred and degassed with nitrogen for 5 min. Then 1 mmol of acid chloride **6**, 1.05 mmol of alkyne **1**, and 0.14 mL (1.00 mmol) of NEt_3 were successively added. The reaction mixture was then stirred at room temperature for 1-2 h until the complete consumption of alkyne (monitored by TLC). Then 1.20 mmol of amine **4** (10.0 mmol for entry 1, 2.00 mmol for amine **4g**) in 5 mL of methanol was added. The reaction mixture was stirred at room temp for 3 h (secondary amines) or heated to reflux temp for 3 h (primary amines) until the conversion was complete (monitored by TLC, R_f ~ 0.8 for ynone **7** and R_f ~ 0.4 for β-enaminone **11** in HE/EA 4:1). The solvents were evaporated and the residue was chromatographed on neutral aluminium oxide (HE/EA 4:1) to give the enaminones **11** as light yellow oils or solids (see Table 34 for experimental details).

Table 34. Experimental Details of the Synthesis of *β*-Enaminones 11

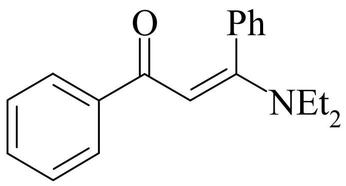
Entry	Alkyne **1**	Acid chloride **6**	Amine **4**	*β*-Enaminone **11** (Yield %)
1	0.14 mL (1.05 mmol) of **1f**	141 mg (1.00 mmol) of **6f**	1.00 mL (10.0 mmol) of **4b**	150 mg (74 %) of **11a**
2	0.11 mL (1.05 mmol) of **1a**	141 mg (1.00 mmol) of **6f**	0.12 mL (1.20 mmol) of **4b**	270 mg (97 %) of **11b**
3	0.11 mL (1.05 mmol) of **1a**	141 mg (1.00 mmol) of **6f**	0.10 mL (1.20 mmol) of **4a**	264 mg (95 %) of **11c**
4	0.11 mL (1.05 mmol) of **1a**	141 mg (1.00 mmol) of **6f**	0.11 mL (1.20 mmol) of **4c**	290 mg (99 %) of **11d**
5	0.11 mL (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	0.12 mL (1.20 mmol) of **4b**	272 mg (95 %) of **11e**
6	0.11 mL (1.05 mmol) of **1a**	175 mg (1.00 mmol) of **6g**	0.12 mL (1.20 mmol) of **4b**	305 mg (97 %) of **11f**
7	0.11 mL (1.05 mmol) of **1a**	121 mg (1.00 mmol) of **6h**	0.12 mL (1.20 mmol) of **4b**	190 mg (75 %) of **11g**
8	0.12 mL (1.05 mmol) of **1b**	141 mg (1.00 mmol) of **6f**	0.12 mL (1.20 mmol) of **4b**	250 mg (97 %) of **11h**
9	0.11 mL (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	0.12 mL (1.20 mmol) of **4e**	270 mg (95 %) of **11i**
10	0.11 mL (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	0.13 mL (1.20 mmol) of **4f**	310 mg (97 %) of **11j**
11	0.11 mL (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	290 mg (78 %) of **11k**
12	0.12 mL (1.05 mmol) of **1b**	167 mg (1.00 mmol) of **6i**	0.55 mL (5.00 mmol) of **4f**	220 mg (69 %) of **11l**

(*E*)-3-Diethylamino-1-phenyl-propenone (11a)



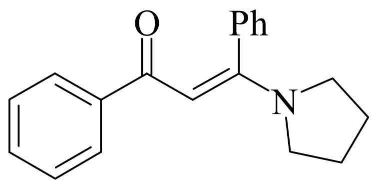
Only *E* (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.19 (t, J = 7.2 Hz, 6 H), 3.30 (q, J = 7.2 Hz, 4 H), 5.74 (d, J = 12.5 Hz, 1 H), 7.37-7.42 (m, 3 H), 7.79 (d, J = 12.5 Hz, 1 H), 7.84-7.88 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.6 (CH_3), 14.7 (CH_3), 42.7 (CH_2), 50.4 (CH_2), 91.6 (CH), 127.4 (CH), 128.3 (CH), 130.6 (CH), 140.7 ($C_{quat.}$), 152.3 (CH), 188.6 ($C_{quat.}$). EI +Q1MS (*m/z* (%)): 203 (M^+, 46), 186 (M^+ - OH, 30), 105 ($PhCO^+$, 100). IR (Film): $\tilde{\nu}$ 2975, 2934, 1639, 1582, 1365, 1219, 1051, 707 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 246 nm (11200), 340 nm (19400). HRMS calcd. for $C_{13}H_{17}NO$, 203.1306; found 203.1314.

(*E*)-3-Diethylamino-1,3-diphenyl-propenone (11b)



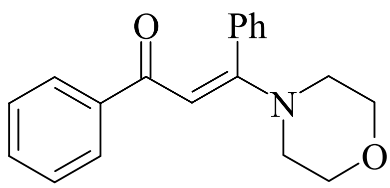
E/Z = 30:1 (^{1}H NMR). Sticky yellow crystals, Mp. 52-53 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16-1.29 (m, 6 H), 3.26-3.48 (m, 4 H), 5.98 (s, 1 H), 7.26 (d, J = 4.5 Hz, 2 H), 7.35-3.45 (m, 6 H), 7.86 (d, J = 4.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.2 (CH_3), 44.0 (CH_2), 92.9 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 130.1 (CH), 137.0 ($C_{quat.}$), 141.9 ($C_{quat.}$), 162.9 ($C_{quat.}$), 186.7 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 279 (M^+, 20), 262 (M^+ - OH, 100), 250 (M^+ - C_2H_5, 15), 174 (M^+ - PhCO, 37), 105 ($PhCO^+$, 44). IR (Film): $\tilde{\nu}$ 3440, 2967, 1627, 1574, 1519, 1354, 1218, 769 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 246 nm (13300), 342 nm (19800). HRMS calcd. for $C_{19}H_{21}NO$: 279.1618. Found: 279.1613.

(*E*)-1,3-Diphenyl-3-pyrrolidin-1-yl-propenone (11c)



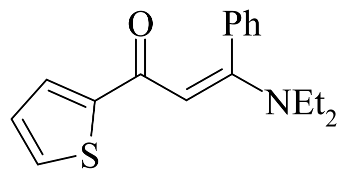
E/Z = 5:1 (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.81-1.85 (m, 2 H), 1.93-2.03 (m, 2 H), 3.03-3.11 (m, 2 H), 3.38-3.47 (m, 2 H), 5.81 (s, 1 H), 7.26 (d, J = 4.0 Hz, 2 H), 7.31-7.42 (m, 6 H), 7.86 (d, J = 4.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.0 (CH_2), 25.2 (CH_2), 48.5 (CH_2), 49.8 (CH_2), 93.0 (CH), 127.1 (CH), 127.7 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 130.3 (CH), 138.0 ($C_{quat.}$), 141.8 ($C_{quat.}$), 161.8 ($C_{quat.}$), 186.6 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 277 (M^+, 15), 260 (M^+ - OH, 31), 105 ($PhCO^+$, 100). IR (Film): $\tilde{\nu}$ 3057, 2971, 2872, 1627, 1575, 1520, 1340, 1213, 939, 765, 700 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 246 nm (13300), 346 nm (18000).

(*E*)-3-Morpholin-4-yl-1,3-diphenyl-propenone (11d)



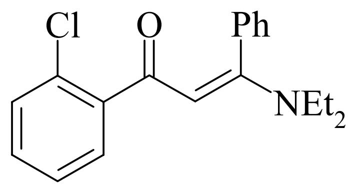
E/Z = 4:1 (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): major isomer δ 3.21 (t, J = 2.9 Hz, 4 H), 3.72 (t, J = 2.9 Hz, 4 H), 5.99 (s, 1 H), 7.24-7.87 (m, 10 H); minor isomer 3.39 (t, J = 2.9 Hz, 4 H), 3.83 (t, J = 2.9 Hz, 4 H), 5.69 (s, 1 H), 7.24-7.87 (m, 10 H). ^{13}C NMR ($CDCl_3$, 75 MHz): major isomer δ 48.2 (CH_2), 66.5 (CH_2), 97.3 (CH), 127.1 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.6 (CH), 130.3 (CH), 136.0 ($C_{quat.}$), 141.0 ($C_{quat.}$), 164.4 ($C_{quat.}$), 189.1 ($C_{quat.}$); minor isomer δ 52.1 (CH_2), 67.3 (CH_2), 98.2 (CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 129.6 (CH), 132.4 ($C_{quat.}$), 138.5 ($C_{quat.}$), 164.1 ($C_{quat.}$), 185.6 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 293 (M^+, 9), 276 (M^+ - OH, 100), 105 ($PhCO^+$, 45). IR (Film): $\tilde{\nu}$ 3056, 2959, 2853, 1628, 1534, 1207, 1123, 923, 767 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 250 nm (12500), 340 nm (15800).

(*E*)-3-Diethylamino-3-phenyl-1-thiophen-2-yl-propenone (11e)



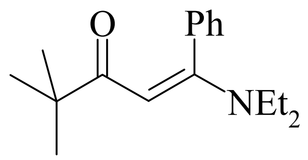
E/Z = 14:1 (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): major isomer δ 0.95-1.20 (m, 6 H), 2.98-3.41 (m, 4 H), 5.80 (s, 1 H), 6.94 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.12-7.18 (m, 2 H), 7.26-7.38 (m, 4 H), 7.48 (dd, J = 3.7 Hz, J = 1.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): major isomer δ 13.4 (CH_3), 44.2 (CH_2), 92.1 (CH), 127.1 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.5 (CH), 131.9 (CH), 136.8 ($C_{quat.}$), 149.4 ($C_{quat.}$), 163.4 ($C_{quat.}$), 178.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 285 (M^+, 33), 268 (M^+ - OH, 100), 174 (M+ - 2-ThCO$^+$, 22), 111 (2-ThCO$^+$, 42). IR (Film): $\tilde{\nu}$ 2974, 1612, 1518, 1358, 801, 704 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 258 nm (10400), 284 nm (6300), 354 nm (22200). HRMS calcd. for $C_{17}H_{19}NOS$: 285.1183. Found: 285.1174.

(*E*)-1-(2-Chloro-phenyl)-3-diethylamino-3-phenyl-propenone (11f)



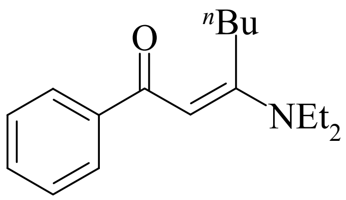
Only *E* (^{1}H NMR). Colorless crystals, Mp. 80-81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.02-1.29 (m, 6 H), 3.33-3.54 (m, 4 H), 5.61 (s, 1 H), 7.03-7.52 (m, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3 (CH_3), 44.1 (CH_2), 99.0 (CH), 125.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 129.0 (CH), 129.2 (CH), 130.2 ($C_{quat.}$), 135.7 ($C_{quat.}$), 142.9 ($C_{quat.}$), 162.9 ($C_{quat.}$), 189.5 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 315 (M^+ (^{37}Cl), 12), 313 (M^+ (^{35}Cl), 35), 298 (M^+ (^{37}Cl) - OH, 34), 296 (M^+ (^{35}Cl) - OH, 100), 139 (*o*-$ClC_6H_4CO^+$, 40). IR (KBr): $\tilde{\nu}$ 2976, 1627, 1589, 1517, 1464, 1359, 1217, 1076, 795 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 246 nm (8500), 328 nm (19400). HRMS calcd. for $C_{19}H_{20}ClNO$ (^{37}Cl): 315.1199. Found: 315.1221. Calcd. for $C_{19}H_{20}ClNO$ (^{35}Cl): 313.1229. Found: 313.1272. Anal. calcd. for $C_{19}H_{20}ClNO$ (313.80): C 72.72, H 6.42, N 4.46. Found: C 72.60, H 6.42, N 4.51.

(*E*)-1-Diethylamino-4,4-dimethyl-1-phenyl-pent-1-en-3-one (11g) (compound is not pure)



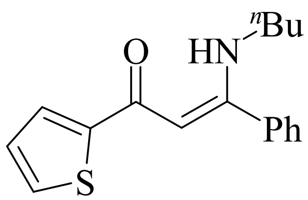
Only *E* (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 15 H), 3.14-3.29 (m, 4 H), 5.46 (s, 1 H), 7.10-7.14 (m, 2 H), 7.31-7.41 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.1 (CH_3), 27.6 (CH_3), 42.6 ($C_{quat.}$), 43.7 (CH_2), 91.5 (CH), 127.1 (CH), 127.7 (CH), 128.1 (CH), 137.4 ($C_{quat.}$), 161.4 ($C_{quat.}$), 201.2 ($C_{quat.}$).

(*E*)-3-Diethylamino-1-phenylhept-2-en-1-one (11h)



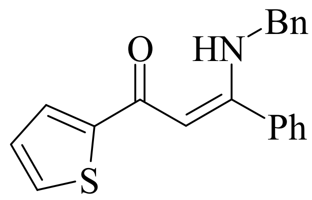
Only *E* (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 6 H), 1.38-1.51 (m, 4 H), 3.00-3.14 (m, 2 H), 3.33 (q, J = 7.1 Hz, 4 H), 5.66 (s, 1 H), 7.34-7.39 (m, 3 H), 7.80-7.85 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.1 (CH_3), 13.8 (CH_3), 23.1 (CH_2), 28.6 (CH_2), 31.0 (CH_2), 44.0 (CH_2), 90.7 (CH), 127.1 (CH), 127.8 (CH), 129.8 (CH), 143.3 ($C_{quat.}$), 166.2 ($C_{quat.}$), 186.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 259 (M^+, 12), 242 (M^+ - OH, 83), 105 ($PhCO^+$, 100). IR (Film): $\tilde{\nu}$ 2958, 2932, 2872, 1606, 1575, 1532, 1356, 1217, 1091, 768 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 248 nm (9700), 330 nm (17000).

(*Z*)-3-Butylamino-3-phenyl-1-thiophen-2-yl-propenone (11i)



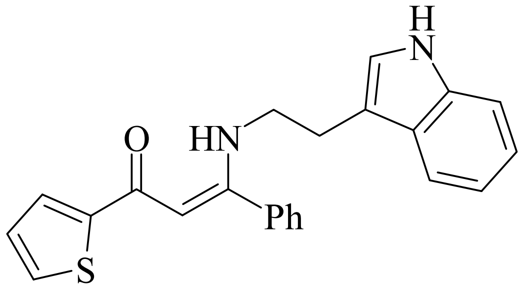
Only *Z* (^{1}H NMR). Yellow crystals, Mp. 57-58 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (t, J = 7.4 Hz, 3 H), 1.30-1.43 (m, 2 H), 1.48-1.59 (m, 2 H), 3.19 (q, J = 6.6 Hz, 2 H), 5.62 (s, 1 H), 7.05 (dd, J = 5.1, J = 3.7 Hz, 1 H), 7.38-7.48 (m, 6 H), 7.53 (dd, J = 3.7, J = 1.1 Hz, 1 H), 11.08 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6 (CH_3), 19.8 (CH_2), 32.7 (CH_2), 44.5 (CH_2), 92.8 (CH), 127.4 (CH), 127.6 (CH), 127.6 (CH), 128.5 (CH), 129.4 (CH), 129.8 (CH), 135.4 ($C_{quat.}$), 147.1 ($C_{quat.}$), 166.4 ($C_{quat.}$), 181.0 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 285 (M^+, 100), 268 (M^+ - OH, 49), 111 (2-ThCO$^+$, 63). IR (KBr): ṽ 2950, 2928, 1591, 1576, 1376, 1232, 703 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 254 nm (9100), 280 nm (5100), 368 nm (22500). Anal. calcd. for $C_{17}H_{19}NOS$ (285.41): C 71.54, H 6.71, N 4.91. Found: C 71.44, H 6.68, N 4.99.

(*Z*)-3-Benzylamino-3-phenyl-1-thiophen-2-yl-propenone (11j)



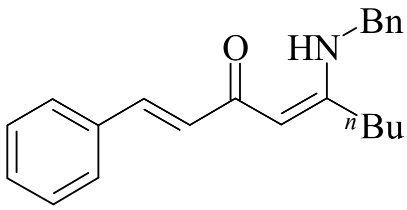
Only *Z* (^{1}H NMR). Yellow crystals, Mp. 110-111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.38 (d, J = 6.3 Hz, 2 H), 5.72 (s, 1 H), 7.07 (dd, J = 5.1, J = 3.7 Hz, 1 H), 7.19-7.50 (m, 11 H), 7.58 (dd, J = 3.7, 1.1 Hz, 1 H), 11.36 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.5 (CH_2), 93.7 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 127.82 (CH), 128.6 (CH), 128.7 (CH), 129.6 (CH), 130.2 (CH), 135.3 ($C_{quat.}$), 138.3 ($C_{quat.}$), 147.1 ($C_{quat.}$), 166.4 ($C_{quat.}$), 181.7 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 319 (M^+, 100), 302 (M^+ - OH, 23), 91 (C_7H_7, 65). IR (KBr): ṽ 3060, 3026, 1590, 1569, 1334, 1232, 1077, 853, 700 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 252 nm (9800), 288 nm (3900), 368 nm (24000). Anal. calcd. for $C_{20}H_{17}NOS$ (319.43): C 75.20, H 5.36, N 4.38, S 10.04. Found: C 75.12, H 5.50, N 4.58, S 9.75.

(*Z*)-3-[2-(1H-Indol-3-yl)-ethylamino]-3-phenyl-1-thiophen-2-yl-propenone (11k)



Only *Z* (^{1}H NMR). Yellow crystals, Mp. 61-62 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.98 (t, J = 7.0 Hz, 2 H), 3.51 (q, J = 6.8 Hz, 2 H), 5.61 (s, 1 H), 7.00-7.49 (m, 12 H), 7.55 (dd, J = 3.7, 1.1 Hz, 1 H), 8.32 (s, 1 H), 11.00 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 (CH_2), 45.1 (CH_2), 93.0 (CH), 111.1 (CH), 119.8 ($C_{quat.}$), 118.1 (CH), 119.1 (CH), 121.7 (CH), 122.5 (CH), 126.9 ($C_{quat.}$), 127.4 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 129.2 (CH), 129.7 (CH), 135.2 ($C_{quat.}$), 136.2 ($C_{quat.}$), 147.0 ($C_{quat.}$), 166.5 ($C_{quat.}$), 181.1 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 372 (M^+, 17), 242 (M^+ - C_9H_8N, 100). IR (KBr): $\tilde{\nu}$ 2925, 1590, 1568, 1484, 1416, 1332, 1234, 743 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) 256 nm (12100), 280 nm (10300), 368 nm (22100). HRMS calcd. for $C_{23}H_{20}N_2OS$: 372.1292. Found: 372.1331. Anal. calcd. for $C_{23}H_{20}N_2OS$ (372.49): C 74.16, H 5.41, N 7.52. Found: C 73.58, H 5.32, N 7.68.

(*1E,4Z*)-5-Benzylamino-1-phenyl-nona-1,4-dien-3-one (11l)



Only *Z* (^{1}H NMR). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, J = 7.2 Hz, 3 H), 1.33-1.46 (m, 2 H), 1.51-1.61 (m, 2 H), 2.29 (t, J = 8.0 Hz, 2 H), 4.53 (d, J = 6.2 Hz, 2 H), 5.24 (s, 1 H), 6.70 (d, J = 15.8 Hz, 1 H), 7.25-7.38 (m, 8 H), 7.48-7.54 (m, 3 H), 11.89 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7 (CH_3), 22.5 (CH_2), 30.1 (CH_2), 31.7 (CH_2), 46.7 (CH_2), 96.4 (CH), 126.9 (CH), 127.5 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 130.0 (CH), 136.0 ($C_{quat.}$), 137.2 (CH), 137.7 ($C_{quat.}$), 168.9 ($C_{quat.}$), 185.7 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 319 (M^+, 20), 302 (M^+ - OH, 9), 290 (M^+ - C_2H_5, 11), 277 (M^+ - C_3H_6, 46), 249 (M^+ - C_2H_5, 31), 131 (C_6H_5CH=$CHCO^+$, 35), 91 (C_7H_7, 100). HRMS calcd. for $C_{22}H_{25}NO$: 319.1936. Found: 319.1922.

6.6 General Procedure for the Synthesis of Pyrimidines 12a-s

A stirred mixture of 14 mg (0.02 mmol) of $PdCl_2(PPh_3)_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF or CH_3CN was stirred and degassed with nitrogen for 5 min. Then 1 mmol of acid chloride **6**, 1.05 mmol of alkyne **1**, and 0.14 mL (1.00 mmol) of NEt_3 were successively added. The reaction mixture was then stirred at room temperature for 1-3 h until the complete consumption of alkyne (monitored by TLC). Afterwards 973 mg (3.40 mmol for alkyne **1f**) or 687 mg (2.40 mmol for all other alkynes **1**) of $Na_2CO_3 \times 10\ H_2O$ and 1.20 mmol (2.50 mmol for guanidine hydrochloride **10a**) of amidinium hydrochloride **10** (0.60 mmol of 2-methyl-2-thiopseudourea sulfate for **10e**) were added to the suspension and the reaction mixture was heated to reflux temp for 12-14 h. After cooling to room temp the crude products were purified by chromatography on silica gel to give the analytically pure pyrimidines **12**. Crystallization was achieved from pentane/CH_2Cl_2 or methanol, (see Table 35 for experimental details).

Table 35. Experimental Details of the Synthesis of Pyrimidines 12

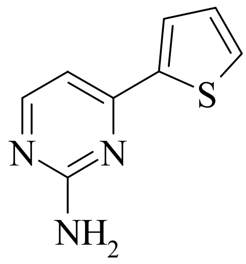
Entry	Alkyne **1**	Acid chloride **6**	Amidinium salt **10**	Solvent	$Na_2CO_3 \cdot 10\ H_2O$	Pyrimidine **12** (Yield %)
1	0.14 mL (1.05 mmol) of **1f**	147 mg (1.00 mmol) of **6e**	240 mg (2.50 mmol) of **10a**	5 mL of CH_3CN and 5mL of CH_3OH[a]	973 mg	90 mg (51 %) of **12a**[b]
2	0.12 mL (1.05 mmol) of **1b**	141 mg (1.00 mmol) of **6f**	195 mg (1.20 mmol) of **10b**	5 mL of THF	687 mg	198 mg (67 %) of **12b**[c]
3	103 mg (1.00 mmol) of **1g**	141 mg (1.00 mmol) of **6f**	195 mg (1.20 mmol) of **10b**	5 mL of CH_3CN	687 mg	150 mg (48 %) of **12c**[d]
4	0.11 mL (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	224 mg (1.20 mmol) of **10c**	5 mL of CH_3CN	687 mg	170 mg (49 %) of **12d**[d]
5	0.12 mL (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	224 mg (1.20 mmol) of **10c**	5 mL of THF	687 mg	264 mg (84 %) of **12e**[d]
6	0.14 mL (1.05 mmol) of **1f**	147 mg (1.00 mmol) of **6e**	224 mg (1.20 mmol) of **10c**	5 mL of THF and 5mL of CH_3OH[a]	973 mg	217 mg (81 %) of **12f**[e]

Table 35. Continued

Entry	Alkyne **1**	Acid chloride **6**	Amidinium salt **10**	Solvent	$Na_2CO_3 \cdot 10\ H_2O$	Pyrimidine **12** (Yield %)
7	0.14 mL (1.05 mmol) of **1f**	147 mg (1.00 mmol) of **6e**	281 mg (1.20 mmol) of **10d**	5 mL of THF and 5mL of CH_3OH[a]	973 mg	121 mg (38 %) of **12g**[e]
8	171 mg (1.00 mmol) of **1h**	147 mg (1.00 mmol) of **6e**	170 mg (0.60 mmol) of **10e**	5 mL of THF	687 mg	199 mg (56 %) of **12h**[f]
9	171 mg (1.00 mmol) of **1h**	147 mg (1.00 mmol) of **6e**	113 mg (1.20 mmol) of **10f**	5 mL of THF	687 mg	113 mg (35 %) of **12i**[e]
10	0.12 mL (1.05 mmol) of **1b**	121 mg (1.00 mmol) of **6h**	195 mg (1.20 mmol) of **10b**	5 mL of THF	687 mg	71 mg (26 %) of **12j**[g]
11	0.12 mL (1.05 mmol) of **1b**	121 mg (1.00 mmol) of **6h**	241 mg (1.20 mmol) of **10g**	5 mL of THF	687 mg	100 mg (33 %) of **12k**[h]
12	0.14 mL (1.05 mmol) of **1f**	121 mg (1.00 mmol) of **6a**	240 mg (2.50 mmol) of **10a**	5 mL of CH_3CN and 5mL of CH_3OH[a]	973 mg	83 mg (44 %) of **12l**[b]
13	0.14 mL (1.05 mmol) of **1f**	171 mg (1.00 mmol) of **6j**	240 mg (2.50 mmol) of **10a**	5 mL of CH_3CN and 5mL of CH_3OH[a]	973 mg	99 mg (49 %) of **12m**[b]
14	0.12 mL (1.05 mmol) of **1b**	141 mg (1.00 mmol) of **6f**	230 mg (1.20 mmol) of **10h**	5 mL of THF	687 mg	194 mg (60 %) of **12n**[d]
15	0.14 mL (1.05 mmol) of **1f**	147 mg (1.00 mmol) of **6e**	241 mg (1.20 mmol) of **10g**	5 mL of THF and 5mL of CH_3OH[a]	973 mg	85 mg (30 %) of **12o**[e]

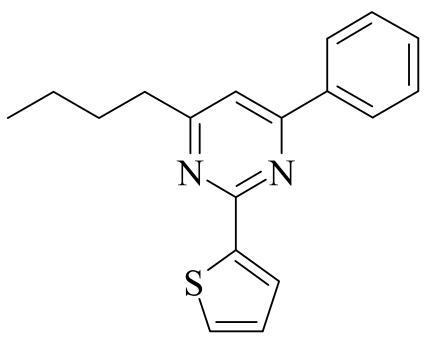
[a]Methanol was added only after completing of the first step. [b]Chromatography on silica gel (EA). [c]Chromatography on silica gel (HE/EA 8:1). [d]Chromatography on silica gel (HE/EA 6:1). [e]Chromatography on silica gel (HE/EA 4:1). [f]Chromatography on silica gel (HE to HE/EA 8:1). [g]Chromatography on silica gel (HE/EA 9:1 to 4:1). [h]Chromatography on silica gel (HE/EA 9:1).

4-Thiophen-2-yl-pyrimidin-2-ylamine (12a)



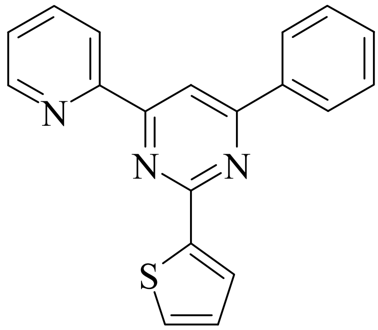
Colorless crystals, Mp. 189-190 °C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.67 (s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.19 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.73 (dd, J = 5.2 Hz, J = 1.2 Hz, 1 H), 7.89 (dd, J = 3.7 Hz, J = 1.2 Hz, 1 H), 8.25 (d, J = 5.2 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 104.3 (CH), 127.5 (CH), 128.4 (CH), 129.8 (CH), 142.8 (C_{quat}), 158.7 (CH), 158.9 (C_{quat}), 163.5 (C_{quat}). EI MS (m/z (%)): 177 (M, 100), 176 (M^+ – H, 44), 135 (M^+ - H_2NCN, 23.5). IR (KBr): $\tilde{\nu}$ 3344, 3186, 1643, 1557, 1461 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 248 (14379). Anal. calcd. for $C_8H_7N_3S$ (177.23): C 54.22, H 3.98, N 23.71. Found: C 54.03, H 4.02, N 23.58.

4-Butyl-6-phenyl-2-thiophen-2-yl-pyrimidine (12b)



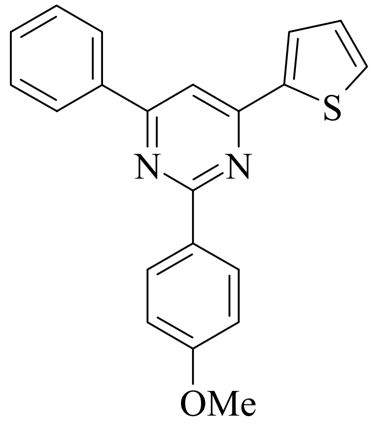
Yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.87 (t, J = 7.2 Hz, 3 H), 1.26-1.38 (m, 2 H), 1.64-1.75 (m, 2 H), 2.71 (t, J = 7.6 Hz, 2 H), 7.04 (dd, J = 3.7, 5.1 Hz, 1 H), 7.24 (s, 1 H), 7.36-7.40 (m, 4 H), 8.02-8.07 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.4 (CH_2), 30.8 (CH_2), 37.6 (CH_2), 112.8 (CH), 127.1 (CH), 128.0 (CH), 128.7 (CH), 128.7 (CH), 129.4 (CH), 130.6 (CH), 137.0 (C_{quat}), 144.1 (C_{quat}), 161.1 (C_{quat}), 163.6 (C_{quat}), 171.6 (C_{quat}). FAB$^+$ MS (m/z (%)): 295 ($(M + H)^+$, 100), 265 ($(M + H)^+$ - C_2H_6, 8), 252 ($(M + H)^+$ - C_3H_7, 29). IR (neat): ṽ 2956, 2929, 2870, 1601, 1575, 1530, 1438, 1376 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 260 nm (19500), 294 (19100). HRMS calcd. for $C_{18}H_{18}N_2S$ + H: 295.1267. Found: 295.1250.

4-Phenyl-6-pyridin-2-yl-2-thiophen-2-yl-pyrimidine (12c)



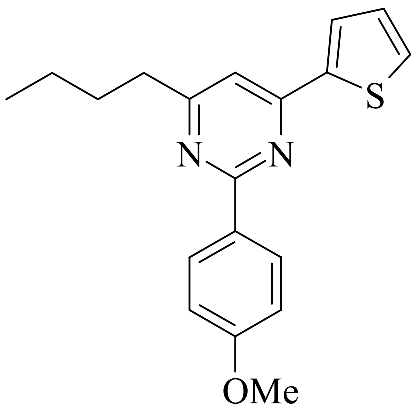
Yellow crystals, Mp. 174 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.20 (dd, J = 3.7, J = 5.0 Hz, 1 H), 7.43 (ddd, J = 1.1, J = 4.8, J = 7.7 Hz, 1 H), 7.50-7.58 (m, 4 H), 7.91 (dt, J = 1.9, J = 7.8 Hz, 1 H), 8.21 (dd, J = 1.5, J = 3.7 Hz, 1 H), 8.31-8.37 (m, 2 H), 8.65-8.69 (m, 2 H), 8.74-8.77 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.9 (CH), 121.7 (CH), 125.1 (CH), 127.2 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 129.4 (CH), 130.7 (CH), 136.7 (C_{quat}), 136.8 (CH), 143.9 (C_{quat}), 149.2 (CH), 154.1 (C_{quat}), 161.1 (C_{quat}), 163.4 (C_{quat}), 165.0 (C_{quat}). FAB$^+$ MS (m/z (%)): 316 ($(M + H)^+$, 100). IR (KBr): ṽ 1577 cm^{-1}, 1568, 1532, 1365, 765 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 242 nm (26800), 252 (31500), 272 (36200), 282 (37300), 290 (35000), 302 (28000), 338 (9300). Anal. calcd. for $C_{19}H_{13}N_3S$ (315.40): C 72.36, H 4.15, N 13.32. Found: C 71.01, H 4.13, N 12.99.

2-(4-Methoxy-phenyl)-4-phenyl-6-thiophen-2-yl-pyrimidine (12d)



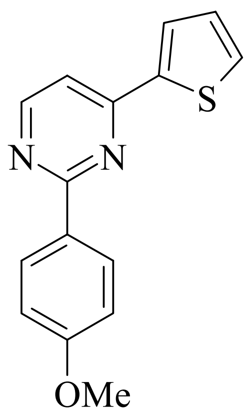
Colorless crystals, Mp. 136 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.82 (s, 3 H), 6.96 (d, J = 8.9 Hz, 2 H), 7.12 (dd, J = 5.1 Hz, J = 3.8 Hz, 1 H), 7.45-7.47 (m, 4 H), 7.71 (s, 1 H), 7.83 (dd, J = 3.8 Hz, J = 1.1 Hz, 1 H), 8.15-8.17 (m, 2 H), 8.55 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.7 (CH_3), 107.9 (CH), 113.8 (CH), 127.1 (CH), 127.3 (CH), 128.3 (CH), 128.9 (CH), 129.8 (CH), 130.2 (CH), 130.3 (C_{quat}), 130.8 (CH), 137.8 (C_{quat}), 143.4 (C_{quat}), 159.6 (C_{quat}), 162.0 (C_{quat}), 164.1 (C_{quat}), 164.4 (C_{quat}). FAB^{+} MS (*m/z* (%)): 345 ((M + H)$^{+}$, 100). IR (KBr): $\tilde{\nu}$ 2918, 1569, 1528, 1513, 1367, 1251 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 270 nm (24100), 278 (24900), 294 (3300), 332 (9000), 362 (400). HRMS calcd. for $C_{21}H_{16}N_2OS$ + H: 345.1062. Found: 345.1044. Anal. calcd. for $C_{21}H_{16}N_2OS$ (344.4): C 73.23, H 4.68, N 8.13; Found: C 73.10, H 4.66, N 8.21.

4-Butyl-2-(4-methoxy-phenyl)-6-thiophen-2-yl-pyrimidine (12e)



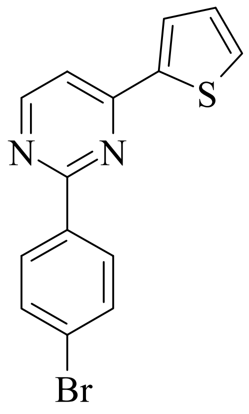
Yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.84 (t, J = 7.2 Hz, 3 H), 1.26-1.35 (m, 2 H), 1.60-1.69 (m, 2 H), 2.65 (t, J = 7.7 Hz, 2 H), 3.71 (s, 3 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.98 (dd, J = 3.7, 4.9 Hz, 1 H), 7.10 (s, 1 H), 7.33 (dd, J = 1.1, 4.9 Hz, 1 H), 7.62 (dd, J = 1.1, 3.7 Hz, 1 H), 8.40 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.4 (CH_2), 30.7 (CH_2), 37.7 (CH_2), 55.2 (CH_3), 110.6 (CH), 113.6 (CH), 126.6 (CH), 128.0 (CH), 129.2 (CH), 129.9 (CH), 130.4 (C_{quat}), 143.4 (C_{quat}), 158.4 (C_{quat}), 161.6 (C_{quat}), 163.7 (C_{quat}), 171.1 (C_{quat}). FAB$^+$ MS (m/z (%)): 325 ((M + H)$^+$, 100), 282 ((M + H)$^+$ - C_3H_7, 39). IR (neat): $\tilde{\nu}$ 2956, 2930, 1607, 1588, 1571, 1530, 1380, 1252, 1168 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 292 nm (30200), 328 (6300). HRMS calcd. for $C_{19}H_{20}N_2OS$ + H: 325.1366. Found: 325.1374.

2-(4-Methoxy-phenyl)-4-thiophen-2-yl-pyrimidine (12f)



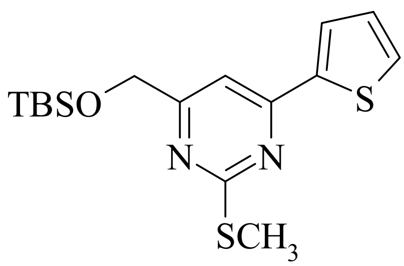
Colorless crystals, Mp. 82 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.80 (s, 3 H), 6.93 (d, J = 9.1 Hz, 2 H), 7.08 (dd, J = 3.7, 5.1 Hz, 1 H), 7.28 (d, J = 5.4 Hz, 1 H), 7.45 (dd, J = 1.1, 5.1 Hz, 1 H), 7.71 (dd, J = 1.1, 3.7 Hz, 1 H), 8.41 (d, J = 9.1 Hz, 2 H), 8.62 (d, J = 5.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.3 (CH_3), 112.0 (CH), 113.9 (CH), 127.4 (CH), 128.3 (CH), 129.9 (CH), 130.1 (CH), 143.0 (C_{quat}), 157.1 (CH), 159.0 (C_{quat}), 162.0 (C_{quat}), 164.1 (C_{quat}). FAB$^+$ MS (m/z (%)): 269 ((M + H)$^+$, 100). IR (KBr): $\tilde{\nu}$ 1562, 1416, 1252 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 296 nm (34500), 330 (9000). Anal. calcd. for $C_{15}H_{12}N_2OS$ (268.3): C 67.14, H 4.51, N 10.44. Found: C 66.73, H 4.51, N 10.29.

2-(4-Brom-phenyl)-4-thiophen-2-yl-pyrimidine (12g)



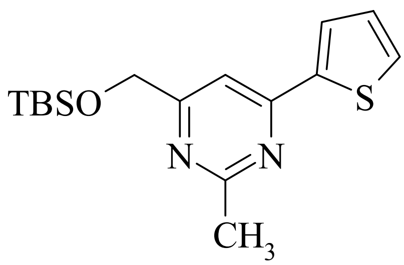
Orange crystals, Mp. 123 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.12 (t, J = 4.2 Hz, 1 H), 7.39 (d, J = 5.2 Hz, 1 H), 7.48 (d, J = 4.9 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 3.2 Hz, 1 H), 8.32 (d, J = 8.5 Hz, 2 H), 8.66 (d, J = 5.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 113.0(CH), 125.7 (C_{quat}), 127.8 (CH), 128.5 (CH), 130.0 (CH), 130.5 (CH), 131.7 (CH), 136.1 (C_{quat}), 142.5 (C_{quat}), 157.3 (CH), 159.2 (C_{quat}), 163.5 (C_{quat}). FAB$^+$ MS (m/z (%)): 319 ((M + H)$^+$ (^{81}Br), 100), 317 ((M + H)$^+$ (^{79}Br), 95). IR (KBr): $\tilde{\nu}$ 1581, 1557, 1441, 1421, 1401, 818 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 270 nm (28700), 280 (25700), 312 (15800), 326 (11600). Anal. calcd. for $C_{14}H_9BrN_2S$ (317.2): C 53.01, H 2.86, N 8.83. Found: C 53.01, H 3.03, N 8.72.

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methylsulfanyl-6-thiophen-2-yl-pyrimidine (12h)



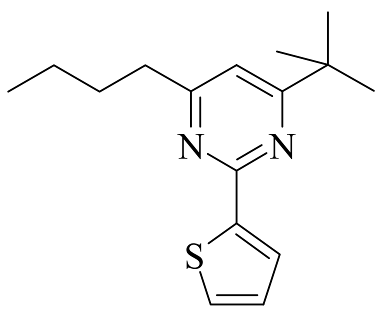
Light yellow crystals, Mp. 76 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.00 (s, 6 H), 0.82 (s, 9 H), 2.61 (s, 3 H), 4.59 (s, 2 H), 7.01 (dd, J = 3.8, 5.0 Hz, 1 H), 7.31 (s, 1 H), 7.36 (dd, J = 1.1, 5.0 Hz, 1 H), 7.62 (dd, J = 1.1, 3.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -5.4 (CH_3), 14.1 (CH_3), 18.4 (C_{quat}), 25.9 (CH_3), 65.2 (CH_2), 106.2 (CH), 127.5 (CH), 128.3 (CH), 130.0 (CH), 142.7 (C_{quat}), 159.4 (C_{quat}), 171.0 (C_{quat}), 171.6 (C_{quat}). FAB$^+$ MS (m/z (%)): 353 ((M + H)$^+$, 100), 295 ((M + H)$^+$ - C_4H_{10}). IR (KBr): $\tilde{\nu}$ 2951, 2928, 2855, 1547, 1529, 1434, 1349, 1269, 1219, 1129, 859, 779 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 242 nm (8400), 262 (15900), 296 (11400), 304 (10700), 324 (9600), 336 (7800). Anal. calcd. for $C_{10}H_{10}N_2OS_2$ (352.6): C 54.50, H 6.86, N 7.94. Found: C 54.51, H 6.87, N 7.80.

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-6-thiophen-2-yl-pyrimidine (12i)



Brown oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.01 (s, 6 H), 0.84 (s, 9 H), 2.55 (s, 3 H), 4.61 (s, 2 H), 7.01 (dd, J = 3.7, 5.1 Hz, 1 H), 7.36 (d, J = 5.1 Hz, 1 H), 7.47 (s, 1 H), 7.63 (d, J = 4.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -5.4 (CH_3), 18.4 (C_{quat}), 25.8 (CH_3), 25.9 (CH_3), 65.2 (CH_2), 108.0 (CH), 127.2 (CH), 128.3 (CH), 129.7 (CH), 143.0 (C_{quat}), 159.5 (C_{quat}), 167.5 (C_{quat}), 170.6 (C_{quat}). FAB$^+$ MS (m/z (%)): 321 ((M + H)$^+$, 100), 263 ((M + H)$^+$ - C_4H_{10}, 89). HRMS calcd. for $C_{16}H_{24}N_2OSSi$ + H: 321.1446. Found: 321.1504.

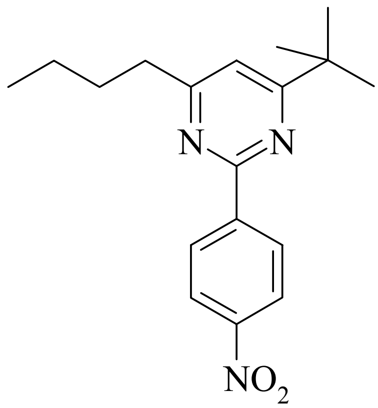
4-Butyl-6-*tert*-butyl-2-thiophen-2-yl-pyrimidine (12j)



Yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.89 (t, J = 7.4 Hz, 3 H), 1.28 (s, 9 H), 1.28-1.37 (m, 2 H), 1.60-1.70 (m, 2 H), 2.66 (t, J = 7.6 Hz, 2 H), 6.8 (s, 1 H), 7.02 (dd, J = 3.7, 5.1 Hz, 1 H), 7.33 (d, J = 4.7 Hz, 1 H), 7.94 (d, J = 3.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7

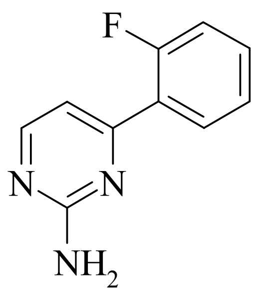
(CH_3), 21.7(CH_2), 29.2 (CH_3), 30.8 (CH_2), 37.1 (C_{quat}), 37.5 (CH_2), 112.3 (CH), 127.6 (CH), 128.0 (CH), 128.7 (CH), 144.5 (C_{quat}), 160.1 (C_{quat}), 170.7 (C_{quat}), 177.2 (C_{quat}). FAB^+ MS (*m/z* (%)): 275 ($(M+H)^+$, 100), 232 ($(M + H)^+$ - C_3H_7, 44). HRMS calcd. for $C_{16}H_{22}N_2S$ + H: 275.1572. Found: 275.1608.

4-Butyl-6-tert-butyl-2-(4-nitro-phenyl)-pyrimidine (12k)



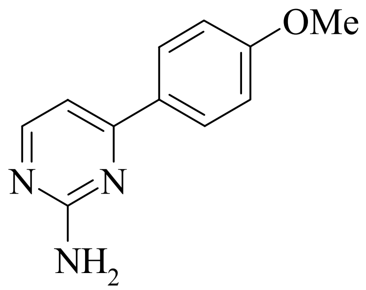
Orange crystals, Mp. 85 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.84 (t, J = 7.3 Hz, 3 H), 1.34 (s, 9 H), 1.35 – 1.38 (m, 2 H), 2.71 – 2.74 (m, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), 7.05 (s, 1 H), 8.21 (d, J = 9.0 Hz, 2 H), 8.61 (d, J = 8.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 29.5 (CH_3), 31.0 (CH_2), 37.6 (C_{quat}), 37.9 (CH_2), 114.2 (CH), 123.5 (CH), 129.1 (CH), 144.4 (C_{quat}), 149.0 (C_{quat}), 161.1 (C_{quat}), 171.3 (C_{quat}), 177.9 (C_{quat}). FAB^+ MS (*m/z* (%)): 314 ($(M + H)^+$, 100), 271 ($(M + H)^+$ - C_3H_7, 16). HRMS calcd. for $C_{18}H_{23}N_3O_2$ + H: 314.1858. Found: 314.1830.

4-(2-Fluorophenyl)-2-yl-pyrimidin-2-ylamin (12l)



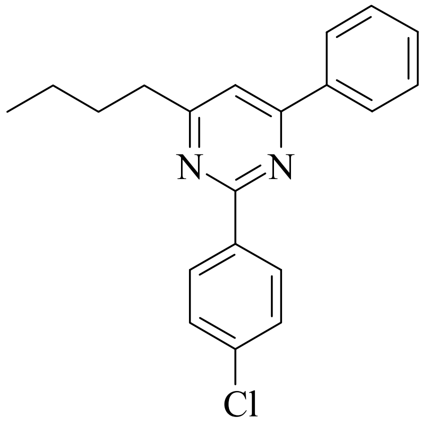
Beige crystals, Mp. 164-165 °C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.75 (s, 2 H), 6.92-6.99 (m, 1 H), 7.28-7.40 (m, 2 H), 7.45-7.65 (m, 1 H), 7.88-8.02 (m, 1 H), 8.33 (d, J = 5.4 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 109.5 (d, ^3J(C, F) = 9 Hz, CH), 116.2 (d, ^2J(C, F) = 22 Hz, CH), 124.4 (d, ^4J(C, F) = 3 Hz, CH), 125.4 (d, ^2J(C, F) = 11 Hz, C_{quat}), 130.1 (d, ^4J(C, F) = 3 Hz, CH), 131.8 (d, ^3J(C, F) = 9 Hz, CH), 158.8 (CH), 160.2 (C_{quat}), 160.3 (d, ^1J(C, F) = 248 Hz, C_{quat}), 163.8 (C_{quat}). EI MS (*m/z* (%)): 189 (M^+, 100), 188 (M^+ – H, 41), 170 (M^+ - F, 29), 120 (C_8H_5F, 10). IR (KBr): $\tilde{\nu}$ 3330, 3160, 1657, 1614, 1576, 1461, 1215, 816, 762 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 236 nm (17100), 310 (6800). HRMS calcd. for $C_{18}H_{23}N_3O_2$ + H: 189.0702. Found: 189.0684. Anal. calcd. for $C_{10}H_8FN_3$ (189.19): C 63.49, H 4.26, N 22.21. Found: C 63.32, H 4.23, N 21.92.

4-(4-Methoxyphenyl)-2-yl-pyrimidin-2-ylamin (12m)



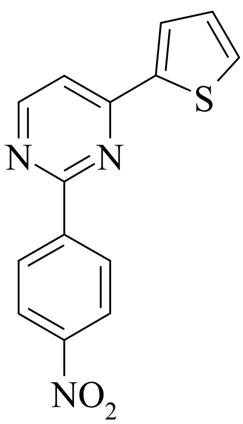
Colorless crystals, Mp. 191-192 °C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.83 (s, 3 H), 6.58 (s, 2 H), 7.02-7.08 (m, 3 H), 8.05 (d, J = 9.1 Hz, 2 H), 8.25 (d, J = 5.4 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.3 (CH_3), 105.0 (CH), 114.0 (CH), 128.2 (CH), 129.3 (C_{quat}), 158.7 (CH), 161.2 (C_{quat}), 163.1 (C_{quat}), 169.7 (C_{quat}). EI MS (*m/z* (%)): 201 (M^+, 100), 200 (M^+ – H, 66), 186 (M^+ - CH_3, 9). IR (KBr): $\tilde{\nu}$ 3467, 3342, 3191, 1610, 1581, 1457, 1253, 1179, 807 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 240 nm (9100), 276 nm (14700), 294 nm (11400), 316 nm (15900). Anal. calcd. for $C_{11}H_{11}N_3O$ (201.2): C 65.66, H 5.51, N 20.88. Found: C 65.47, H 5.55, N 20.60.

4-Butyl-2-(4-chlor-phenyl)-6-phenyl-pyrimidine (12n)



Colorless crystals, Mp. 56-57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, J = 7.3 Hz, 3 H), 1.40-1.50 (m, 2 H), 1.78-1.88 (m, 2 H), 2.87 (t, J = 7.7 Hz, 2 H), 7.25-7.56 (m, 6 H), 8.16-8.21 (m, 2 H), 8.55 (d, J = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 22.5 (CH_2), 31.0 (CH_2), 37.9 (CH_2), 113.6 (CH), 127.21 (CH), 128.6 (CH), 128.9 (CH), 129.7 (CH), 130.7 (CH), 136.3 (C_{quat}), 136.6 (C_{quat}), 137.1 (C_{quat}), 163.1 (C_{quat}), 163.6 (C_{quat}), 171.5 (C_{quat}). EI +Q1MS (*m/z* (%)): 325 (M^+(^{37}Cl), 0.3), 323 (M^+(^{35}Cl), 0.9), 282 (M^+(^{37}Cl), - C_3H_7, 31), 280 (M^+(^{35}Cl), - C_3H_7, 100). IR (KBr): $\tilde{\nu}$ 2956, 2929, 2868, 1588, 1566, 1534, 1379, 1089, 1015, 843, 768, 693 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 266 nm (33900), 302 nm (6500). Anal. calcd. for $C_{20}H_{19}ClN_2$ (322.84): C 74.41, H 5.93, N 8.68. Found: C 74.17, H 5.96, N 8.62.

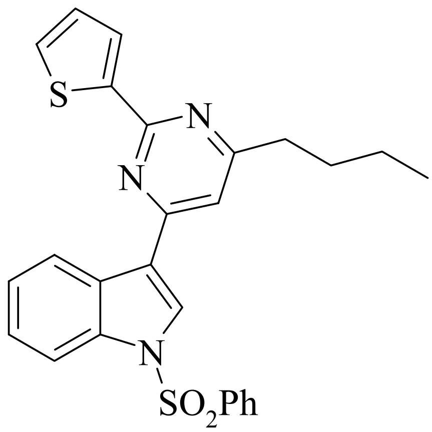
2-(4-Nitro-phenyl)-4-thiophen-2-yl-pyrimidin (12o)



Brown crystals, Mp. 195 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.19-7.23 (m, 1 H), 7.54 (d, J = 5.2 Hz, 1H), 7.60 (dd, J = 5.1 Hz, J = 1.1 Hz, 1 H), 7.86 (dd, J = 3.8 Hz, J = 1.1 Hz, 1 H), 8.35 (d, J = 9.1 Hz, 2 H), 8.71 (d, J = 9.1 Hz, 2 H), 8.80 (d, J = 5.1 Hz, 1 H). ^{13}C NMR, ($CDCl_3$, 75 MHz): δ 113.6 (CH), 123.5 (CH), 127.7 (CH), 128.4 (CH), 128.9 (CH), 130.5 (CH), 141.9 (C_{quat}), 143.0 (C_{quat}), 149.2 (C_{quat}), 157.6 (CH), 159.2 (C_{quat}), 162.3 (C_{quat}). FAB^{+} MS (m/z (%)): 284 ($(M+H)^{+}$, 17). IR (KBr): $\tilde{\nu}$ 2916, 2851, 1637, 1574, 1562, 1521, 1444, 1345 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 274 nm (17000), 306 nm (25000), 362 nm (200). HRMS calcd. for ($C_{14}H_9N_3O_2S$+H): 284.0490. Found: 284.0511. Anal. calcd. for $C_{14}H_9N_3O_2S$ (283.31): C 59.35, H 3.20, N 14.83. Found: C 58.88, H 3.31, N 14.42.

1-Benzenesulfonyl-3-(6-butyl-2-thiophen-2-yl-pyrimidin-4-yl)-1H-indole (12p)

In a screw cap pressure vessel 14.0 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7.0 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF. Then 0.14 mL (1.00 mmol) of Et_3N as well as 320 mg (1.00 mmol) of 1-(phenylsulfonyl)indole-3-yl carbonyl chloride (**6k**) and 0.12 mL (1.05 mmol) 1-hexyne (**1b**) were successively added to the solution. The reaction mixture was stirred for 3 h. Finally, 687.0 mg (2.40 mmol) of Na_2CO_3×10 H_2O and 195 mg (1.20 mmol) of 2-thienyl amidinium chloride **10b** were added to the suspension and the reaction mixture was heated to reflux temp for 6 h. After cooling to room temp the crude product was purified by chromatography on silica gel (n-hexane/ethyl acetate 3:1) to give 290 mg (61 %) of analytically pure **12p** as colorless crystals.

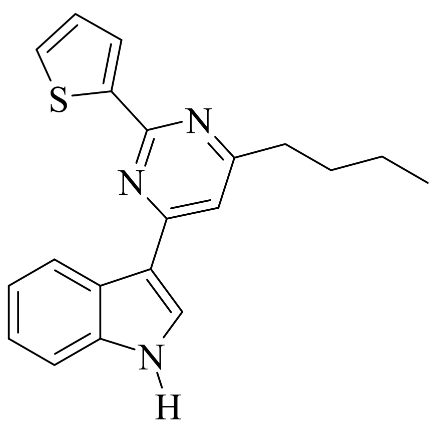


Colorless crystals, Mp. 159-160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00 (t, J = 7.3 Hz, 3 H), 1.41-1.53 (m, 2 H), 1.77-1.87 (m, 2 H), 2.83 (t, J = 7.7 Hz, 2 H), 7.16 (dd, J = 5.0 Hz, J = 1.3 Hz, 1 H), 7.30 (s, 1 H), 7.38-7.60 (m, 6 H), 7.94-8.09 (m, 4 H), 8.26 (s, 1 H), 8.61-8.64 (m, 1

H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 30.9 (CH_2), 37.7 (CH_2), 113.3 (CH), 113.4 (CH), 120.7 (C_{quat}), 123.1 (CH), 124.3 (CH), 125.5 (CH), 126.9 (CH), 127.0 (CH), 128.1 (CH), 128.3 (C_{quat}), 128.7 (CH), 129.5 (CH), 134.3 (CH), 135.6 (C_{quat}), 137.9 (C_{quat}), 144.2 (C_{quat}), 159.8 (C_{quat}), 161.1 (C_{quat}), 171.3 (C_{quat}). EI MS (*m/z* (%)): 474 (M^+, 4), 431 ($M^+ - C_3H_7$, 100). IR (KBr): $\tilde{\nu}$ 2956, 2929, 2869, 1580, 1527, 1440, 1375, 1176, 1106, 966, 749 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 260 nm (19100), 268 (18700), 300 (30700). Anal. calcd. for $C_{26}H_{23}N_3O_2S_2$ (473.6): C 65.94, H 4.89, N 8.87. Found: C 65.67, H 4.87, N 8.85.

3-(6-Butyl-2-thiophen-2-yl-pyrimidin-4-yl)-1H-indole (12q)

In a screw cap pressure vessel 14.0 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7.0 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed THF. Then 0.14 mL (1.00 mmol) of Et_3N as well as 320 mg (1.00 mmol) of 1-(phenylsulfonyl)indole-3-ylacid chloride (**6k**) and 0.12 mL (1.05 mmol) of 1-hexyne (**1b**) were successively added to the solution. The reaction mixture was stirred for 3 h. Finally, 1.43 g (5.00 mmol) of $Na_2CO_3 \times 10\ H_2O$ and 195 mg (1.20 mmol) of 2-thienyl amidinium chloride **10b** suspended in 5 mL of methanol and 4 ml H_2O were added to the suspension and the reaction mixture was heated to reflux temp for 14 h. After cooling to room temp the crude product was purified by chromatography on silica gel (n-hexane/ethyl acetate 2:1) to give 200 mg (60 %) of analytically pure **12q** as colorless crystals.

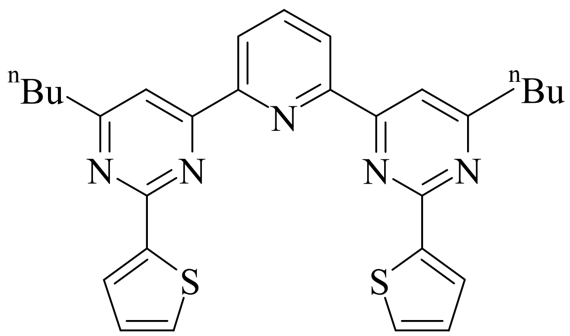


Colorless crystals, Mp. 166-167 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.94 (t, J = 7.4 Hz, 3 H), 1.33-1.43 (m, 2 H), 1.69-1.79 (m, 2 H), 2.72 (t, J = 7.6 Hz, 2 H), 7.21-7.24 (m, 3 H), 7.47-7.50 (m, 1 H), 7.63 (s, 1 H), 7.73 (dd, J = 4.9 Hz, J = 1.2 Hz, 1 H), 7.99 (dd, J = 3.4 Hz, J = 1.2 Hz, 1 H), 8.45 (s, 1 H), 8.68-8.71 (m, 1 H), 11.88 (s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.9 (CH_3), 21.9 (CH_2), 30.4 (CH_2), 36.8 (CH_2), 111.8 (CH), 112.1 (CH), 113.0

(C_{quat}), 120.8 (CH), 122.0 (CH), 122.2 (CH), 125.4 (C_{quat}), 127.9 (CH), 128.3 (CH), 129.2 (CH), 129.8 (CH), 137.2 (C_{quat}), 144.4 (C_{quat}), 160.0 (C_{quat}), 162.1 (C_{quat}), 169.4 (C_{quat}). EI MS (*m/z* (%)): 334(M^+ + 1, 7), 333 (M^+, 9), 291 ($M^+ – C_3H_7$, 100). IR (KBr): $\tilde{\nu}$ 2956, 1581, 1519, 1376, 765 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 262 (16100), 282 (22200), 302 (28200), 328 (20500). Anal. calcd. for $C_{20}H_{19}N_3S$ (333.5): C 72.04, H 5.74, N 12.60. Found: C 71.76, H 5.73, N 12.49.

2,6-Bis-(4-butyl-2-thiophen-2-yl-pyrimidyl)-pyridine (12r)

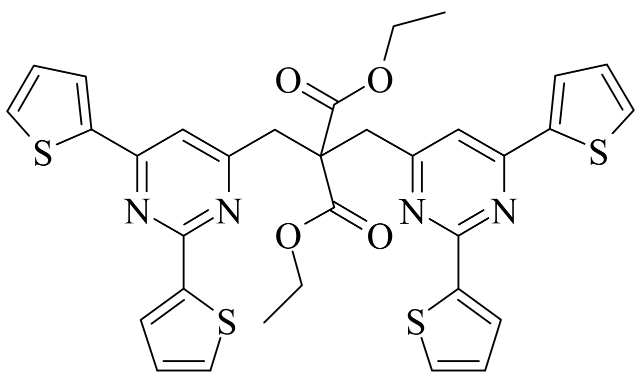
In a screw cap pressure vessel 14.0 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7.0 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed CH_3CN. Then 0.17 mL (1.25 mmol) of Et_3N as well as 102 mg (0.50 mmol) of pyridine 2,6-dicarbonyl dichloride (**6l**) and 0.17 mL (1.50 mmol) 1-hexyne (**1b**) were successively added to the solution. The reaction mixture was stirred overnight. Finally, 687 mg (2.40 mmol) of $Na_2CO_3\times10\ H_2O$ and 195 mg (1.20 mmol) of 2-thienyl amidinium chloride **10b** were added to the suspension and the reaction mixture was heated to reflux temp for 14 h. After cooling to room temp the crude product was purified by chromatography on silica gel (n-hexane/ethyl acetate 4:1) to give 44 mg (17 %) of the analytically pure bispyrimidyl pyridine **12r** as colorless crystals.



Colorless crystals, Mp. 158-159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (t, J = 7.3 Hz, 6 H), 1.48-1.59 (m, 4 H), 1.79-1.88 (m, 4 H), 2.98 (t, J = 7.6 Hz, 4 H), 7.21 (dd, J = 4.9, 3.7 Hz, 2 H), 7.52 (dd, J = 4.9, 1.2 Hz, 2 H), 8.11 (t, J = 8.1 Hz, 1 H), 8.17 (dd, J = 3.7, 1.2 Hz, 2 H), 8.20 (s, 2 H), 8.73 (d, J = 7.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 22.5 (CH_2), 30.8 (CH_2), 37.9 (CH_2), 113.3 (CH), 123.4 (CH), 128.1 (CH), 128.8 (CH), 129.5 (CH), 138.2 (CH), 143.9 (C_{quat}), 153.9 (C_{quat}), 161.0 (C_{quat}), 162.2 (C_{quat}), 172.5 (C_{quat}). FAB$^+$ MS (*m/z* (%)): 512 ($(M + H)^+$, 100), 482 ($(M + H)^+ - C_2H_6$). IR (KBr): $\tilde{\nu}$ 2958, 1573, 1537, 1437, 1378, 706 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 264 nm (46000). Anal. calcd. for $C_{29}H_{29}N_5S_2$ (511.7): C 68.07, H 5.71, N 13.69. Found: C 67.68, H 5.74, N 13.47.

2,2-Bis-(2,6-di-thiophen-2-yl-pyrimidin-4-ylmethyl)-malonic acid diethyl ester (12s)

In a screw cap pressure vessel 28.0 mg (0.04 mmol) of $Pd(PPh_3)_2Cl_2$, and 14.0 mg (0.08 mmol) of CuI were dissolved in 10 mL of degassed THF. Then 0.34 mL (2.50 mmol) of Et_3N as well as 294 mg (2.00 mmol) of 2-thienylacid chloride (**6e**) and 236 mg (1.00 mmol) of 2,2-di-prop-2-ynyl-malonic acid diethyl ester (**1i**) were added successively to the solution. The reaction mixture was stirred overnight. Finally, 1.43 g (5.00 mmol) of $Na_2CO_3 \times 10\ H_2O$ and 390 mg (2.40 mmol) of 2-thienyl amidinium chloride **10b** were added to the suspension and the reaction mixture was heated to reflux temp for 14 h. After cooling to room temp the crude product was purified by chromatography on silica gel (n-hexane/ethyl acetate 4:1) to give 140 mg (21 %) of the analytically pure bispyrimidyl pyridine **12s** as colorless crystals.



Colorless crystals, Mp. 158-159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, J = 7.2 Hz, 6 H), 3.65 (s, 4 H), 4.31 (q, J = 7.2 Hz, 4 H), 7.07 (dd, J = 4.9 Hz, J = 3.7 Hz, 2 H), 7.11 (dd, J = 5.1 Hz, J = 3.7 Hz, 2 H), 7.16 (s, 2 H), 7.45 (dd, J = 5.1 Hz, J = 1.2 Hz, 2 H), 7.48 (dd, J = 4.9 Hz, J = 1.1 Hz, 2 H), 7.64 (dd, J = 3.7 Hz, J = 1.1 Hz, 2 H), 8.03 (dd, J = 3.7 Hz, J = 1.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (CH_3), 38.5 (CH_2), 56.1 (C_{quat}), 61.6 (CH_2), 112.6 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 129.2 (CH), 129.7 (CH), 129.8 (CH), 142.1 (C_{quat}), 143.2 (C_{quat}), 158.7 (C_{quat}), 160.6 (C_{quat}), 166.4 (C_{quat}), 169.9 (C_{quat}). EI MS (*m/z* (%)): 672 ((M^+, 1), 599 (M^+ - CO_2Et), 415 (CH_2(2,4-bis(2-Th))-pyrimidine, 100). IR (KBr): $\tilde{\nu}$ 2979, 1733, 1578, 1528, 1432, 1379, 712 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 302 nm (61000). Anal. calcd. for $C_{33}H_{28}N_4O_4S_4$ (672.87): C 58.91, H 4.19, N 8.33. Found: C 58.53, H 4.21, N 8.34.

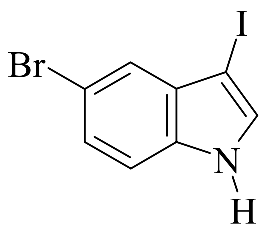
6.7 General Procedure for the Synthesis of Iodoindoles 14[140]

A solution of I_2 (4.73 g, 18.64 mmol) in 35 mL of dry DMF was added dropwise into the solution of indole **13** (18.46 mmol) and KOH (2.59 g, 46.13 mmol) in 35 ml of dry DMF at r.t. (at 0°C for indol **13c**) under nitrogen, in a Schlenk flask covered with alu-folia and then stirred for 45 min at the room temperature. The reaction mixture was poured into 450 mL of ice water containing 0.15 g of Na_2SO_3. The white precipitate was immediately formed, was filtered and washed with cold water, dried at the high vacuum, giving iodidole **14** that still contains the small amount of DMF, the product due to its relative instability (should be stored under nitrogen, in a refrigerator at 0 °C) was not further dried, but used directly for the next step (see Table 36 for experimental details).

Table 36. Experimental Details of the Synthesis of Iodoindoles 14

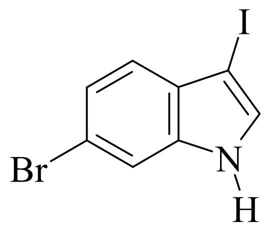
Indole **13**	Iodine	KOH	Product (Yield %)
20.0 g (171 mmol) of **13a**	43.9 g (173 mmol)	23.9 g (427 mmol)	32.8 g (79 %) of **14a**
2.50 g (12.8 mmol) of **13b**	3.27 g (12.9 mmol)	1.79 g (31.9 mmol)	3.92 g (96 %) of **14b**
3.62 g (18.5 mmol) of **13c**	4.73 g (18.6 mmol)	2.59 g (46.1 mmol)	5.93 g (99 %) of **14c**
2.50 g (21.2 mmol) of **13d**	5.43 g (21.4 mmol)	2.97 g (52.9 mmol)	4.84 g (94 %) of **14d**

5-Bromo-3-iodo-1H-indole (14b)



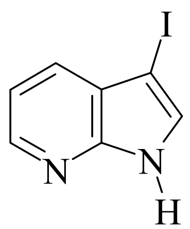
Grey solid, Mp 97.5-98.5 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.25 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.9 Hz, 1H), 7.39 (d, ^{3}J = 8.7 Hz, 1H), 7.45 (d, ^{4}J = 2.2 Hz, 1H), 7.52 (s, 1H), 10.83 (br s, 1H, NH). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.2 (C_{quat}), 113.9 (C_{quat}), 114.6 (CH), 123.5 (CH), 126.1 (CH), 132.1 (CH), 132.6 (C_{quat}), 136.0 (C_{quat}). EI +Q1MS (*m/z* (%)): 323 (M^+, (^{81}Br), 100), 321 (M^+, (^{79}Br), 95), 242 ($(M-Br)^+$, 6), 196 ($(M-I)^+$, (^{81}Br), 22), 194 ($(M-I)^+$, (^{79}Br), 23). IR (KBr): $\tilde{\nu}$ 3122, 3102, 1453, 1440, 1401, 1328, 1298, 1237, 1186, 1099, 883, 863, 797, 774, 676, 583, 494, 466, 418 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 284 nm (5640), 290 nm (5670), 300 nm (4170). Anal. calc. for C_8H_5BrIN (321.94): C 29.85, H 1.57, N 4.35. Found: C 30.28, H 1.81, N 4.49.

6-Bromo-3-iodo-1H-indole (14c)



Beige solid, Mp. 106-107 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.26-7.31 (m, 2H), 7.53 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 10.81 (br s, 1H, NH). ^{13}C NMR (acetone-d_6, 75 MHz): δ 56.3 (C_{quat}), 115.4 (CH), 116.5 (C_{quat}), 122.7 (CH), 124.1 (CH), 129.9 (C_{quat}), 131.5 (CH), 137.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 323 (M^+, (^{81}Br), 100), 321 (M^+, (^{79}Br), 95), 242 ($(M-Br)^+$, 4), 196 ($(M-I)^+$, (^{81}Br), 22), 194 ($(M-I)^+$, (^{79}Br), 23), 115 ($(M-I-Br)^+$, 38). IR (KBr): $\tilde{\nu}$ 1606, 1470, 1303, 1225, 1092, 960, 894, 775 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 286 nm (7500), 294 nm (6200). Anal. calc. for C_8H_5BrIN (321.94): C 29.85, H 1.57, N 4.35. Found: C 29.91, H 1.63, N 4.34.

3-Iodo-1H-pyrrolo[2,3-b]-pyridine (14d)



Beige solid, Mp. 177-180 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.16 (dd, ^3J = 8.1 Hz, ^3J = 4.8 Hz, 1H), 7.68 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H), 7.71 (s, 1H), 8.25 (dd, ^3J = 4.8, ^4J = 1.5 Hz, 1H), 12.1 (br s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 54.2 (C_{quat}), 116.4 (CH), 121.9 (C_{quat}), 128.0 (CH), 130.4 (CH), 143.7 (CH), 147.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 244 (M^+, 100), 117 ($(M-I)^+$, 18). IR (KBr): $\tilde{\nu}$ 3125, 3071, 3058, 3015, 2984, 2918, 2860, 2817, 1583, 1412, 1314, 1285, 965, 804, 789, 766, 642, 489 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 288 nm (7320), 296 nm (6030). Anal. calc. for $C_7H_5IN_2$ (244.04): C 34.45, H 2.07, N 11.48, I 52.00. Found: C 34.83, H 2.28, N 11.43, I 52.34.

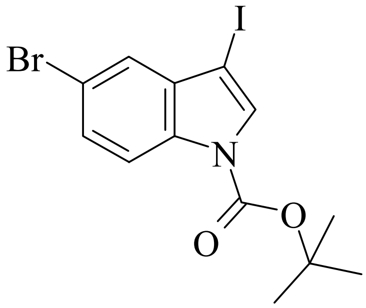
6.8 General Procedure for the Synthesis of Boc-protected Iodoindoles 15[140]

(41.14 mmol) of iodoindole **14** were dissolved in 200 mL of dry CH_2Cl_2 and treated with 17 mL of dry triethylamine and 0.5 g (4.10 mmol) of DMAP. Then, 10.0 g, (45.82 mmol) of Boc_2O in 50 mL of dry CH_2Cl_2 was added dropwise into the solution, without the external cooling. The reaction mixture was stirred for the other 2 h at the room temperature. The solution was washed twice with water containing 1.0 g of sodium sulphite, dried with Na_2SO_4 and evaporated, applied to column chromatography on aluminium oxide giving Boc-protected iodoindole **15** (see Table 37 for experimental details).

Table 37. Experimental Details of the Synthesis of BOC-protected Iodoindoles 15

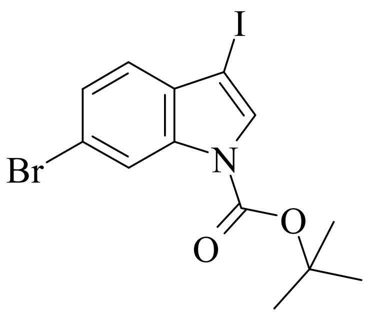
Iodoindole **14**	Boc_2O	NEt_3	Product (Yield %)	Eluent
10.0 g (41.1 mmol) of **14a**	10.0 g (45.8 mmol)	17.0 mL (121 mmol)	11.3 g (80 %) of **15a**	HE:EA 9:1
3.84 g (11.9 mmol) of **14b**	3.05 g (13.3 mmol)	5.00 mL (35.7 mmol)	4.31 g (86 %) of **15b**	HE:EA 9:1
5.50 g (17.0 mmol) of **14c**	4.37 g (19.0 mmol)	7.20 mL (51.4 mmol)	5.55 g (77 %) of **15c**	HE:EA 12:1
4.77 g (19.5 mmol) of **14d**	4.75 g (21.8 mmol)	8.50 mL (60.7 mmol)	4.83 g (72 %) of **15d**	HE:EA 4:1

5-Bromo-3-iodo-indole-1-carboxylic acid *tert*-butyl ester (15b)



Colorless solid, Mp 120 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.69 (s, 9H), 7.49-7.58 (m, 2H), 7.90 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 28.0 (CH_3), 63.8 (C_{quat}), 85.6 (C_{quat}), 117.0 (C_{quat}), 117.6 (CH), 124.5 (CH), 128.8 (CH), 132.6 (CH), 134.6 (C_{quat}), 134.8 (C_{quat}), 148.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 422.8 (M^+, (^{81}Br), 30), 420.8 (M^+, (^{79}Br), 28), 366.7 ($(M+H-C_4H_9)^+$, (^{81}Br), 71), 364.8 ($(M+H-C_4H_9)^+$, (^{79}Br), 68), 322.7 ($(M+H-C_4H_9-CO_2)^+$, (^{81}Br), 100), 320.8 ($(M+H-C_4H_9-CO_2)^+$, (^{79}Br), 97), 195.9 ($(M+H-C_4H_9-CO_2-I)^+$, (^{81}Br), 11), 193.9 ($(M+H-C_4H_9-CO_2-I)^+$, (^{79}Br), 12), 57.0 ($C_4H_9^+$, 98). IR (KBr): $\tilde{\nu}$ 3156, 2980, 1751, 1736, 1475, 1456, 1443, 1395, 1363, 1270, 1249, 1205, 1156, 1063, 1052, 1036, 857, 792, 761, 620 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 242 nm (22500), 274 nm (8090), 296 nm (6330), 304 nm (6330). Anal. calc. for $C_{13}H_{13}BrINO_2$ (422.06): C 37.00, H 3.10, N 3.32. Found: C 36.97, H 3.23, N 3.59.

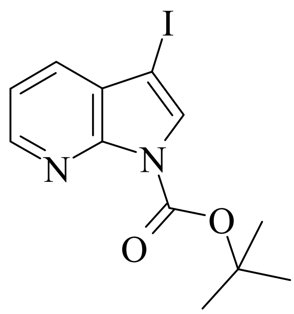
6-Bromo-3-iodo-indole-1-carboxylic acid *tert*-butyl ester (15c)



Colorless solid, Mp 151-152 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.70 (s, 9H), 7.33 (d, J = 8.4 Hz, 1H), 7.50 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H), 7.86 (s, 1H), 8.35 (d, J = 1.7 Hz, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 28.1 (CH_3), 64.9 (C_{quat}), 85.9 (C_{quat}), 118.7 (CH), 119.5 (C_{quat}), 123.7 (CH), 127.3 (CH), 132.1 (CH), 136.4 (C_{quat}), 149.0 (C_{quat}), 151.0 (C_{quat}). EI +Q1MS

(m/z (%)): 422.8 (M^+, (^{81}Br), 5), 420.8 (M^+, (^{79}Br), 5), 366.7 ($(M+H-C_4H_9)^+$, (^{81}Br), 12), 364.8 ($(M+H-C_4H_9)^+$, (^{79}Br), 12), 322.7 ($(M+H-C_4H_9-CO_2)^+$, (^{81}Br), 19), 320.8 ($(M+H-C_4H_9-CO_2)^+$, (^{79}Br), 20), 57 ($C_4H_9^+$, 100). IR (KBr): ṽ 3146, 2984, 2929, 1735, 1428, 1373, 1317, 1207, 1073, 939, 843, 805, 764 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 240 nm (21400), 278 nm (12700), 290 nm (10700), 300 nm (8000). Anal. calc. for $C_{13}H_{13}BrINO_2$ (422.06): C 37.00, H 3.10, N 3.32. Found: C 37.25, H 3.20, N 3.37.

3-Iodo-pyrrolo[2,3-b]pyridine-1-carboxylic acid *tert*-butyl ester (15d)



Yellow oil. (acetone-d_6, 300 MHz): δ 1.67 (s, 9H, CH_3), 7.36 (dd, J = 8.1 Hz, J = 4.8 Hz, 1 H), 7.75 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.99 (s, 1H), 8.44 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 28.1 (CH_3), 61.9 (C_{quat}), 84.8 (C_{quat}), 120.1 (CH), 125.8 (C_{quat}), 130.1 (CH), 132.1 (CH), 146.6 (CH), 147.8 (C_{quat}), 147.9 (C_{quat}). EI + MS (m/z (%)): 344 (M^+, 7), 271 ($C_8H_4ON_2I^+$, 3), 245 ($C_7H_6N_2I^+$, 10), 244 ($C_7H_5N_2I^+$, 100), 217 ($(M-I)^+$, 5), 162 ($C_8H_6O_2N_2^+$, 13), 144 ($C_8H_4ON_2^+$, 1), 127 (I^+, 2), 117 ($C_7H_5N_2^+$, 14), 116 ($C_7H_4N_2^+$, 8), 57 ($C_4H_9^+$, 22). IR (KBr): ṽ 3132, 2977, 1758, 1732, 1568, 1523, 1398, 1308, 1250, 1154, 938, 840, 766 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 238 nm (16100), 276 nm (8100), 280 nm (8400), 292 nm (8100). Calc. HRMS for $C_{12}H_{13}IN_2O_2$: 344.0022. Found: 344.0020.

6.9 General Procedure for the Synthesis of (TMS)-ynones 7f-i

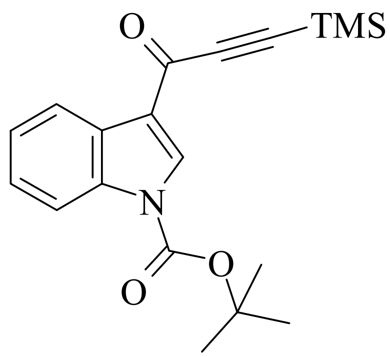
In a Schlenk flask 35 mg (0.05 mmol) of $Pd(PPh_3)_2Cl_2$, 8 mg (0.01 mmol) of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (for **15d** without $Pd(dppf)Cl_2 \cdot CH_2Cl_2$), 4 mg (0.02 mmol) of CuI, (1.00 mmol) of Boc-protected iodoindole **15,** 5 mL of THF were placed under nitrogen. Carbon monoxide was bubbled through the solution for 5 minutes and then 0.21 mL (1.50 mmol) of trimethylsilylacetylene and 0.14 mL (1.00 mmol) of triethylamine were successively added.

The reaction mixture became dark-red and was further stirred at the room temperature for 48 h under 1 atm pressure of carbon monoxide. The reaction mixture was diluted with brine (20 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried with sodium sulfate, evaporated and applied to column chromatography on silica gel, giving rise to (TMS)-ynone **7f-i** (see Table 38 for experimental details).

Table 38. Experimental Details of the Synthesis of (TMS)-ynones 7f-i

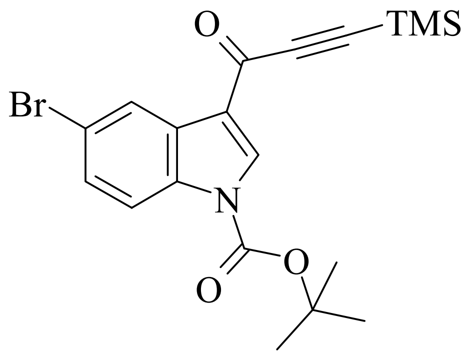
(Boc)-protected iodoindole **15**	TMSA	NEt_3	Product (Yield %)	Eluent
2.00 g (5.83 mmol) of **15a**	1.22 mL (8.74 mmol)	0.82 mL (5.83 mmol)	1.36 g (68 %) of **7f**	HE:EA 9:1
422 mg (1.00 mmol) of **15b**	0.21 mL (1.50 mmol)	0.14 mL (1.00 mmol)	287 mg (68 %) of **7g**	HE:EA 12:1
2.11 g (5.00 mmol) of **15c**	1.05 mL (7.50 mmol)	0.70 mL (5.00 mmol)	1.34 g (64 %) of **7h**	HE:EA 15:1
344 mg (1.00 mmol) of **15d**	0.21 mL (1.50 mmol)	0.14 mL (1.00 mmol)	216 mg (63 %) of **7i**	HE:EA 4:1

3-(3-Trimethylsilanyl-propynoyl)-indole-1-carboxylic acid *tert*-butyl ester (7f)



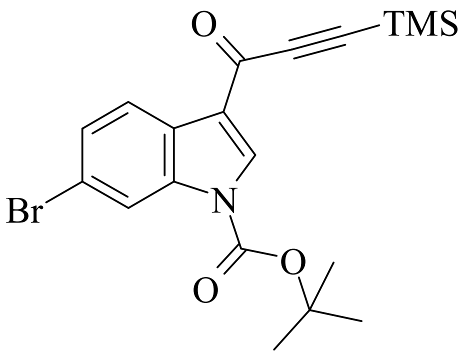
Yellow solid, Mp. 126.3-126.4 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 0.35 (s, 9H), 1.74 (s, 9H), 7.35-7.48 (m, 2H), 8.16-8.27 (m, 2H), 8.44 (s, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ -0.8 (CH_3), 27.9 (CH_3), 86.4 (C_{quat}), 96.0 (C_{quat}), 102.0 (C_{quat}), 116.0 (CH), 122.0 (C_{quat}), 122.6 (CH), 125.3 (CH), 126.6 (CH), 127.1 (C_{quat}), 136.7 (C_{quat}), 137.1 (CH), 149.3 (C_{quat}), 171.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 341 (M^+,23), 285 ($(M+H-C_4H_9)^+$, 100), 241 ($(M+H-C_4H_9-CO_2)^+$, 91), 226 (21), 198 (22), 57 ($C_4H_9^+$, 56). IR (KBr): $\tilde{\nu}$ 3148, 2979, 2959, 2160, 1744, 1625, 1546, 1481, 1450, 1396, 1373, 1359, 1310, 1282, 1243, 1187, 1157, 1111, 957, 857, 765, 744 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 250 nm (17700), 318 nm (12500). Anal. calc. for $C_{19}H_{23}NO_3Si$ (341.49): C 66.83, H 6.79, N 4.10. Found: C 66.84, H 6.88, N 4.14.

5-Bromo-3-(3-trimethylsilanyl-propynoyl)-indole-1-carboxylic acid *tert*-butyl ester (7g)



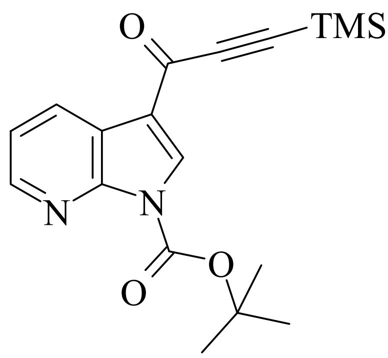
Colorless solid, Mp 157-159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.32 (s, 9H), 1.70 (s, 9H), 7.47 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 8.36 (s, 1H), 8.48 (d, J = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.7 (CH_3, -Si(CH_3)$_3$), 28.0 (CH_3, -C(CH_3)$_3$), 86.1 (C_{quat}), 97.0 (C_{quat}), 101.3 (C_{quat}), 116.5 (CH), 118.4 (C_{quat}), 120.8 (C_{quat}), 125.0 (CH), 128.1 (C_{quat}), 128.9 (CH), 134.6 (C_{quat}), 136.4 (CH), 148.4 (C_{quat}), 171.5 (C_{quat}). EI +Q1MS (*m/z* (%)): 421 ((M)$^+$, (^{81}Br), 5), 419 ((M)$^+$, (^{79}Br), 7), 365 (M-C_4H_9)$^+$, (^{81}Br), 58), 363 (M-C_4H_9)$^+$, (^{79}Br), 49), 321 (M-C_4H_9-CO_2+H)$^+$, (^{81}Br), 100), 319 (M-C_4H_9-CO_2+H)$^+$, (^{79}Br), 84), 306 ((M+H-Si(CH_3)$_3$-CO_2)$^+$, (^{81}Br), 23), 304 ((M+H-Si(CH_3)$_3$-CO_2)$^+$, (^{79}Br), 19), 57 ($C_4H_9^+$, 99). IR (KBr): $\tilde{\nu}$ 1755, 1633, 1542, 1443, 1370, 1234, 1117, 1034, 847, 761 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 254 nm (21000), 314 nm (15000). Anal. calc. for $C_{19}H_{22}BrNO_3Si$ (420.38): C 54.29, H 5.28, N 3.33, Br 19.01. Found: C 54.00, H 5.33, N 3.37, Br 19.27.

6-Bromo-3-(3-trimethylsilanyl-propynoyl)-indole-1-carboxylic acid *tert*-butyl ester (7h)



Colorless solid, Mp 169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.31 (s, 9H), 1.70 (s, 9H), 7.46 (dd, J = 8.5 Hz, J = 1.8 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.33 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.9 (CH_3, -Si(CH_3)$_3$), 27.8 (CH_3, -C(CH_3)$_3$), 85.9 (C_{quat}), 96.5 (C_{quat}), 101.0 (C_{quat}), 118.2 (CH), 119.5 (C_{quat}), 121.2 (C_{quat}), 123.3 (CH), 125.1 (C_{quat}), 127.7 (CH), 135.9 (CH), 136.2 (C_{quat}), 148.1 (C_{quat}), 171.4 (C_{quat}). EI +Q1MS (*m/z* (%)): 421 ((M)$^+$, (^{81}Br), 2), 419 ((M)$^+$, (^{79}Br), 2), 365 (M-C_4H_9)$^+$, (^{81}Br), 12), 363 (M-C_4H_9)$^+$, (^{79}Br), 13), 321 (M-C_4H_9-CO_2+H)$^+$, (^{81}Br), 8), 319 (M-C_4H_9-CO_2+H)$^+$, (^{79}Br), 10), 57 ($C_4H_9^+$, 100). IR (KBr): $\tilde{\nu}$ 2979, 1741, 1634, 1540, 1464, 1358, 1241, 1147, 1111, 956, 845, 762 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 258 nm (26200), 306 nm (12300). Anal. calc. for $C_{19}H_{22}BrNO_3Si$ (420.38): C 54.29, H 5.28, N 3.33. Found: C 53.93, H 5.13, N 3.48.

3-(3-Trimethylsilanyl-propynoyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid *tert*-butyl ester (7i)



Colorless solid, Mp 126-128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.32 (s, 9H), 1.70 (s, 9H), 7.31 (dd, J= 8.1 Hz, J = 4.8 Hz, 1H), 8.43 (s, 1H), 8.55 (dd, J = 5.0 Hz, J = 1.7 Hz, 1H), 8.59

(dd, J = 7.7 Hz, J = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.7 (CH_3), 27.9 (CH_3), 85.8 (C_{quat}), 97.3 (C_{quat}), 100.8 (C_{quat}), 119.2 (C_{quat}), 119.6 (C_{quat}), 120.4 (CH), 131.0 (CH), 135.9 (CH), 146.7 (CH), 147.0 (C_{quat}), 148.4 (C_{quat}), 171.6 (C_{quat}). EI+ Q1MS (*m/z* (%)): 343 ($(M+H)^+$, 33), 342 (M^+, 10), 287 ($(M-C_4H_7)^+$, 66), 242 ($(M-C_4H_7-CO_2)^+$, 100), 227 ($(M-C_5H_{10}-CO_2)^+$, 61), 199 ($(M-Si-C_5H_{10}-CO_2)^+$, 69), 57 ($C_4H_9^+$, 98). IR (KBr): $\tilde{\nu}$ 3141, 2984, 2155, 1738, 1634, 1542, 1479, 1405, 1380, 1374, 1355, 1272, 1258, 1192, 1144, 1107, 1066, 955, 858, 805, 780, 769, 736 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 246 nm (16800), 276 nm (13600), 292 (17400). Anal. calc. for $C_{18}H_{22}N_2O_3Si$ (342.47): C 63.13, H 6.48, N 8.18. Found: C 63.20, H 6.44, N 8.32.

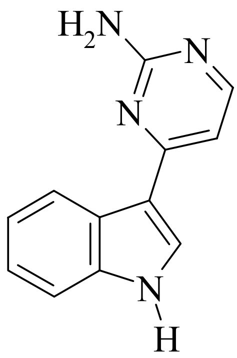
6.10 General Procedure for the Synthesis of Meridianins

(3.30 mmol) of (TMS)-ynone **7f-i** were dissolved in 11 mL of acetonitrile. Then 400 mg (3.74 mmol) of sodium carbonate, 11 mL of tert-butanol and 1.88 mL (9.4 mmol) of 5 M solution of guanidine (prepared by dissolving 9.55 g (0.10 mol) of guanidine hydrochloride in 20 mL water and neutralizing with 4.1 g (0.10 mol) of sodium hydroxide just before using) were added to the solution successively. The reaction mixture was stirred at 80 °C for 38 h. After complete conversion to meridianin (TLC), the reaction mixture was diluted with brine (75 mL), extracted with dichloromethane (5×40 mL). The combined organic layers were dried over sodium sulfate, evaporated and applied to column chromatography on deactivated (ethanol/ammonia 9:1) silica gel eluting with ethylacetate-ethanol (9:1), giving rise to meridianines **16a-d**, as the light yellow solids. Purification was achieved by dissolving in ethylacetate and precipitation with pentane (see Table 39 for experimental details).

Table 39. Experimental Details of the Synthesis of Meridianins

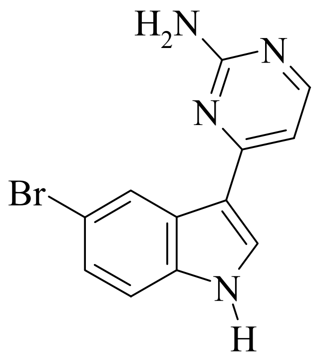
(TMS)-ynone **7**	Guanidine (5M solution in water)	Product (Yield %)
171 mg (0.44 mmol) of **7f**	0.22 mL (1.10 mmol)	61 mg (66 %) of **16a**
185 mg (0.44 mmol) of **7g**	0.22 mL (1.10 mmol)	287 mg (68 %) of **16b**
1.39 g (3.30 mmol) of **7h**	1.88 mL (9.40 mmol)	750 mg (78 %) of **16c**
221 mg (0.65 mmol) of **7i**	0.32 mL (1.61 mmol)	75 mg (59 %) of **16d**

4-(1H-Indol-3-yl)-pyrimidin-2-ylamine (Meridianin G, 16a)



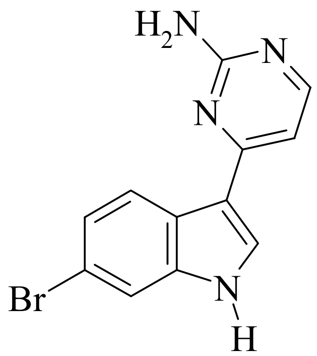
Yellow solid, Mp 190-192 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.42 (br s, 2H, NH_2), 7.02 (d, J = 5.5 Hz, 1H), 7.15 (m, 2H), 7.45 (d, J = 7.4 Hz, 1H), 8.11 (d, ^{3}J = 5.1 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 7.0 Hz, 1H), 11.67 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.3 (CH), 111.8 (CH), 113.7 (C_{quat}), 120.2 (CH), 121.9 (CH), 122.4 (CH), 125.3 (C_{quat}), 128.2 (CH), 137.0 (C_{quat}), 157.0 (CH), 162.6 (C_{quat}), 163.4 (C_{quat}).

4-(5-Bromo-1H-indol-3-yl)-pyrimidin-2-ylamine (Meridianin C, 16b)



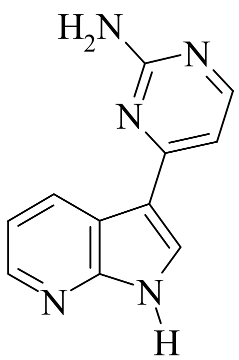
Yellow solid, Mp 241-243 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.52 (br s, 2H, NH_2), 7.00 (d, J = 5.1 Hz, 1H), 7.29 (dd, J = 8.5 Hz, J = 1.8 Hz, 1H), 7.41 (d, ^{3}J = 8.8 Hz, 1H), 8.10 (d, J = 5.1 Hz, 1H), 8.26 (br s, 1H), 8.76 (d, J = 1.8 Hz, 1H), 11.87 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.3 (CH), 113.3 (C_{quat}), 113.4 (C_{quat}), 113.8 (CH), 124.5 (CH), 124.6 (CH), 127.1 (C_{quat}), 129.6 (CH), 135.8 (C_{quat}), 157.2 (CH), 162.3 (C_{quat}), 163.6 (C_{quat}). Anal. calc. for $C_{12}H_9BrN_4$ (289.14): C 49.85, H 3.14, N 19.38. Found: C 50.10, H 3.24, N 18.87.

4-(6-Bromo-1H-indol-3-yl)-pyrimidin-2-ylamine (Meridianin D, 16c)



Yeollow solid, Mp 224-226 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.47 (br s, 2H, NH_2), 7.00 (d, J = 5.5 Hz, 1H), 7.23 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 5.5 Hz, 1H), 8.23 (s, 1H), 8.56 (d, J = 8.8 Hz, 1H), 11.79 (br s, 1H, NH).. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.2 (CH), 113.8 (C_{quat}), 114.4 (CH), 114.6 (C_{quat}), 123.0 (CH), 124.1 (CH), 124.4 (C_{quat}), 129.0 (CH), 137.8 (C_{quat}), 157.1 (CH), 162.1 (C_{quat}), 163.5 (C_{quat}). Anal. calc. for $C_{12}H_9BrN_4{\cdot}0.5H_2O$ (298.14): C 48.34, H 3.38, N 18.79. Found: C 48.77, H 3.13, N 18.75.

4-(1H-Pyrrolo[2,3-b]pyrimidin-3-yl)-pyrimidin-2-ylamine (16d)



Light yellow solid, Mp. 286-289 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.49 (s, 2H, NH_2), 7.06 (d, J = 5.1 Hz, 1H), 7.18 (dd, J = 8.1 Hz, J = 4.8 Hz, 1H), 8.14 (d, J = 5.1 Hz, 1H), 8.29 (dd, J = 4.6 Hz, J = 1.7 Hz, 1H), 8.34 (s, 1H), 8.93 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H), 12.18 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.0 (CH), 112.4 (C_{quat}), 116.6 (CH), 117.8 (CH), 128.3 (CH), 130.7 (CH), 143.4 (CH), 143.4 (C_{quat}), 157.2 (CH), 162.0 (C_{quat}), 163.5 (C_{quat}). EI+ Q1MS (m/z (%)): 211 (M^+, 100), 210 $(M-H)^+$, 39), 195 ($(M-NH_2)^+$, 3).

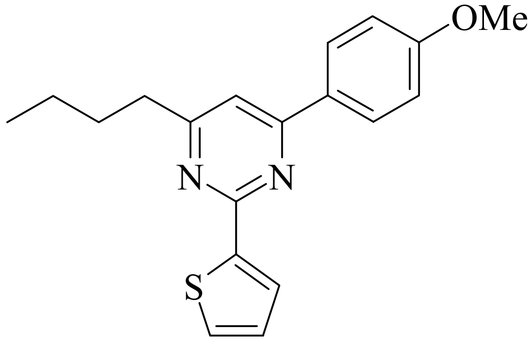
6.11 General Procedure for the Synthesis of Pyrimidines 12t-x via Carbonylative Coupling

In a Schlenk flask 35 mg (0.05 mmol) of $Pd(PPh_3)_2Cl_2$, 4 mg (0.02 mmol) of CuI, (for EWG aryl iodide **17e** only 7 mg (0.01 mmol) of $Pd(PPh_3)_2Cl_2$ was used as a catalyst) (1.00 mmol) of aryl iodide **17**, 5 mL of THF were placed under nitrogen. Carbon monoxide was bubbled through the solution for 5 minutes and then 1.20 mmol of alkyne **1**, and 0.28 mL (2.00 mmol) of NEt_3 were successively added. The reaction mixture was then stirred at the room temperature under pressure of CO (1 atm) for 48 h until the complete consumption of aryl iodide (monitored by TLC). Afterwards 265 mg (2.50 mmol) of Na_2CO_3 and 1.20 mmol of amidinium hydrochloride (nitrate for **10i**) **10**, 0.5 mL of water and 5 mL of CH_3CN were added to the suspension and the reaction mixture was heated to reflux temp for 12-24 h. After cooling to room temperature the crude product was purified by chromatography on silica gel to give the analytically pure pyrimidines **12**. Crystallization was achieved from pentane/CH_2Cl_2 or methanol (see Table 40 for experimental details).

Table 40. Experimental Details of the Synthesis of Pyrimidines via Carbonylative Coupling

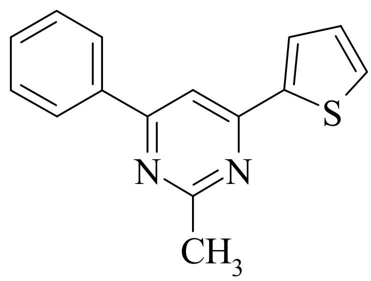
Alkyne **1**	Aryl iodide **17**	Amidinium salt **10**	Pyrimidine **12** (Yield %)	Eluent
0.14 mL (1.20 mmol) of **1b**	234 mg (1.00 mmol) of **17a**	195 mg (1.20 mmol) of **10b**	166 mg (51 %) of **12t**	HE:EA 6:1
0.20 mL (1.80 mmol) of **1a**	315 mg (1.50 mmol) of **17b**	170 mg (1.80 mmol) of **10f**	210 mg (56 %) of **12u**	HE:EA 9:1
0.21 mL (1.80 mmol) of **1b**	327 mg (1.50 mmol) of **17c**	463 mg (1.80 mmol) of **10i**	165 mg (29 %) of **12v**	HE:EA 4:1
0.20 mL (1.80 mmol) of **1a**	393 mg (1.50 mmol) of **17d**	170 mg (1.80 mmol) of **10f**	195 mg (43 %) of **12w**	HE:EA 9:1→4:1
0.14 mL (1.20 mmol) of **1b**	229 mg (1.00 mmol) of **17e**	195 mg (1.20 mmol) of **10b**	90 mg (28 %) of **12x**	HE:EA 9:1

4-Butyl-6-(4-methoxy-phenyl)-2-thiophen-2-yl-pyrimidine (12t)



Light-yellow solid, Mp 84-86 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.97 (t, J = 7.4 Hz, 3 H), 1.38-1.56 (m, 2 H), 1.74-1.85 (m, 2 H), 2.80 (t, J = 7.9 Hz, 2 H), 3.87 (s, 3 H), 7.01 (d, J = 8.9 Hz, 2 H), 7.14 (dd, J = 5.0 Hz, J = 3.7 Hz, 1 H), 7.29 (s, 1 H), 7.45 (dd, J = 5.0 Hz, J = 1.1 Hz, 1 H), 8.08 (dd, J = 3.7 Hz, J = 1.1 Hz, 1 H), 8.14 (d, J = 8.9 Hz, 2 H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 13.9 (CH$_3$), 22.5 (CH$_2$), 30.9 (CH$_2$), 37.8 (CH$_2$), 55.4 (CH$_3$), 111.6 (CH), 114.1 (CH), 128.0 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.5 (C$_{quat}$), 144.4 (C$_{quat}$), 161.0 (C$_{quat}$), 161.8 (C$_{quat}$), 163.1 (C$_{quat}$), 171.4 (C$_{quat}$). EI+ Q1MS (*m/z* (%)): 324 (M$^+$, 2), 309 ((M-CH$_3$)$^+$, 4), 295 ((M-C$_2$H$_5$)$^+$, 7), 282 (M-C$_3$H$_6$)$^+$, 100). IR (KBr): ṽ 2953, 2932, 1608, 1585, 1528, 1406, 1253, 1183, 1030, 834, 710 cm^{-1}. UV/Vis (CH$_2$Cl$_2$): λ_{max} (ε): 270 nm (18800), 294 nm (32900). Anal. calc. for C$_{19}$H$_{20}$N$_2$OS (324.25): C 70.34, H 6.21, N 8.63, S 9.88. Found: C 69.95, H 6.17, N 8.59, S 9.86.

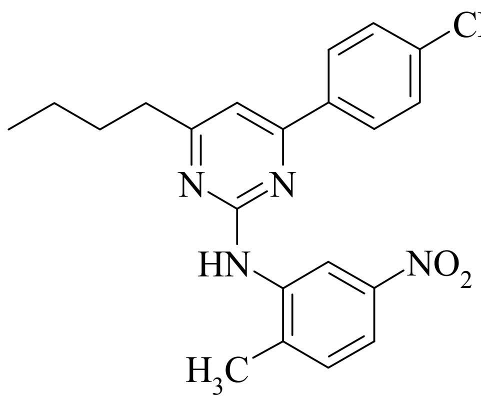
2-Methyl-4-phenyl-6-thiophen-2-yl-pyrimidine (12u)



Colorless solid, Mp 85-86 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.81 (s, 3H), 7.18 (dd, J = 5.0 Hz, J = 3.7 Hz, 1H), 7.49-7.56 (m, 4H), 7.76 (s, 1H), 7.84 (dd, J = 3.7 Hz, J = 1.1 Hz, 1H), 8.06-8.13 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 26.1 (CH$_3$), 107.9 (CH), 126.9 (CH), 127.0 (CH), 128.1 (CH), 128.7 (CH), 129.5 (CH), 130.5 (CH), 137.1 (C$_{quat}$), 142.7 (C$_{quat}$), 159.3 (C$_{quat}$), 164.5 (C$_{quat}$), 168.4 (C$_{quat}$). EI+ Q1MS (*m/z* (%)): 252 (M$^+$, 100), 211 ((M-CH$_3$CN)$^+$, 10). IR (KBr): ṽ 3077, 1602, 1524, 1431, 1398, 1241, 1082, 987, 778, 723 cm^{-1}. UV/Vis

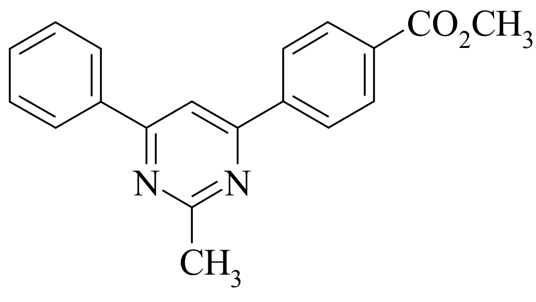
(CH_2Cl_2): λ_{max} (ε): 260 nm (19900), 318 nm (21300), 332 nm (15400). Anal. calc. for $C_{15}H_{12}N_2S$ (252.34): C 71.40, H 4.79, N 11.10, S 12.71. Found: C 71.21, H 4.80, N 10.90, S 12.90.

(4-Butyl-6-*p*-tolyl-pyrimidine-2-yl)-(2-methyl-5-nitro-phenyl)-amine (12v)



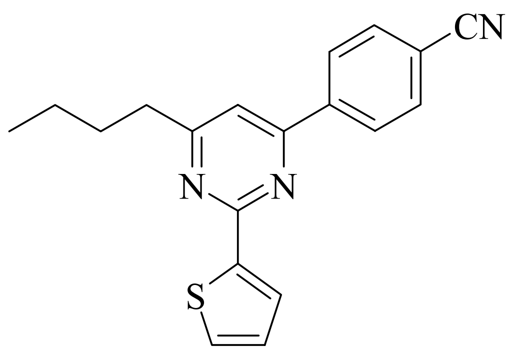
Yellow crystals, Mp 108 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, J = 7.4 Hz, 3 H), 1.38-1.51 (m, 2 H), 1.74-1.85 (m, 2 H), 2.42 (s, 3H), 2.44 (s, 3H), 2.72 (t, J = 7.7 Hz, 2 H), 7.07 (s, 1H), 7.12 (s, 1H), 7.26-7.35 (m, 3 H), 7.79 (dd, J = 8.2 Hz, J = 2.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 2H), 9.71 (d, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 18.3 (CH_3), 21.4 (CH_3), 22.5 (CH_2), 30.8 (CH_2), 37.8 (CH_2), 108.2 (CH), 114.1 (CH), 116.3 (CH), 127.1 (CH), 129.6 (CH), 130.4 (CH), 132.4 (C_{quat}), 134.1 (C_{quat}), 139.1 (C_{quat}), 141.2 (C_{quat}), 147.1 (C_{quat}), 159.6 (C_{quat}), 164.8 (C_{quat}), 172.8 (C_{quat}). EI+ Q1MS (m/z (%)): 376 (M^+, 20), 361 ($(M-CH_3)^+$, 11), 347 ($(M-C_2H_5)^+$, 13), 334 ($(M-C_3H_6)^+$, 100). IR (KBr): $\tilde{\nu}$ 3443, 3119, 2955, 2927, 1594, 1576, 1537, 1436, 1344, 1187, 819 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 282 nm (38700), 318 nm (6100), 346 nm (3300), 364 nm (3300). Anal. calc. for $C_{22}H_{24}N_4O_2$ (376.46): C 70.19, H 6.43, N 14.88. Found: C 69.57, H 6.45, N 14.45.

4-(2-Methyl-6-phenyl-pyrimidin-4-yl)-benzoic acid methyl ester (12w)



Colorless solid, Mp 159-160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.87 (s, 3H), 3.95 (s, 3H), 7.49-7.54 (m, 3 H), 7.91 (s, 1H), 8.10-8.15 (m, 2H), 8.17-8.20 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.5 (CH_3), 52.3 (CH_3), 110.4 (CH), 127.2 (CH), 127.3 (CH), 129.0 (CH), 130.1 (CH), 130.8 (CH), 131.9 (C_{quat}), 137.2 (C_{quat}), 141.6 (C_{quat}), 163.6 (C_{quat}), 165.2 (C_{quat}), 166.6 (C_{quat}), 168.8 (C_{quat}). EI+ Q1MS (*m/z* (%)): 304 (M^+, 100), 273 ($(M-CH_3O)^+$, 49), 245 ($(M-CO_2CH_3)^+$, 15). IR (KBr): $\tilde{\nu}$ 1712, 1587, 1532, 1368, 1290, 1120, 750 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 254 nm (22400), 296 nm (21000). Anal. calc. for $C_{19}H_{16}N_2O_2$ (304.35): C 74.98, H 5.30, N 9.20. Found: C 74.52, H 5.30, N 9.11.

4-(6-Butyl-2-thiohen-2-yl-pyrimidin-4-yl)-benzonitrile (12x)



Colorless solid, Mp 110-112 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, J = 7.0 Hz, 3 H), 1.38-1.52 (m, 2 H), 1.75-1.86 (m, 2 H), 2.85 (t, J = 7.7 Hz, 2 H), 7.15 (dd, J = 5.1 Hz, J = 3.7 Hz, 1H), 7.36 (s, 1H), 7.49 (dd, J = 5.1 Hz, J = 1.1 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 8.10 (dd, J = 3.7 Hz, J = 1.1 Hz, 1H), 8.26 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 30.8 (CH_2), 37.8 (CH_2), 101.5 (C_{quat}), 113.2 (CH), 113.9 (C_{quat}), 118.3 (C_{quat}), 127.7 (CH), 128.2 (CH), 129.1 (CH), 129.9 (CH), 132.6 (CH), 141.0 (C_{quat}), 143.5 (C_{quat}), 161.3 (C_{quat}), 172.4 (C_{quat}). EI+ Q1MS (*m/z* (%)): 319 (M^+, 2), 304 ($(M-CH_3)^+$, 3), 290 ($(M-C_2H_5)^+$, 16), 277 $(M-C_3H_6)^+$, 100). IR (KBr): $\tilde{\nu}$ 3066, 2961, 2930, 2858, 2229, 1583, 1530, 1399, 1335, 844, 725 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 262 nm (28400), 294 nm (24600). Anal. calc. for $C_{19}H_{17}N_3S$ (319.43): C 71.44, H 5.36, N 13.15. Found: C 70.95, H 5.31, N 12.91.

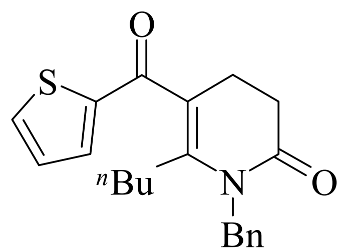
6.12 General Procedure for the CAA Sequence

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF. Then 0.14 mL (1.00 mmol) of triethylamine, as well as (1 mmol) of acid chloride **6** and 0.12 mL (1.05 mmol) of hexyne **1b** were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 1.2 mmol of amine **4** was added and the reaction mixture was heated at 70 °C for 24 h. After complete conversion of ynone to enaminone (TLC), acryloyl chloride **18a** (1.2-2.1 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temp the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with hexane-ethylacetate 2:1 (**19a,b**) or ether (**19c**), to give the analytically pure δ-lactam **19** as oils (see Table 41 for experimental details).

Table 41. Experimental Details for CAA Sequence

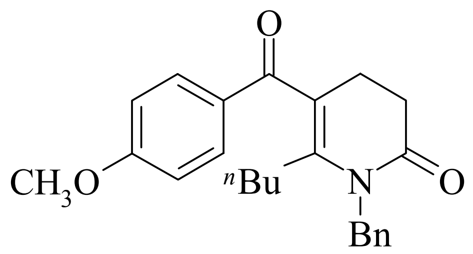
Alkyne **1**	Acid chloride **6**	Amine **4**	Acryloyl Chloride **18a**	Product (Yield %)
0.12 mL (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	0.13 mL (1.20 mmol) of **4f**	0.10 mL (1.20 mmol) of **18a**	110 mg (31 %) of **19a**
0.12 mL (1.05 mmol) of **1b**	171 mg (1.00 mmol) of **6a**	0.13 mL (1.20 mmol) of **4f**	0.12 mL (1.50 mmol) of **18a**	238 mg (63 %) of **19b**
0.12 mL (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	0.20 mL (1.20 mmol) of **4h**	0.17 mL (2.10 mmol) of **18a**	295 mg (69 %) of **19c**

1-Benzyl-6-butyl-5-(thiophene-2-carbonyl)-3,4-dihydro-1H-pyridin-2-one (19a)



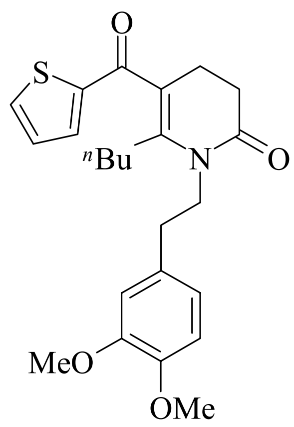
Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73 (t, J = 7.2 Hz, 3 H), 1.10-1.23 (m, 2 H), 1.28-1.40 (m, 2 H), 2.12-2.18 (m, 2 H), 2.57 (s, 4 H), 4.89 (s, 2 H), 6.94 (dd, J = 4.9 Hz, J = 3.8 Hz, 1 H), 7.09-7.28 (m, 6 H), 7.51 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6 (CH_3), 22.2 (CH_2), 23.6 (CH_2), 29.5 (CH_2), 31.1 (CH_2), 31.9 (CH_2), 44.0 (CH_2), 119.2 (C_{quat}), 126.3 (CH), 127.2 (CH), 127.9 (CH), 128.7 (CH), 132.6 (CH), 133.9 (CH), 137.7 (C_{quat}), 144.5 (C_{quat}), 145.7 (C_{quat}), 171.1 (C_{quat}), 188.3 (C_{quat}). FAB$^+$ MS (m/z (%)): 353 (M^+, 37), 320 (M^+ - HS, 100), 111 (2-ThCO$^+$, 32). IR (KBr): ṽ 2957, 2930, 1683, 1634, 1515, 1454, 1412, 1373, 1286, 1180, 843, 729 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 264 nm (8600), 304 nm (8100). Calc. HRMS for $C_{21}H_{23}NO_2S$: 353.1444. Found: 353.1470.

1-Benzyl-6-butyl-5-(*p*-methoxybenzoyl)-3,4-dihydro-1H-pyridin-2-one (19b)



Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (t, J = 7.4 Hz, 3 H), 1.14-1.27 (m, 2 H), 1.33-1.46 (m, 2 H), 2.15 (t, J = 7.7 Hz, 2 H), 2.49-1.57 (m, 2 H), 2.61-2.69 (m, 2 H), 3.83 (s, 3 H), 4.98 (s, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 7.19-7.39 (m, 5 H), 7.61 (d, J = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.7 (CH_3), 22.3 (CH_2), 23.6 (CH_2), 29.4 (CH_2), 31.1 (CH_2), 32.0 (CH_2), 44.1 (CH_2), 55.5 (CH_3), 113.8 (CH), 119.5 (C_{quat}), 126.5 (CH), 127.3 (CH), 128.8 (CH), 130.4 (C_{quat}), 131.2 (CH), 137.7 (C_{quat}), 144.7 (C_{quat}), 163.2 (C_{quat}), 171.1 (C_{quat}), 195.5 (C_{quat}). EI+ Q1MS (m/z (%)): 377 (M^+, 576), 360 (M^+ - OH, 36), 334 (M^+ - C_3H_7, 56), 135 (p-$CH_3OC_6H_4CO^+$, 100). IR (KBr): ṽ 2957, 2931, 1679, 1599, 1372, 1257, 1143, 1029 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 288 nm (15400). Calc. HRMS for $C_{24}H_{27}NO_3$: 377.1991. Found: 377.1988.

1-[3,4-Dimethoxyphenylethyl]-6-butyl-5-(thiophene-2-carbonyl)-3,4-dihydro-1H-pyridin-2-one (19c)



Colorless oil (~90% pure). R_f= 0.65 (Ether). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.84 (t, J = 7.1 Hz, 3 H), 1.05-1.35 (m, 4 H), 2.16-2.24 (m, 2 H), 2.39 (s, 4 H), 2.70-2.78 (m, 2 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.79-3.87 (m, 2 H), 6.64-6.70 (m, 3 H), 7.00 (dd, J = 4.9 Hz, J = 3.8 Hz, 1 H), 7.20 (dd, J = 3.8 Hz, J = 1.2 Hz, 1 H), 7.54 (dd, J = 4.9 Hz, J = 1.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3 (CH_3), 21.8 (CH_2), 23.2 (CH_2), 28.7 (CH_2), 30.3 (CH_2), 31.4 (CH_2), 36.8 (CH_2), 42.1 (CH_2), 55.4 (CH_3), 55.5 (CH_3), 110.9 (CH), 111.8 (CH), 118.2 (C_{quat}), 120.5 (CH), 127.6 (CH), 130.5 (C_{quat}), 132.3 (CH), 133.6 (CH), 144.1 (C_{quat}), 145.0 (C_{quat}), 147.4 (C_{quat}), 148.5 (C_{quat}), 170.6 (C_{quat}), 188.0 (C_{quat}).

6.13 General Procedure for the CAAPS Sequence

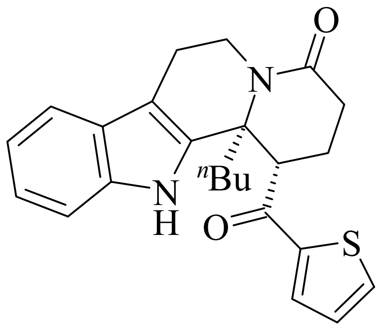
In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF or toluene. Then 0.14 mL (1.00 mmol) of triethylamine, as well as (1 mmol) of acid chloride **6** and (1.05 mmol) of alkyne **1** were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 2.0 mmol of amine **4g** or **4i** was added (for **20i-j** the excess of **4g** was reduced to 1.1 mmol, adding 0.15 mL (1.00 mmol) of DBU at the sane time) and the reaction mixture was heated at 70 °C (THF) or 100 °C (toluene) for 10 h. After complete conversion of ynone to enaminone (TLC), α,β-unsaturated acid chlorides **18** (5.0 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temp the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel, to give the analytically pure tetrahydro-β-carbolines **20** as solids (see Table 42 for experimental details).

Table 42. Experimental Details for CAAPS Sequence

Alkyne **1**	Acid chloride **6**	Amine **4**	Acryloyl Chloride	Product (Yield %)	Eluent
0.12 mL[a] (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	210 mg (52 %) of **20a**	Ether
0.12 mL[a] (1.05 mmol) of **1b**	186 mg (1.00 mmol) of **6b**	320 mg (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	192 mg (43 %) of **20b**	Ether
0.12 mL[a] (1.05 mmol) of **1b**	171 mg (1.00 mmol) of **6a**	320 mg (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	254 mg (59 %) of **20c**	Ether
0.11 mL[a] (1.05 mmol) of **1a**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	175 mg (41 %) of **20d**	Ether
0.12 mL[a] (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	0.48 mL (5.00 mmol) of **18b**	210 mg (50 %) of **20e**	HE/EA 1:1
0.12 mL[a] (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	0.48 mL (5.00 mmol) of **18c**	185 mg (44 %) of **20f** and 40 mg (10 %) of **20f'**	HE/EA 2:1
0.14 mL[a] (1.05 mmol) of **1f**	147 mg (1.00 mmol) of **6e**	320 mg[c] (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	140 mg (32 %) of **20g**	EA
179 mg[a] (1.05 mmol) of **1h**	147 mg (1.00 mmol) of **6e**	320 mg (2.00 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	148 mg (30 %) of **20h**	HE/EA 1:1
0.12 mL[a] (1.05 mmol) of **1b**	318 mg (1.00 mmol) of **6k**	175 mg[d] (1.10 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	206 mg (36 %) of **20i**	Ether→EA
0.12 mL[a] (1.05 mmol) of **1b**	107 mg (1.00 mmol) of **6m**	175 mg[d] (1.10 mmol) of **4g**	0.41 mL (5.00 mmol) of **18a**	130 mg (36 %) of **20j**	Ether
0.12 mL[b] (1.05 mmol) of **1b**	147 mg (1.00 mmol) of **6e**	510 mg[e] (2.00 mmol) of **4i**	0.80 mL (9.76 mmol) of **18a**	210 mg (45 %) of **20k**	Ether

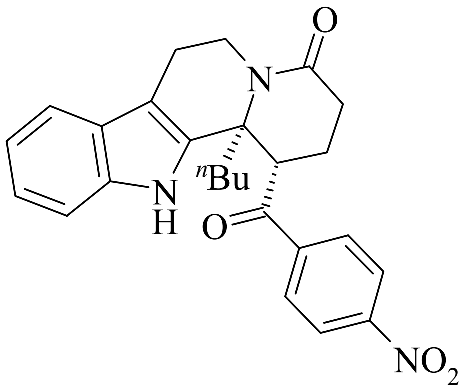
[a] the reaction was carried out in THF as a solvent; [b] the reaction was carried out in toluene as a solvent; [c] *n*-Bu_4NF (1 mL, 1 *M* solution in THF) was added after the coupling step and the reaction mixture was stirred for 5 min before amine **4g** was added; [d] DBU (0.15 mL, 1 mmol) was added with trypatmine **4g**; [e] Amine **4i** (as a hydrochloride) was added with additional amounts of triethylamine (0.28 mL, 2.00 mmol).

***rac*-12b-Butyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a] quinolizin-4-one (20a)**



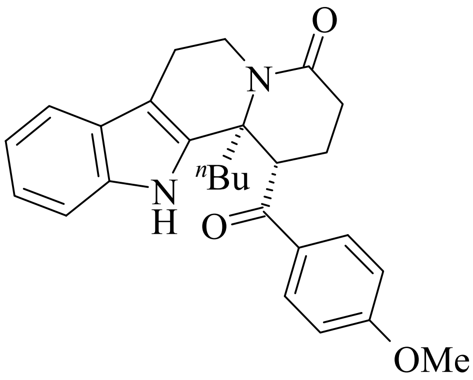
Colorless crystals, Mp. 250-251 °C. R_f = 0.37 (diethyl ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.83 (t, J = 7.4 Hz, 3 H), 1.02-1.11 (m, 1 H), 1.22-1.37 (m, 3 H), 2.10-2.23 (m, 2 H), 2.34-2.44 (m, 1 H), 2.72-2.88 (m, 5 H), 2.97 (dt, J = 12.2 Hz, J = 3.8 Hz, 1 H), 3.73 (dd, J = 13.2 Hz, J = 5.0 Hz, 1 H), 5.22 (dd, J = 13.2 Hz, J = 5.0 Hz, 1 H), 6.90 (dd, J = 4.9 Hz, J = 3.7 Hz, 1 H), 7.03-7.09 (m, 2 H), 7.13-7.16 (m, 1 H), 7.38 (dd, J = 3.7 Hz, J = 1.1 Hz, 1 H), 7.44-7.49 (m, 1 H), 7.54 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H), 8.00 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 20.1 (CH_2), 21.8 (CH_2), 23.3 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 35.9 (CH_2), 40.0 (CH_2), 55.0 (CH), 61.9 (C_{quat}), 110.0 (CH), 118.2 (CH), 119.5 (CH), 122.2 (CH), 126.0 (C_{quat}), 128.5 (CH), 132.5 (CH), 133.9 (C_{quat}), 135.2 (CH), 135.8 (C_{quat}), 143.9 (C_{quat}), 145.2 (C_{quat}), 169.6 (C_{quat}), 195.5 (C_{quat}). FAB$^+$ MS (*m/z* (%)): 407 (MH^+, 100), 349 (MH^+ - C_4H_9, 90). IR (KBr): $\tilde{\nu}$ 2955, 2869, 1626, 1413, 1238, 731 cm^{-1}. Anal. calcd. for $C_{24}H_{26}N_2O_2S$ (406.6): C 70.91, H 6.45, N 6.89. Found: C 70.64, H 6.44, N 6.92.

rac-12b-Butyl-1-(4-nitrophenyl-1-carbonyl)-2,3,6,7,12,12b-hexahydro-_1H_-indolo[2,3-a] quinolizin-4-one (20b)



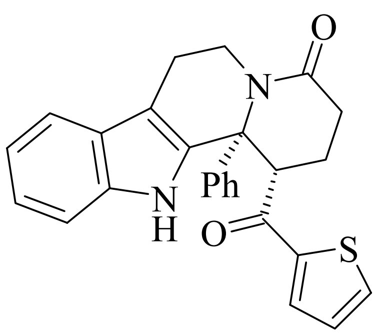
Yellow crystals, Mp. 195-197 °C. R_f = 0.26 (diethyl ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 7.1 Hz, 3 H), 1.01-1.18 (m, 1 H), 1.22-1.41 (m, 3 H), 2.00 (ddd, J = 18.4 Hz, J = 9.0 Hz, J = 4.4 Hz, 1 H), 2.21 (dt, J = 18.4 Hz, J = 4.4 Hz, 1 H), 2.29-2.39 (m, 1 H), 2.65 (dt, J = 18.0 Hz, J = 4.0 Hz, 1 H), 2.74-2.85 (m, 3 H), 2.90 (ddd, J = 15.1 Hz, J = 3.3 Hz, J = 1.3 Hz, 1 H), 2.99 (dt, J = 12.4 Hz, J = 3.4 Hz, 1 H), 3.92 (dd, J = 13.4 Hz, J = 5.0 Hz, 1 H), 5.24 (ddd, J = 12.7 Hz, J = 4.7 Hz, J = 1.3 Hz, 1 H), 7.03-7.08 (m, 3 H), 7.47-7.50 (m, 1 H), 7.68 (d, J = 9.0 Hz, 2 H), 7.83 (s, 1 H), 8.05 (d, J = 9.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 21.0 (CH_2), 21.1 (CH_2), 23.3 (CH_2), 27.0 (CH_2), 29.3 (CH_2), 35.5 (CH_2), 40.1 (CH_2), 54.1 (CH), 61.8 (C_{quat}), 110.1 (C_{quat}), 111.6 (CH), 118.2 (CH), 119.8 (CH), 122.4 (CH), 123.6 (CH), 125.9 (C_{quat}), 128.6 (CH), 133.4 (C_{quat}), 135.6 (C_{quat}), 141.1 (C_{quat}), 150.1 (C_{quat}), 169.1 (C_{quat}), 201.8 (C_{quat}). FAB$^+$ MS (m/z (%)): 446 (MH^+, 100), 388 (MH^+ - C_4H_9, 75). IR (KBr): $\tilde{\nu}$ 2957, 2868, 1618, 1527, 1347, 1235 746 cm^{-1}. Anal. calcd. for $C_{24}H_{27}N_3O_4$ (445.5): C 70.10, H 6.11, N 9.43. Found: C 69.79, H 6.05, N 9.41.

rac-12b-Phenyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-_1H_-indolo[2,3-a] quinolizin-4-one (20c)



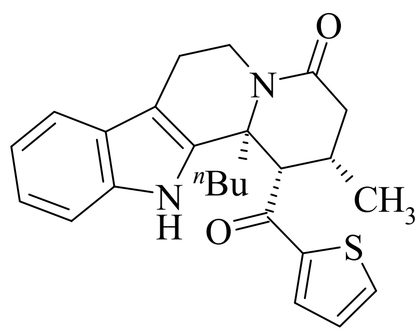
Colorless crystals, Mp. 201-202 °C. R_f = 0.25 (diethyl ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 7.0 Hz, 3 H), 1.05-1.20 (m, 1 H), 1.24-1.40 (m, 3 H), 1.96-2.12 (m, 1 H), 2.20-2.40 (m, 2 H), 2.75-2.90 (m, 5 H), 2.98 (dt, J = 12.0 Hz, J = 4.0 Hz, 1 H), 3.74 (s, 3 H), 3.93 (dd, J = 13.2 Hz, J = 4.9 Hz, 1 H), 5.27 (ddd, J = 12.8 Hz, J = 4.8 Hz, J = 1.5 Hz, 1 H), 6.74 (d, J = 9.0 Hz, 2 H), 7.04-7.17 (m, 3 H), 7.46-7.52 (m, 1 H), 7.66 (d, J = 9.0 Hz, 2 H), 8.27 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 20.9 (CH_2), 21.5 (CH_2), 23.2 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 35.7 (CH_2), 39.8 (CH_2), 52.6 (CH), 55.3 (CH_3), 62.0 (C_{quat}), 110.7 (C_{quat}), 111.0 (CH), 113.7 (CH), 118.0 (CH), 119.3 (CH), 121.8 (CH), 125.9 (C_{quat}), 129.4 (C_{quat}), 130.3 (CH), 134.3 (C_{quat}), 135.7 (C_{quat}), 163.7 (C_{quat}), 169.6 (C_{quat}), 201.5 (C_{quat}). EI +Q1MS (*m/z* (%)): 430 (M^+, 13), 373 (MH^+ - C_4H_9, 32), 135 (4-MeOPhCO$^+$, 100). IR (KBr): $\tilde{\nu}$ 2957, 2868, 1600, 1426, 1261, 1173, 1029, 843, 745, 593, 505 cm^{-1}. Anal. calcd. for $C_{27}H_{30}N_2O_3$ (430.6): C 75.32, H 7.02, N 6.51. Found: C 74.93, H 7.01, N 6.46.

rac-12b-Phenyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-_1H_-indolo[2,3-a] quinolizin-4-one (20d)



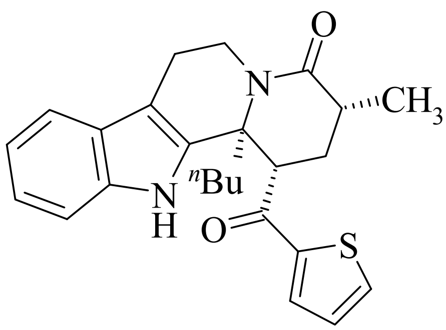
Colorless crystals, Mp. 315-316 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.80-1.90 (m, 1 H), 1.92-1.99 (m, 1 H), 2.26 (dd, J = 17.7 Hz, J = 5.4 Hz, 1 H), 2.41 (dd, J = 14.9 Hz, J = 4.2 Hz, 1 H), 2.78 (ddd, J = 17.7 Hz, J = 12.9 Hz, J = 6.8 Hz, 1 H), 2.91 (dt, J = 15.1 Hz, J = 5.6 Hz, 1 H), 2.99 (dt, J = 12.1 Hz, J = 4.4 Hz, 1 H), 4.66 (dd, J = 12.7 Hz, J = 5.6 Hz, 1 H), 4.81 (t, J = 3.6 Hz, 1 H), 6.98-7.03 (m, 2 H), 7.10-7.18 (m, 4 H), 7.27 (d, J = 7.6 Hz, 2 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.52 (d, J = 8.3 Hz, 1 H), 7.87 (dd, J = 4.9 Hz, J = 1.1 Hz, 1 H), 8.06 (dd, J = 3.9 Hz, J = 1.1 Hz, 1 H), 11.76 (s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.8 (CH_2), 21.8 (CH_2), 28.9 (CH_2), 39.0 (CH_2), 47.2 (CH), 66.7 (C_{quat}), 109.5 (C_{quat}), 111.4 (CH), 118.1 (CH), 119.0 (CH), 121.8 (CH), 126.6 (C_{quat}), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.3 (CH), 134.0 (CH), 135.8 (C_{quat}), 136.0 (CH), 136.1 (C_{quat}), 141.3 (C_{quat}), 144.7 (C_{quat}), 171.7 (C_{quat}), 192.1 (C_{quat}). FAB$^+$ MS (m/z (%)): 426 (M^+, 100), 349 (M^+ - Ph, 18), 111 (2-ThCO$^+$, 70). IR (KBr): $\tilde{\nu}$ 1651, 1611, 1456, 1413, 1351, 1236, 1215, 745, 702 cm^{-1}. Anal. calcd. for $C_{26}H_{22}N_2O_2S$ (426.5): C 73.21, H 5.20, N 6.57. Found: C 72.55, H 5.26, N 6.52.

***rac*-12b-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a] quinolizin-4-one (20e)**



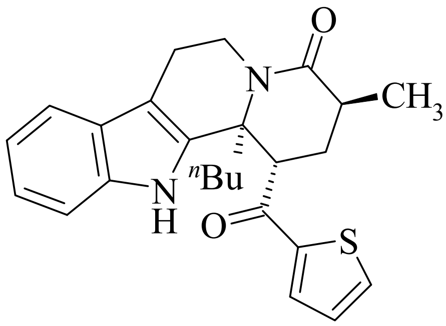
Colorless crystals Mp. 301-302 °C. R_f = 0.32 (HE/EA = 1/1). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.50 (t, J = 7.8 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H), 0.85 (dd, J = 14.7 Hz, J = 7.3 Hz, 1 H), 0.94-1.04 (m, 1 H), 1.08-1.18 (m, 1 H), 1.24-1.34 (m, 1 H), 1.82 (dt, J = 12.8 Hz, J = 3.6 Hz, 1 H), 1.88-1.96 (m, 1 H), 2.07-2.24 (m, 3 H), 2.55 (dd, J = 15.6 Hz, J = 5.0 Hz, 1 H), 2.80 (ddd, J = 15.6 Hz, J = 11.5 Hz, J = 6.9 Hz, 1 H), 3.41 (dt, J = 12.4 Hz, J = 5.0 Hz, 1 H), 4.66 (d, J = 3.7 Hz, 1 H), 4.76 (dd, J = 13.7 Hz, J = 6.9 Hz, 1 H), 6.97 (t, J = 7.4 Hz, 1 H), 7.10 (t, J = 7.4 Hz, 1 H), 7.35-7.43 (m, 3 H), 8.11 (dd, J = 5.0 Hz, J = 0.9 Hz, 1 H), 8.53 (dd, J = 3.7 Hz, J = 0.9 Hz, 1 H), 11.16 (s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.9 (CH_3), 19.0 (CH_3), 19.5 (CH_2), 21.9 (CH_2), 26.2 (CH_2), 27.0 (CH), 35.5 (CH_2), 36.1 (CH_2), 38.4 (CH_2), 48.8 (CH), 63.0 (C_{quat}), 107.0 (C_{quat}), 110.9 (CH), 117.5 (CH), 118.4 (CH), 121.0 (CH), 126.8 (C_{quat}), 128.7 (CH), 134.4 (CH), 135.3 (C_{quat}), 136.5 (C_{quat}), 137.4 (CH), 147.3 (C_{quat}), 170.2 (C_{quat}), 192.7 (C_{quat}). EI +Q1MS (*m/z* (%)): 420 (M^+, 28), 363 (M^+ - C_4H_9, 100), 111 (2-$ThCO^+$, 29). IR (KBr): ṽ 2958, 1615, 1415, 1233, 742 cm^{-1}. Anal. calcd. for $C_{25}H_{28}N_2O_2S$ x 0.4 CH_3OH (433.4): C 70.40, H 6.88, N 6.46. Found: C 70.60, H 6.68, N 6.66.

***rac*-12b-Butyl-3-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a] quinolizin-4-one Major Diastereomer 20f** (*syn-syn/syn-anti* = 4.5:1)



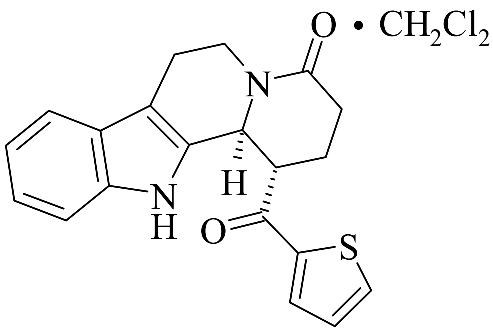
Colorless crystals, Mp. 209-210 °C. R_f = 0.35 (HE/EA = 2/1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.82 (t, J = 7.0 Hz, 3 H), 1.04-1.16 (m, 1 H), 1.22-1.36 (m, 3 H), 1.39 (d, J = 7.0 Hz, 3 H), 1.84 (ddd, J = 14.1 Hz, J = 5.7 Hz, J = 4.4 Hz, 1 H), 2.31 (ddd, J = 14.5 Hz, J = 12.4 Hz, J = 4.2 Hz, 1 H), 2.62 (dt, J = 13.7 Hz, J = 9.8 Hz, 1 H), 2.68-2.78 (m, 2 H), 2.81-2.88 (m, 2 H), 2.96 (dt, J = 12.4 Hz, J = 3.7 Hz, 1 H), 3.75 (dd, J = 13.1 Hz, J = 6.0 Hz, 1 H), 5.23 (ddd, J = 12.8 Hz, J = 4.8 Hz, J = 1.6 Hz, 1 H), 6.91 (dd, J = 4.9 Hz, J = 3.9 Hz, 1 H), 7.03-7.10 (m, 2 H), 7.14-7.16 (m, 1 H), 7.38 (dd, J = 3.9 Hz, J = 1.0 Hz, 1 H), 7.47 (d, J = 7.0 Hz, 1 H), 7.54 (dd, J = 4.9 Hz, J = 1.0 Hz, 1 H), 7.99 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0 (CH_3), 19.7 (CH_3), 21.0 (CH_2), 23.3 (CH_2), 27.2 (CH_2), 30.9 (CH_2), 33.9 (CH), 35.4 (CH_2), 40.1 (CH_2), 53.9 (CH), 62.4 (C_{quat}), 111.0 (C_{quat}), 111.1 (CH), 118.1 (CH), 119.5 (CH), 122.1 (CH), 126.1 (C_{quat}), 128.4 (CH), 132.5 (CH), 134.5 (C_{quat}), 135.0 (C_{quat}), 135.1 (CH), 143.9 (C_{quat}), 173.0 (C_{quat}), 195.4 (C_{quat}). EI +Q1MS (*m/z* (%)): 420 (M^+, 5), 363 (M^+ - C_4H_9, 100), 111 (2-$ThCO^+$, 43). IR (KBr): ṽ 3439, 3281, 2957, 2930, 1644, 1462, 1414, 1351, 1301, 1237, 742, 729 cm^{-1}. Anal. calcd. for $C_{25}H_{28}N_2O_2S$ (420.6): C 71.40, H 6.71, N 6.66. Found: C 71.11, H 6.68, N 6.67.

Minor Diastereomer 20f'



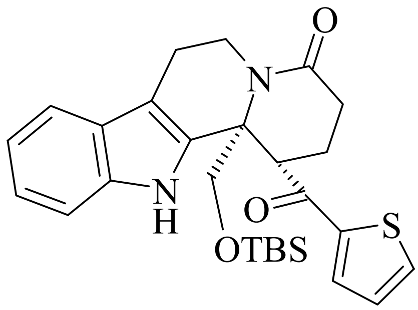
Colorless crystals, Mp.213-214 °C. R_f = 0.30 (HE/EA = 2/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (t, J = 7.2 Hz, 3 H), 0.86-0.92 (m, 1 H), 1.00-1.37 (m, 4 H), 1.42 (d, J = 6.0 Hz, 3 H), 2.08-2.32 (m, 3 H), 2.70-2.90 (m, 3 H), 3.02 (t, J = 11.3 Hz, 1 H), 3.77 (dd, J = 11.7 Hz, J = 3.7 Hz, 1 H), 5.22 (d, J = 12.1 Hz, 1 H), 6.92-6.98 (m, 1 H), 6.96-7.12 (m, 2 H), 7.13-7.18 (m, 1 H), 7.40-7.50 (m, 2 H), 7.58 (d, J = 4.5 Hz, 1 H), 7.95 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 19.3 (CH_3), 24.8 (CH_2), 24.9 (CH_2), 27.6 (CH_2), 30.8 (CH_2), 36.1 (CH), 37.8 (CH_2), 40.0 (CH_2), 54.8 (CH), 62.0 (C_{quat}), 110.8 (C_{quat}), 111.0 (CH), 118.2 (CH), 119.5 (CH), 122.1 (CH), 126.0 (C_{quat}), 128.5 (CH), 132.5 (CH), 134.4 (C_{quat}), 135.0 (CH), 135.6 (C_{quat}), 143.6 (C_{quat}), 172.9 (C_{quat}), 195.5 (C_{quat}). IR (KBr): $\tilde{\nu}$ 2957, 2931, 1627, 1463, 1414, 1350, 1237, 744, 728 cm^{-1}. EI +Q1MS (*m/z* (%)): 420 (M^+, 11), 363 (M^+ - C_4H_9, 100), 111 (2-ThCO$^+$, 80). Anal. calcd. for $C_{25}H_{28}N_2O_2S$ (420.6): C 71.40, H 6.71, N 6.66. Found: C 71.04, H 6.92, N 6.53.

***rac*-1-(Thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a]quinolizin-4-one (20g)**



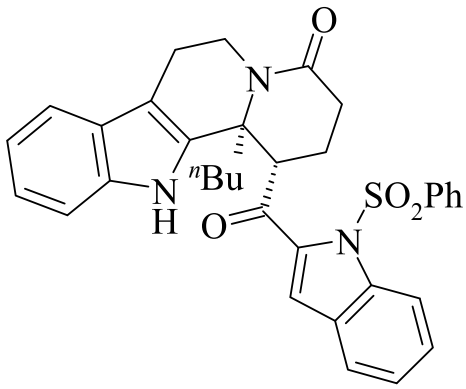
Yellow crystals Mp. 133-134 °C. R_f = 0.48 (EA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.02-2.11 (m, 1 H), 2.24-2.30 (m, 1 H), 2.55-2.90 (m, 5 H), 3.60 (ddd, J = 12.0 Hz, J = 10.0 Hz, J = 3.2 Hz, 1 H), 5.13-5.19 (m, 1 H), 5.29 (s, 2 H (CH_2Cl_2)), 5.44 (d, J = 10.0 Hz, 1 H), 7.06 (dt, J = 7.9 Hz, J = 1.2 Hz, 1 H), 7.06 (dt, J = 7.4 Hz, J = 1.2 Hz, 1 H), 7.15-7.19 (m, 2 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.74-7.77 (m, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.2 (CH_2), 26.4 (CH_2), 31.9 (CH_2), 40.7 (CH_2), 50.7 (CH), 55.0 (CH), 111.3 (CH), 118.3 (CH), 119.9 (CH), 122.4 (CH), 126.5 (C_{quat}), 128.4 (CH), 132.0 (C_{quat}), 133.3 (CH), 135.8 (CH), 136.2 (C_{quat}), 142.2 (C_{quat}), 155.8 (C_{quat}), 168.3 (C_{quat}), 197.0 (C_{quat}). EI +Q1MS (*m/z* (%)): 350 (M^+, 77), 239 (M^+ - 2-ThCO, 100), 111 (2-ThCO$^+$, 25). IR (KBr): $\tilde{\nu}$ 3372, 1641, 1413, 1251, 1235, 1061, 753 cm^{-1}. Anal. calcd. for $C_{20}H_{18}N_2O_2S \cdot CH_2Cl_2$ (434.1): C 57.93, H 4.63, N 6.43, S 7.37, Cl 16.29. Found: C 58.04, H 4.66, N 6.48, S 7.31, Cl 16.51.

***rac*-12b-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a]quinolizin-4-one (20h)**



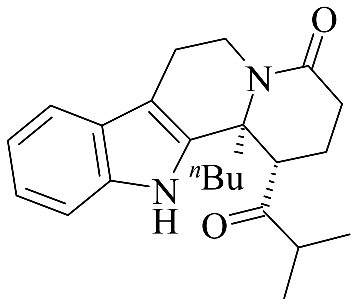
Colorless crystals Mp. 288-289 °C. R_f= 0.45 (HE/EA = 1/1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 2.00-2.10 (m, 1 H), 2.65-2.87 (m, 5 H), 2.95 (dt, J = 12.0 Hz, J = 4.2 Hz, 1 H), 3.80-3.88 (m, 1 H), 4.08 (d, J = 10.6 Hz, 1 H), 4.97 (d, J = 10.6 Hz, 1 H), 5.17 (dd, J = 12.8 Hz, J = 3.3 Hz, 1 H), 7.02-7.12 (m, 3 H), 7.17 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 3.5 Hz, 1 H), 7.65 (d, J = 4.6 Hz, 1 H), 7.95 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.2 (C_{quat}), 21.2 (CH_2), 23.7 (CH_2), 25.8 (CH_3), 31.3 (CH_2), 36.7 (CH_2), 52.6 (CH), 62.3 (C_{quat}), 65.0 (CH_2), 110.6 (C_{quat}), 111.2 (CH), 118.4 (CH), 119.8 (CH), 122.4 (CH), 126.0 (C_{quat}), 128.6 (CH), 132.8 (CH), 133.7 (C_{quat}), 135.3 (CH), 135.8 (C_{quat}), 143.6 (C_{quat}), 170.2 (C_{quat}), 196.4 (C_{quat}). FAB$^+$ MS (*m/z* (%)): 494 (M^+, 4), 349 (M^+ - TBSOCH$_2$, 100), 111 (2-ThCO$^+$, 25). IR (KBr): $\tilde{\nu}$ 2953, 2855, 1623, 1412, 1253, 1103, 841, 742 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 270 nm (17000), 280 nm (15600), 290 nm (14200). Anal. calcd. for $C_{27}H_{34}N_2O_3SSi$ (494.73): C 65.55, H 6.93, N 5.66. Found: C 65.23, H 6.87, N 5.78.

rac-1-(1-Benzenesulfonyl-1H-indole-3-carbonyl)-12b-butyl-2,3,6,7,12,12b-hexahydro-*1H*-indolo[2,3-a]quinolizin-4-one (20i)



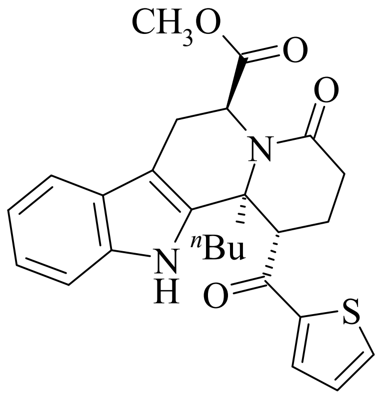
Colorless crystals, Mp. 286-288 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.83 (t, J = 7.4 Hz, 3 H), 1.03-1.12 (m, 1 H), 1.24-1.40 (m, 3 H), 2.06-2.14 (m, 1 H), 2.20-2.27 (m, 1 H), 2.37-2.47 (m, 1 H), 2.71-2.93 (m, 5 H), 2.99 (dt, J = 12.0 Hz, J = 4.0 Hz, 1 H), 3.67 (dd, J = 13.4 Hz, J = 5.4 Hz, 1 H), 5.25 (dd, J = 12.7 Hz, J = 4.4 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.02 (dt, J = 8.4 Hz, J = 1.3 Hz, 1 H), 7.08 (dt, J = 7.0 Hz, J = 1.0 Hz, 1 H), 7.30-7.37 (m, 4 H), 7.48-7.53 (m, 2 H), 7.57 (dd, J = 8.7 Hz, J = 1.0 Hz, 2 H), 7.73 (dd, J = 7.0 Hz, J = 1.3 Hz, 1 H), 7.81 (s, 1 H), 7.92 (s, 1 H), 8.31 (dd, J = 6.4 Hz, J = 1.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 21.0 (CH_2), 21.7 (CH_2), 23.3 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 36.0 (CH_2), 40.0 (CH_2), 55.7 (CH), 61.9 (C_{quat}), 111.0 (CH), 111.2 (C_{quat}), 113.0 (CH), 118.4 (CH), 119.6 (CH), 120.8 (C_{quat}), 122.2 (CH), 122.7 (CH), 125.0 (CH), 125.9 (CH), 126.1 (C_{quat}), 127.0 (CH), 127.3 (C_{quat}), 129.7 (CH), 131.8 (CH), 134.3 (C_{quat}), 134.5 (CH), 134.6 (C_{quat}), 135.7 (C_{quat}), 136.9 (C_{quat}), 169.7 (C_{quat}), 198.6 (C_{quat}). EI +Q1MS (*m/z* (%)): 579 (M^+, 22), 522 (M^+ - C_4H_9, 64), 284 ($PhSO_2$Ind-3-CO^+, 100). IR (KBr): $\tilde{\nu}$ 2960, 2932, 1844, 1619, 1535, 1448, 1381, 1235, 1188, 1172, 748, 732 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 282 nm (15000), 290 nm (14500). Anal. calcd. for $C_{34}H_{33}N_3O_4S$ (579.72): C 70.44, H 5.74, N 7.25, S 5.53. Found: C 70.06, H 5.65, N 7.28, S 5.58.

rac-12b-Butyl-1-isobutyryl-2,3,6,7,12,12b-hexahydro-_1H_-indolo[2,3-a]quinolizin-4-one (20j)



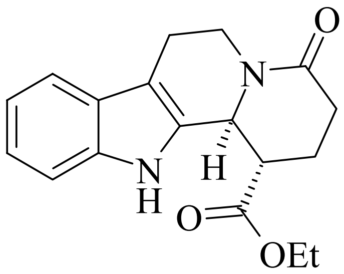
Colorless crystals, Mp. 194-196 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.69 (d, J = 6.7 Hz, 3 H), 0.80 (t, J = 7.2 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.97-1.07 (m, 1 H), 1.20-1.32 (m, 3 H), 1.96 (ddd, J = 18.1 Hz, J = 9.0 Hz, J = 4.7 Hz, 1 H), 2.08 (dt, J = 14.2 Hz, J = 4.0 Hz, 1 H), 2.13-2.21 (m, 1 H), 2.28 (spt, J = 7.0 Hz, 1 H), 2.60 (dt, J = 12.4 Hz, J = 3.4 Hz, 1 H), 2.66-2.76 (m, 3 H), 2.83 (ddd, J = 15.4 Hz, J = 3.4 Hz, J = 1.6 Hz, 1 H), 2.91 (dt, J = 12.4 Hz, J = 3.7 Hz, 1 H), 3.16 (dd, J = 13.7 Hz, J = 5.0 Hz, 1 H), 5.16 (ddd, J = 12.7 Hz, J = 4.8 Hz, J = 1.5 Hz, 1 H), 7.11 (dt, J = 8.0 Hz, J = 1.0 Hz, 1 H), 7.16 (dt, J = 7.7 Hz, J = 1.0 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.70 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9 (CH_3), 17.5 (CH_3), 20.4 (CH_2), 20.9 (CH_2), 23.2 (CH_2), 27.0 (CH_2), 29.4 (CH_2), 35.4 (CH_2), 39.9 (CH_2), 42.4 (CH), 56.8 (CH), 61.4 (C_{quat}), 110.9 (CH), 111.1 (C_{quat}), 118.3 (CH), 119.7 (CH), 122.4 (CH), 126.2 (C_{quat}), 134.0 (C_{quat}), 135.8 (C_{quat}), 169.4 (C_{quat}), 218.3 (C_{quat}). EI +Q1MS (*m/z* (%)): 366 (M^+, 16), 309 (M^+ - C_4H_9, 72), 239 (M^+ - C_4H_9 - ^{i}PrCO, 100). IR (KBr): $\tilde{\nu}$ 3267, 2960, 2932, 2871, 1708, 1624, 1466, 1433, 1405, 744 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 276 nm (8500), 282 nm (8200), 292 nm (5200). Anal. calcd. for $C_{23}H_{30}N_2O_2 \cdot 0.2CH_2Cl_2$ (383.50): C 72.66, H 7.99, N 7.30, Cl 3.70. Found: C 71.61, H 7.89, N 7.27, Cl 1.61.

(6*S*, 4*S*, 12b*S*)-12b-Butyl-4-oxo-1-(thiophene-2-carbonyl)-1,2,3,4,6,7,12,12b-octahydro-indolo-[2,3-*a*]quinolizin-6-carboxylic acid methyl ester (20k)



Colorless crystals Mp. 139-140 °C. R_f = 0.45 (diethyl ether). $[\alpha]_D^{24}$: +178° (c=2.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.60-0.70 (m, 1 H), 0.76 (t, J = 7.1 Hz, 3 H), 1.14-1.25 (m, 3 H), 2.24 (dt, J = 14.0 Hz, J = 4.0 Hz, 1 H), 2.31-2.37 (m, 2 H), 2.61-2.66 (m, 1 H), 2.82-2.86 (m, 2 H), 3.10 (dd, J = 15.8 Hz, J = 6.9 Hz, 1 H), 3.45 (dd, J = 15.8 Hz, J = 2.7 Hz, 1 H), 3.67 (s, 3H), 4.90 (t, J = 9.9 Hz, 1 H), 5.52 (dd, J = 6.8 Hz, J = 2.7 Hz, 1 H), 7.05-7.13 (m, 3 H), 7.18-7.19 (m, 1 H), 7.45 (dd, J = 6.3 Hz, J = 1.8 Hz, 1 H), 7.68 (dd, J = 4.9 Hz, J = 1.0 Hz, 1 H), 7.79 (dd, J = 3.8 Hz, J = 1.0 Hz, 1 H), 8.16 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 23.0 (CH_2), 25.5 (CH_2), 30.0 (CH_2), 37.3 (CH_2), 52.0 (CH), 52.6 (CH_3), 54.8 (CH), 62.9 (C_{quat}), 107.6 (C_{quat}), 111.3 (CH), 118.2 (CH), 119.6 (CH), 122.4 (CH), 125.2 (C_{quat}), 128.9 (CH), 133.9 (CH), 134.1 (C_{quat}), 135.9 (CH), 136.1 (C_{quat}), 144.4 (C_{quat}), 172.8 (C_{quat}), 197.9 (C_{quat}). EI +Q1MS (*m/z* (%)): 464 (M^+, 10), 407 (M^+ - C_4H_9, 100), 111 (2-ThCO$^+$, 57). IR (KBr): $\tilde{\nu}$ 3428, 2955, 2931, 1739, 1650, 1414, 1239, 1060, 741 cm^{-1}. Anal. calcd. for $C_{26}H_{28}N_2O_4S \cdot 0.5\ CH_2Cl_2$ (507.1): C 62.72, H 5.77, N 5.52, S 6.32, Cl 6.99. Found: C 62.72, H 5.78, N 5.36, S 6.39, Cl 7.18.

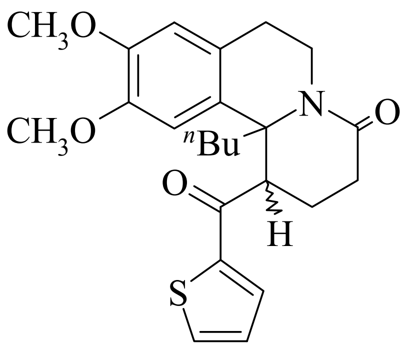
4-Oxo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine-1-carboxylic acid ethyl ester (20l)



In a screw cap pressure vessel 0.2 mL (2.00 mmol) of ethyl propiolate **1j**, and 320 mg (2.00 mmol) of tryptamine **4g** were dissolved in 10 mL of THF. The reaction mixture was heated at 65 °C for 3 h. After complete conversion 0.18 mL (2.20 mmol) of acryloyl chloride **18a** was added and the reaction mixture was heated at 70 °C for 6 h. After cooling to room temp the reaction mixture was diluted with methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with ether → ethylacetate to give the analytically pure quinolizinone **20l** as colorless crystals (crystallization was achieved from pentane/CH_2Cl_2).

Syn/*anti* = 9:1 (^{1}H NMR, minor diastereomer not listed). Colorless crystals, Mp.186-187°C. R_f= 0.50 (EA). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (t, J = 7.1 Hz, 3 H), 2.02-2.12 (m, 1 H), 2.22-2.28 (m, 1 H), 2.42-2.49 (m, 1 H), 2.65 (ddd, J = 17.6 Hz, J = 4.9 Hz, J = 2.9 Hz, 1 H), 2.74 (d, J = 11.2 Hz, 1 H), 2.80-2.90 (m, 3 H), 4.39 (q, J = 7.1 Hz, 2 H), 5.10-5.15 (m, 2 H), 7.11 (dt, J = 7.8 Hz, J = 1.0 Hz, 1 H), 7.18 (dt, J = 8.3 Hz, J = 1.0 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.50 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.2 (CH_3), 21.0 (CH_2), 23.8 (CH_2), 31.5 (CH_2), 41.0 (CH_2), 46.1 (CH), 55.3 (CH), 62.0 (CH_2), 111.9 (C_{quat}), 111.2 (CH), 118.4 (CH), 119.8 (CH), 122.3 (CH), 126.5 (C_{quat}), 132.5 (C_{quat}), 136.1 (C_{quat}), 168.5 (C_{quat}), 174.8 (C_{quat}). EI +Q1MS (*m/z* (%)): 312 (M^+, 100), 256 (M^+ - C_4H_9, 100), 256 (M^+ - CH_2CH_2CO, 80), 239 (M^+ - CO_2Et, 36). IR (KBr): $\tilde{\nu}$ 2930, 1723, 1619, 1467, 1444, 1327, 1299, 1160, 739 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 282 nm (8100). Anal. calcd. for $C_{18}H_{20}N_2O_3$ (312.37): C 69.21, H 6.45, N 8.97. Found: C 68.19, H 6.41, N 8.81.

11b-Butyl-9,10-dimethoxy-1-(thiophene-2-carbonyl)-1,2,3,6,7,11b-hexahydro-pyrido[2,1-*a*]isoquinolin-4-one (20m)



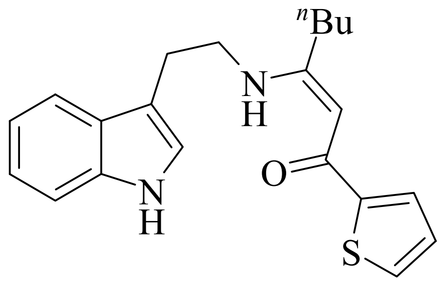
In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in 5 mL of degassed toluene. Then 0.14 mL (1.00 mmol) of triethylamine, 147 mg (1.00 mmol) of thiophene acid chloride **6e** and 0.12 mL (1.05 mmol) of hexyne **1b** were added. The reaction mixture was stirred for 3 h at room temperature until consumption of alkyne (that was verified by TLC HE/EA 9/1). Afterwards 0.2 mL (1.20 mmol) of homoveratryl amine **4h** was added and the reaction mixture was heated at 100 °C for 10 h. After complete conversion of alkynone to enaminone (TLC HE/EA 4/1; for alkynone R_f~0.7 for enaminone R_f~0.2) acryloyl chloride **18a** 0.17 mL (2.00 mmol) was added and the reaction mixture was heated at 70 °C for 3 h (TLC ether; for the aza-annulation product **19c** Rf~0.65). Afterwards 0.30 mL(4.00 mmol) of CF_3CO_2H was added and the reaction mixture was heated until consumption of the aza-annulation product **19c** (TLC in EA; for **20m** R_f~0.5, for the both diastereomers). The reaction mixture was quenched with K_2CO_3 solution, extracted with CH_2Cl_2, dried, evaporated and applied to column chromatography eluting with ethylacetate.

dr = 1.4:1. Yellow solid, Mp.67-68 °C. R_f= 0.50 (EA). ^{1}H NMR ($CDCl_3$, 300 MHz): Major diastereomer: δ 0.84 (t, J = 7.3 Hz, 3 H), 1.04-1.14 (m, 1 H), 1.20-1.34 (m, 4 H), 1.80-2.15 (m, 3 H), 2.44-2.92 (m, 6 H), 3.50 (s, 3 H), 3.76 (s, 3 H), 5.04-5.14 (m, 1 H), 6.42 (s, 1 H), 6.55 (s, 1 H), 6.80-6.85 (m, 1 H), 6.95-7.02 (m, 1 H), 7.46-7.51 (m, 1 H). Minor diastereomer: δ 3.63 (s, 3 H), 3.75 (s, 3 H), 6.46 (s, 1 H), 6.59 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): Major diastereomer: δ 13.9 (CH_3), 20.2 (CH_2), 23.2 (CH_2), 26.6 (CH_2), 28.9 (CH_2), 30.0 (CH_2), 35.4 (CH_2), 39.6 (CH_2), 54.8 (CH), 55.6 (CH_3), 55.8 (CH_3), 64.5 (C_{quat}), 109.8 (CH), 111.7 (CH), 128.5 (C_{quat}), 128.6 (CH), 129.5 (C_{quat}), 132.0 (CH), 134.9 (CH), 145.6 (C_{quat}), 147.3 (C_{quat}), 169.6 (C_{quat}), 194.4 (C_{quat}). Minor diastereomer: δ 13.8 (CH_3), 19.9 (CH_2), 23.3 (CH_2), 27.3

(CH_2), 27.4 (CH_2), 28.6 (CH_2), 37.2 (CH_2), 43.6 (CH_2), 51.0 (CH), 55.7 (CH_3), 56.1 (CH_3), 62.7 (C_{quat}), 108.9 (CH), 111.5 (CH), 128.4 (C_{quat}), 129.0 (CH), 129.4 (C_{quat}), 132.1 (CH), 133.5 (CH), 144.0 (C_{quat}), 147.6 (C_{quat}), 169.4 (C_{quat}), 192.1 (C_{quat}). EI +Q1MS (*m/z* (%)): 427 (M^+, 6), 370 (M^+ - C_4H_9, 100), 111 (2-ThCO$^+$, 66). IR (KBr): $\tilde{\nu}$ 3440, 2955, 2934, 2870, 1737, 1562, 1414, 1260, 1221, 726 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 282 nm (8500). Calc. HRMS for $C_{24}H_{29}NO_4S$: 427.1817. Found: 427.1788.

6.14 Splitting Protocol

(*Z*)-3-[2-(1H-Indol-3-yl)-ethylamino]-1-thiophen-2-yl-heptenone (11m)



In a Schlenk flask a stirred mixture of 140 mg (0.20 mmol) of $Pd(PPh_3)_2Cl_2$, and 70 mg (0.40 mmol) of CuI in 30.0 mL of THF was degassed for 5 min. Then 1.40 mL (10.0 mmol) of triethylamine, 1.07 mL (10.0 mmol) of thiophene acid chloride **6e** and 1.2 mL (10.5 mmol) of hexyne **1b** were added. The reaction mixture was stirred for 2 h under nitrogen at room temperature until the hexyne was completely consumed (monitored by TLC). Then 1.92 g (12.0 mmol) of tryptamine **4g** and 30.0 mL of methanol were added. The reaction mixture was heated to reflux temp for 3 h until the conversion was complete (monitored by TLC). The solvents were evaporated and the residue was chromatographed on silica gel (hexane/ethylacetate 2:1) to afford 2.86 g (81 %) of the enaminone **11m** as a yellow oil.

Yellow oil, R_f= 0.50 (HE/EA 2/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, J = 7.2 Hz, 3 H), 1.36-1.48 (m, 2 H), 1.51-1.62 (m, 2 H), 2.26 (t, J = 7.6 Hz, 2 H), 3.12 (t, J = 6.8 Hz, 2 H), 3.65 (q, J = 6.6 Hz, 2 H), 5.68 (s, 1 H), 7.06-7.11 (m, 2 H), 7.18-7.26 (m, 2 H), 7.31-7.36 (m, 1 H), 7.43 (d, J = 5.1 Hz, 1 H), 7.63-7.67 (m, 2 H), 9.12 (s, 1 H), 11.40 (t, J = 5.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5 (CH_3), 22.4 (CH_2), 25.9 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 43.3 (CH_2), 90.5 (CH), 111.0 (C_{quat}), 111.4 (CH), 117.8 (CH), 118.8 (CH), 121.4 (CH), 122.9

(CH), 126.6 (C_{quat}), 126.8 (CH), 127.4 (CH), 129.1 (CH), 136.2 (C_{quat}), 147.0 (C_{quat}), 168.8 (C_{quat}), 180.3 (C_{quat}).

Synthesis of indolo[2,3-a]quinolizin-4-ones 20a or 20f via aza-annulation-PS sequence.

In a screw cap pressure vessel 353 mg (1.00 mmol) of enaminone **11m** was dissolved in 5 mL of degassed THF. Then *α,β*-unsaturated chloride **18a** or **18c** (1.2 mmol) was added and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temp the reaction mixture was diluted with 5 mL of methanol, stirred for 10 min, evaporated and applied to column chromatography on silica gel eluting with ether (compound **20a**), hexane-ethylacetate 2:1 (compounds **20f)** to give 345 mg (85 %) of compound **20a** as colorless crystals or 312 mg (75 %) of compound **210** (the ratio of diastereomers 4.5:1, the diastereomers were separated by column chromatography) (crystallization was achieved from pentane/CH_2Cl_2). For the characterization, see the CAAPS sequence.

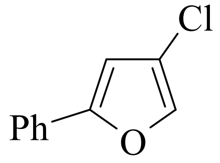
6.15 General Procedure for the β-Chlorofuran Synthesis

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF. Then 1.00 mmol of acid chloride **6**, 1.00 mmol of THP protected propargyl alcohol **1**, as well as 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 117 mg (2.00 mmol) of sodium chloride, 209 mg (1.10 mmol) of *p*-toluenesulphonic acid monohydrate and 3 mL of methanol were added and the reaction mixture was heated at 60 °C for 20 h. After complete conversion of ynone to furan (TLC), the reaction mixture was diluted with saturated solution of $NaHCO_3$ (20 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried over sodium sulfate, evaporated and applied to column chromatography on the neutral aluminium oxide eluting with hexane-ethylacetate (12:1) to give the analytically pure *β*-chlorofurans **21** as oils or solids (crystallization was achieved from hexane) (see Table 43 for experimental details).

Table 43. Experimental Details for the *β*-Chlorofuran Synthesis

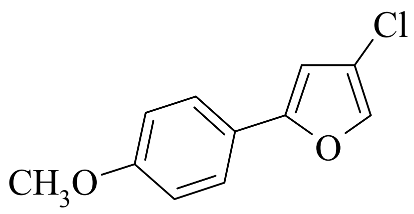
Acid Chloride **6**	Alkyne **1**	Product **21** (Yield %)	Eluent
141mg of **6f**	141 mg of **1k**	113 mg (63%) of **21a**	HE:EA 9:1 $R_f = 0.75$
171 mg of **6a**	141 mg of **1k**	138 mg (71%) of **21b**	HE:EA 9:1 $R_f = 0.60$
141 mg of **6f**	168 mg of **1l**	145 mg (70%) of **21c**	HE:EA 9:1 $R_f = 0.87$
147 mg of **6e**	168 mg of **1l**	125 mg (59%) of **21d**	HE:EA 9:1 $R_f = 0.72$
167 mg of **6i**	168 mg of **1l**	170 mg (73%) of **21e**	HE:EA 9:1 $R_f = 0.70$
159 mg of **6j**	141 mg of **1k**	92 mg (47%) of **21f**	HE:EA 9:1 $R_f = 0.66$
186 mg of **6b**	141 mg of **1k**	56 mg (24%) of **21g**	HE:EA 4:1 $R_f = 0.78$
145 mg of **6n**	141 mg of **1k**	117 mg (64%) of **21h**	HE:EA 9:1 $R_f = 0.77$

4-Chloro-2-phenyl-furan *(*21a)



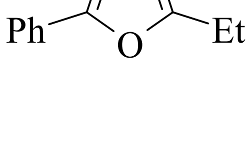
Colorless solid (sublimates under high vacuum), Mp. 53-54 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 6.68 (d, J = 0.7 Hz, 1 H), 7.24-7.34 (m, 1 H), 7.37-7.44 (m, 2 H), 7.49 (d, J = 0.7 Hz, 1 H), 7.61-7.65 (m, 2 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 106.8 (CH), 117.8 (C_{quat}), 124.2 (CH), 128.6 (CH), 129.2 (CH), 130.3 (C_{quat}), 138.5 (CH), 154.7 (C_{quat}). EI +Q1MS (m/z (%)):180 (M^+(^{37}Cl), 33), 178 (M^+(^{35}Cl), 100), 149 (M^+(^{35}Cl), - CHO, 29), 115 (M^+ - COCl, 57). IR (KBr): $\tilde{\nu}$ 3143, 1569, 1518 1445, 1355, 1282, 1205, 1121, 1071, 1014, 941, 908, 804, 764, 689, 588 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 282 nm (19740), 298 nm (1006). Anal. calcd. for $C_{10}H_7ClO$ (178.62): C 67.24, H 3.95. Found: C 67.52, H 4.44.

4-Chloro-2-(4-methoxy-phenyl)-furan (21b)



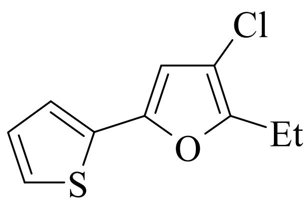
Colorless solid, Mp. 82-83 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 3.81 (s, 3H), 6.52 (d, J = 1.1 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.43 (d, J = 1.1 Hz, 1 H), 7.55 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 55.7 (CH_3), 105.2 (CH), 114.6 (CH), 117.7 (C_{quat}), 123.2 (C_{quat}), 125.7 (CH), 137.8 (CH), 154.8 (C_{quat}), 160.2 (C_{quat}). EI +Q1MS (m/z (%)): 210 (M^+(^{37}Cl), 33), 208 (M^+(^{35}Cl), 100), 195 (M^+(^{37}Cl), - CH_3, 17), 193 (M^+(^{35}Cl), - CH_3, 51), 179 (M^+(^{35}Cl), - CHO, 11), 145 (M^+ - COCl, 49). IR (KBr): $\tilde{\nu}$ 1614, 1526, 1496, 1296, 1279, 1252, 1126, 1035, 909, 835, 794, 592 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 284 nm (23770), 306 nm (11510). Anal. calcd. for $C_{11}H_9ClO_2$ (208.65): C 63.32, H 4.35, Cl 16.99. Found: C 63.34, H 4.38, 17.01.

3-Chloro-2-ethyl-5-phenyl-furan (21c)



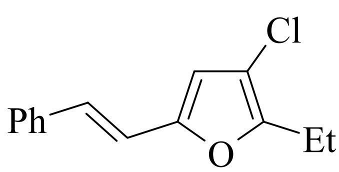
Colorless oil. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 1.29 (t, J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2 H), 6.60 (s, 1 H), 7.24-7.32 (m, 1 H), 7.35-7.42 (m, 2 H), 7.58-7.64 (m, 2 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 12.4 (CH_3), 19.5 (CH_2), 107.0 (CH), 112.2 (C_{quat}), 123.8 (CH), 128.0 (CH), 129.1 (CH), 130.7 (C_{quat}), 151.7 (C_{quat}), 152.5 (C_{quat}). EI +Q1MS (*m/z* (%)): 208 (M^+(^{37}Cl), 16), 206 (M^+(^{35}Cl), 44), 193 (M^+(^{37}Cl), - CH_3, 33), 191 (M^+(^{35}Cl), - CH_3, 100). IR (Film): $\tilde{\nu}$ 1597, 1556, 1488, 1449, 1290, 1099, 1039, 926, 796, 757, 689 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 292 nm (19000), 308 nm (11470). Calc. HRMS for $C_{12}H_{11}{}^{37}ClO$: 208.0469. Found: 208.0462; calc. HRMS for $C_{12}H_{11}{}^{35}ClO$: 206.0498. Found: 206.0479.

3-Chloro-2-ethyl-5-thiophen-2-yl-furan (21d)



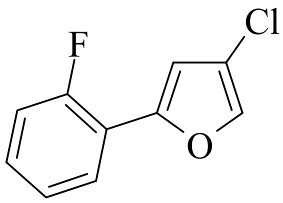
Yellow oil. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 1.25 (t, J = 7.6 Hz, 3H), 2.69 (q, J = 7.6 Hz, 2 H), 6.44 (s, 1 H), 7.03 (dd, J = 5.1 Hz, J = 3.7 Hz, 1 H), 7.22 (dd, J = 3.7 Hz, J = 1.1 Hz, 1 H), 7.25 (dd, J = 5.1 Hz, J = 1.1 Hz, 1 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 12.3 (CH_3), 19.4 (CH_2), 106.7 (CH), 112.0 (C_{quat}), 123.1 (CH), 124.8 (CH), 128.1 (CH), 133.4 (C_{quat}), 147.4 (C_{quat}), 152.1 (C_{quat}). EI +Q1MS (*m/z* (%)): 214 (M^+(^{37}Cl), 23), 212 (M^+(^{35}Cl), 69), 199 (M^+(^{37}Cl), - CH_3, 33), 197 (M^+(^{35}Cl), - CH_3, 100). IR (Film): $\tilde{\nu}$ 1614, 1426, 1095, 1025, 992, 848, 786, 695 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 244 nm (4150), 310 nm (14750), 330 nm (7370). Calc. HRMS for $C_{10}H_9{}^{37}ClOS$: 214.0033. Found: 214.0005; calc. HRMS for $C_{10}H_9{}^{35}ClOS$: 212.0063. Found: 212.0036.

3-Chloro-2-ethyl-5-styryl-furan (21e)



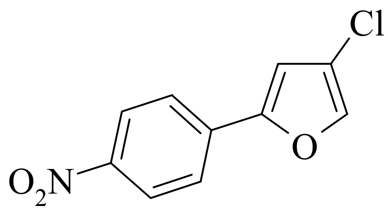
Yellow oil. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 1.29 (t, J = 7.6 Hz, 3H), 2.69 (q, J = 7.6 Hz, 2 H), 6.29 (s, 1 H), 6.79 (d, J = 16.5 Hz, 1 H), 6.99 (d, J = 16.5 Hz, 1 H), 7.21-7.27 (m, 1 H), 7.30-7.38 (m, 2 H), 7.42-7.48 (m, 2 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 12.3 (CH_3), 19.5 (CH_2), 110.2 (CH), 112.1 (C_{quat}), 116.2 (CH), 126.7 (CH), 127.4 (CH), 128.1 (CH), 129.1 (CH), 137.1 (C_{quat}), 151.0 (C_{quat}), 152.6 (C_{quat}). EI +Q1MS (*m/z* (%)): 234 (M^+(^{37}Cl), 28), 232 (M^+(^{35}Cl), 83), 219 (M^+(^{37}Cl), - CH_3, 35), 217 (M^+(^{35}Cl), - CH_3, 100). IR (Film): $\tilde{\nu}$ 2976, 2938, 1597, 1494, 1447, 1280, 1119, 1028, 955, 787, 748, 692, 579 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 314 nm (13670), 328 nm (13000), 346 nm (18590). Calc. HRMS for $C_{14}H_{13}{}^{37}ClO$: 234.0625. Found: 234.0617; calc. HRMS for $C_{14}H_{13}{}^{35}ClO$: 232.0655. Found: 232.0664.

4-Chloro-2-(2-fluoro-phenyl)-furan (21f)



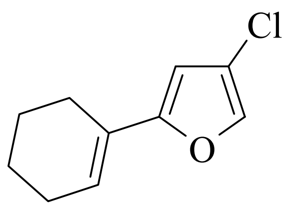
Colorless crystals, Mp. 38-39 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 6.83 (d, J = 3.8 Hz, 1 H), 7.10-7.35 (m, 3 H), 7.52 (s, 1 H), 7.78 (dt, J = 7.5 Hz, J = 1.9 Hz, 1 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 111.6 (d, J = 11.9 Hz, CH), 116.4 (d, J = 21.5 Hz, CH), 118.0 (C_{quat}), 118.5 (d, J = 11.9 Hz, C_{quat}), 124.9 (d, J = 3.4 Hz, CH), 126.3 (d, J = 2.8 Hz, CH), 129.8 (d, J = 8.5 Hz, CH), 138.5 (d, J = 1.1 Hz, CH), 148.7 (C_{quat}), 159.0 (d, J = 251.0 Hz, C_{quat}). EI +Q1MS (*m/z* (%)): 199 (M^+(^{37}Cl), 33), 196 (M^+(^{35}Cl), 100), 169 (M^+(^{37}Cl), - CHO, 12), 167 (M^+(^{35}Cl), - CHO, 37), 133 (M^+, - COCl, 90). IR (KBr): $\tilde{\nu}$ 3150, 3071, 2920, 1590, 1519, 1487, 1354, 1264, 1206, 1128, 1104, 1036, 1014, 943, 910, 819, 760, 590 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 268 nm (22730), 278 nm (23860), 290 nm (19880), 298 nm (16480), 330 nm (4550). Calc. HRMS for $C_{10}H_6{}^{37}ClFO$: 198.0062. Found: 198.0024; calc. HRMS for $C_{10}H_6{}^{35}ClFO$: 196.0091. Found: 196.0085.

4-Chloro-2-(4-nitro-phenyl)-furan (21g)



Yellow solid, Mp. 128-130 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 6.89 (d, J = 0.7 Hz, 1 H), 7.59 (d, J = 0.7 Hz, 1 H), 7.77 (d, J = 8.8 Hz, 2 H), 8.24 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 110.3 (CH), 118.6 (C_{quat}), 124.6 (CH), 124.7 (CH), 135.8 (C_{quat}), 140.6 (CH), 147.5 (C_{quat}), 152.4 (C_{quat}). EI +Q1MS (m/z (%)): 225 (M^+(^{37}Cl), 33), 223 (M^+(^{35}Cl), 100), 195 (M^+(^{37}Cl), - NO, 7), 193 (M^+(^{35}Cl), - NO, 20). IR (KBr): $\tilde{\nu}$ 1602, 1577, 1511, 1339, 1110, 943, 910, 853, 801, 586 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 242 nm (10490), 346 nm (18800). Anal. calcd. for $C_{10}H_6ClNO_3$ (223.62): C 53.71, H 2.70, N 6.26, Cl 15.85. Found: C 53.75, H 2.86, N 6.27, Cl 15.91.

4-Chloro-2-cyclohex-1-enyl-furan (21h)



Yellow oil. ^{1}H NMR (Acetone-d_6, 300 MHz): δ 1.58-1.76 (m, 4 H), 2.14-2.28 (m, 4 H), 6.27-6.31 (m, 1 H), 6.34 (s, 1 H), 7.58 (s, 1 H). ^{13}C NMR (Acetone-d_6, 75 MHz): δ 22.7 (CH_2), 22.9 (CH_2), 25.2 (CH_2), 25.7 (CH_2), 105.8 (CH), 117.3 (C_{quat}), 124.6 (CH), 127.6 (C_{quat}), 138.3 (CH), 156.7 (C_{quat}). EI +Q1MS (m/z (%)): 184 (M^+(^{37}Cl), 32), 182 (M^+(^{35}Cl), 100), 169 (M^+(^{37}Cl), - CH_3, 10), 167 (M^+(^{35}Cl), - CH_3, 23), 156 (M^+(^{37}Cl), - C_2H_4, 13), 154 (M^+(^{35}Cl), - C_2H_4, 45), 147 (M^+ - Cl, 45). IR (KBr): $\tilde{\nu}$ 2932, 2860, 2662, 1778, 1720, 1569, 1448, 1338, 1252, 1120, 942, 786, 737, 589 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 270 nm (7270), 284 nm (480). Calc. HRMS for $C_{10}H_{11}{}^{37}ClO$: 184.0469. Found: 184.0463; calc. HRMS for $C_{10}H_{11}{}^{35}ClO$: 182.0498. Found: 182.0501.

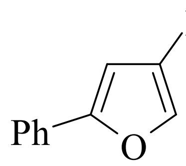
6.16 General Procedure for the β-Iodofuran Synthesis

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF. Then 1.00 mmol of acid chloride **6**, 1.00 mmol of THP protected propargyl alcohol **1**, as well as 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 750 mg (5.00 mmol) of sodium iodide, 209 mg (1.10 mmol) of *p*-toluenesulphonic acid monohydrate and 3 mL of methanol were added and the reaction mixture was stirred at the r.t. for 2 h. After complete conversion of ynone to furan (TLC), the reaction mixture was diluted with saturated solution of $NaHCO_3$ (10 mL) and Na_2SO_3 (10 mL), and extracted with dichloromethane (5×20 mL). The combined organic layers were dried over sodium sulfate, evaporated and applied to column chromatography on the neutral aluminium oxide eluting with hexane-ethylacetate (12:1) to give the analytically pure *β*-iodofurans **21** as oils or solids (crystallization was achieved from hexane) (see Table 44 for experimental details).

Table 44. Experimental Details for the *β*-Iodofuran Synthesis

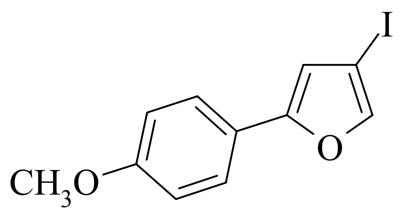
Acid Chloride **6**	Alkyne **1**	Product **21** (Yield %)	Eluent
141mg of **6f**	141 mg of **1k**	170 mg (63 %) of **21i**	HE:EA 9:1 $R_f = 0.75$
171 mg of **6a**	141 mg of **1k**	190 mg (63 %) of **21j**	HE:EA 9:1 $R_f = 0.60$
147 mg of **6e**	168 mg of **1l**	150 mg (49 %) of **21k**	HE:EA 9:1 $R_f = 0.72$
167 mg of **6i**	141 mg of **1k**	180 mg (61 %) of **21l**	HE:EA 9:1 $R_f = 0.73$
186 mg of **6b**	141 mg of **1k**	128 mg (40 %) of **21m**	HE:EA 4:1 $R_f = 0.78$
141mg of **6f**	168 mg of **1l**	215 mg (72 %) of **21n**	HE:EA 9:1 $R_f = 0.87$
141mg of **6f**	247 mg of **1m**	147 mg (39 %) of **21o**	HE:EA 9:1 $R_f = 0.50$
107 mg of **6m**	247 mg of **1m**	101 mg (29 %) of **21p**	HE:EA 9:1 $R_f = 0.61$

4-Iodo-2-phenyl-furan (21i)



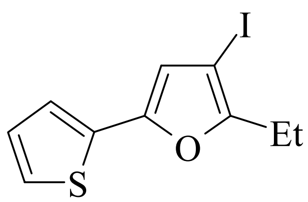
Colorless solid, Mp. 64 °C. ^{1}H NMR (acetone-d_6, 300 MHz): 7.02 (d, J = 0.7 Hz, 1H), 7.28-7.37 (m, 1H), 7.40-7.48 (m, 2H), 7.70-7.74 (m, 2H), 7.75 (d, ^{4}J = 0.7 Hz, 1H).. ^{13}C NMR (acetone-d_6, 75 MHz): .δ 66.5 (C_{quat}), 112.9 (CH), 124.5 (CH), 128.9 (CH), 129.6 (CH), 130.4 (C_{quat}), 146.4 (CH), 156.2 (C_{quat}).

4-Iodo-2-(4-methoxy-phenyl)-furan (21j)



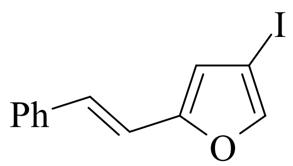
Colorless solid, Mp. 84-85 ^{o}C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.83 (s, 3H), 6.84 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.67 (s, 1 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.7 (CH_3), 66.5 (C_{quat}), 111.3 (CH), 115.2 (CH), 123.4 (C_{quat}), 126.2 (CH), 145.7 (CH), 156.6 (C_{quat}), 160.7 (C_{quat}). EI +Q1MS (m/z (%)): 300 (M^+, 100), 285 (M^+- CH_3, 12), 173 (M^+ - I, 20), 145 (M^+ - COI, 25). IR (KBr): $\tilde{\nu}$ 3107, 2958, 1612, 1513, 1485, 1291, 1255, 1181, 1103, 1036, 910, 833, 795, 588 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 288 nm (27140), 306 nm (15710). Anal. calcd. for $C_{11}H_9O_2I$ (300.10): C 44.03, H 3.02. Found: C 44.42, H 3.24.

2-Ethyl-3-iodo-5-thiophen-2-yl-furan (21k)



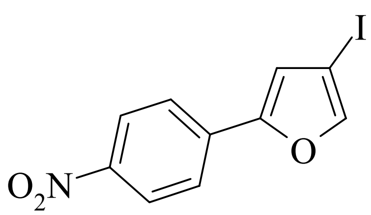
Light yellow oil. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.23 (t, ^{3}J = 7.5 Hz, 3H), 2.73 (q, ^{3}J = 7.5 Hz, 2 H), 6.70 (s, 1 H), 7.09 (dd, J = 5.0 Hz, J = 3.5 Hz, 1H), 7.33 (dd, J = 3.7 Hz, J = 1.1 Hz, 1H), 7.44 (dd, J = 5.1 Hz, J = 1.1 Hz, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 12.8 (CH_3), 21.6 (CH_2), 63.7 (C_{quat}), 113.2 (CH), 123.9 (CH), 125.7 (CH), 128.7 (CH), 133.4 (C_{quat}), 150.2 (C_{quat}), 157.7 (C_{quat}). EI +MS (m/z (%)): 304 (M^+, 92), 289 (M^+ - CH_3, 100), 177 (M^+ - I, 2), 111 ($C_4H_3SCO^+$, 25). IR (KBr): $\tilde{\nu}$ 3117, 2973, 1426, 1131, 1063, 1016, 1007, 1001, 988, 950, 847, 824, 791, 696 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 302 nm (15200), 312 (16200), 330 (9170). Calc. HRMS for $C_{10}H_9OSI$: 303.9419. Found: 303.9412.

3-Iodo-2-styryl-furan (21l)



Colorless solid, Mp. 79 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.65 (s, 1H), 7.05 (d, J = 16.5 Hz, 1H), 7.12 (d, J = 16.5 Hz, 1H), 7.24-7.31 (m, 1H), 7.33-7.41 (m, 2H), 7.54-7.59 (m, 2H) 7.68 (s, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 66.3 (C_{quat}), 115.8 (CH), 116.2 (CH), 127.1 (CH), 127.3 (CH), 128.7 (CH), 129.3 (CH), 129.5 (CH), 137.4 (C_{quat}), 146.3 (CH), 155.7 (C_{quat}). EI +Q1MS (m/z (%)): 296 (M^+, 100), 169 (M^+-I, 22), 141 (M^+ - COI, 70). IR (KBr): $\tilde{\nu}$ 3140, 3125, 3083, 3059, 3036, 1630, 1446, 1247, 957, 928, 911, 799, 747, 692, 586 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 310 nm (27900), 322 nm (32960), 336 nm (22870). Anal. calcd. for $C_{12}H_9IO$ (296.11): C 48.68, H 3.06. Found: C 48.93, H 3.23.

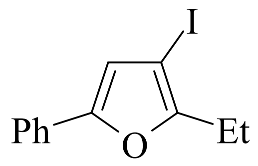
4-Iodo-2-(4-nitro-phenyl)-furan (21m)



Yellow crystals, Mp. 160 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.35 (s, 1H), 7.90 (d, ^{4}J = 0.7 Hz, 1H), 7.97 (d, J = 9.2 Hz, 2H), 8.31 (d, J = 9.2 Hz, 2H). ^{13}C NMR (acetone-d_6, 75

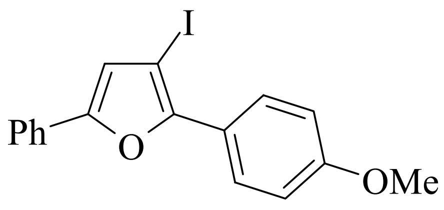
MHz): δ 67.1 (C_{quat}), 116.8 (CH), 125.0 (CH), 125.2 (CH), 135.9 (C_{quat}), 147.8 (C_{quat}), 148.4 (CH), 154.0 (C_{quat}). EI + MS (m/z (%)): 315 (M^+, 100), 285 (M^+ - NO, 10). IR (KBr): ṽ 3135, 1600, 1569, 1514, 1336, 1279, 1143, 1111, 1098, 1023, 913, 854, 827, 816, 773, 752, 692, 587, 515 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε). 244 nm (9240), 350 nm (18020). Anal. calcd. for $C_{10}H_6NO_3I$ (315.07): C 38.12, H 1.92, N 4.45. Found: C 38.22, H 2.09, N 4.38.

2-Ethyl-3-iodo-5-phenyl-furan (21n)



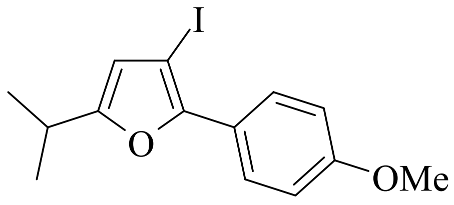
Light yellow liquid. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.26 (t, ^3J = 7.7 Hz, 3 H), 2.76 (q, ^4J = 7.7 Hz, 2H), 6.89 (s, 1H), 7.26-7.32 (m, 1H), 7.38-7.45 (m, 2 H), 7.66-7.71 (m, 2 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 12.8 (CH_3), 21.6 (CH_2), 63.9 (C_{quat}), 113.6 (CH), 124.2 (CH), 128.5 (CH), 129.7 (CH), 131.0 (C_{quat}), 154.4 (C_{quat}), 158.1 (C_{quat}). EI +MS (m/z (%)): 298 (M^+, 94), 283 (M^+ - CH_3, 100), 105 ($C_6H_5CO^+$, 22), 77 ($C_6H_5^+$, 13). IR (KBr): ṽ 2973, 1550, 1487, 1444, 1281, 1142, 1065, 1008, 754, 686 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 294 nm (15300), 308 (10400). Calc. HRMS for $C_{12}H_{11}IO$: 297.9855. Found: 297.9861.

3-Iodo-2-(4-methoxy-phenyl)-5-phenyl-furan (21o)



Colorless crystals, Mp. 116 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.87 (s, 3 H), 7.08 (d, J = 8.8 Hz, 2 H), 7.11 (s, 1 H), 7.30-7.37 (m, 1 H), 7.42-7.49 (m, 2H), 7.78-7.83 (m, 2H), 8.04 (d, J = 8.8 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.7 (CH_3), 62.1 (C_{quat}), 114.9 (CH), 116.7 (CH), 123.7 (C_{quat}), 124.5 (CH), 128.5 (CH), 128.8 (CH), 129.7 (CH), 130.6 (C_{quat}), 150.2 (C_{quat}), 154.4 (C_{quat}), 160.8 (C_{quat}). EI +Q1MS (m/z (%)): 376 (M^+, 100), 361 (M^+ - CH_3, 22), 221 (M^+ - I - CH_3 - CH, 48), 105 ($C_6H_5CO^+$, 18), 77 ($C_6H_5^+$, 12). IR (KBr): ṽ 1607, 1541, 1494, 1440, 1294, 1254, 1180, 1069, 1055, 1026, 945, 831, 797, 760, 688, 663 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 238 nm (14500), 252 nm (12000), 328 nm (24600), 350 nm (13000). Anal. calcd. for $C_{17}H_{13}IO_2$ (376.20): C 54.28, H 3.48. Found: C 54.35, H 3.49.

3-Iodo-5-isopropyl-2-(4-methoxy-phenyl)-furan (21p)



Colorless oil. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.27 (d, J = 7.0 Hz, 6 H), 2.99 (dspt, J = 7.0 Hz, J = 1.1 Hz, 1H), 3.85 (s, 3 H), 6.27 (d, J = 1.1 Hz, 1 H), 7.03 (d, J = 9.2 Hz, 2H), 7.88 (d, J = 9.2 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 21.0 (CH_3), 28.4 (CH), 55.5 (CH_3), 60.2 (C_{quat}), 114.4 (CH), 114.6 (CH), 124.0 (C_{quat}), 128.1 (CH), 153.7 (C_{quat}), 160.3 (C_{quat}), 162.5 (C_{quat}). EI + MS (*m/z* (%)): 342 (M^+, 88), 327 (M^+ - CH_3, 100). IR (KBr): $\tilde{\nu}$ 2964, 1607, 1550, 1492, 1280, 1247, 1176, 1032, 941, 826 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε) 286 (19300), 296 (17600), 314 (8820). Calc. for HRMS $C_{14}H_{15}IO_2$: 342.0117. Found: 342.0125.

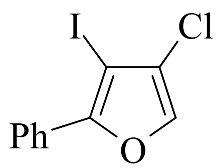
6.17 General Procedure for the 3-Chloro-4-iodofuran Synthesis

In a screw cap pressure vessel 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF. Then 1.00 mmol of acid chloride **6**, 1.00 mmol of THP protected propargyl alcohol **1**, as well as 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 293 mg (5.00 mmol) of sodium chloride, 244 mg (1.5 mmol) for entries 1, 2, 3 or 406 mg (2.5 mmol) for entry 4 of iodine monochloride, 209 mg (1.10 mmol) of *p*-toluenesulphonic acid monohydrate and 3 mL of methanol were added and the reaction mixture was stirred at the r.t. for 4 h. After complete conversion of ynone to furan (TLC), the reaction mixture was diluted with saturated solution of $NaHCO_3$ (20 mL) and Na_2SO_3 (20 mL), and extracted with dichloromethane (5×20 mL). The combined organic layers were dried with sodium sulfate, evaporated and applied to column chromatography on the neutral aluminium oxide eluting with hexane-ethylacetate (12:1) to give the analytically pure 3-chloro-4-iodofurans **22** as oils or solids (crystallization was achieved from hexane) (see Table 45 for experimental details).

Table 45. Experimental Details for the Synthesis of 3-Chloro-4-iodofurans

Acid Chloride **6**	Alkyne **1**	Product **22** (Yield %)	Eluent
141mg of **6f**	141 mg of **1k**	160 mg (52%) of **22a**	HE:EA 9:1 R_f = 0.75
171 mg of **6a**	168 mg of **1l**	232 mg (64%) of **22b**	HE:EA 9:1 R_f = 0.62
167 mg of **6i**	168 mg of **1l**	205 mg (57%) of **22c**	HE:EA 9:1 R_f = 0.81
171 mg of **6a**	247 mg of **1m**	226 mg (51%) of **22d**	HE:EA 6:1 R_f = 0.79
186 mg of **6b**	141 mg of **1k**	107 mg (31%) of **22e**	HE:EA 6:1→4:1
171 mg of **6a**	141 mg of **1k**	140 mg (42%) of **22f**	HE:EA 15:1
147 mg of **6e**	141 mg of **1k**	98 mg (31%) of **22g**	HE:EA 20:1

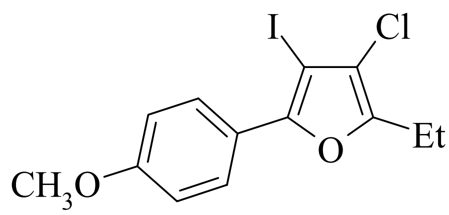
4-Chloro-3-iodo-2-phenyl-furan (22a)



Colorless oil. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.41-7.56 (m, 3H), 7.97-8.02 (m, 3H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 67.9 (C_{quat}), 123.5 (C_{quat}), 127.0 (CH), 129.4 (CH), 129.8

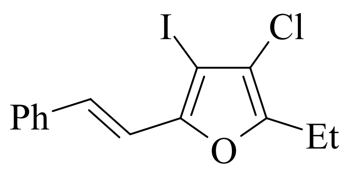
(CH), 130.5 (C_{quat}), 139.6 (CH), 153.5 (C_{quat}). EI + MS (*m/z* (%)): 306 (M^+ (^{37}Cl), 31), 304 (M^+ (^{35}Cl), 100), 179 ($(M-I)^+$ (^{37}Cl), 9), 177 ($(M-I)^+$ (^{35}Cl), 26). IR (KBr): ṽ 3149, 1522, 1480, 1444, 1209, 1147, 1053, 1027, 978, 907, 764, 690, 668, 593 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 276 nm (13700), 288 (12200), 302 (7150). Calc. HRMS for $C_{10}H_6O^{37}ClI$: 305.9122. Found: 305.9127. Calc. HRMS for $C_{10}H_6O^{35}ClI$: 303.9152. Found: 303.9154.

3-Chloro-2-ethyl-4-iodo-5-(4-methoxy-phenyl)-furan (22b)



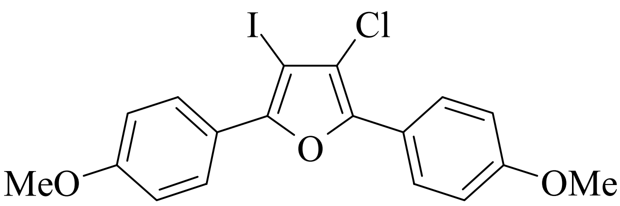
Yellow oil. ^1H NMR (acetone-d_6, 300 MHz): δ 1.26 (t, J = 7.6 Hz, 3H), 2.80 (q, J = 7.6 Hz, 2H), 3.86 (s, 3H), 7.05 (d, J = 9.1 Hz, 2H), 7.90 (d, J = 9.1 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 12.2 (CH_3), 20.2 (CH_2), 55.7 (CH_3), 66.2 (C_{quat}), 114.8 (CH), 117.6 (C_{quat}), 123.4 (C_{quat}), 126.7 (C_{quat}), 128.4 (CH), 152.2 (C_{quat}), 161.0 (C_{quat}). EI + MS (*m/z* (%)): 364 (M^+ (^{37}Cl), 37), 362 (M^+ (^{35}Cl), 100), 349 ($(M-CH_3)^+$ (^{37}Cl), 19), 345 ($(M-CH_3)^+$ (^{35}Cl), 57), 237 ($(M-I)^+$ (^{37}Cl), 8), 235 ($(M-I)^+$ (^{35}Cl), 25). Calc. HRMS for $C_{13}H_{12}O_2{}^{37}ClI$: 363.9541. Found: 363.9521. Calc. HRMS for $C_{13}H_{12}O_2{}^{35}ClI$: 361.9571. Found: 361.9561.

3-Chloro-2-ethyl-4-iodo-5-styryl-furan (22c)



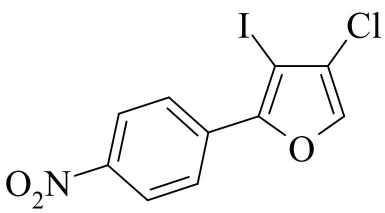
Yellow oil. ^1H NMR (acetone-d_6, 300 MHz): δ 1.27 (t, J = 7.7 Hz, 3H), 2.80 (q, J = 7.7 Hz, 2H), 6.97 (d, J = 16.5 Hz, 1H), 7.18 (d, J = 16.5 Hz, 1H), 7.27-7.34 (m, 1H), 7.36-7.42 (m, 2H), 7.59-7.64 (m, 2H).^{13}C NMR (acetone-d_6, 75 MHz): δ 12.0 (CH_3), 20.2 (CH_2), 72.2 (C_{quat}), 115.4 (CH), 117.4 (C_{quat}), 127.4 (CH), 129.0 (CH), 129.6 (CH), 130.3 (CH), 137.2 (C_{quat}), 152.0 (C_{quat}), 153.3 (C_{quat}). EI +Q1MS (*m/z* (%)): 360 (M^+ (^{37}Cl), 37), 358 (M^+ (^{35}Cl), 100), 345 ($(M-CH_3)^+$ (^{37}Cl), 17), 343 ($(M-CH_3)^+$ (^{35}Cl), 42). IR (KBr): ṽ 2975, 2936, 1586, 1493, 1458, 1447, 1319, 1268, 1092, 1062, 990, 954, 749, 691, 595 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε):310 nm (15800), 326 nm (26300), 338 nm (32100), 356 nm (23700). Calc. HRMS for $C_{14}H_{12}O^{37}ClI$: 359.9591. Found: 359.9609. Calc. HRMS for $C_{14}H_{12}O^{35}ClI$: 357.9621. Found: 357.9627.

3-Chloro-4-iodo-2,5-bis-(4-methoxy-phenyl)-furan (22d)



Colorless crystals, Mp. 129 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.86 (s, 3H), 3.87 (s, 3H), 7.04-7.11 (m, 4H), 7.93 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.6 (CH_3), 55.7 (CH_3), 69.0 (C_{quat}), 114.8 (CH), 115.0 (CH), 116.9 (C_{quat}), 122.1 (C_{quat}), 123.0 (C_{quat}), 147.4 (C_{quat}), 151.2 (C_{quat}), 160.8 (C_{quat}), 161.1 (C_{quat}). EI +Q1MS (*m/z* (%)): 442 (M^+ (^{37}Cl), 28), 440 (M^+ (^{35}Cl), 100), 427 ($(M\text{-}CH_3)^+$ (^{37}Cl), 5), 425 ($(M\text{-}CH_3)^+$ (^{35}Cl), 18), 313 ($(M\text{-}I)^+$ (^{35}Cl), 1), 285 ($(M - COI)^+$ (^{37}Cl), 24), 283 ($(M\text{-} COI)^+$ (^{35}Cl), 77), 135 (p-$MeOC_6H_4CO^+$, 48). IR (KBr): ṽ 1613, 1504, 1495, 1299, 1284, 1250, 1180, 1086, 1029, 940, 828 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 260 nm (23700), 324 nm (26200). Anal. calc. For $C_{18}H_{14}ClIO_3$ (440.67): C 49.06, H 3.20. Found: C 48.74, H 3.30.

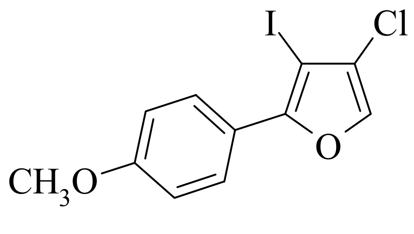
4-Chloro-3-iodo-2-(4-nitro-phenyl)-furan (22e)



Yellow crystals, Mp. 105-106 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.12 (s, 1H), 8.28 (d, J = 9.2 Hz, 2H), 8.37 (d, J = 9.2 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 71.9 (C_{quat}), 124.5 (C_{quat}), 124.7 (CH), 127.3 (CH), 136.0 (C_{quat}), 141.2 (CH), 148.3 (C_{quat}), 151.2 (C_{quat}). EI + MS (*m/z* (%)): 351 (M^+ (^{37}Cl), 31), 349 (M^+ (^{35}Cl), 100), 321 ($(M\text{-}NO)^+$ (^{37}Cl), 4), 319 ((M-

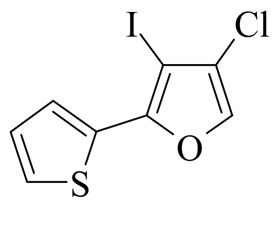
$NO)^+$ (^{35}Cl), 12), 224 ($(M-I)^+$ (^{37}Cl), 7), 222 ($(M-I)^+$ (^{35}Cl), 21). IR (KBr): $\tilde{\nu}$ 1598, 1509, 1338, 910, 852 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 240 nm (9900), 350 (18500). Anal. calc. For $C_{10}H_5ClINO_3$ (349.51): C 34.37, H 1.44, N 4.01. Found: C 34.48, H 1.60, N 3.98.

4-Chloro-3-iodo-2-(4-methoxy-phenyl)-furan (22f)



Colorless crystals, Mp. 53-54 °C. ^1H NMR (acetone-d_6, 300 MHz): δ 3.68 (s, 3H), 6.88 (d, J = 9.1 Hz, 2H), 7.73 (s, 1H), 7.72 (d, J = 9.1 Hz, 2H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.7 (CH_3), 66.3 (C_{quat}), 114.9 (CH), 123.1 (C_{quat}), 123.3 (C_{quat}), 128.7 (CH), 139.0 (CH), 148.1 (C_{quat}), 161.2 (C_{quat}). EI + MS (m/z (%)): 336 (M^+ (^{37}Cl), 31), 334 (M^+ (^{35}Cl), 100), 209 ($(M-I)^+$ (^{37}Cl), 7), 207 ($(M-I)^+$ (^{35}Cl), 21), 181 ($(M-COI)^+$ (^{37}Cl), 30), 179 ($(M-COI)^+$ (^{35}Cl), 94). IR (KBr): $\tilde{\nu}$ 3101, 2973, 2859, 1610, 1528, 1489, 1256, 1179, 1022, 841 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 282 nm (18000). Anal. calc. For $C_{11}H_8ClIO_2$ (334.54): C 39.49, H 2.41. Found: C 39.86, H 2.55.

4-Chloro-3-iodo-5-thiophen-2-yl-furan (22g)



Colorless oil. ^1H NMR (CD_2Cl_2, 300 MHz): δ 7.18 (dd, J = 5.1 Hz, J = 3.7 Hz, 1H), 7.46 (dd, J = 5.1 Hz, J = 1.1 Hz, 1H), 7.56 (s, 1H), 7.76 (dd, J = 3.7 Hz, J = 1.1 Hz, 1H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 67.0 (C_{quat}), 123.2 (C_{quat}), 126.0 (CH), 126.5 (CH), 127.8 (CH), 131.8 (C_{quat}), 137.6 (CH), 150.4 (C_{quat}). EI + MS (m/z (%)): 312 (M^+ (^{37}Cl), 31), 310 (M^+ (^{35}Cl), 100), 185 ($(M-I)^+$ (^{37}Cl), 10), 183 ($(M-I)^+$ (^{35}Cl), 26), 157 ($(M-COI)^+$ (^{37}Cl), 17), 155 ($(M-COI)^+$ (^{35}Cl), 30). IR (KBr): $\tilde{\nu}$ 3148, 3106, 1578, 1535, 1421, 1314, 1247, 1038, 970, 746, 589 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 298 nm (14500), 308 nm (15100), 326 nm (8900). Calc.

HRMS for $C_8H_4O^{37}ClIS$: 311.8686. Found: 311.8716. Calc. HRMS for $C_8H_4O^{35}ClIS$: 309.8716. Found: 309.8723.

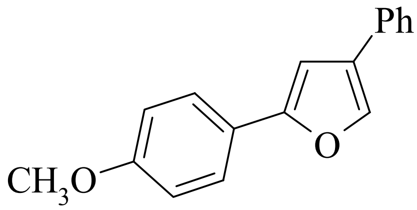
6.18 General Procedure for the 2,3,5-Trisubstituted Furan Synthesis

In a screw cap pressure vessel 35 mg (0.05 mmol) of $Pd(PPh_3)_2Cl_2$, and 7 mg (0.04 mmol) of CuI were dissolved in a 5 mL of degassed THF. Then 1.00 mmol of acid chloride **6**, 1.00 mmol of THP protected propargylic alcohol **1**, as well as 0.14 mL (1.00 mmol) of triethylamine were successively added to the solution. The reaction mixture was stirred for 2 h at the room temperature until the conversion was complete (monitored by TLC). Afterwards 750 mg (5.00 mmol) of sodium iodide, 209 mg (1.10 mmol) of *p*-toluenesulphonic acid monohydrate and 3 mL of methanol were added and the reaction mixture was stirred at the r.t. for 2 h. After complete conversion of ynone to β-iodofuran (TLC), 4 mL of 2 M solution of sodium carbonate (8 mmol) and 1.05 mmol of boronic acid **23** were added and the reaction mixture was heated at 90 °C for 24-50 h. Then the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried with sodium sulfate, evaporated and applied to column chromatography on the silica gel eluting with hexane-ethylacetate (20:1 → 9:1) to give the analytically pure 2,3,5-trisubstituted furans **24** as oils or solids (crystallization was achieved from hexane) (see Table 46 for experimental details).

Table 46. Experimental Details for the Synthesis of 2,3,5-Trisubstituted furans

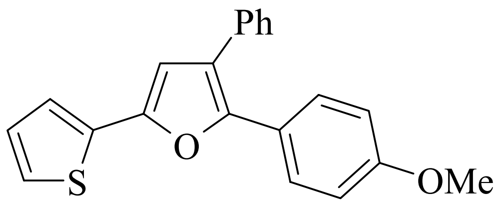
Acid Chloride **6**	Alkyne **1**	Boronic acid **23**	Product **25** (Yield %)	Eluent
171 mg of **6a**	141 mg of **1k**	128 mg of **23a**	115 mg (50%) of **24a**	HE:EA 9:1 $R_f = 0.42$
147 mg of **6e**	247 mg of **1m**	128 mg of **23a**	174 mg (52%) of **24b**	HE:EA 9:1 $R_f = 0.62$
167 mg of **6i**	168 mg of **1l**	137 mg of **23b**	117 mg (42%) of **24c**	HE:EA 20:1
107 mg of **6m**	141 mg of **1k**	188 mg of **23c**	122 mg (52%) of **24d**	HE:EA 20:1 $R_f = 0.62$

2-(4-Methoxy-phenyl)-4-phenyl-furan (24a)



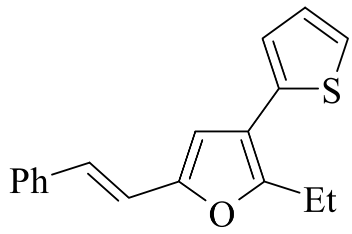
Colorless solid, Mp 129 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.84 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 0.7 Hz, 1H), 7.24-7.31 (m, 1H), 7.36-7.44 (m, 2H), 7.63-7.68 (m, 2H), 7.72 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 0.7 Hz, 1H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 55.6 (CH_3), 103.3 (CH), 115.1 (CH), 124.5 (C_{quat}), 126.1 (CH), 126.5 (CH), 127.8 (CH), 129.3 (C_{quat}), 129.6 (CH), 133.4 (C_{quat}), 138.6 (CH), 155.8 (C_{quat}), 160.4 (C_{quat}). EI +Q1MS (*m/z* (%)): 250 (M^+, 100), 235 ($(M-CH_3)^+$, 14), 221 ($(M-CHO)^+$, 15). IR (KBr): $\tilde{\nu}$ 1611, 1500, 1251, 1179, 1037, 1023, 913, 838, 804, 749, 692 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 248 nm (15300), 280 nm (23600), 290 nm (20800). Anal calc. for $C_{17}H_{14}O_2$ (250.30): C 81.58, H 5.64. Found: C 81.20, H 5.63.

2-(4-Methoxy-phenyl)-3-phenyl-5-thiophen-2-yl-furan (24b)



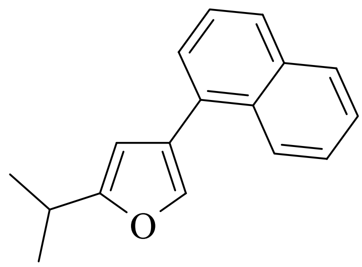
Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 3H), 6.68 (s, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 5.1, J = 3.7, 1H), 7.23-7.27 (m, 1H), 7.31-7.42 (m, 4H), 7.44-7.49 (m, 2H), 7.54 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.1 (CH_3), 109.0 (CH), 113.7 (CH), 122.3 (CH), 122.8 (C_{quat}), 123.5 (C_{quat}), 123.9 (CH), 127.0 (CH), 127.51 (CH), 127.54 (CH), 128.43 (CH), 128.47 (CH), 133.5 (C_{quat}), 134.0 (C_{quat}), 147.5 (C_{quat}), 147.57 (C_{quat}), 159.0 (C_{quat}). EI +Q1MS (*m/z* (%)): 332 (M^+, 100), 317 ($(M-CH_3)^+$, 31). IR (KBr): $\tilde{\nu}$ 3108, 3069, 2930, 2834, 1641, 1515, 1300, 1253, 1138, 1049, 834, 765, 698 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 272 nm (12900), 308 nm (16200), 338 nm (19100). Calc. HRMS for $C_{21}H_{16}O_2S$: 332.0871. Found: 332.0860.

2-Ethyl-5-styryl-3-thiophen-2-yl)-furan (24c)



Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, J = 7.5 Hz, 3H), 2.94 (q, J = 7.4 Hz, 2H), 6.50 (s, 1H), 6.87 (d, J = 16.5, 1H), 7.02-7.10 (m, 3H), 7.23-7.30 (m, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.50 (d, J = 7.0 Hz, 2 H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5 (CH_3), 20.7 (CH_2), 109.6 (CH), 116.0 (CH), 116.1 (C_{quat}), 123.5 (CH), 123.6 (CH), 126.1 (CH), 126.5 (CH), 127.2 (CH), 127.3 (CH), 128.5 (CH), 135.5 (C_{quat}), 136.9 (C_{quat}), 150.9 (C_{quat}), 152.8 (C_{quat}). EI +Q1MS (*m/z* (%)): 282 (M^+, (^{34}S), 6), 280 (M^+, (^{32}S), 100), 267 ($(M-CH_3)^+$, (^{34}S), 10), 265 ($(M-CH_3)^+$, (^{32}S), 69), 223 ($(M-C_3H_5CO)^+$, 11).

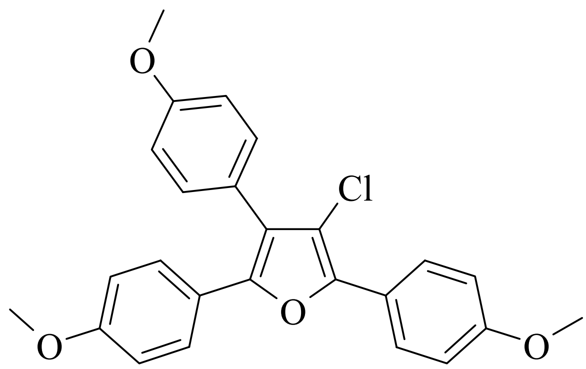
2-Isopropyl-4-naphthalen-1-yl-furan (24d)



Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (d, J = 7.0 Hz, 6H), 3.06 (sptd, J = 7.0 Hz, J = 0.7 Hz, 1H), 6.32 (d, J = 1.1 Hz, 1H), 7.45-7.53 (m, 4H), 7.55 (d, J = 1.1 Hz, 1H), 7.79-7.85 (m, 1H), 7.86-7.93 (m, 1H), 8.19-8.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9 (CH_3), 27.8 (CH), 105.5 (CH), 124.9 (C_{quat}), 125.2 (CH), 125.56 (CH), 125.58 (CH), 125.8 (CH), 126.4 (CH), 127.3 (CH), 128.2 (CH), 131.2 (C_{quat}), 131.6 (C_{quat}), 133.7 (C_{quat}), 138.2 (CH), 161.8 (C_{quat}). EI +Q1MS (*m/z* (%)): 236 (M^+, 100), 221 ($(M-CH_3)^+$, 93), 193 (M^+ - C_2H_3O, 15), 178 (M^+ - C_3H_6O, 15). IR (KBr): $\tilde{\nu}$ 3046, 2966, 2877, 1590, 1544, 1502, 1458, 1385, 1149, 1125, 936, 930, 799, 777, 653 cm^{-1}. UV/Vis (CH_2Cl_2): λ_{max} (ε): 294 nm (6900). Calc. HRMS for $C_{17}H_{16}O$: 236.1201. Found: 236.1190.

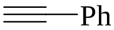
6.19 Synthesis of 3-Chloro-2,4,5-tris-(4-methoxy-phenyl)-furan (25)

In a screw cap pressure vessel 35 mg (0.05 mmol) of $Pd(PPh_3)_2Cl_2$, and 441 mg (1.00 mmol) of 3-chloro-4-iodo-2,5-bis-(4-methoxy-phenyl)-furan (**22d**) were dissolved in a mixture of 5 mL of degassed THF and 5 mL of degassed methanol. Then 4 mL of 2 M solution of sodium carbonate (8.00 mmol) and 160 mg (1.05 mmol) of *p*-methoxyphenylboronic acid (**23d**) were added and the reaction mixture was heated at 90 °C for 24 h. Then the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried over sodium sulfate, evaporated and applied to column chromatography on the neutral aluminium oxide eluting with hexane-ethylacetate (9:1) to give 226 mg (51%) of **25** as a colorless solid.



Colorless solid, Mp 128 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.74 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 6.92 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 9.2 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.08 (CH_3), 55.14 (CH_3), 55.23 (CH_3), 111.9 (C_{quat}), 114.2 (CH), 114.38 (CH), 114.41 (CH), 121.18 (C_{quat}), 121.35 (C_{quat}), 122.18 (C_{quat}), 122.53 (C_{quat}), 125.8 (C_{quat}), 126.32 (CH), 126.63 (CH), 131.2 (CH), 145.0 (C_{quat}), 146.5 (C_{quat}), 159.07 (C_{quat}), 159.08 (C_{quat}), 159.12 (C_{quat}). EI +Q1MS (*m/z* (%)): 422 (M^+, (^{37}Cl), 22), 420 (M^+ (^{35}Cl), 100), 407 ($(M\text{-}CH_3)^+$, (^{37}Cl), 5), 405 ($(M\text{-}CH_3)^+$, (^{35}Cl), 18), 135 ($CH_3OC_6H_4CO^+$, 17). IR (KBr): 1612, 1598, 1519, 1505, 1463, 1441, 1298, 1291, 1277, 1251, 1176, 1079, 1032, 945, 833. UV/Vis (CH_2Cl_2): λ_{max} (ε): 268 nm (22300), 322 nm (15300), 334 nm (26300). Anal calc. for $C_{25}H_{21}ClO_4$ (420.90): C 71.34, H 5.03, Cl 8.42. Found: C 70.96, H 5.05, Cl 8.72.

7 Molecule Contents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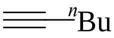
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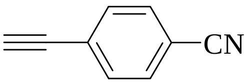
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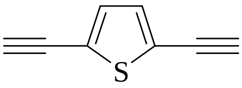
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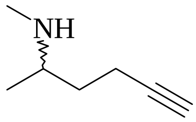
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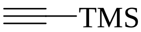
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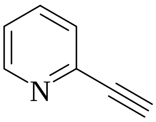
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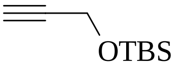
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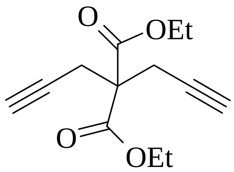
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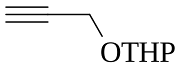
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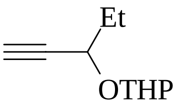
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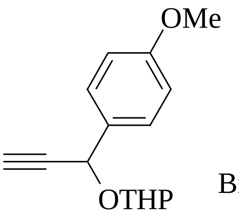
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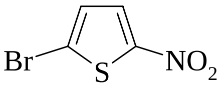
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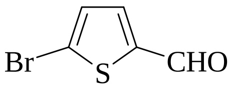
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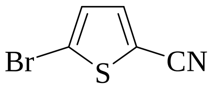
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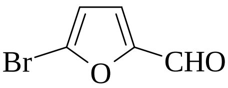
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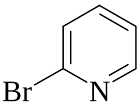
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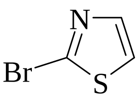
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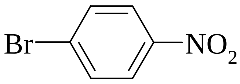
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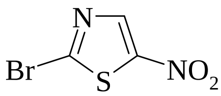
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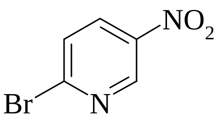
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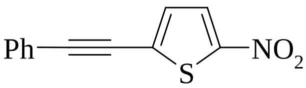
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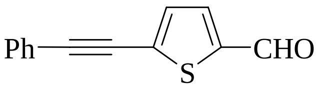
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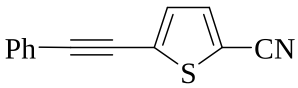
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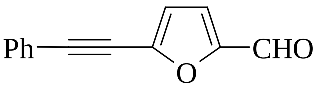
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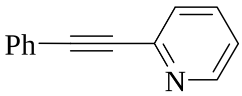
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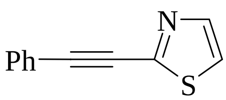
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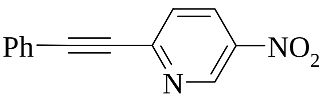
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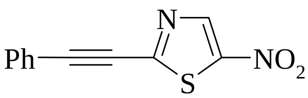
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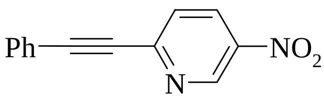
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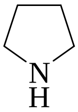
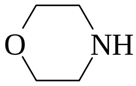


4a

Et_2NH

4b



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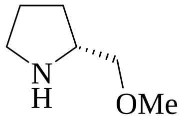


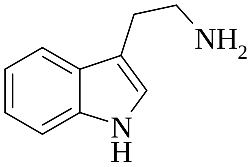
4d

$^{n}BuNH_2$

4e

$BnNH_2$

4f



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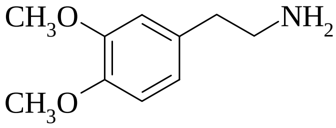

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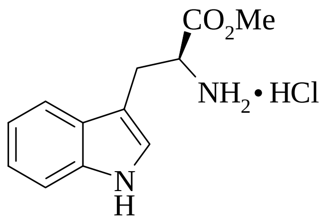

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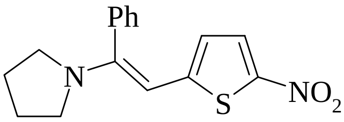

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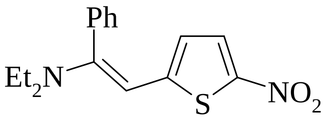

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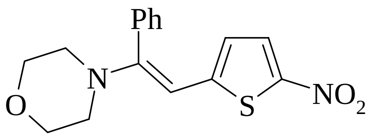

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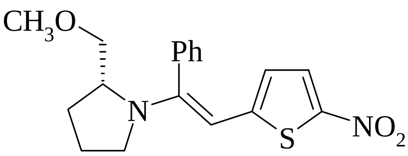

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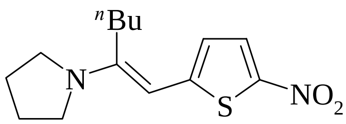

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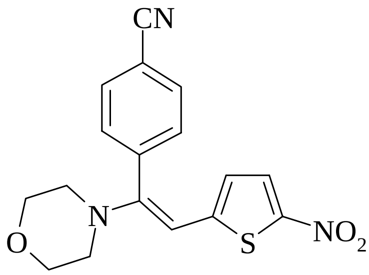

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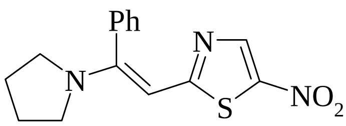

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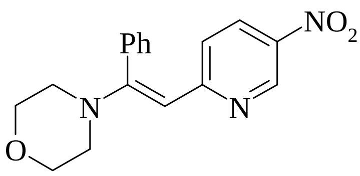

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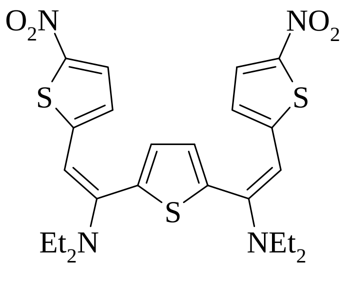

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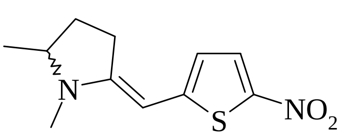

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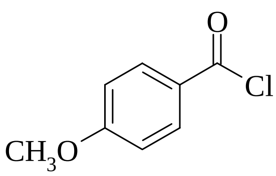

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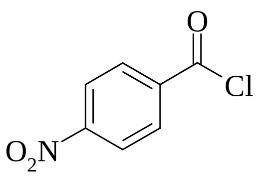

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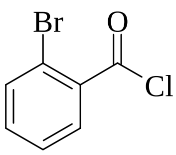

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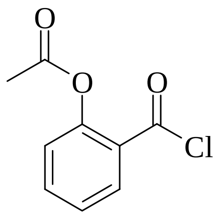
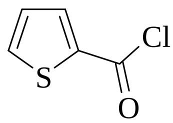
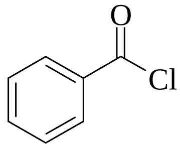
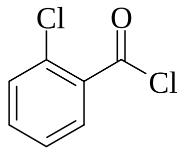
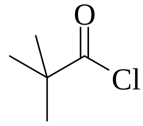
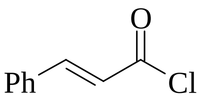
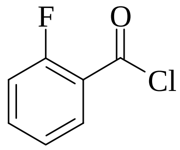
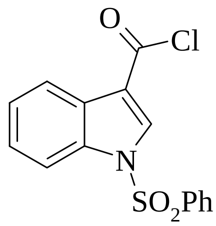
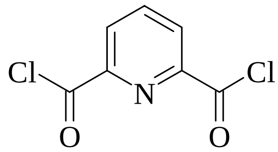
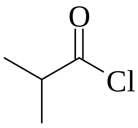
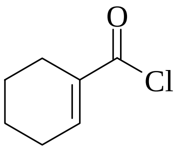
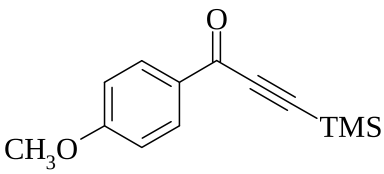
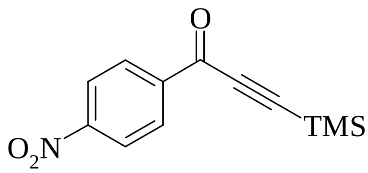






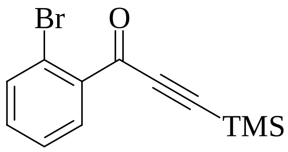
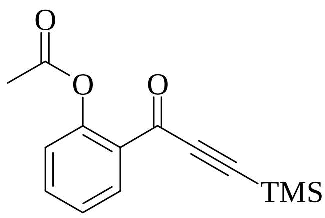
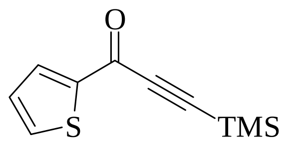
6d **6e** **6f** **6g** **6h**

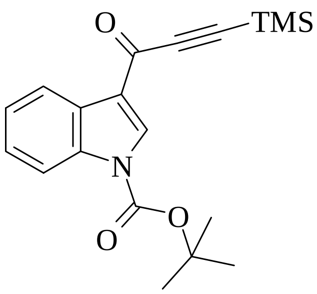
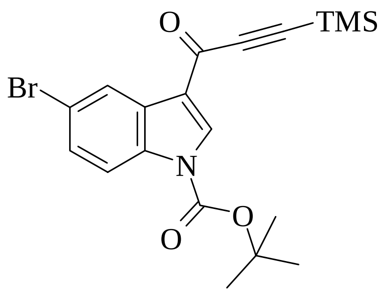
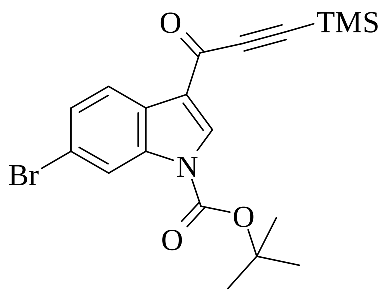
6i **6j** **6k** **6l**

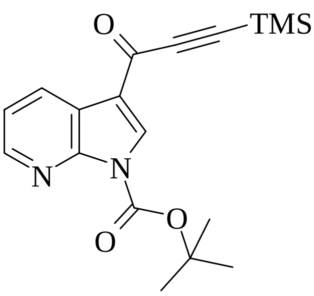
6m **6n** **7a** **7b**

7c **7d** **7e**

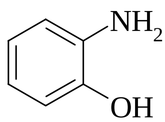
7f **7g** **7h**



7i

$NH_2OH{\bullet}HCl$

8a



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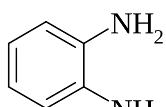
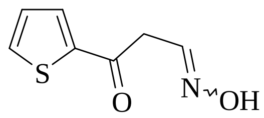


8c



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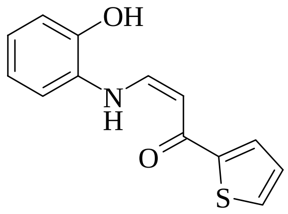

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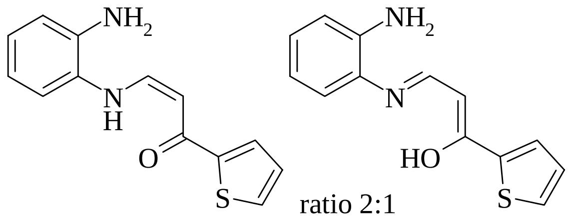

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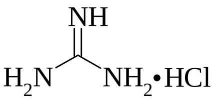

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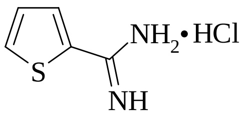

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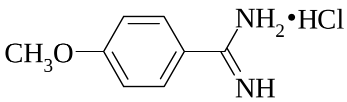

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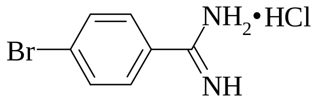

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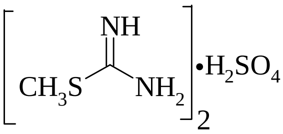

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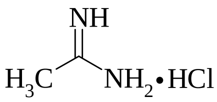

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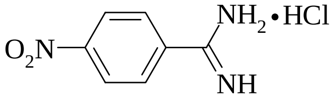
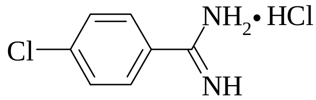
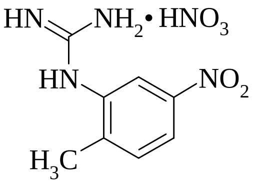


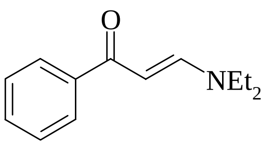
10g



10h



10i



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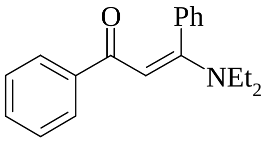

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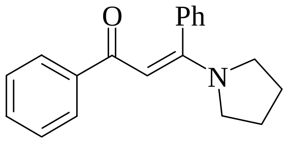

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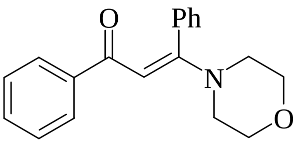

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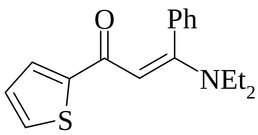

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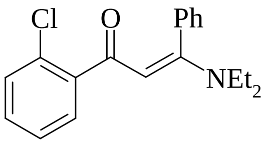

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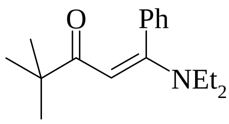

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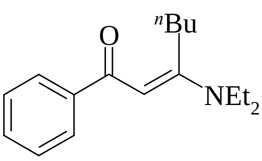

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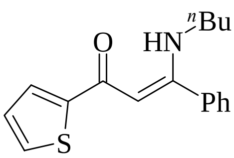

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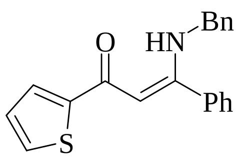

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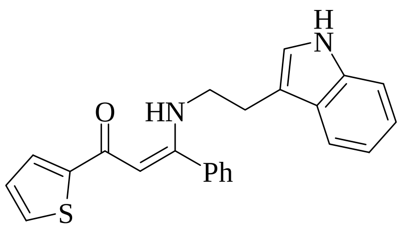

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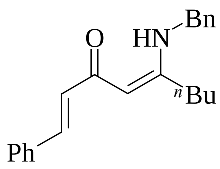

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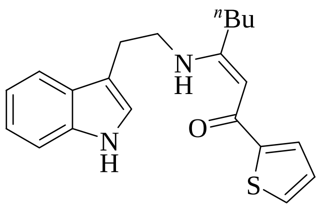

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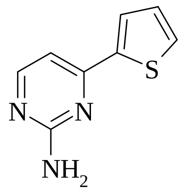

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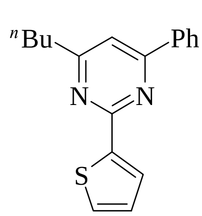

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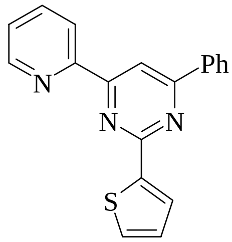

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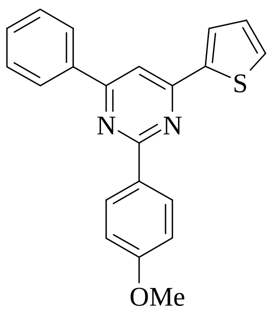

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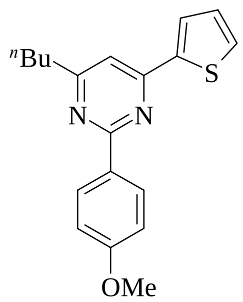

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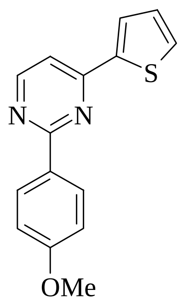

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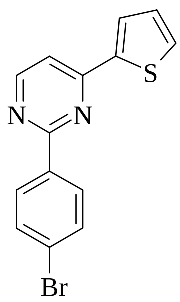

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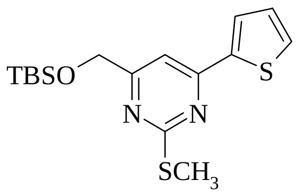

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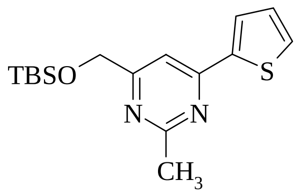

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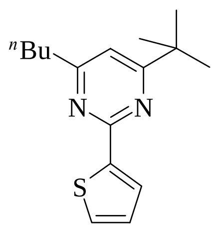

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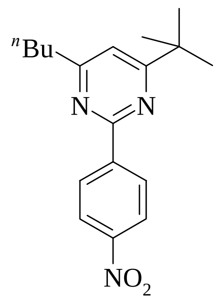

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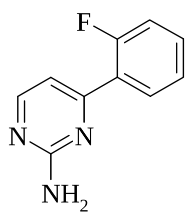

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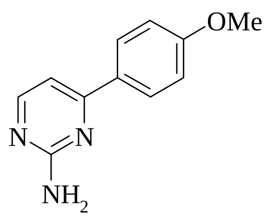

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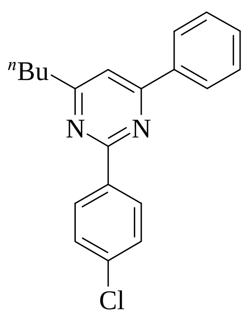

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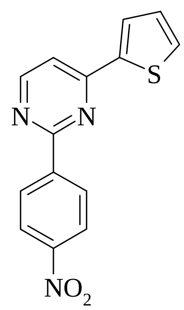

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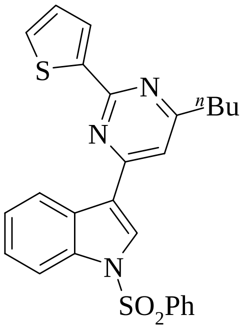

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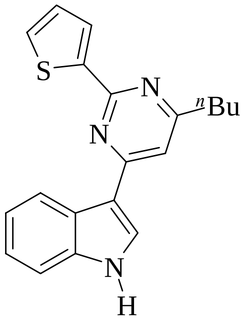

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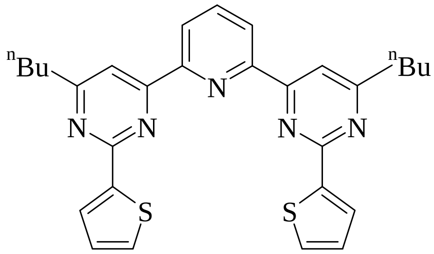

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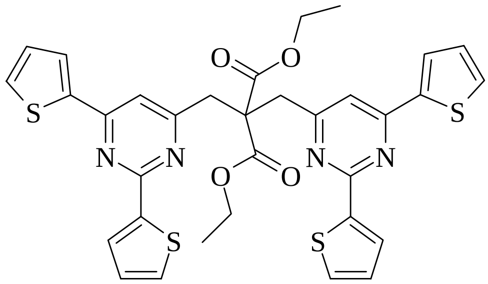

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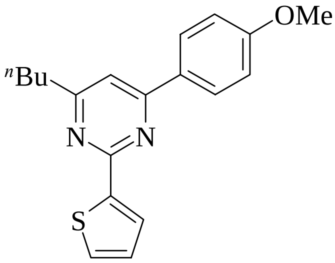

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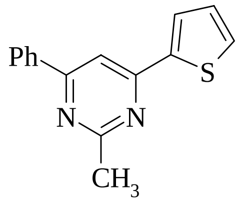

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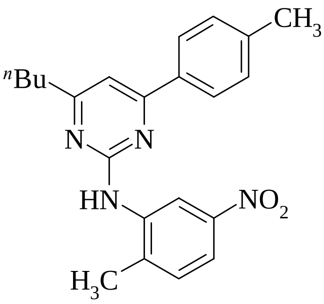

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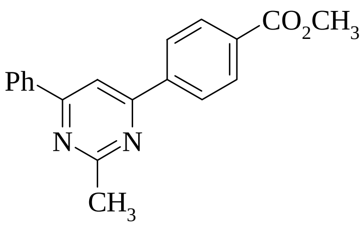

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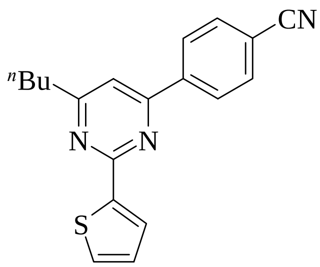

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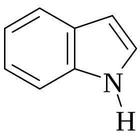

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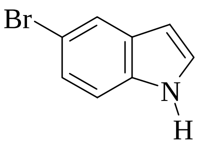

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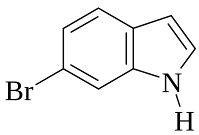

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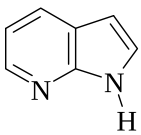

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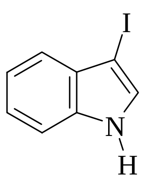

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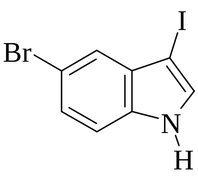

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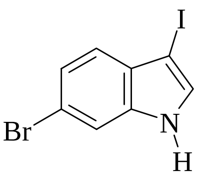

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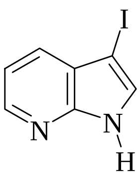

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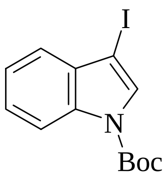

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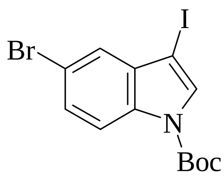

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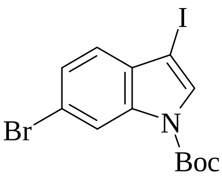

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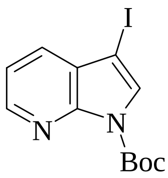

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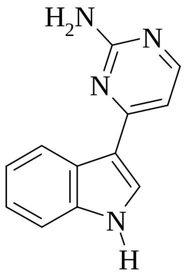

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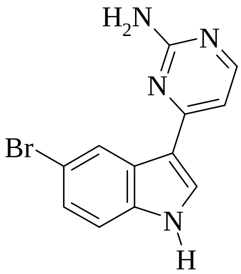

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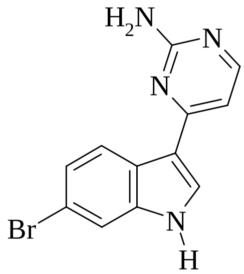

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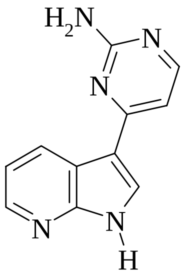

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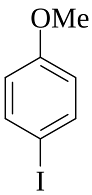

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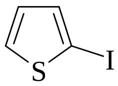

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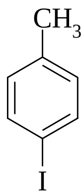

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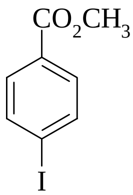

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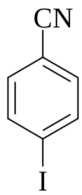

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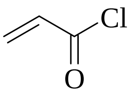

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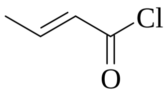

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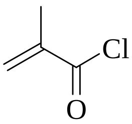

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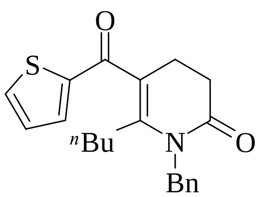

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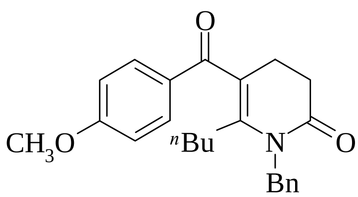

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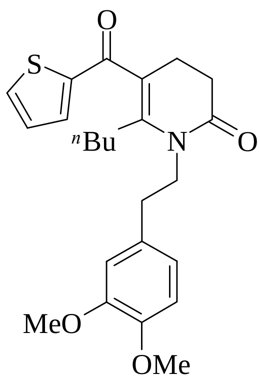

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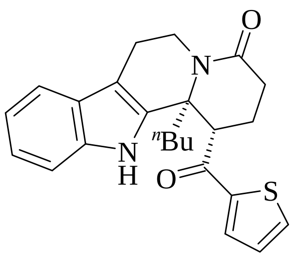

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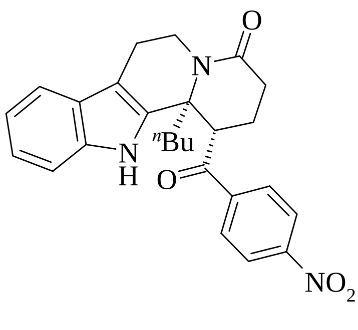

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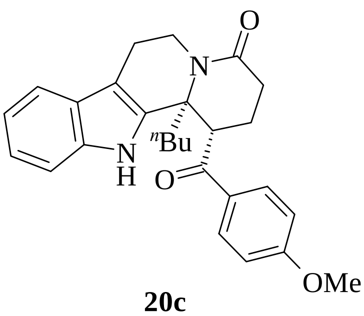

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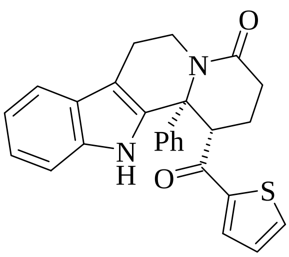

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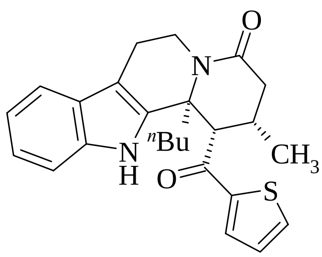

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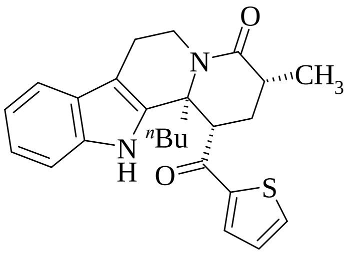

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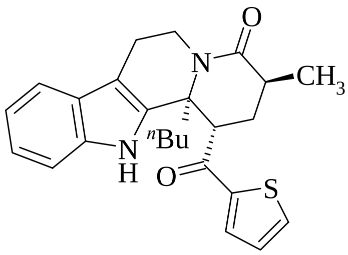

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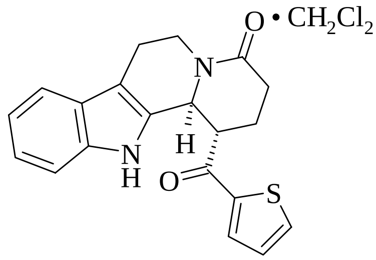

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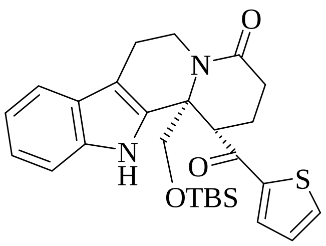

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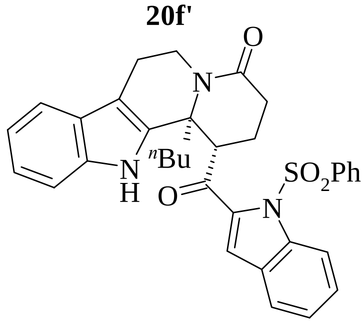

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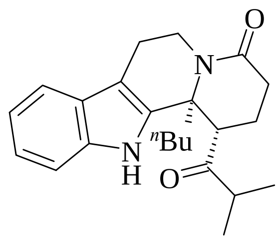

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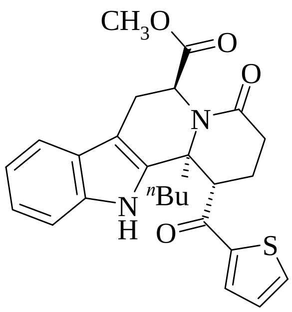

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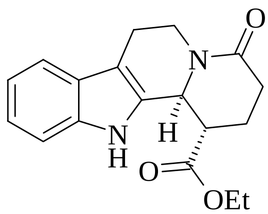

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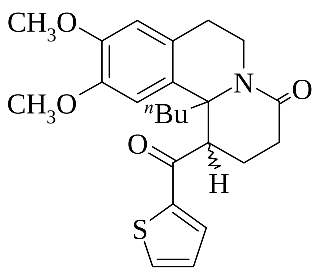

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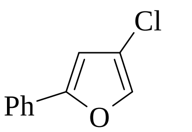

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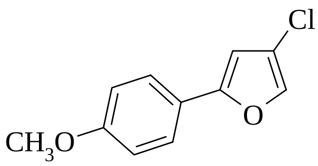

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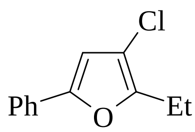

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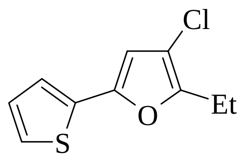

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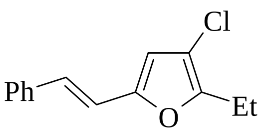

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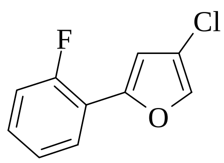

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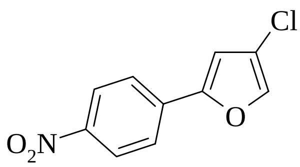

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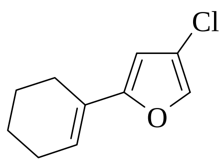

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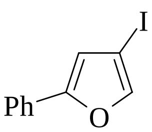

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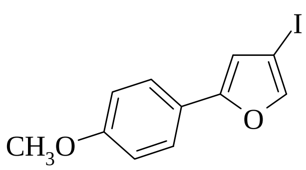

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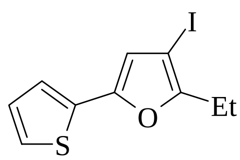

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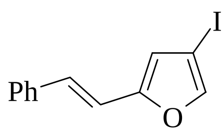

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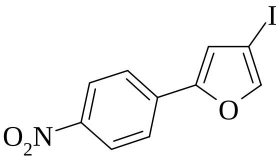

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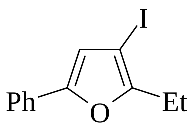

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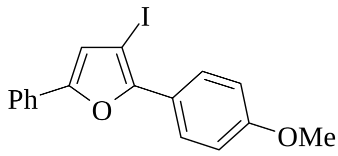

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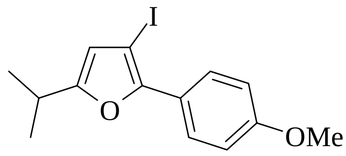

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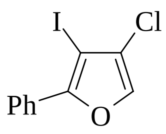

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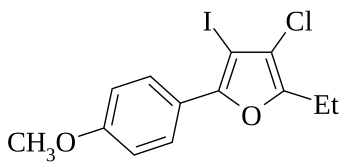

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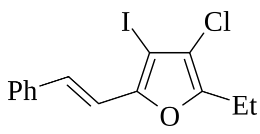

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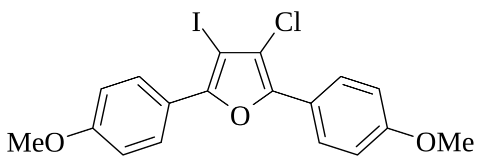

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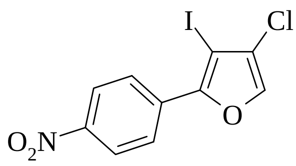

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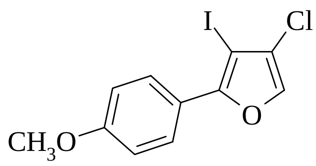

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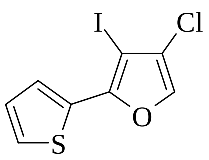

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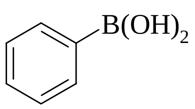

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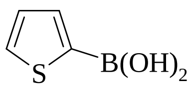

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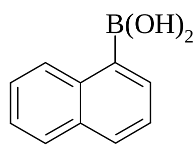

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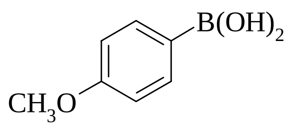

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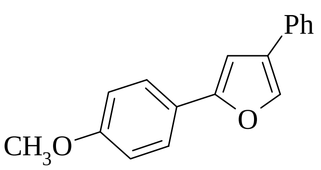

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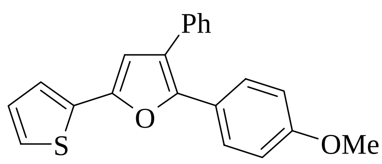

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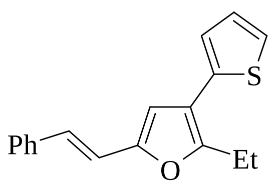

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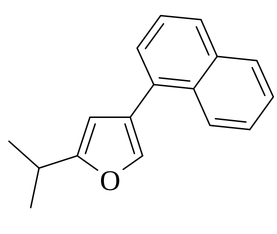

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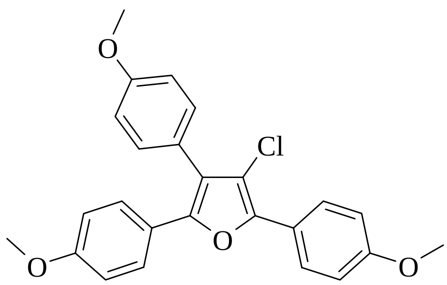

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8 Crystal Data

Table 47. Crystal Data and Structure Refinement for (*E*)-1-[2-(5-nitrothien-2-yl)-1-phenyl-vinyl] pyrrolidine 5a

Empirical Formula	$C_{16}H_{16}N_2O_2S$
Formula Weight	300.37
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 9.1983(2) Å α = 90 °.
	b = 13.5431(3) Å β = 92.909(1) °.
	c = 12.1129(2) Å γ = 90 °.
Volume	1507.00(5) $Å^3$
Z	4
Density (calculated)	1.32 g/cm^3
Absorption coefficient	0.22 mm^{-1}
Crystal size	0.57 x 0.08 x 0.08 mm
θ_{min} / θ_{max}	2.3 to 27.5 °.
Reflections collected	15325
Independent reflections	3451 [R(int) = 0.0391]
Absorption correction	semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3451/ 0 /190
Goodness-of-fit on F^2	1.03
Final R indices ($I>2\sigma(I)$)	R_1 = 0.035 and R_2 = 0.077
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.29 and -0.24 eA^{-3}

Table 48. Crystal Data and Structure Refinement for (*E*)-Diethyl-[2-(5-nitrothien-2-yl)-1-phenyl-vinyl] amine 5b

Empirical Formula	$C_{16}H_{18}N_2O_2S$	
Formula Weight	302.38	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.2306(1) Å	α = 90 °.
	b = 12.6911(3) Å	β = 107.121(1) °.
	c = 13.6270(3) Å	γ = 90 °.
Volume	1525.61(5) $Å^3$	
Z	4	
Density (calculated)	1.32 g/cm^3	
Absorption coefficient	0.22 mm^{-1}	
Crystal size	0.35 x 0.21 x 0.18 mm	
θ_{min} / θ_{max}	1.6 to 24.1 °.	
Reflections collected	12245	
Independent reflections	4843 [R(int) = 0.0679]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.9618 and 0.9276	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4843/ 1 /383	
Goodness-of-fit on F^2	1.05	
Final R indices (I>2σ(I))	R_1 = 0.058 and R_2 = 0.130	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.45 and -0.56 eA^{-3}	

Table 49. Crystal Data and Structure Refinement for (*E*)-4-[2-(5-nitrothien-2-yl)-1-phenyl-vinyl] morpholine 5c

Empirical Formula	$C_{16}H_{16}N_2O_3S$	
Formula Weight	316.38	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.4125(1) Å	α = 98.318(1) °.
	b = 10.9522(1) Å	β = 99.741(1) °.
	c = 15.4517(2) Å	γ = 99.615(1) °.
Volume	1523.15(3) $Å^3$	
Z	4	
Density (calculated)	1.37 g/cm^3	
Absorption coefficient	0.22 mm^{-1}	
Crystal size	0.39 x 0.30 x 0.21 mm	
θ_{min} / θ_{max}	1.9 to 27.5 °.	
Reflections collected	15977	
Independent reflections	6915 [R(int) = 0.0281]	
Absorption correction	semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	6915/ 1 /397	
Goodness-of-fit on F^2	1.03	
Final R indices (I>2σ(I))	R_1 = 0.045 and R_2 = 0.127	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.61 and -0.37 eA^{-3}	

Table 50. Crystal Data and Structure Refinement for (*E,E*)-2,5-Bis[2-(5-nitrothien-2-yl)-1-diethylamino-vinyl] thiophene 5i

Empirical Formula	$C_{24}H_{28}N_4O_4S_3$
Formula Weight	532.68
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.8981(4) Å α = 90 °.
	b = 9.4414(4) Å β = 112.067(2) °.
	c = 12.3127(5) Å γ = 90 °.
Volume	1281.82(9) $Å^3$
Z	2
Density (calculated)	1.38 g/cm^3
Absorption coefficient	0.33 mm^{-1}
Crystal size	0.52 x 0.06 x 0.02 mm
θ_{min} / θ_{max}	1.8 to 24.1 °.
Reflections collected	10266
Independent reflections	4075 [R(int) = 0.0632]
Absorption correction	none
Max. and min. transmission	0.9935 and 0.8482
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4075/ 34 /325
Goodness-of-fit on F^2	0.98
Final R indices ($I>2\sigma(I)$)	R_1 = 0.045 and R_2 = 0.065
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.20 and -0.21 eA^{-3}

Table 51. Crystal Data and Structure Refinement for 3-(3-Trimethylsilanyl-propynoyl)-pyrrolo[2,3-b]pyridine-1-carboxylic acid *tert*-butyl ester 7i

Empirical Formula	$C_{18}H_{22}N_2O_3Si$	
Formula Weight	342.47	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.8618(5) Å	α = 107.562(1) °.
	b = 10.0262(5) Å	β = 103.513(1) °.
	c = 11.1585(6) Å	γ = 103.262(1) °.
Volume	967.76(9) Å^3	
Z	2	
Density (calculated)	1.17 g/cm^3	
Absorption coefficient	0.14 mm^{-1}	
Crystal size	0.40 x 0.30 x 0.24 mm	
θ_{min} / θ_{max}	2.0 to 26.4 °.	
Reflections collected	9354	
Independent reflections	3954 [R(int) = 0.0282]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.95	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3954/ 0 /223	
Goodness-of-fit on F^2	1.05	
Final R indices ($I>2\sigma(I)$)	R_1 = 0.045 and R_2 = 0.110	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.27 and -0.30 eA^{-3}	

Table 52. Crystal Data and Structure Refinement for 12b-Butyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one 20a

Empirical Formula	$C_{24}H_{26}N_2O_2S{*}CH_2Cl_2$
Formula Weight	491.45
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pna2_1$
Unit cell dimensions	a = 24.2176(8) Å α = 90 °.
	b = 14.5820(5) Å β = 90 °.
	c = 14.2040(5) Å γ = 90 °.
Volume	5016.0(3) $Å^3$
Z	8
Density (calculated)	1.30 g/cm^3
Absorption coefficient	0.37 mm^{-1}
Crystal size	0.34 x 0.34 x 0.18 mm
θ_{min} / θ_{max}	1.6 to 22.0 °.
Reflections collected	31357
Independent reflections	6126 [R(int) = 0.0396]
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.89
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6126/ 8/578
Goodness-of-fit on F^2	1.07
Final R indices (I>2σ(I))	R_1 = 0.059 and R_2 = 0.153
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.59 and -0.49 eA^{-3}

Table 53. Crystal Data and Structure Refinement for 12b-Butyl-1-(4-nitrophenyl-1-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one 20b

Empirical Formula	$C_{26}H_{27}N_3O_4$	
Formula Weight	445.51	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.7620(1) Å	α = 90 °.
	b = 13.0069(1) Å	β = 97.724(1) °.
	c = 14.7316(2) Å	γ = 90 °.
Volume	2233.30(4) $Å^3$	
Z	4	
Density (calculated)	1.33 g/cm^3	
Absorption coefficient	0.09 mm^{-1}	
Crystal size	0.40 x 0.34 x 0.11 mm	
θ_{min} / θ_{max}	2.1 to 27.5 °.	
Reflections collected	22678	
Independent reflections	5107 [R(int) = 0.0294]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.96	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5107/ 0/298	
Goodness-of-fit on F^2	1.03	
Final R indices ($I>2\sigma(I)$)	R_1 = 0.041 and R_2 = 0.100	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.33 and -0.27 eA^{-3}	

Table 54. Crystal Data and Structure Refinement for 12b-Butyl-1-(4-methoxyphenyl-1-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one 20c

Empirical Formula	$C_{27}H_{30}N_2O_3$	
Formula Weight	430.53	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 15.6913(1) Å	α = 90 °.
	b = 16.5338(2) Å	β = 99.574(1) °.
	c = 18.1420(2) Å	γ = 90 °.
Volume	4641.15(8) Å^3	
Z	8	
Density (calculated)	1.23 g/cm^3	
Absorption coefficient	0.08 mm^{-1}	
Crystal size	0.46 x 0.33 x 0.30 mm	
θ_{min} / θ_{max}	1.8 to 27.5 °.	
Reflections collected	23712	
Independent reflections	5323 [R(int) = 0.0371]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.96	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5323/ 2/ 300	
Goodness-of-fit on F^2	1.01	
Final R indices (I>2σ(I))	R_1 = 0.049 and R_2 = 0.120	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.22 and -0.18 eA^{-3}	

Table 55. Crystal Data and Structure Refinement for 12b-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one 20e

Empirical Formula	$C_{25}H_{28}N_2O_2S$	
Formula Weight	420.55	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.8924(2) Å	α = 90 °.
	b = 10.3918(2) Å	β = 95.472(1) °.
	c = 23.1132(4) Å	γ = 90 °.
Volume	2365.21(8) $Å^3$	
Z	4	
Density (calculated)	1.17 g/cm^3	
Absorption coefficient	0.16 mm^{-1}	
Crystal size	0.40 x 0.28 x 0.08 mm	
θ_{min} / θ_{max}	1.8 to 27.5 °.	
Reflections collected	23864	
Independent reflections	5407 [R(int) = 0.0363]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.94	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5407/ 0/ 300	
Goodness-of-fit on F^2	1.03	
Final R indices ($I>2\sigma(I)$)	R_1 = 0.041 and R_2 = 0.103	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.25 and -0.50 eA^{-3}	

Table 56. Crystal Data and Structure Refinement for 12b-Butyl-2-methyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one (major diastereomer) 20f

Empirical Formula	$C_{25}H_{28}N_2O_2S$
Formula Weight	420.55
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 8.6239(1) Å α = 90 °.
	b = 22.0514(4) Å β = 100.164(1) °.
	c = 13.2225(1) Å γ = 90 °.
Volume	2475.05(6) Å^3
Z	4
Density (calculated)	1.13 g/cm^3
Absorption coefficient	0.15 mm^{-1}
Crystal size	0.50 x 0.26 x 0.22 mm
θ_{min} / θ_{max}	1.9 to 27.5 °.
Reflections collected	25612
Independent reflections	5688 [R(int) = 0.0437]
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.97 and 0.93
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5688/ 12/ 324
Goodness-of-fit on F^2	1.04
Final R indices (I>2σ(I))	R_1 = 0.068 and R_2 = 0.191
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.65 and -0.58 eA^{-3}

Table 57. Crystal Data and Structure Refinement for (6*S*, 4*S*, 12b*S*,)-12b-Butyl-4-oxo-1-(thiophene-2-carbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-6-carboxylic acid methyl ester 20k

Empirical Formula	$C_{26}H_{28}N_2O_4S{*}CH_2Cl_2$	
Formula Weight	549.49	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.022(1) Å	α = 90 °.
	b = 14.950(1) Å	β = 94.869(2) °.
	c = 14.663(1) Å	γ = 90 °.
Volume	2625.9(4) $Å^3$	
Z	4	
Density (calculated)	1.39 g/cm^3	
Absorption coefficient	0.36 mm^{-1}	
Crystal size	0.21 x 0.15 x 0.12 mm	
θ_{min} / θ_{max}	2.0 to 26.4 °.	
Reflections collected	23151	
Independent reflections	10561 [R(int) = 0.0423]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.96 and 0.93	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	10561/ 1/ 871	
Goodness-of-fit on F^2	1.06	
Final R indices (I>2σ(I))	R_1 = 0.050 and R_2 = 0.107	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.46 and -0.24 eA^{-3}	

Table 58. Crystal Data and Structure Refinement for 4-oxo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine-1-carboxylic acid ethyl ester (major diastereomer) 20l

Empirical Formula	$C_{18}H_{20}N_2O_3$
Formula Weight	312.36
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.5257(3) Å α = 90 °.
	b = 12.9651(4) Å β = 94.770(1) °.
	c = 10.7417(3) Å γ = 90 °.
Volume	1599.59(8) $Å^3$
Z	4
Density (calculated)	1.30 g/cm^3
Absorption coefficient	0.09 mm^{-1}
Crystal size	0.42 x 0.22 x 0.16 mm
θ_{min} / θ_{max}	1.8 to 27.5 °.
Reflections collected	16235
Independent reflections	3648 [R(int) = 0.0298]
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.96
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3648/ 0/ 288
Goodness-of-fit on F^2	1.03
Final R indices ($I>2\sigma(I)$)	R_1 = 0.036 and R_2 = 0.089
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.19 and -0.24 eA^{-3}

Table 59. Crystal Data and Structure Refinement for 4-Iodo-2-(4-nitro-phenyl)-furan 21m

Empirical Formula	$C_{10}H_6INO_3$	
Formula Weight	315.06	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$	
Unit cell dimensions	a = 8.2679(1) Å	α = 84.927(1) °.
	b = 11.0675(1) Å	β = 83.749(1) °.
	c = 22.2477(2) Å	γ = 88.385(1) °.
Volume	2015.39(4) $Å^3$	
Z	8	
Density (calculated)	2.08 g/cm^3	
Absorption coefficient	3.16 mm^{-1}	
Crystal size	0.50 x 0.34 x 0.30 mm	
θ_{min} / θ_{max}	0.9 to 27.5 °.	
Reflections collected	20833	
Independent reflections	9160 [R(int) = 0.0201]	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.45 and 0.30	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	9160/ 0 /542	
Goodness-of-fit on F^2	1.10	
Final R indices ($I>2\sigma(I)$)	R_1 = 0.021 and R_2 = 0.049	
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	0.69 and -0.35 eA^{-3}	

Table 60. Crystal Data and Structure Refinement for 4-Chloro-3-iodo-2-(4-nitro-phenyl)-furan 22e

Empirical Formula	$C_{10}H_5ClINO_3$
Formula Weight	349.50
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 7.0636(7) Å α = 90 °.
	b = 10.335(1) Å β = 92.961(2) °.
	c = 14.921(1) Å γ = 90 °.
Volume	1087.8(2) $Å^3$
Z	4
Density (calculated)	2.13 g/cm^3
Absorption coefficient	3.18 mm^{-1}
Crystal size	0.28 x 0.18 x 0.09 mm
θ_{min} / θ_{max}	2.7 to 28.3 °.
Reflections collected	10899
Independent reflections	2711 [R(int) = 0.0228]
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.76 and 0.47
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2711/ 0 /165
Goodness-of-fit on F^2	1.20
Final R indices ($I>2\sigma(I)$)	R_1 = 0.035 and R_2 = 0.085
$(\Delta\rho)_{max}$ und $(\Delta\rho)_{min}$	1.22 and -0.30 eA^{-3}

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