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Synthesis of substituted 1*H*-pyrrolo[3,2-*c*]pyridines and 1*H*-pyrrolo[2,3-*b*]pyridines

Master Thesis

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Master of Science

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Supervisor:

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Institute of Organic Chemistry

Graz University of Technology

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Meinen Eltern und Rene

„Erfahrung ist die gemeinsame Mutter aller Wissenschaften und Künste.“

Leonardo da Vinci
(1452-1519)

DANKSAGUNG

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Abstract

Pyrrolopyridines are bicyclic ring systems combining an electron-withdrawing pyridine ring with an electron-releasing pyrrole ring. These compounds display biological as well as physicochemical activities. Furthermore, pyrrolo[3,2-*c*]pyridine known as 5-azaindole and pyrrolo[2,3-*b*]pyridine known as 7-azaindole are substrates for probing the active site of a novel enzyme – nitrile reductase queF – which has recently been found in the biosynthetic pathway to the modified nucleoside queuosine. This enzyme is capable of reducing a nitrile group to its corresponding primary amine, however, exhibits high substrate selectivity towards its natural substrate 2-amino-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one ($preQ_0$).

In this master thesis, substituted pyrrolo[2,3-*b*]pyridines and substituted pyrrolo[3,2-*c*]pyridines were synthesised as they bear high structural resemblance to $preQ_0$.The substrates synthesized differ from the natural substrate only in the absence of one ring nitrogen and might possibly be bound in the active site.

Substituted 5-azaindole was prepared starting from a *N*-protected 2-substituted pyrrole. In the first step a carboxylic acid moiety was introduced by Knoevenagel condensation. The carboxylic acid moiety is then converted to an azide group, followed by subsequent Curtius rearrangement to yield 5-azaindole. Depending on the protection group used in the pyrrole starting material, the final 5-azaindole showed either an *N*-1 benzyl or *N*-1 phenylsulfonyl protecting group, leading to a decrease of polarity compared to unsubstituted pyrrolepyridine.

Additionally, pyrrolo[2,3-*b*]pyridines as well as pyrrolo[3,2-*c*]pyridines were synthesised in condensation reactions starting from substituted pyridine precursors, first used for the preparation of 5- and 7-azaindoles in this work.

Kurzfassung

Pyrrolopyridine sind bizyklische Ringsysteme, bestehend aus einem elektronendefizienten Pyridinring und einem elektronenüberschüssigen Pyrrolring. Diese Verbindungen weisen sowohl biologische, als auch physikochemische Eigenschaften auf. Vor allem Pyrrol[3,2-*c*]pyridin auch bekannt als 5-Azaindol und Pyrrol[2,3-*b*]pyridin genannt 7-Azaindol, sind interessante Substrate für ein neues Enzym, Nitrilreduktase, welches erst kürzlich im Biosyntheseweg zu Queuosin, einem modifizierten Nukleosid, entdeckt wurde. Dieses Enzym ist in der Lage Nitrilgruppen zu ihrem entsprechenden primären Amin zu reduzieren und weist eine hohe Substratselektivität gegenüber seinem natürlichen Substrat 2-Amino-5-cyano-7*H*-pyrrol[2,3-*d*]pyrimidin-4-on (preQ$_0$) auf.

In dieser Masterarbeit wurden sowohl substituierte Pyrrol[2,3-*b*]pyridine, als auch substituierte Pyrrol[3,2-*c*]pyridine hergestellt, da diese eine hohe strukturelle Ähnlichkeit zum natürlichen Substrat preQ$_0$ aufweisen. Die Synthese substituierter 5-Azaindole beginnt mit der Einführung einer Carbonsäuregruppe in ein *N*-geschütztes 2-substituiertes Pyrrol mittels Knoevenagel Kondensation. Anschließend wird die Carboxygruppe in ein Azid umgewandelt, gefolgt von einer Curtius Umlagerung zur Herstellung des 5-Azaindoles. Die *N*-1 Position im somit synthetisierten bizykischen Ringsystem ist, je nach Schutzgruppe am Pyrrol, mit einer Benzylgruppe oder einer Phyenylsulfonylgruppe geschützt, was zu einer Verminderung der Polarität im Vergleich zum unsubstituierten Pyrrolpyridin führt. Desweiteren wurden Pyrrolo[2,3-*b*]pyridine und Pyrrolo[3,2-*c*]pyridine durch Kondensationsreaktionen an Pyridine auf einem bislang noch nicht veröffentlichten Reaktionsweg hergestellt.

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1 Aim of this work

The aim of this master thesis is the synthesis of substituted pyrrolopyridines, in particular the development of synthetic ways to pyrrolo[3,2-*c*]pyridine (5-azaindole) and pyrrolo[2,3-*b*]pyridine (7-azaindole). These substituted pyrrolopyridines will later be used in investigations of the substrate scope of a novel enzyme, nitrile reductase queF.

This novel enzyme, capable of reducing a nitrile group to its corresponding primary amine, has recently been found in the biosynthetic pathway to the modified nucleoside queuosine.[1] Various nitrile transforming enzymes, e.g. oxynitrilases[2], nitrilases and nitrile hydratases[3] are already used in biotransformation reactions, a nitrile reducing enzyme would be a valuable contribution. Consequently, in our group, nitrile reductase queF was investigated regarding its applicability as biocatalyst. However, the enzyme exhibits high substrate selectivity towards its natural substrate 2-amino-5-cyano-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one ($preQ_0$).[4] Therefore, pyrrolo[2,3-*b*]pyridines and pyrrolo[3,2-*c*]pyridines are interesting substrates for nitrile reductase queF, as they differ from its natural substrate $preQ_0$ only in the absence of one ring nitrogen.

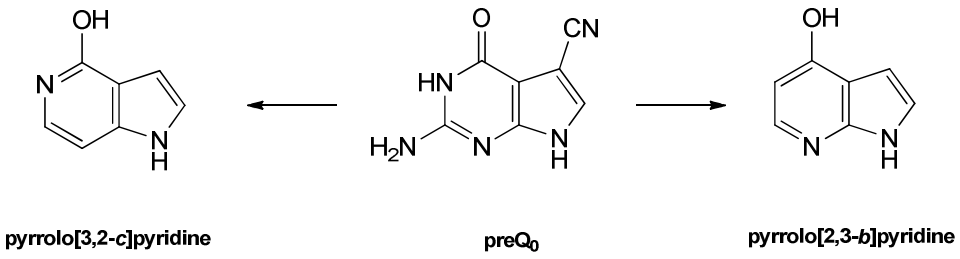
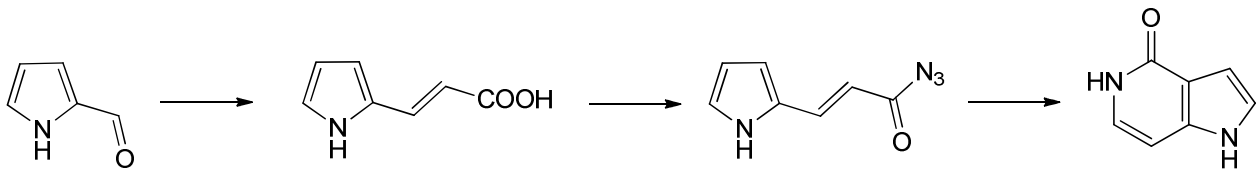


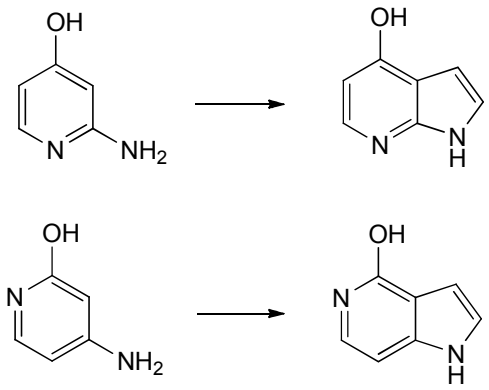
Figure 1: natural substrate $preQ_0$ and the parent pyrrolopyridines

Synthetic pathways to substituted pyrrolopyridines commonly start form pyrrole precursors.[5] Here pyrrolo[3,2-*c*]pyridine was prepared starting from 2-substituted pyrrole, followed by a Knoevenagel condensation to insert a carboxylic acid, conversion to azide group and subsequent Curtius rearrangement (Scheme 1). This synthesis was successfully repeated in my master thesis.



Scheme 1: Synthesis of pyrrolo[3,2-*c*]pyridine ensuing from 2-substituted pyrrole

Additionally to syntheses starting from pyrrole-precursors, substituted pyrrolo[3,2-*c*]pyridines and pyrrolo[2,3-*b*]pyridines were prepared starting from pyridine precursors, on a pathway not yet discussed in literature. Here, in analogy to syntheses known for pyrrolo[2,3-*d*]pyrimidines[6] and first applied for pyrrolopyridines in this master thesis, the bicycle is formed by condensation of a suitable fragment with a 2- or 4-substituted hydroxypyridine as precuror, which led to 5-azaindole as well as to 7-azaindole as depicted in Scheme 2.

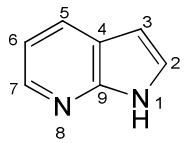


Scheme 2: Synthesis of pyrrolo[2,3-*b*]pyridine and pyrrolo[3,2-*c*]pyridine starting from 2- or 4- substituted hydroxypyridine

2 Introduction

2.1 Nomenclature

The first nomenclature for the fused pyrrole-pyridine system was introduced by Perkin and Robinson[7] in which they termed these compounds pyrindoles and numbed the ring as depicted in Figure 2.

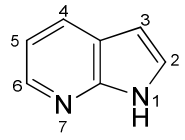


I

Figure 2: Numbering of pyrindole

In 1976 Kruber[8] introduced the aza designation for 7-azaindole and this system is used most frequently and consequently replaced the pyrindole nomenclature. Kruber's azaindole nomenclature is based on the principles used in constructing the name of indole compounds, and adding the aza-designation for the additional ring nitrogen atoms.[9]

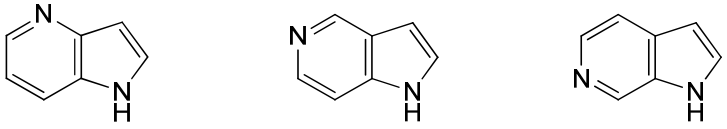
The Ring Index and *Chemical Abstracts* classify the system as pyrrolopyridine, as shown in Figure 3.[10]



II

Figure 3: Nomenclature of pyrrolo[3,2-*c*]pyridine

Consequently, 4-azaindole (**III**) is 1*H*-pyrrolo[3,2-*b*]pyridine, 5-azaindole (**IV**) is 1*H*-pyrrolo[3,2-*c*]pyridine, 6-azaindole (**V**) is 1*H*-pyrrolo[2,3-*c*]pyridine (Figure 4) and 7-azaindole (**II**) is 1*H*-pyrrolo[2,3-*b*]pyridine (Figure 3).[10]



III **IV** **V**

Figure 4: Nomenclature of the three other pyrrolopyridines

Furthermore, azaindoles can be named as diaza-analogues of indene, e.g. 1-4-diazaindene.[9]

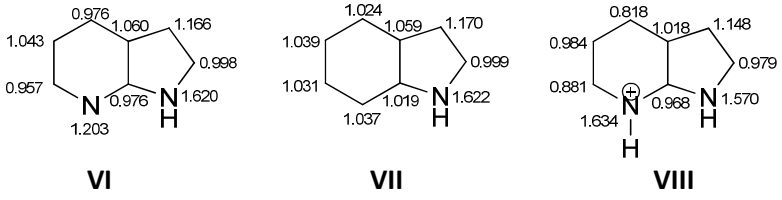
2.2 Chemical Properties

In order to understand the different chemical properties of pyrrolopyridines (azaindoles) compared to pyrrole and pyridine itself, the nature of these two compounds should be explained. Pyrrole, a five-membered aromatic ring, is due to the nucleophilic character of its ring more reactive towards electrophiles than pyridine, but it undergoes aromatic substitution reactions, like Friedel-Crafts, nitrations or halogenations rather than addition reactions. On the one hand it is observed that during a reaction with reagents like bromine all four free positions would be attacked, but on the other hand more selective reagents as $POCl_3$ and DMF (Vilsmeier reaction) commonly react with position 2 or 5. Only if these positions are blocked the other two positions become available.[11]

In comparison to pyrrole, pyridine is less inclined to electophilic aromatic substitutions because the energy of the orbitals in the π-system is lower and an electrophilic attack is difficult. Additionaly, the nitrogen lone pair is basic and a reasonably good nucleophile. Reagents for electrophilic substitutions are generally acidic, hence they protonate the nitrogen atom and a totally unreactive pyridinium ion results. Only if the pyridine ring is activated by electron-donating substituents such as $-NH_2$ or -OMe, pyridines can undergo electrophilic substitution. In contrast, the nitrogen atom renders pyridines more reactive towards nucleophilic substitutions, especially at the 2- and 4-postions, as the LUMO energy of the π-system of pyridine is lowered.[11]

A pyrrolopyridine combines and maintains chemical properties of both rings, but with lower reactivity. Electrophilic reagents attack the pyrrole ring in 3-position like indole, however with greater difficulty.[10]

The lowered reactivity is explained by π-electron density diagrams of 7-azaindole and indole calculated by the LCAO-MO method by Bochvar *et al.* (Scheme 3).[12] The electron density of the 3-position in 7-azaindole (**VI**) is slightly lower than calculated for indole (**VII**), if 7-azaindole is protonated at position 7 (**VIII**) the electron density further decreases, which accordingly explains the lowered reactivity towards electrophilic reagents.[10] The introduction of electron-acceptor groups into position 1 of the azaindole molecule negatively affects the electrophilic substitutions in position 3, whereas electron-donor groups facilitate the substitutions.[9]

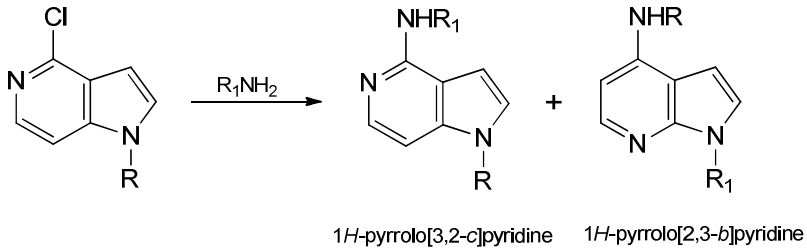


VI **VII** **VIII**

Scheme 3: π-electron density diagrams of 7-azaindole (VI), indole(VII) and protonated 7-azaindole (VIII) [9,10]

A comparison of the molecular diagrams of pyridine and 7-azaindole indicates that the electron density in the pyridine ring is higher in positions 4 and 6 than in positions 2 and 4 in pyridine itself resulting in a decreased tendency to nucleophilic attack.[9,10]

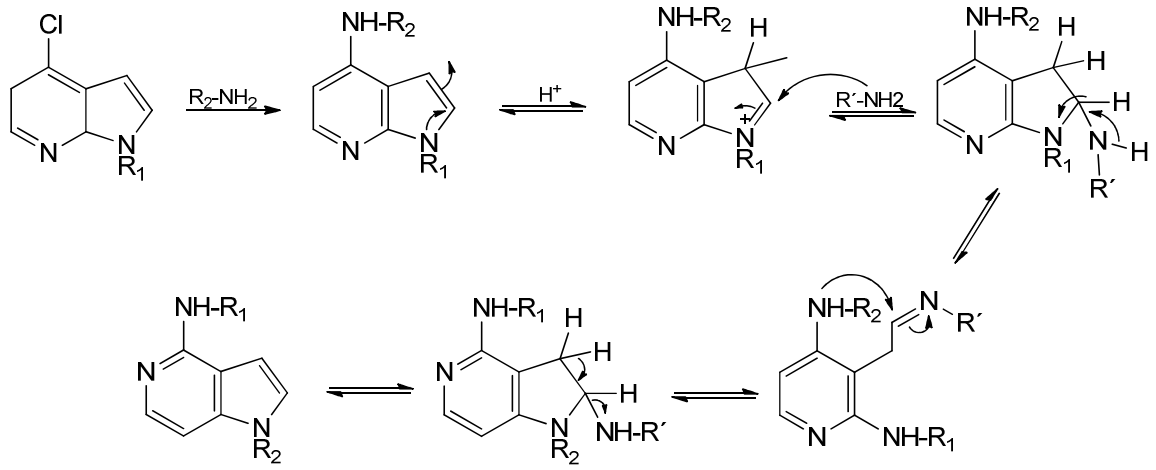
Studies of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) systems showed that reactions with 4-substituted 7-azaindoles lead to nucleophilic substitution-rearrangements. Bisagni *et al*.[13] reported that a nucleophilic displacement of a 4-chloro group of *N*-1 substituted pyrrolo[3,2-c]pyridines by benzylamine or other primary alkylamines yielded a mixture of two isomeric compounds, as depicted in Scheme 4.



Scheme 4: Mixture of two isomeric compounds after nucleophilic substitutuion-rearrangement

The presence of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) derivatives in the resulting mixture proved that a secondary reaction took place by opening and subsequent closing of the pyrrole ring of the intermediate 1*H*-pyrrolo[3,2-*c*]pyridine, which led the reaction to an equilibrium indicating that the isomerization is reversible.[14] Girgis *et al*.[14] reported that also in the case of *N*-1 unsubstituted 4-chloro- (or activated 4-hydroxy-)pyrrolo[2,3-*b*]pyridines, in some cases, rearrangement to the *N*-1-substituted pyrrolo[3,2-*c*]pyridines takes place.

A mechanism for the rearrangement to the 7-azaindole system, involving a Schifff base intermediate, was proposed (Scheme 5). These intermediates were never isolated, however, the formation of Schiff bases was supported by the fact that reactions with primary amines generally gave the rearrangement products, while reactions with secondary amines gave simple substitution products. Secondary amines normally do not form Schiff bases without dealkylation and under these reaction conditions a dealkylation does not proceed and thus only substitution takes place.[15]



Scheme 5: Mechanism proposed for the rearrangement of 7-azaindole to 5-azaindole[15]

Even *N*-1-unsubstituted 4-chloro- or activated 4-hydroxypyrrolo[2,3-*b*]pyridines underwent nucleophilic displacement when they were treated with a variety of amines. In some cases also rearrangements to *N*-1-substituted pyrrolo[3,2-*c*]pyridines took place.[15]

Girgis *et al*.[14] investigated the influence of resonance or field effects of various substituted anilines concerning rearrangement *versus* nucleophilic displacement products and ease of reaction and product yield. Thus, they chose several *para*-substituted anilines, on the one hand having electron-withdrawing (-F, -Cl, $-NO_2$), and on the other hand having electron-donating substituents ($-CH_3$, $-OCH_3$) compared to hydrogen. It turned out, reactions of these anilines always led to displacement-rearrangement products with satisfying product yields for both, withdrawing and donating substituents in the aniline reactants. However, reactions proceeded with different rates, under the same conditions. Anilines bearing electron-donating groups reacted in less than half the time compared to those substituted with electron withdrawing groups. One potential reason for the increased rate of reaction with electron-donating groups might be the enhanced nucleophilicity and basicity of the amine functionality by resonance (for the $-OCH_3$ group) or field effects (for the $-CH_3$ group). The initial displacement step and the subsequent attack on the pyrrole ring resulting in ring-opening and rearrangement would be preferential by the augmented nucleophilicity of the amino group.[15]

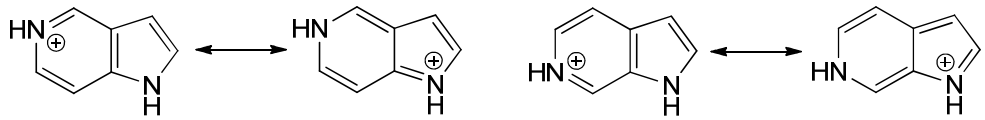
Furthermore, the amine used in the substitution reaction showed a significant influence, using simple primary alkylamines led to displacement-rearrangement products, while reactions with secondary amines led to substitution products without rearrangement.[15]

Compared to indole, which shows hardly any basic properties as the lone pair of the nitrogen atom is involved in the π-electron system, azaindoles exhibit relative basic strengths, as shown in Table 1.

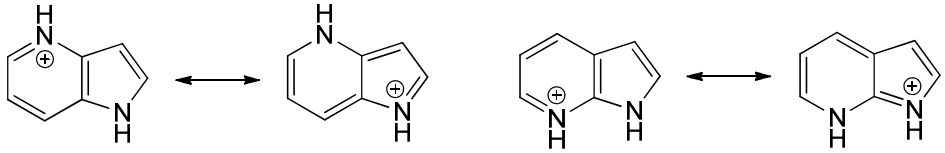
Table 1: Ionization constants of azaindoles, measured in water at 20°C [15]

Compound	pK_a (basic) 20°C
4-Azaindole	6.94
5-Azaindole	8.26
6-Azaindole	7.95
7-Azaindole	4.59

The basic strength of azaindoles originates in the resonance stabilization of the cations. Thus, *para*-quinonoid resonance structures lead to greater stabilization and produce stronger bases than *ortho*-quinonoid forms. 7-azaindole is a weaker base than the other azaindoles because of the inductive effect of *N*-1 defined by the proximity of the two nitrogen atoms. The fractional positive charge on *N*-1 is possibly exerting a coulombic repulsion on an approaching proton.



Scheme 6: ***para*-quinonoid forms of 5-azaindole (left) and 6-azaindole (right)**



Scheme 7: ***para*-quinonoid forms of 4-azaindole (left) and 7-azaindole (right)**

2.3 Syntheses of azaindoles

2.3.1 Syntheses starting from pyridine derivatives

Various synthetic methods have been reported for the preparation of substituted indoles[16]. However, only a limited number of synthetic strategies for azaindoles are described in literature, even though azaindoles are of interest in synthetic organic and medicinal chemistry due to their potential biological properties.[17] Table 2 gives an overview of the different synthetic strategies to azaindoles by using classical methods of indole syntheses. Some of these methods are described in more detail in the subsequent chapter.

Table 2: Different preparation methods for azaindoles

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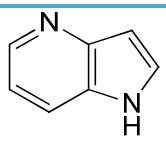
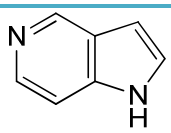
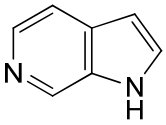
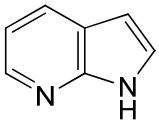
	 4-azaindole	 5-azaindole	 6-azaindole	 7-azaindole
Fischer Synthesis	++++	--	++++	--
Madelung Synthesis	++	+++	+++	++++
Lorenz Synthesis	++++	++	++	++++
Reissert Synthesis	+++	+++	++++	++
Batcho-Leimgruber Synthesis	+++	+++	++++	++
Hemestsberger-Knittel Synthesis	++	+++	++++	+++
Bartoli-Synthesis	+++	++	++++	--
Larock-Synthesis	++++	++++	++++	++++
Hegedus-Mori-Heck Synthesis	++++	++++	++++	++++

The Fischer reaction is one of the most general preparation methods for preparing various indole compounds and as well a good method for synthesising 7-substituted 6-azaindole and 5-substituted 4-azaindole, as described in chapter 2.3.1.2.[26]

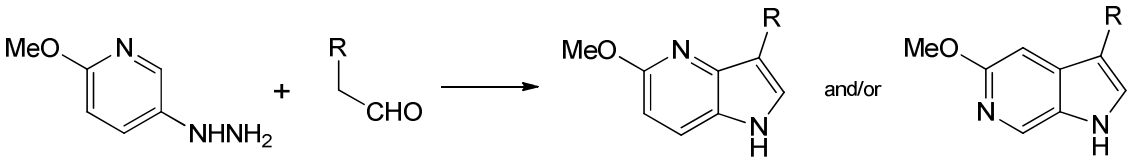


Figure 5: Fischer synthesis

A commonly used method for the preparation of azaindole compounds, especially 7-azaindoles, is the Madelung synthesis, described in more detail in chapter 2.3.1.1.[9]

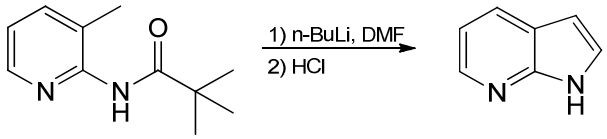


Figure 6: Madelung synthesis

A modification of the Madelung synthesis is the Lorenz reaction using sodium anilide as a base, allowing the preparation of 4- and 7-azaindoles in good yields. [25]

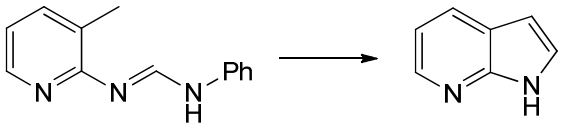


Figure 7: Lorenz synthesis

The Reissert reaction is commonly applied for the synthesis of indoles from *o*-nitrotoluene, but rarely for the preparation of azaindoles.[10] However, 6-azaindole-2-carboxylate was successfully prepared in 85% yield using the Reissert reaction. 4-methyl-3-nitropyridine was treated with diethyl oxalate in the presence of sodium ethoxide producing a pyruvate intermediate, which was subsequently subjected to hydrogenation with a palladium on charcoal catalyst, allowing intramolecular cyclisation.[16]

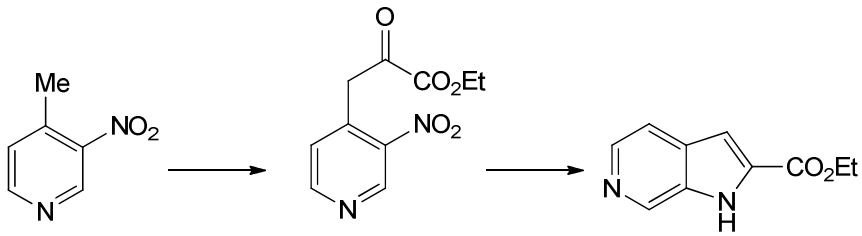


Figure 8: Reissert synthesis

The Batcho-Leimgruber synthesis is a well known preparation method for indoles starting from *o*-nitrotoluenes.[18] In the first step an enamine is formed using *N*,*N*-dimethylformamide dimethyl acetal and pyrrolidine. The addition of amine allows lower temperatures. In the second step the desired indole is formed by reductive cyclisation.[19] This reaction type is also an adequate method for the preparation of 4-, 5- and 6-azaindoles.

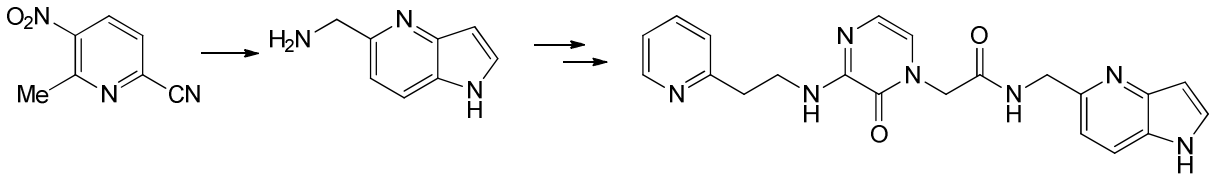


Figure 9: Batcho-Leimgruber synthesis[17]

The Hemetsberger-Knittel reaction was used for a preparation of various 4-substituted 5-, 6-, or 7-azaindole-2-carboxylates. Pyridine-carboxaldehyde derivatives were treated with methyl azidoacetate in presence of MeONa, producing azidopyridineacrylates. The corresponding azaindoles were achieved by thermal cyclisation in good yields.[16]

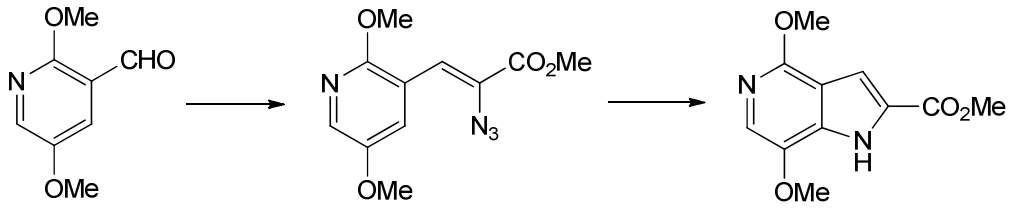


Figure 10: Hemetsberger-Knittel synthesis[20]

The Bartoli cyclisation was extensivly studied for the synthesis of indole derivatives from nitrobenzene, these approaches were applied to the synthesis of 7-substituted 4- and 6-azaindoles. 2-Methoxy-3-nitropyridine was treated with vinylmagnesium bromide in THF at -78°C, yielding the desired azaindole.[16, 21]

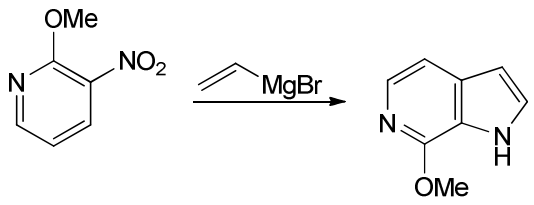


Figure 11: Bartoli synthesis

The Larock synthesis can be applied for the generation of 2, 3-substituted 4-, 5-, 6- or 7-azaindoles using 3-indopyridin-2-amine and a disubstituted alkyne as starting materials.[22]

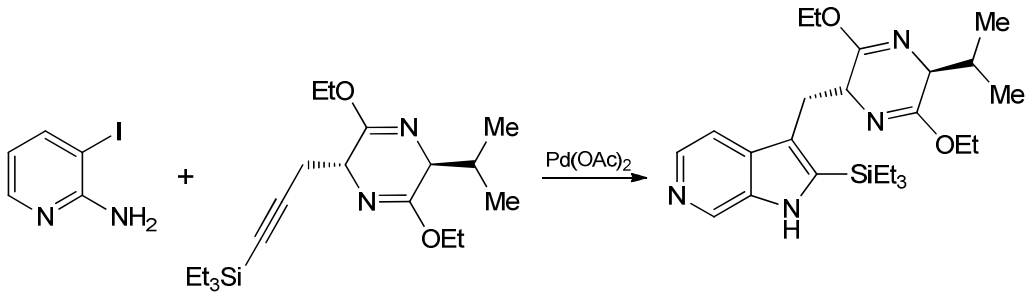


Figure 12: Larock synthesis

Using an intramolecular Heck reaction, the preparation of 2, 3-substituted 4-, 5- , 6- and 7-azaindoles is possible with the so called Hegedus-Mori-Heck synthesis in satisfactory yields.[23]

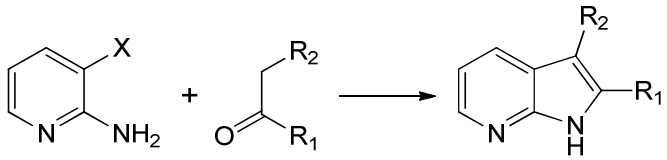
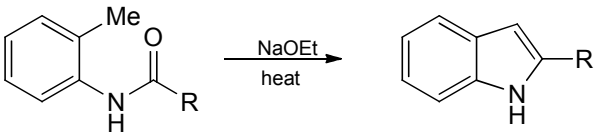


Figure 13: Hegedus-Mori-Heck synthesis

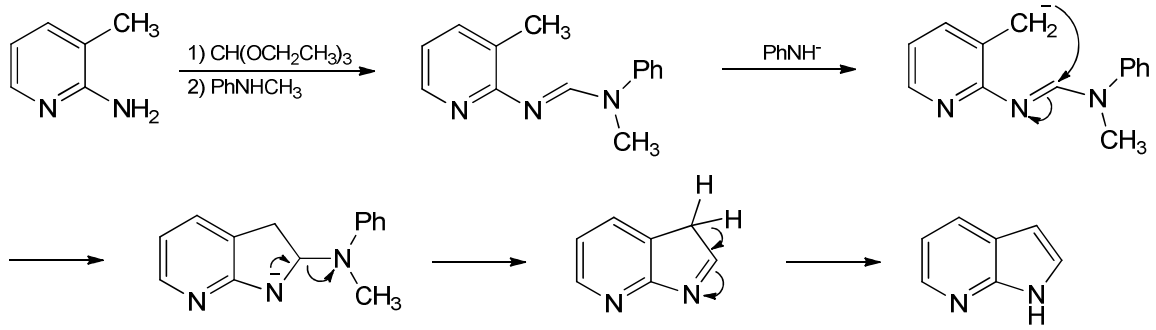
2.3.1.1 Madelung synthesis (Lorenz synthesis)

One of the most successful methods for the preparation of azaindoles is the Madelung synthesis[24] which produces substituted or unsubstituted azaindole compounds by intramolecular cyclization of 2-methyl-formanilide using strong base at high temperature.[9, 10]



Scheme 8: Madelung synthesis[24]

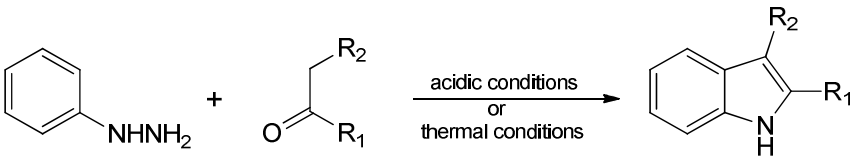
Various modifications to optimize the yield are known, however, often proved to be not reproducible. Lorenz *et al.* obtained good results using sodium anilide as base. Starting from amidine, prepared by the reaction of 2-amino-3-pyridine with ethyl *ortho*formate and subsequent condensation of the resulting formimidate with *N*-methylaniline, the cyclization was performed with sodium *N*-methylanilide in *N*-methylaniline at approximately 200°C to obtain 7-azaindole in 80 % yield (Scheme 9). 5-azaindole as well as 4-azaindole was analogously prepared in 51 % and 10 % yield, respectively. [25]



Scheme 9: Lorenz synthesis of 7-azaindole[25]

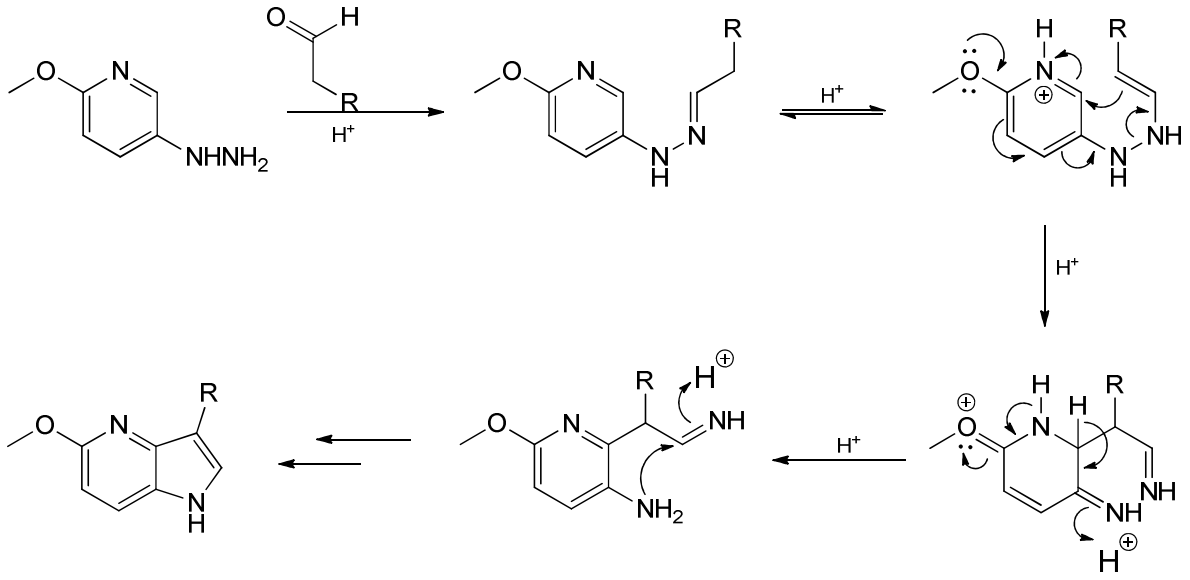
2.3.1.2 Fischer Synthesis: Azaindolization

The best known indole synthesis the Fischer indole cyclization (Scheme 10), however, this method was infrequently used for azaindole chemistry due to the electron-deficient properties of the pyridine ring in the [3,3]-sigmatropic rearrangement step of heterocyclization.[26]



Scheme 10: Fischer synthesis of indoles[27]

Jeanty *et al*.[27] explored the possibility of efficiently producing 4- and 6-azaindoles by Fischer cyclization. 6-methoxypyrid-3-ylhydrazine was used as starting material, as Fischer indole syntheses are significantly more efficient when involving arylhydrazines bearing electron-donating groups.[28, 29] Both azaindole isomers were prepared. Efficient substrates for this rearrangement are linear and cyclic alkyl ketones as well as alkylketals.[27] Additionally, electron-donating groups in pyridylhydrazine were investigated, as they play a significant role during the cyclization as they increase reactivity and regioselectivity. In the absence of electron-donating groups no cyclization was observed. The mesomeric effect of such electron-donating groups is thought to encourage the *N-N* bond cleavage (push effect)[26, 28, 29] and the pyridinium nitrogen may help to create the new *C-C* bond (pull effect)[27].

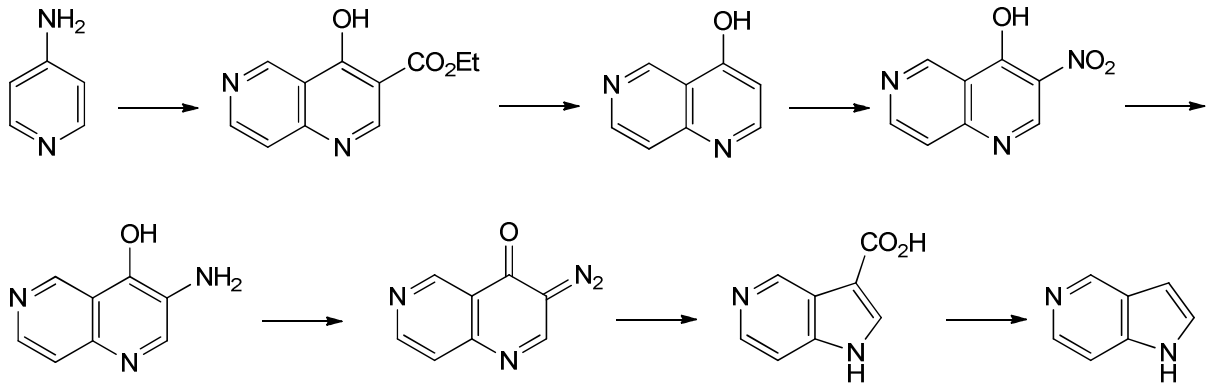


Scheme 11: Azaindole Fischer synthesis from pyrid-3-ylhydrazine[27]

Fischer azaindolization is feasible when the staring material pyridylhydrazine bears electron-donating groups *ortho*- or *para*-position to the hydrazine functionality. Thus, heterocyclization in position 2 of the pyridine ring , or in position 4 in case position 2 is substituted, is preferential.[27]

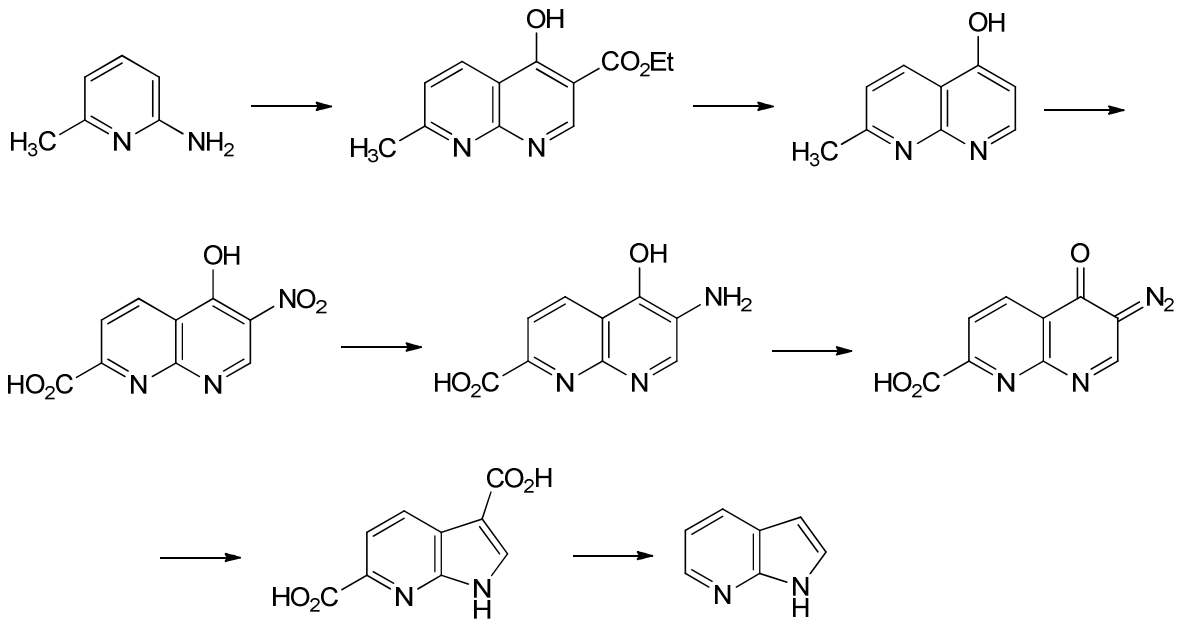
2.3.1.3 Photochemical ring contraction of naphthyridines: Süs and Möller method

Another option preparing pyrrolopyridines is the photochemical method described by Süs and Möller, [30, 31, 32] which allows establishing all four azaindoles in good yields. The syntheses of 4- and 5-azaindole were carried out in analogously, starting with 3- and 4-aminopyridine respectively, which were converted via cyclization into 4-hydroxy-1,5-naphthyridine-3-carboxylic ester or 4-hydroxy-1,6-naphthyridine-3-carboxylic ester by condensation with ethoxymethylmalonic ester, followed by saponification and decarboxylation to obtain the desired 4-hydroxynaphthyridine. The next reaction sequence included the introduction of a nitro group with concentrated nitric acid solely in position 3, reduction of the nitro group to an amino group catalysed by Raney nickel, diazotization with sodium nitrite in *N*-hydochloric acid and in addition the photochemical reaction, which led to 3-carboxylic acid. The final step involved decarboxylation receiving 4- or 5-azaindoles.[30, 32]



Scheme 12: Synthesis of 5-azaindole by Süs and Möller[32]

For the preparation of 7-azaindole, 2-amino-6-methylpyridine was required as starting material, as the methyl group is responsible for the correct cyclization obtaining the 7-methyl-1,8-isomere, whereas 2-amino-pyridine cyclizied to the *N*-atom of the pyridine ring forming a pyridazinderivate.[33] All other steps proceeded identically, as described above, except the methyl group was oxidised to the carboxylic acid during the nitration and was afterwards removed in the last decarboxylation step.[32]

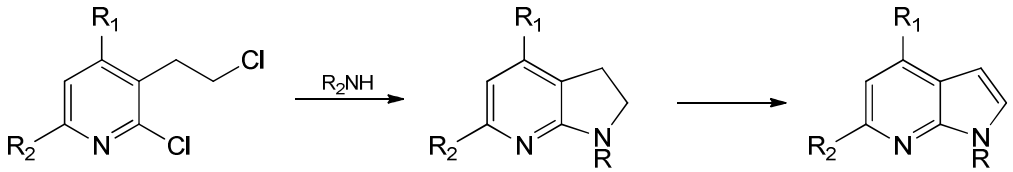


Scheme 13: Synthesis of 7-azaindole by of Süs and Möller

In the case of 6-azaindole[31] 3-amino-pyridine-*N*-oxide was necessary to create the 1,7-naphthyridine derivate, otherwise 3-aminopyridine could only be converted into substituted 1,5-naphthyridine.[33] This method was proven to be adequate in the preparation of unsubstituted azaindoles, however it was not used synthesising substituted pyrrolopyridines.

2.3.1.4 Preparation via azaindolines

Yakhontov and Rubtsov[34] described a new preparation method for substituted 5- and 7-azaindoles, including a novel ring closure of 3-(2´-chloroethyl)pyridine bearing a halogen-substituent in position 2 or 4 with secondary amines. The azaindoline formed was then converted by dehydrogenation, in most cases with chloranil, into a substituted azaindole (Scheme 14).[9]



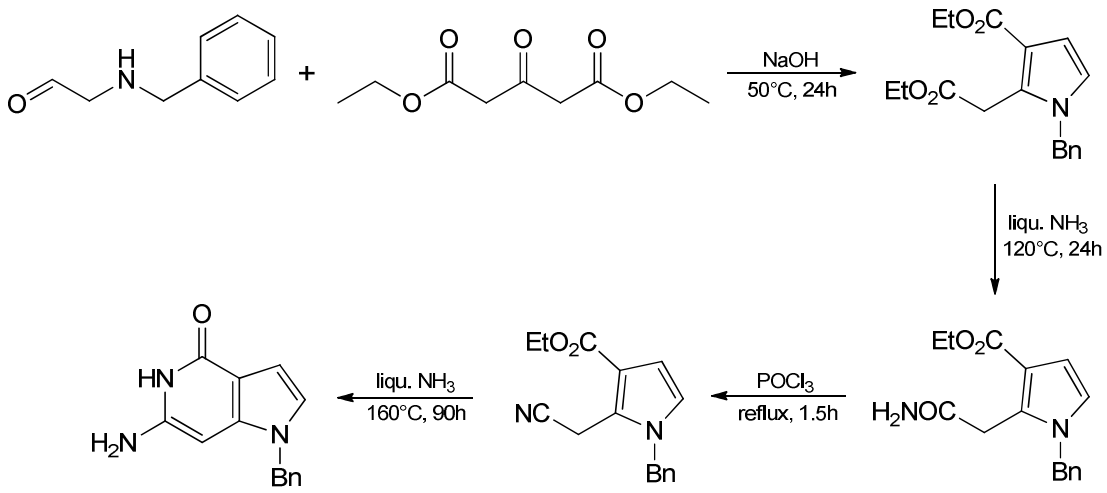
Scheme 14: Synthesis of azaindoles via azaindolines[10] (R_1 = Me, Cl; R_2 = Cl)

Increasing basic strength of secondary amines facilitated the reaction with the pyridine-precursor and consequently the formation of azaindolines derivates. [35, 36] Furthermore, electron-withdrawing

groups in *para*-position of *N*-alkylanilines hinder the reaction, while electron-donating groups enhance the reactivity.[37] Introduction of electron-donors into position 1 of azainodlines promotes dehydrogenation, while electron-acceptors complicate process.[9] Steric hindrance exerts an influence on the reaction, thus aromatic secondary amines encourage the formation of secondary products, particularly vinylpyridine,[9, 35] as well as higher yields for azaindoline derivates were obtained when the alkyl chain is shorter.[35, 36]

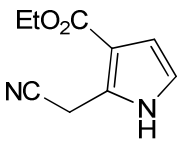
2.3.2 Synthesis starting from pyrrole derivatives

In addition to preparation methods for 5-azaindole starting from pyridines as described in chapter 2.3.1, synthetic routes starting from pyrroles are known. Schneller *et al.* reported the synthesis of 1-substituted 6-amino-1*H*-pyrrolo-[3,2-*c*]pyridine-4(5*H*)-one from a pyrrole precursor, as depicted in Scheme 15.[38]



Scheme 15: Schneller synthesis of 1-substituted 6-amino-1*H*-pyrrolo-[3,2-*c*]pyridine-4(5*H*)-one

The reaction of *N*-benzylaminoacetaldehyde hydrochloride and diethyl acetonedicarboxylate in 20% NaOH solution gave ethyl 1-benzyl -3-(ethoxycarbonyl)pyrrole-2acetate in 28% yield. This pyrrole was then treated with liquid ammonia in a sealed reaction vessel at 120°C to convert the ester-functionality in position 5 of the pyrrole-ring into an amide-functionality which undergoes subsequent dehydration with phosphoruos oxychloride to the corresponding nitrile. The cyclization reaction was achieved by heating the nitrile compound with liquid ammonia in a sealed reaction vessel to obtain the desired 6-amino-1-benzyl-1*H*-pyrrolo[3,2-*c*]pyridine-4-ol in 42% yield as its enol tautomer. Debenzylation was not successful and resulted in recovery of starting material or complete destruction of the heterocyclic compound.[38, 39]



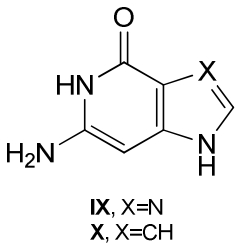
Scheme 16: 3-(ethoxycarbonyl)pyrrole-2-acetonitrile

Reactions of *N*-unsubstituted 3-ethoxycarbonylpyrroles, such as in Scheme 16, were also investigated by Schneller. However, no cyclization was observed when 3-(ethoxycarbonyl)pyrrole-2-acetonitrile

was treated with liquid ammonia at a great number of different temperatures and different durations, as ammonia shows lower nucleophilicity compared to hydroxylamine. To overcome this problem, the electrophilicity of the nitrile carbon of 3-(ethoxycarbonyl)pyrrole-2-acetonitrile was enhanced using acidic conditions. Thus, the pyrrole compound was treated with liquid ammonia containing ammonium chloride in a sealed reaction vessel at 125°C for 24 hours to obtain 5-azaindole in 67% yield. In summary, it was found that nucleophilic reactions take place at the less reactive nitrile site, while the 3-ester functionality is inert towards nucleophilic substitutions.[38, 40]

2.4 Relevance of azaindoles

In 1990s azaindoles were investigated to elucidate the biological nature of 3-deazaguanine (**IX**) which was demonstrated to possess antitumor[41], antiviral[42] and antibacterial[43] properties. It was suggested that the *N*-3 atom of this compound is crucial for its biological activity. Therefore, 3,7-dideazaguanine (5-azaindole, (**X**)) became a useful target compound to establish the biological significance of the *N*-3 atom.[38, 40]



IX, X=N
X, X=CH

Figure 14: 3-Deazaguanine (IX) and 3,7-Dideazaguanine (X)

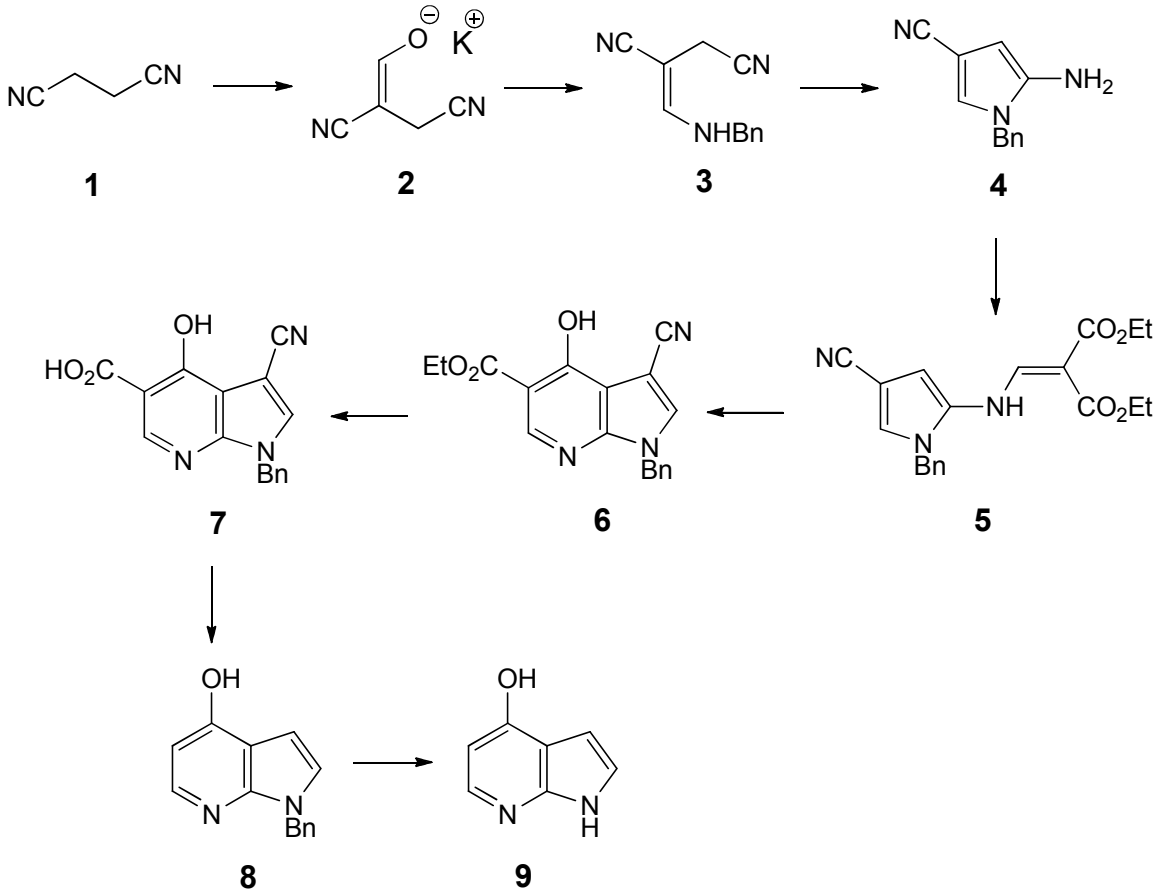
In recent years azaindoles have been highly investigated due to their biological as well as physicochemical activities. These bicyclic systems are prevalent substructures in naturally occurring and synthetic molecules.[27] 7-azaindoles are the most widely studied nitrogen analogues of the indole ring system and were used as an indole bioisostere to improve physicochemical and pharmacokinetic properties of several drug candidates such as dopamine D4 ligands.[44] Over the years, many methods of forming azaindoles have been inspired by several synthetic strategies initially developed for indole ring formation which include the Madelung cyclisation, Reissert synthesis, Lorenz preparation, Fischer-type cyclisation and the Bartoli sequence. Consequently, the azaindole scaffold is the objective of several synthetic studies and the development of an efficient preparation illustrates an active and essential area of research.[27]

3 Results and Discussion

3.1 Syntheses starting from pyrrole derivatives

3.1.1 Synthesis of pyrrolo[2,3-*b*]pyridines (7-azaindoles)

As described in chapter 2.3.2, 5-azaindoles can be synthesized starting from pyrrole, a similar synthetic strategy for the synthesis of 7-azaindoles was published by Brodrick and Wibberly, as depicted in Scheme 17. [45]

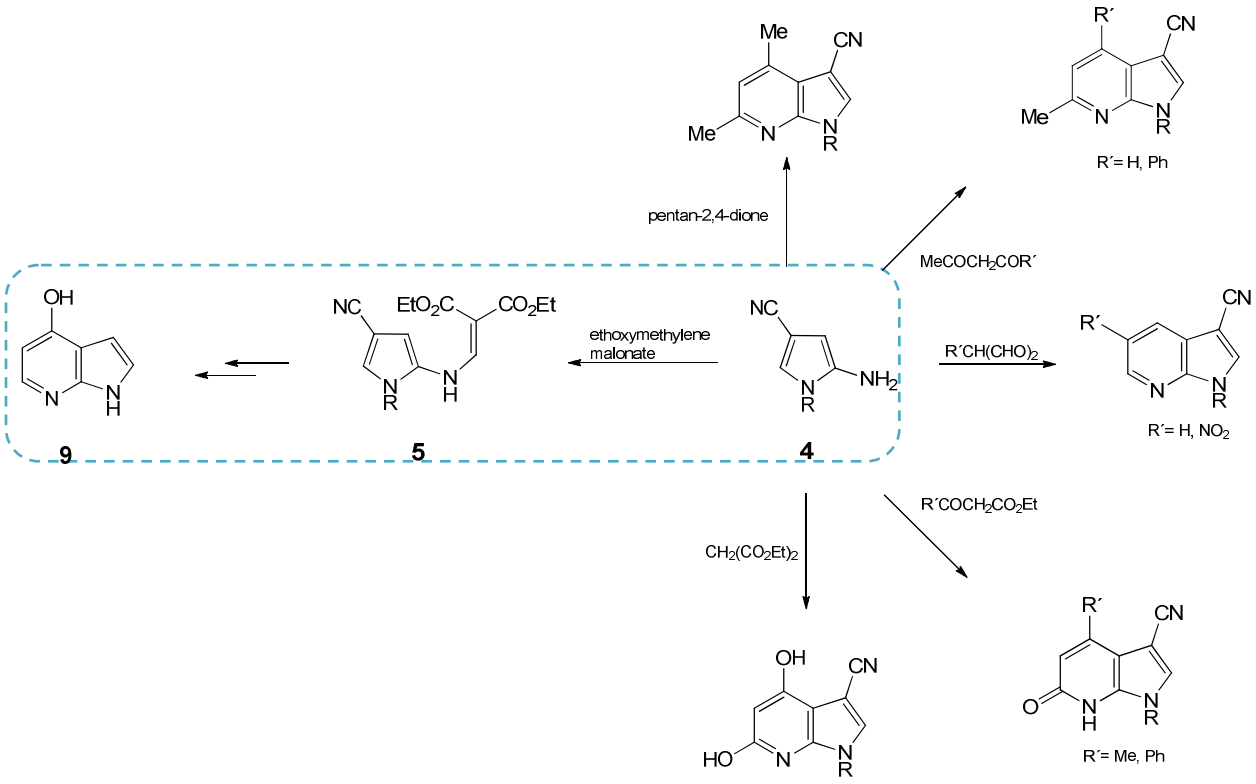


Scheme 17: Synthetic route to compound 9

Their method uses 2-aminopyrroles for the synthesis of 1*H*-pyrrolo[2,3-*b*]pyridine. Simple 2-aminopyridines are known to be highly instable and decompose immediately in air, however, by introducing an electron-withdrawing group, e.g. cyanide, stability can be increased. Reactions starting from methyl 2-aminopyrrole-3-carboxylate or 2-aminopyrrole-3-carbonitrile were not successful, consequently, 2-aminopyrroles with a vacant 3-position were chosen as starting materials. *N*-Benzyl-2-amino-4-cyanopyrrole (**4**), starting material of choice, was prepared from succinonitrile in three steps. Succinonitrile was first subjected to a condensation reaction with ethyl formate and potassium salt **2** was prepared, which in turn was treated with amine to yield

aminomethylensuccinonitrile (**3**). 1-Substituted 2-amino-4-cyanopyrrole (**4**) is then formed in a cyclisation reaction in the presence of potassium ethoxide.

Different substitutents on the 7-azaindole ring system were achieved by condensation of different fragments to the 2-amino-4-cyanopyrrole precursor, as depicted in Scheme 18.[45]



Scheme 18: Various methods for the synthesis of substituted 7-azaindoles[45], R=Bn

In my thesis, the method of choice for the formation of the bicyclic system was the route *via* 2-bisethoxycarbonylvinylaminopyrrole (**5**). Therefore, succinonitrile was condensed with 1.2 equivalents of methyl formate using potassium *t*-butoxide as base and a mixture of *t*-BuOH and toluene in a ratio of 5:1 as solvent. The potassium derivative of formylsuccinonitrile **2,** a yellow solid, was then treated with benzylamine and acetic acid for one hour at 70°C. HPLC-MS measurements confirmed the formation of the aminomethylenesuccinonitrile derivative **3**, however, the formation of the desired product could not be proven by ^{1}H NMR in DMSO-d_6. Furthermore, the reaction did not proceed selectively because the sample contained benzylamine as well as other impurities. One reason for this unselective reaction might be the commercially available potassium *t*-butoxide which was not freshly opened and possibly already unreactive.

Consequently, synthesis of compound **2** was repeated, preparing potassium *t*-butoxide *in situ* from *t*-butanol and potassium which was added dropwise to the reaction mixture containing succinonitrile, methyl formate in *t*-BuOH/toluene in a ratio of 5:1. After stirring the reaction mixture overnight at room temperature compound **2** was dissolved in deionised water and treated with benzylamine for

half an hour to yield compound **3**. After addition of acetic acid the reaction mixture was stirred for further three hours at room temperature. Purification of compound **3** by column chromatography using toluene/acetic acid 4:1 as eluent was not successful, HPLC-MS measurements and ^{1}H-NMR spectroscopy confirmed compound **3** was formed, however, benzylamine and other impurities were present in the sample.

Additionally, potassium hydride was evaluated as a base for the synthesis of compound **2.** A suspension of potassium hydride in diethyl ether was added slowly to a mixture of succinonitrile and methyl formate. The reaction mixture was then directly used for the next synthetic step, the preparation of aminomethylenesuccinonitrile (**3**). Compound 3 was then purified by column chromatography (toluene/ acetic acid 5:1). However, HPLC-MS and ^{1}H NMR spectroscopy showed the desired product contained succinonitrile, which might be due to the absence of the work up of the formylsuccinonitrile derivative **2**.

In summary, it can be stated that reactions using either potassium *t*-butoxide or potassium hydride led to formation of the desired product, however, in each approach the sample contained benzylamine, succinonitrile or other impurities. Hence, the sodium salt of the aminomethylenesuccinonitrile compound **2** was realised using sodium ethoxide as base. The resulting salt was then treated with benzylamine and acetic acid for one hour at 50°C. Unfortunately, no formation of the desired product **3** occurred, as proven by ^{1}H NMR.

Table 3 summarises the reaction conditions for the preparation of the formylsuccinonitrile derivative **2**.

Table 3: Reaction conditions for the formation of the formylsuccinonitrile derivative (2)

Base	Solvents	Temperature	Reaction time [h]	Product (2)	Product identified in HPLC-MS besides byproducts
t-BuOK	*t*-BuOH, toluene	rt	12	potassium-derivative	+
KH	Et_2O	rt	12	potassium-derivative	+
NaOEt	EtOH	rt	12	sodium-derivative	-

Since the resulting product **2** is a salt, the turnover of the reaction cannot be monitored by thin layer chromatography, as salts adsorb strongly on the polar separation material and stay at the baseline. The yield of the first step was not determined in every approach, because in some cases the salt of the formylsuccinonitrile was used for the next synthetic step without work up. Consequently, benzylamine used for the synthesis of compound **3** was used in excess. The desired product **3** was

obtained in 20% to 65% yield in all reactions starting from potassium salt **2**, as summarized in Table 4. However, the desired product **3** contained minor impurities, since the excess of benzylamine, as well as other byproducts, could not be removed by column chromatography.

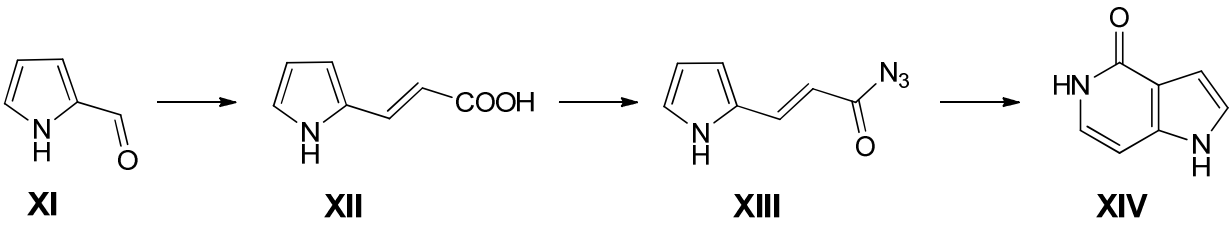
Table 4: Reaction conditions for the formation of the aminomethylenesuccinonitrile compound 3

Reaction	Formylsuccinonitrile – derivate	Temperature	Reaction time [h]
1	potassium	30°C -> 70°C	1
2	potassium	rt	3
3	potassium	rt	2
4	sodium	rt -> 50°C	7

In the following step in the synthetic pathway, depicted in Scheme 17, the substituted pyrrole **4** is prepared from compound **3**. In two subsequent steps the 7-azaindole **6** is formed. To achieve the final product **9** the ester functionality in position 5 is hydrolysed followed by decarboxylation and deprotection of *N*-1. These synthetic steps from compound **3** to the final compound **9** were not pursued in my work, as preparation of compound **3** already proved tedious, as discussed in detail in the previous pages, and six additional reaction steps are required to obtain the desired product **9**. However, an alternative synthetic route to the desired 7-azaindole **9** was investigated, as described in chapter 3.2.1.

3.1.2 Syntheses of pyrrolo[3,2-*c*]pyridines (5-azaindoles)

As described in the previous chapter, 5-azaindoles can be prepared by rearrangement of a suitable pyrrole precursor, as shown in Scheme 19.



XI **XII** **XIII** **XIV**

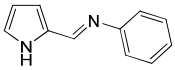
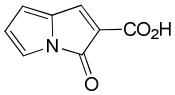
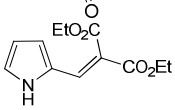
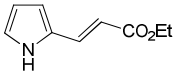
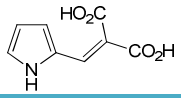
Scheme 19: Synthesis of 5-azainole starting from pyrrole

A carboxylic group was introduced in position 2 of the starting material pyrrole-2-carbaldehyde **XI** by Knoevenagel condensation. This carboxylic group was then converted into an azide functionality, which subsequently undergoes a Curtius rearrangement yielding 5-azaindole **XIV** in the final step. In the following chapter each synthetic step will be explained in detail.

3.1.2.1 Knoevenagel condensation

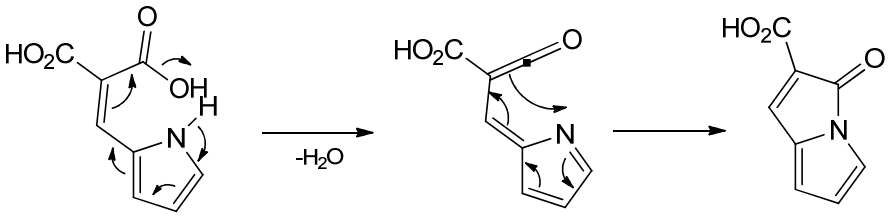
Condensation reactions of aldehydes or ketones with highly diverse C-H acidic compounds, under the influence of weak bases, like tertiary amines, are denoted as Knoevenagel condensation reactions. A Knoevenagel condensation was employed in the first step of the preparation of 5-azaindole to insert a carboxylic functionality in position 2 of a pyrrole derivative. In this reaction malonic acid dissolved in ethanol was treated with pyrrole-2-carbaldehyde using aniline as weak base at room temperature over night. The desired condensation product **XII** was not obtained after work up, but the formation of an imine **10** was observed during the reaction. Aniline reacted with the aldehyde and formed an imine or Schiff base which acted as acceptor in the following reaction. ^{1}H-NMR spectroscopy proved the synthesis of the corresponding Schiff base and shows that no further reaction with the malonic acid occured. For that reason a base study was carried out for the condensation reaction with malonic acid and pyrrole-2-carbaldehyde. The results are summarized in Table 5.

Table 5: Influence of different bases on the Knoevenagel condensation

Base [equiv.]	Solvent	Temperature	Reaction time [h]	Product	Number	Yield [%]	Reference number
aniline [1.8]	EtOH	rt	24		**10**	35	46
piperidine [1.7]	EtOH	rt	24		**11**	53	2
piperidine [1.7]	EtOH	rt	24		**12**	8	2
NaOEt [4.1]	EtOH	rt	12	-		51	2
NaH [1.6]	THF	0°C -> rt	12		**13**	71	47
piperidine [1.0]	pyridine	reflux (140°C)	2	-		-	48
piperidine [0.1]	pyridine	reflux (100°C)	2	-		-	49(a)
piperidine [0.1]	pyridine	reflux (80°C)	2		**14**	41	5

Blue: diethyl malonate used as reagent instead of malonic acid; Green: triethyl phosphonoacateate used as reagent instead of malonic acid

Choosing piperidine as base instead of aniline the corresponding pyrolizin-3-one derivative **11** could be obtained in 53% yield as a brownish solid. Campbell et *al.*[50] reported the successful formation of pyrrolizin-3-ones by pyrolysis of parent propenoates in reasonable yields. Although we did not apply a high temperature protocol, the formation of the pyrrolizin-3-one derivative might be possible and is explained by the following reaction pathway (Scheme 20).



Scheme 20: Mechanism proposed for the synthesis of pyrolizin-3-one derivatives[50]

Furthermore, instead of malonic acid as starting material diethyl malonate was treated with the pyrrole precursor using either piperidine or sodium acetate as base. While the reaction using sodium ehtoxide as base did not yield the desired product, the diester product **12** was successfully obtained in the reaction using piperidine as base, albeit in modest yields of 8%. When in the reaction with pyrrole aldehyde triethyl phosphonoacetate was used instead of malonic acid, and sodium hydride was used as base, formation of the desired monoester **13** was observed. However, a major problem during these previously discussed approaches was the limited solubility of pyrrole-2-carboxaldehyde in ethanol and tetrahydrofuran, respectively. To overcome those solubility problems, pyridine was

used as solvent. Reactions in pyridine as solvent, using either 1.0 equivalents of piperidine as base and 140°C for two hours, or milder reaction conditions of 0.1 equivalents of piperidine and 100°C, did not lead to the desired condensation product. Finally, a further decrease in reaction temperature to 80°C, while maintaining the use of pyridine as solvent and 0.1 equivalents of piperidine as base, provided the desired compound (2-pyrrolylmethylene)malonic acid (**14**). (2-pyrrolylmethylene)malonic acid was isolated in 41% yield as pink solid. Characterisation was carried out by HPLC-MS (Figure 15).

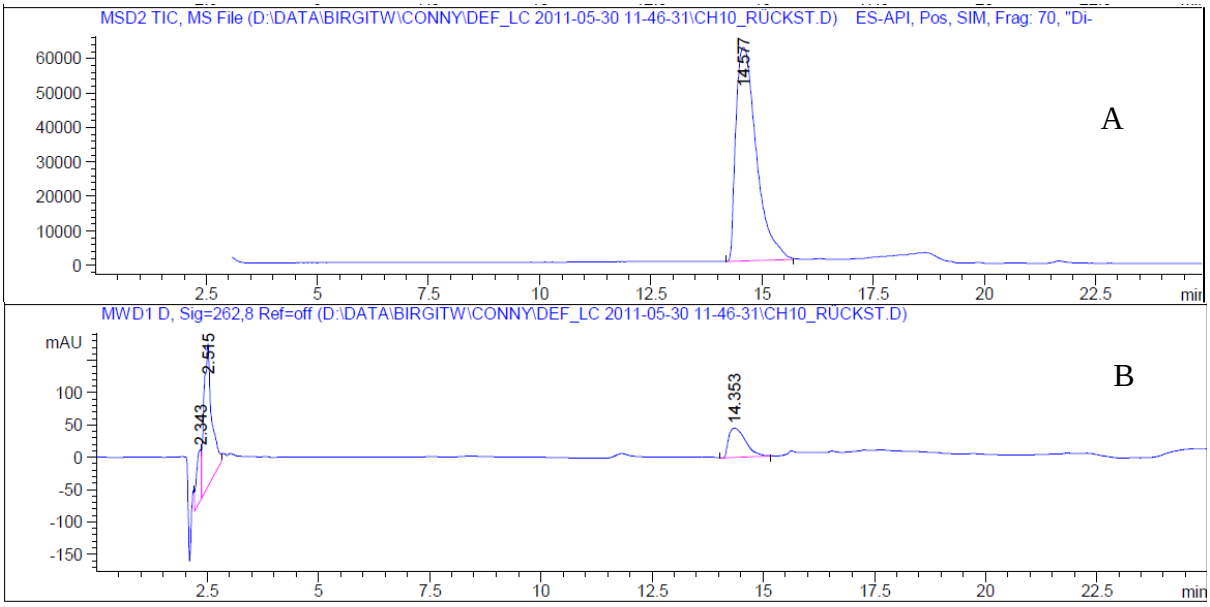
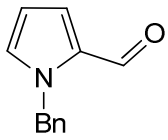


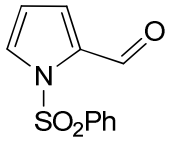
Figure 15: HPLC measurement of (2-pyrrolylmethylene)malonic acid (14): A: SIM-mode, B: UV signal at 262 nm.

The solubility of the diacid **14** turned out to be challenging. Both, aqueous acidic solutions and aqueous basic solutions did not dissolve the compound, neither did common organic solvents, like DMSO, THF or acetone. The reason is possibly the high polarity of the pyrrole derivative. Therefore, derivatisation might improve solubility tremendously. In order to improve solubility, the nitrogen atom in the pyrrolering was protected. The generally used protecting group for pyrrole derivatives described in literature is the benzyl group. Pyrrole-2-carboxaldehyde was dissolved in acetonitrile under nitrogen atmosphere, treated with sodium hydride and stirred for half an hour at room temperature. Afterwards, benzyl bromide was added to the orange reaction mixture, leading to cloudy solution. After work up, the condensation-product **15** was purified by column chromatography. However, a disadvantage of the benzyl protecting group is deprotection, as drastic reaction conditions, using sodium in liquid ammonia, are required. Compared to that, a phenylsulfonyl offers the advantage of facile deprotection by pyrolysis. Introducing the phenylsulfonyl group, the reaction conditions used before for the benzyl group were applied. In this reaction in tetrahydrofuran, using sodium hydride as base and dropwise addition of phenylsulfonyl chloride at 0°C, no product formation was observed, only phenylsulfonyl chloride was isolated.

Consequently, reaction conditions regarding solvent, base, and reaction temperature were optimized. The results are summarized in Table 6.



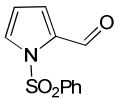
15



16

Scheme 21: Compound 15 and 16

Table 6: Optimization of the reaction conditions for introducing a phenylsulfonyl protecting group

$PhSO_2Cl$ [equiv.]	Base [equiv.]	Solvents	Temperature [°C]	Reaction time [h]	Product	Yield [%] according to HPLC	Reference number
1.2	NaOH [3.0]	DCM	0°C -> rt -> 50°C	12		65	[51]
1.2	NaOH [3.0]	H_2O, DCM	0°C -> rt-> 50°C	12	 **16**	45	[51]
1.4	NaH [1.2]	DMSO	rt	12		10	[52]

Protection of the NH-group was successful using either sodium hydroxide or sodium hydride as base, however with varying yields. Reaction progress was monitored by HPLC-MS.

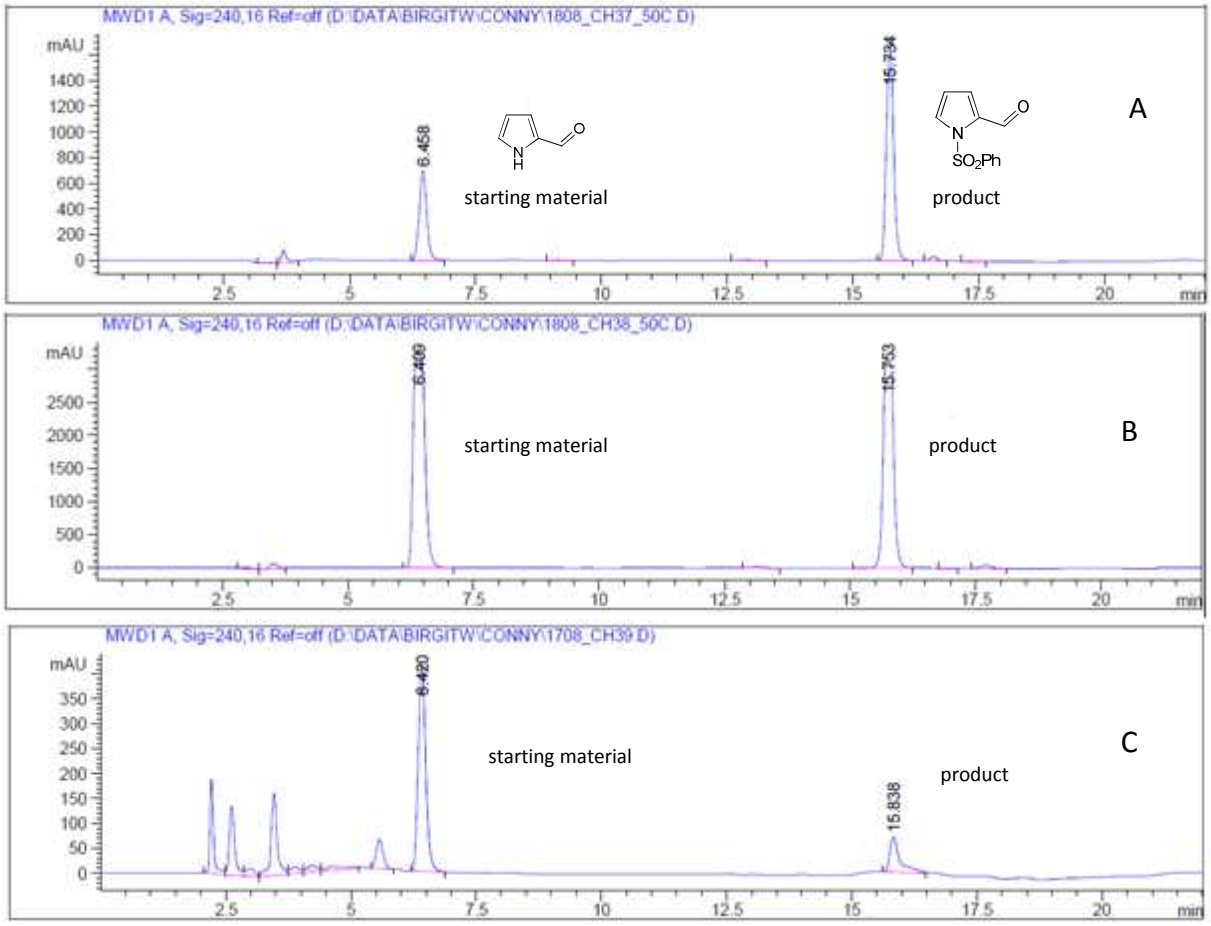


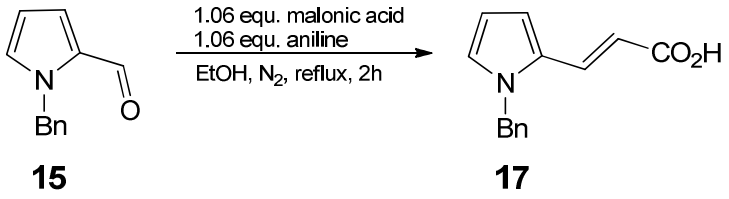
Figure 16: HPLC measurements of compound 16: UV signals at 240 nm; A: reaction with NaOH in DCM, B: reaction with NaOH in H_2O/ DCM, C: reaction with NaH in DMSO.

Best results for the phenylsulfonyl protection were obtained with dichloromethane as solvent and sodium hydroxide as base. The reaction temperature was increase to 50°C after addition of all reagents, and product **16** was purified by column chromatography. Table 7 summarises the reaction yields.

Table 7: Isolated yields for the protection of the NH-group in pyrrole-2-carboxaldehyde

	15	**16**
Yield [%]	66	20

The protection of the NH-group in pyrrole-2-carboxaldehyde solved the solubility problem, consequently the insertion of the carboxylic function by the Knoevenagel condensation was investigated, as shown in Scheme 22.

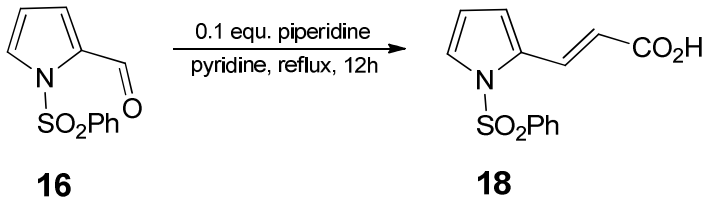


Scheme 22: Synthesis of compound 17

Using benzyl protected pyrrole carbaldehyde **15** the reaction proceeded smoothly, as well as purification was unproblematic. The formation of product **17** took place with malonic acid and aniline in EtOH. The solution was heated to reflux, followed by fast addition of compound **15**. After a reaction time of two hours the mixture was poured onto ice where a brownish precipitate formed which was then recrystallised from toluene.

Similar reaction conditions and reagents were applied to the phenylsulfonyl protected pyrrole carbaldehyde **16**, but did not lead to the desired product, merely the corresponding imine was identified by HPLC-MS measurements.

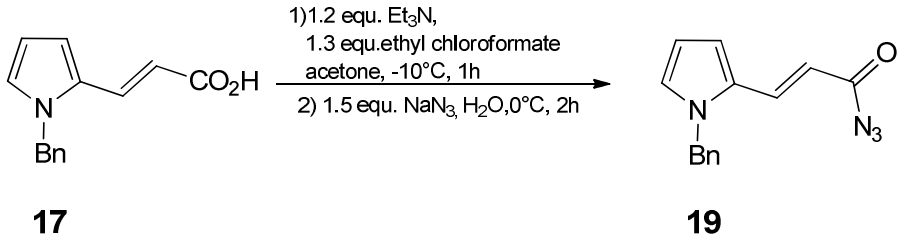
The Doebner modification of the Knoevenagel condensation is a reaction with malonic acid using piperidine as base in 0.1 equivalents in pyridine as solvent for better solubility of the reagents. The resulting unsaturated dicarboxylic acid is then decarboxylated. Applying the Doebner modification product **18** was successfully prepared as a brown solid in 82% yield.



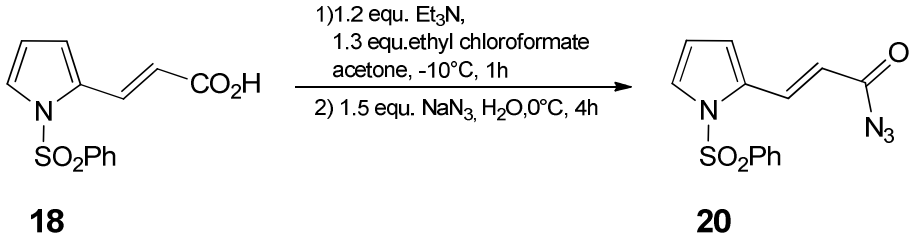
Scheme 23: Synthesis of compound 18

3.1.2.2 Conversion into an azido group

The next step in the synthesis of 5-azaindole is the conversion of the carboxylic group into an azide functionality. The azide moiety is required for the subsequent Curtius rearrangement reaction to form the pyrrolo[3,2-*c*]pyridine. For both, the benzyl- and the phenylsulfonyl protected compound, similar reaction conditions and reagents were used, as shown in Scheme 24 and 25.



Scheme 24: Synthesis of compound 19

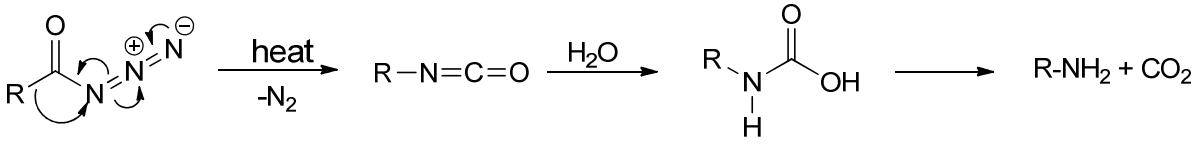


Scheme 25: Synthesis of compound 20

Compounds **17** and **18,** respectively, were dissolved in acetone, triethylamine was added very slowly and the mixture was cooled to -10°C in an ice/NaCl bath. Subsequently ethyl chloroformate was added dropwise and after a reaction time of one hour at -10°C sodium azide dissolved in deionised water was added. After quenching the reaction with deionised water and subsequent extraction with dichloromethane the product (**19** and **20**) was subjected to the next synthetic step without further purification.

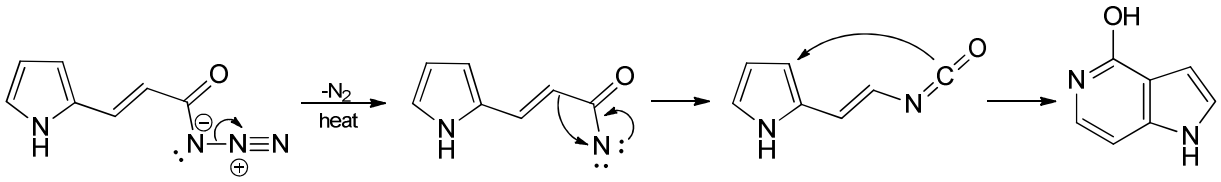
3.1.2.3 Curtius rearrangement

A key step in the synthesis of 5-azaindole is a Curtius rearrangement. The Curtius rearrangement is the thermal decomposition of carboxylic azides to isocyanates. The reaction starts with an acyl azide which is formed by nucleophilic substitution of an acyl chloride by sodium azide. Upon heating, nitrogen (N_2) is released in a thermal decomposition, affording the corresponding nitrene. Nitrenes, like carbenes, are enormously reactive and electrophilic. Substituent R then migrates from the carbon atom to the electron deficient nitrogen atom of the nitrene resulting in isocyanate formation. Isocyanate is unstable in water and carbamic acid is formed which will undergo spontatneous decarboxylation to an amine.[11(b)]



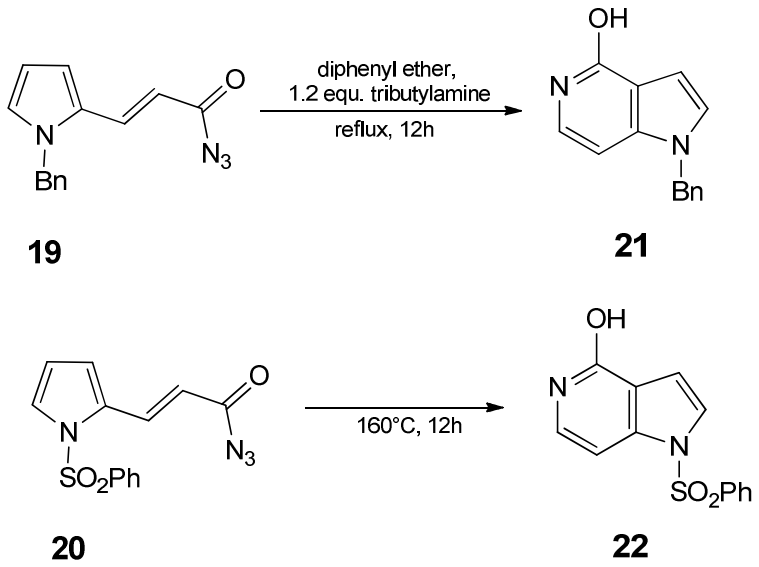
Scheme 26: Curtius degradation from carboxylic acid azides

The 5-azaindole ring system is formed in a Curtius rearrangement of azide **19** or **20**, respectively, and subsequent intramolecular attack of the isocyanate at position 3 of the pyrrole ring. The configuration of the double bond in the azide was found to be not relevant, as both, *cis*- and *trans*-compound were readily converted to the 5-azaindole.



Scheme 27: Curtius rearrangement followed by cyclization

Different reaction conditions were applied for the rearrangement and subsequent cyclisation reaction of compounds **19** and **20**, as depicted in Scheme 28.



Scheme 28: Syntheses of compound 21 and 22

Curtius rearrangements include thermal composition of the nitrene to an isocyanate, consequently high reaction temperatures are inevitable. Therefore, diphenyl ether, a high boiling solvent (bp = 258°C), was chosen as a suitable solvent for the Curtius rearrangement of compound **19**. Azide **19** was added dropwise to the boiling solvent containing 1.2 equivalents of tributylamine. During the reaction decomposition of the azide could be detected by the formation of nitrogen. After a reaction time of 12 hours the majority of the solvent was removed by distillation and product **21** was precipitated by addition of diethyl ether. The resulting brown solid was filtered off and washed with diethyl ether to remove residual diphenyl ether. Nevertheless, the isolation of product **21** was difficult, as diphenylether solidified during filtration, due to its low melting point of 26.9°C. ^{1}H- and

^{13}C-NMR spectroscopy in DMSO-d_6 showed signals of diphenyl ether, which covered any azaindole signals. Complete removal of diphenyl ether was neither possible by recrystallisation from toluene, nor by column chromatography. However, HPLC-MS measurements proved the formation of product **21**.

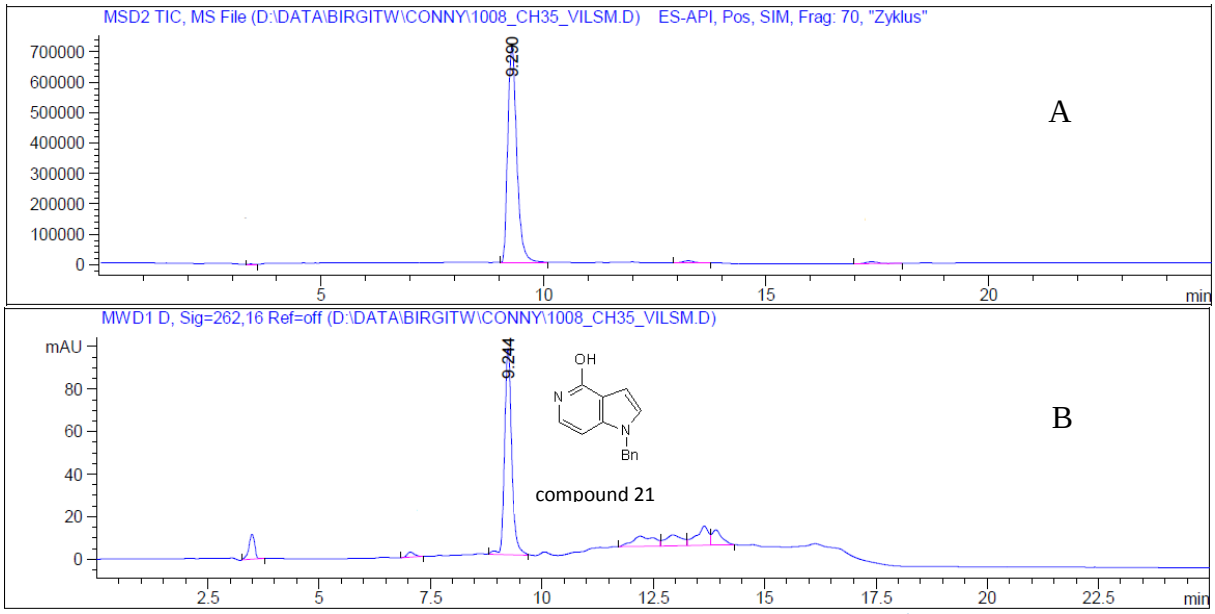


Figure 17: HPLC measurement of compound 21: A: SIM-mode, B: UV signal at 262 nm; (MH^+ = 225.1)

Similar reaction conditions were applied for the Curtius rearrangement of the phenylsulfonyl protected azide **20**. Diphenyl ether and 1.2 equivalents of tributylamine were heated to reflux and the phenylsulfonyl protected azide **20** was added very slowly to the solvent mixture. Solvents were removed by distillation and the product was precipitated as brown solid with diethyl ether. As complete removal of diphenyl ether was not possible and complicated product identification, the cyclisation step was carried out again without the use of solvent. A three-necked flask was heated to an approximate temperature of 160°C with an oil bath and the azide in dichloromethane was added dropwise over a period of two hours. After removing dichloromethane under reduced pressure the resulting brown oil was taken up in diethyl ether in order to precipitate the product. However, the product did not precipitate, so the ether was decanted and the resulting oil was dried under reduced pressure. ^{1}H- and ^{13}C-NMR spectra showed many impurities, thus making an unambiguous product identification difficult. The reaction mixture was washed with hydrochloric acid to remove triethylamine and the final product was recrystallized from toluene. The resulting solid was then purified twice by column chromatography, first with dichloromethane/methanol 40:1 and then with cyclohexane/ethyl acetate 1:3. However, impurities with similar polarity could not be entirely removed. Product **22** was identified by HPLC-MS, however, the majority of the signals in the ^{1}H-NMR spectrum were overlapping with signals of the isocyanate compound.

Unambiguous product identification was neither possible in the reaction using diphenyl ether as solvent nor in the reaction without solvent. In literature, formation of 5-azaindoles starting from azides by Curtius rearrangement and subsequent cyclisation is always described using diphenyl ether as solvent.[53, 54]

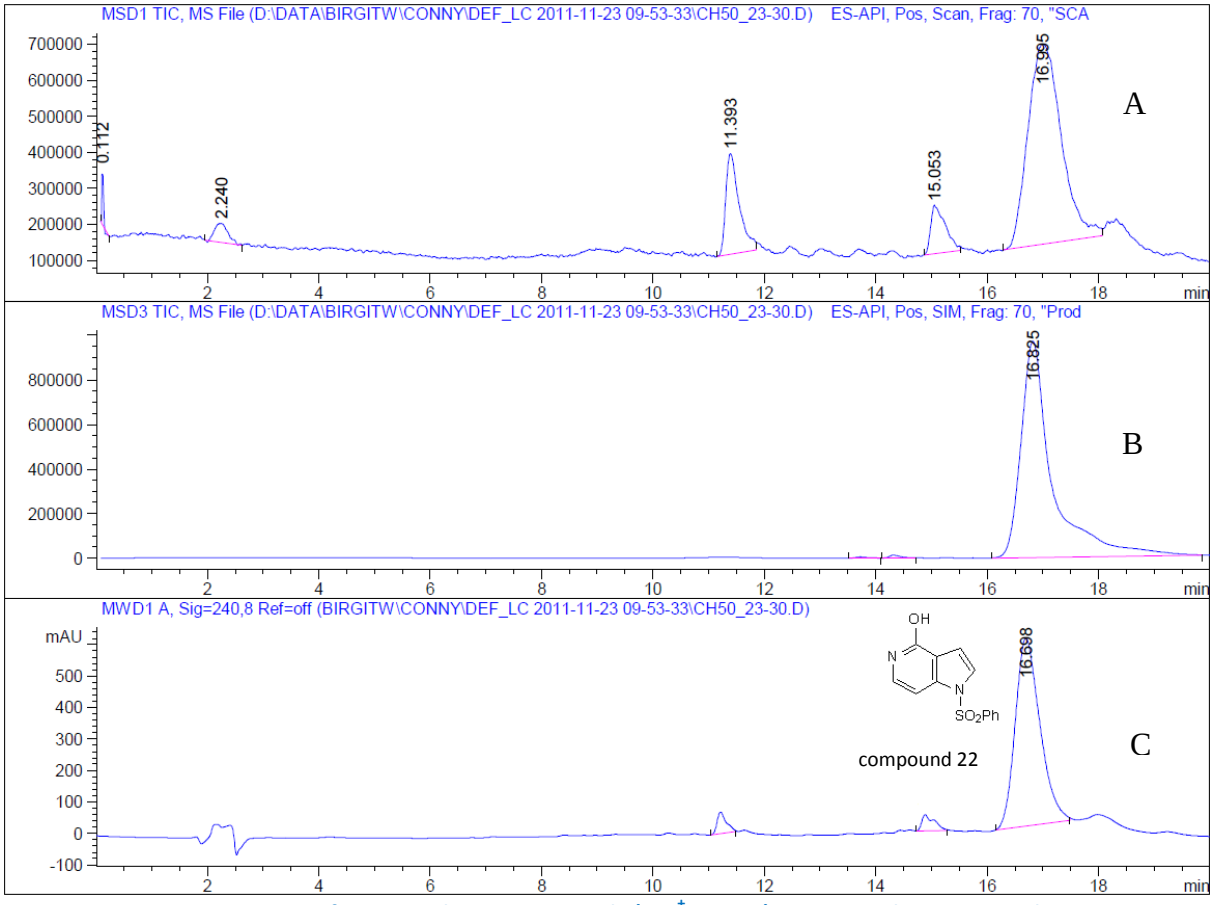
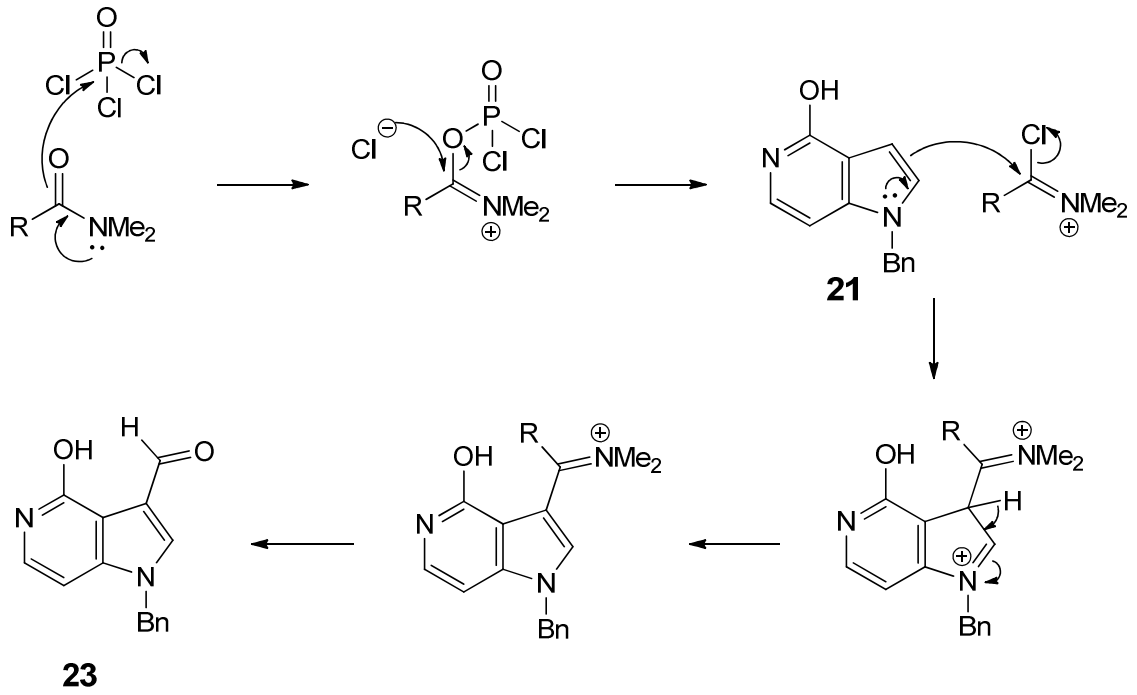


Figure 18: HPLC measurements of compound 22: A: Scan-mode (MH^+ = 275.1), B: SIM-mode, C: UV signal at 240 nm

3.1.2.4 Vilsmeier reaction

Introduction of an aldehyde functionality in position 3 of compound **21** is accomplished by a Vilsmeier-reaction. In this reaction the carbon electrophilicity is increased by adding phosphorus oxychloride and *N*,*N*-dimethylformamide in the absence of a strong acid or Lewis acid. The reaction proceeds in three substeps: formation of an iminium cation, electrophilic substitution and finally hydrolysis of the iminium salt, as depicted in Scheme 29.[11(c)]



Scheme 29: Mechanism of the Vilsmeier reaction for compound 23

In the first step, the formylating agent, the Vilsmeier-Haack reagent, is formed *in situ* from DMF and phosphorus oxy chloride. Subsequently, this iminium salt reacts with the pyrrole ring system *via* electrophilic aromatic substitution yielding an α-chloro amine, which is rapidly hydrolyzed during work up to give the aldehyde.[11(c)]

Different reaction conditions for the synthesis of compound **23** are summarized in Table 8.

Table 8: Reaction conditions for the synthesis of compound 23

Reagent [equiv.]	Solvent	Temperature	Reaction time [h]	Product	Reference number
DMF [1.5]	$POCl_3$	55°C	12	**23**	[55]
$POCl_3$ [1.2]	DMF	rt	12	**21**	[56]
$POCl_3$ [1.0]	DMF	rt -> 50°C rt -> 90°C	12 3	**23**	[49(b)]

In the first reaction, dimethylformamide was chosen as reagent and $POCl_3$ was used as solvent which is unusual for the formylation reaction.[55] Usually, dimethylformamide is used as solvent and $POCl_3$ is added in equimolar amounts. The reaction progress was monitored by HPLC-MS. Only 2% of product **23** was formed besides various unpolar, UV active impurities.

In the second approach, 1.2 equivalents of $POCl_3$ were added dropwise to dimethylformamide at 0°C, followed by slow addition of compound **21**. No conversion was detected after 12 hours at room temperature.

In the third reaction, compound **21** was first dissolved in dimethylformamide and subsequently 1.0 equivalents of $POCl_3$ were added. The reaction was stirred at 50°C for 12 hours or at 90°C for three hours. HPLC-MS measurements revealed that 40% of product **23** was formed at a temperature of 50°C, whereas only a yield of 32% was obtained at a temperature of 90°C. Because of the presence of diphenyl ether in the product from the previous step, compound **23** could not be identified by ^{1}H-NMR, due to the signal overlap in the area of 6 - 7 ppm.

Table 9: Yield of compound 23 at different reaction temperatures

	at 50°C	at 90°C
yield [%] of compound 23	40	32

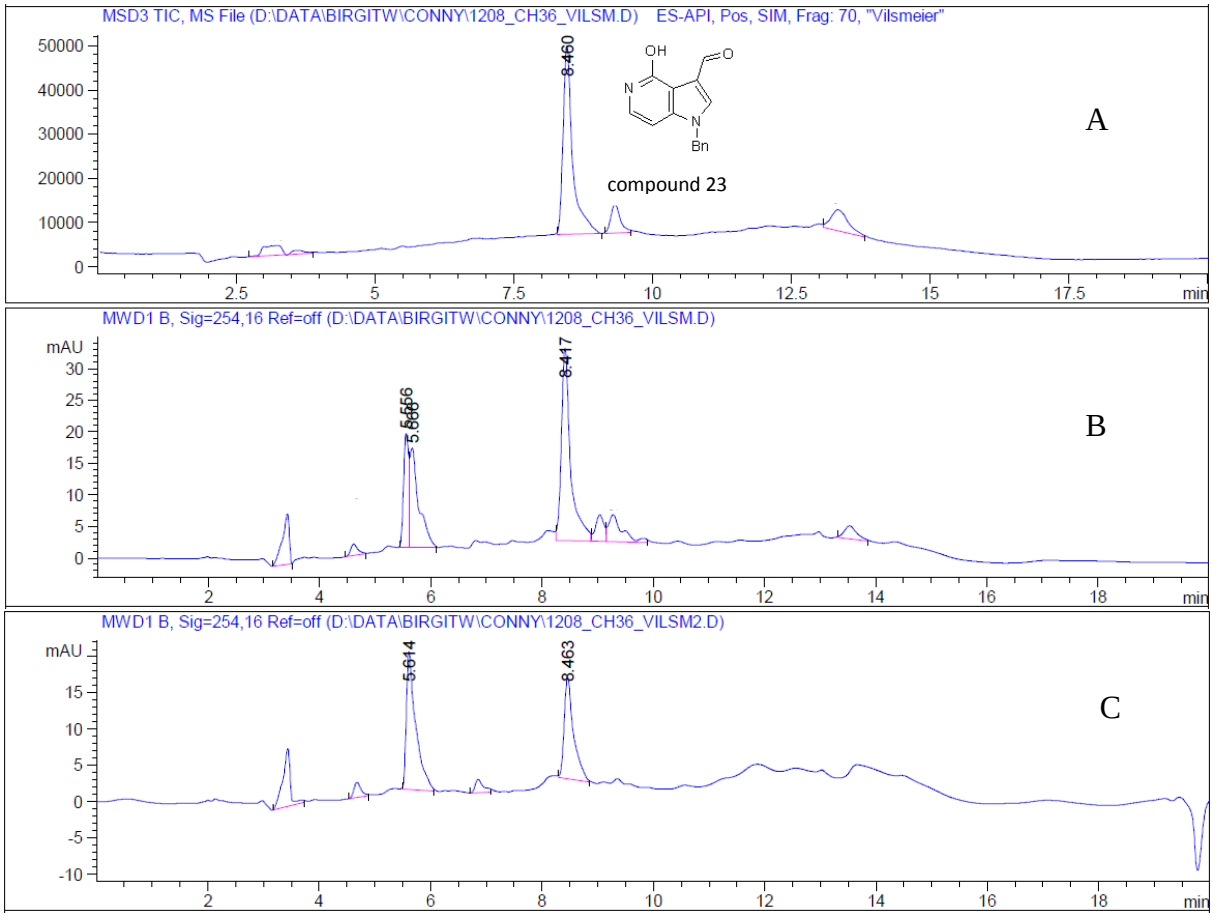


Figure 19: HPLC measurement of compound 23: A: SIM-mode, B: UV signal at 254 nm (reaction at 50°C), C: UV signal at 254 nm (reaction at 90°C); (MH^+ = 253.1)

Due to the high polarity of Vilsmeier product **23** purification by column chromatography was not possible. Therefore, the product mixture was separated by semi-preparative HPLC. Preliminary HPLC-

experiments showed separation of the compounds with an isocratic solvent mixture of methanol/water 40:60. Unfortunately, during semi preparative HPLC separation product and impurity eluted simultanously from the column.

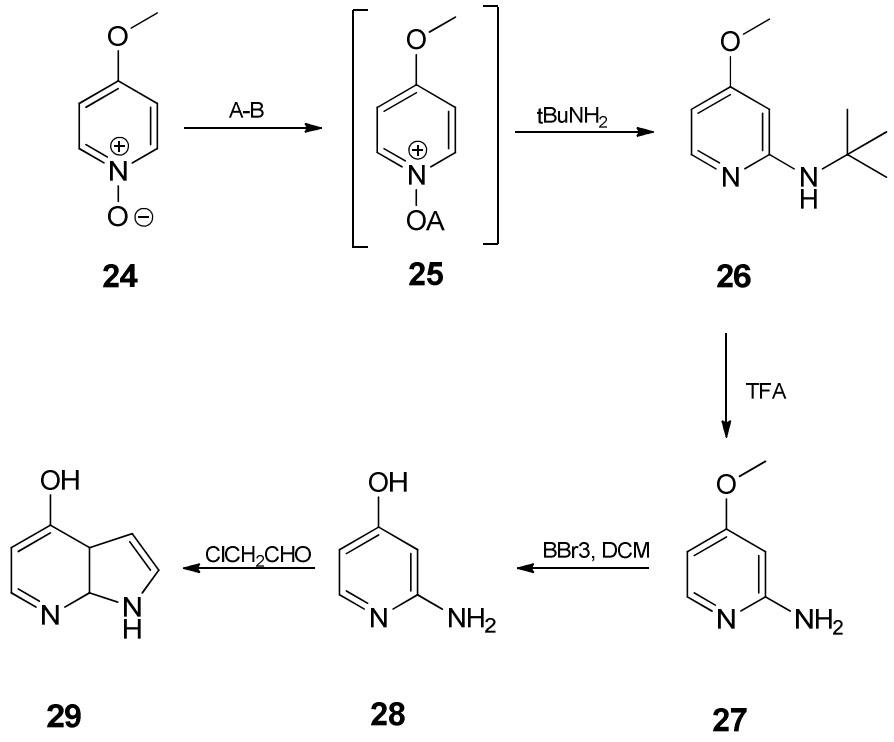
3.2 Syntheses starting from pyridine derivatives

A new preparation method for the synthesis of azaindoles, condensation of 2- or 4-amino hydroxypyridine with chloroacetaldehyde, was investigated. This synthetic method allows convenient and rapid synthesis of azaindoles in only one step.

3.2.1 Syntheses of pyrrolo[2,3-*b*]pyridines (7-azaindoles)

2-aminopyridines and similar compounds illustrate an important substrate class in organic chemistry and drug discovery. Amino-groups are generally introduced by a substitution reaction of 2-halopyridines and analogues, with ammonia, either metal-catalyzed[57] or under high temperature (approximately 200°C) and pressure[58]. Halides in 2-position of the pyridine can be prepared by chlorination of pyridine *N*-oxide, however, mostly in poor 2,4-regioselectivity and/or low yields.[59, 60] The Chichibabin reaction directly generates the 2-aminopyridine from sodium amide and pyridine, but is limited by unsatisfactory yields and low functional group tolerance, based on the strongly basic conditions and high temperatures.

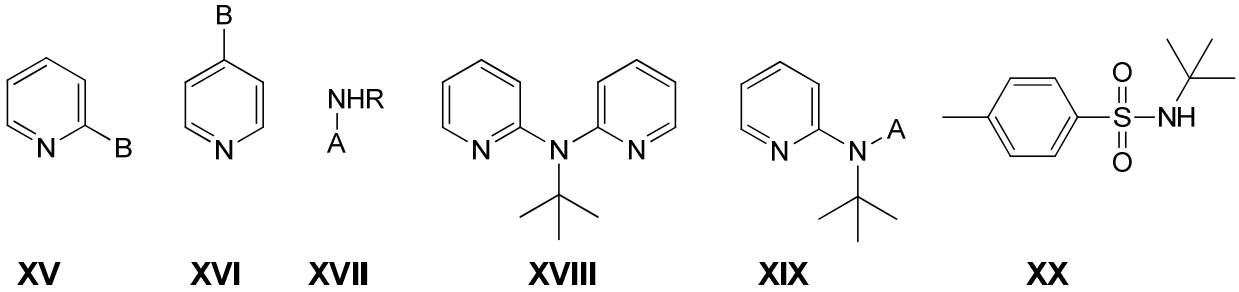
Yin et al[61] reported a new method for the introduction of amino-groups in 2-position of pyridines. Here, pyridine *N*-oxide reacts first with an electrophile to activate position 2 for nucleophilic attack. Nucleophilic addition of position 2 is then possible, allowing the formation of the desired 2-aminopyridine from compound **24**.



Scheme 30: Synthesis of compound 29 (novel synthetic route)

The activated species **25** can be prepared as a stable intermediate in good yields, however, byproducts **XV** and **XVI** form easily in the reaction of compound **25** with counterions B^- (B = Cl, TsO, AcO).

Subsequent treatment of compound **25** with *tert*-butylamine resulted in the formation of compound **26**. In this reaction step, addition of the activating reagent (TsCl, AcCl, Ts_2O) prier to the nucleophile (amine) is prerequisite to avoid formation of byproduct **XVII**. Furthermore, compound **27** can provoke a reaction with the intermediate **25** or the activating reagent, producing compounds **XVIII** and **XIX,** thus lowering the amount of compound **26**.[61] Consequently, the choice of reaction parameters, such as activating reagent, solvent and nucleophile show tremendous influence on the formation of side products.



Scheme 31: Possible byproducts of the reaction of pyridine *N*-oxide with activating reagents and a nucleophile

Yin et al. reported a clean reaction with approximately 61% conversion, containing very little dimerisation or tosylation byproduct, when pyridine *N*-oxide was treated with 1.75 equivalents of TsCl and 4.5 equivalents of *t*-$BuNH_2$ in dichloromethane. In this amination reaction a good 2-/4-regioselectivity was obtained in contrast to poor 2,4-selectivity in chlorination reactions. The only side reaction observed is the reaction between amine and activating reagent to form compound **XX**.[61]

In this thesis, selected reaction conditions for the preparation of compound **27** were chosen and optimized as summarized in Table 10.

Table 10: Reaction parameters for the synthesis of compound 27

Reaction	*t*-$BuNH_2$ [equiv.]	Reagents [equiv.]	Solvents	Temperature	Reaction time [h]	Product 27
1	9.0	TsCl [4.0]	$CHCl_3$	0°C	1	-
2	4.5	TsCl [1.8]	$CHCl_3$	0°C	12	-
3	4.5	TsCl [1.8]	$PhCF_3$, $CHCl_3$	0°C	12	-
4	4.0 + 5.0	Ts_2O [2.0 + 4.0]	$PhCF_3$, $CHCl_3$	0°C	3	+
5	4.0 + 2x 2.5	Ts_2O [2.0 + 2x 1.0]	$PhCF_3$, $CHCl_3$	0°C	12	+

(-) no formation of the desired product 27; (+) formation of product 27

4-methoxy-pyridine-1-oxide was dissolved in chloroform and cooled to 0°C with an ice bath. After addition of 9.0 equivalents *t*-butylamine and 4.0 equivalents tosylchloride the yellow reaction solution was stirred for one hour. Thin layer chromatography (cyclohexane/ethyl acetate 4:1) confirmed conversion. Trifluoroacetic acid was then added to the reaction mixture, which was heated to 70°C to cleave the *t*-butyl group from the amine functionality. The resulting product was purified by column chromatography using cyclohexane/acetic acid 4:1 as eluent. According to ^{1}H- and ^{13}C-NMR spectroscopy only *t*-butyltosylamide **XX** was formed instead of the desired product **27**. Possibly, the reaction time was too short to allow formation of the activated species **25**.

In the next two reactions the amounts of reagents used were reduced to 4.5 equivalents *t*-butylamine and 1.8 equivalents tosylchloride. Reactions were run in either chloroform, or a mixture of chloroform and trifluorotoluene. Trifluorotoluene was reported from Yin et al.[61] as solvent of choice for high conversion to product **27**, however, the solubility of reagent **24** is limited in this solvent. Therefore, chloroform was added to obtain a clear solution. Nevertheless, only the side reaction of tosylchloride and the amine was observed forming *t*-butyltosylamide **XX**. The order of addition of the reagents was changed in the case of using only chloroform as solvent. First, tosylchloride and pyridine *N*-oxide were dissolved in chloroform followed by addition of amine, however, no improvement concerning the formation of the desired intermediate **26** was detected. The reaction mixture was stirred overnight and then trifluoroacetic acid was added. The resulting solid was purified by column chromatography using cyclohexane/ethyl acetate 4:1 as eluent. A

nonploar as well as a polar compound were isolated as white solid. The desired product could not be detected in ^{1}H- and ^{13}C-NMR spectroscopy, however, the nonpolar compound was identified as side product **XX** and the polar compound as dimer **XVIII**.

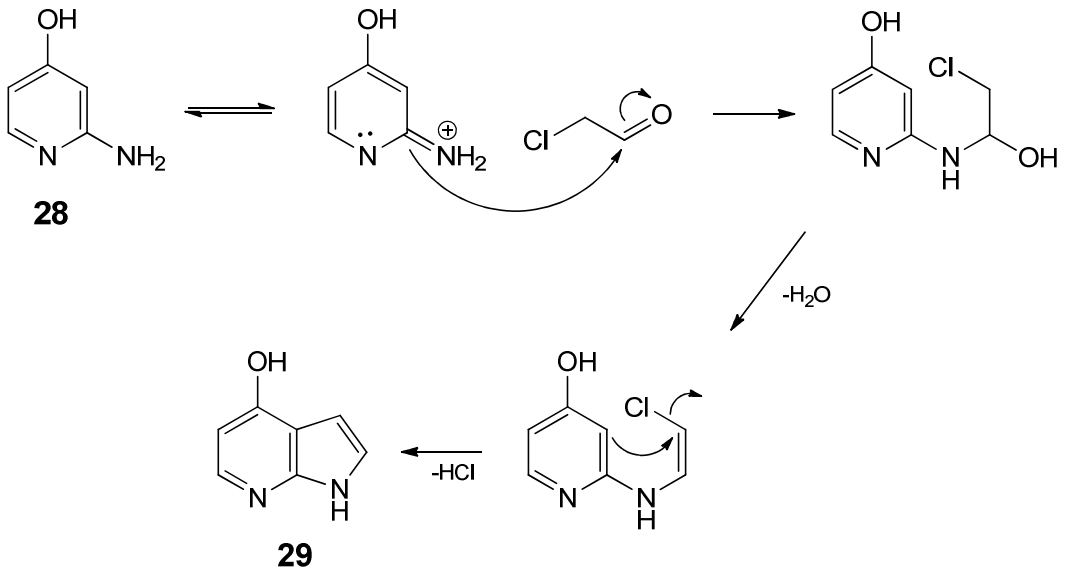
In another modification *p*-toluenesulfonic anhydride was used as activating reagent instead of tosylchloride. 4.0 equivalents tert-butylamine and 2.0 equivalents *p*-toluenesulfonic anhydride were added. After stirring for one hour further 5.0 equivalents of *t*-butylamine and 4.0 equivalents of *p*-toluenesulfonic anhydride were added and the reaction mixture was stirred for additional two hours. The *tert*-butyl group was cleaved using trifluoroacetic acid at 70°C overnight, obtaining 40% of the desired product **27** after purification by column chromatography. However, also the byproduct **XX** was obtained in 22% yield.

Formation of a primary amino group in position 2 of the pyridine could only be achieved with *p*-toluenesulfonic anhydride as electrophile and trifuorotoluene as solvent. Consequently, this reaction method was improved by adding the reagents in smaller amounts and over an extended period of time as illustrated in Table 8 (entry 5). Deprotection with trifluoroacetic acid took place for two days at 40°C. Purification was carried out by column chromatography using cyclohexane/ethyl acetate 4:1 as eluent. Compound **27** was received in 95% yield as a yellowish solid.

In summary, the most efficient preparation method of compound **27** was adding reagents in small amounts and lager equivalents and deprotecting the amino group over a period of two days at lower temperature. A disadvantage of this reaction was tedious product purification from salts and byproducts.

The next step in the synthetic route of preparing 7-azaindole **29** was ether cleavage using boron tribromide solution (1.0 M in dichloromethane)[62] under nitrogen atmosphere. Thus, a boron tribomide solution was cooled to 0°C and after addition of compound **27** the solution was heated to 60°C and stirred over night. The reaction mixture was quenched with saturated sodium bicarbonate-solution and extracted with dichloromethane. The desired product **28** could not be detected in HPLC-MS, consequently these synthetic steps were not further investigated.

In a further attempt, commercially available 2-amino-4-hydroxypyridine **28** was used for the preparation of 7-azaindole **29**. Starting from compound **28** the desired azaindole **29** can be prepared by condensation with chloroacetaldehyde in only one step, as depicted in Scheme 32.



Scheme 32: Proposed mechanism for the cyclisation reaction forming compound 29

Sodium acetate was dissolved in deionised water, treated with compound **28** and heated to 80°C. 1.2 equivalents of chloroacetaldehyde were added dropwise and the brown reaction mixture was stirred overnight at 80°C. After removing the solvent under reduced pressure the resulting solid was purified by column chromatography using dichloromethane/methanol 20:1 as eluent. HPLC-MS measurements of the relevant fractions indicated only minor quantities of the desired product **29**, but formation of a different main product (MH^+ = 177.1).

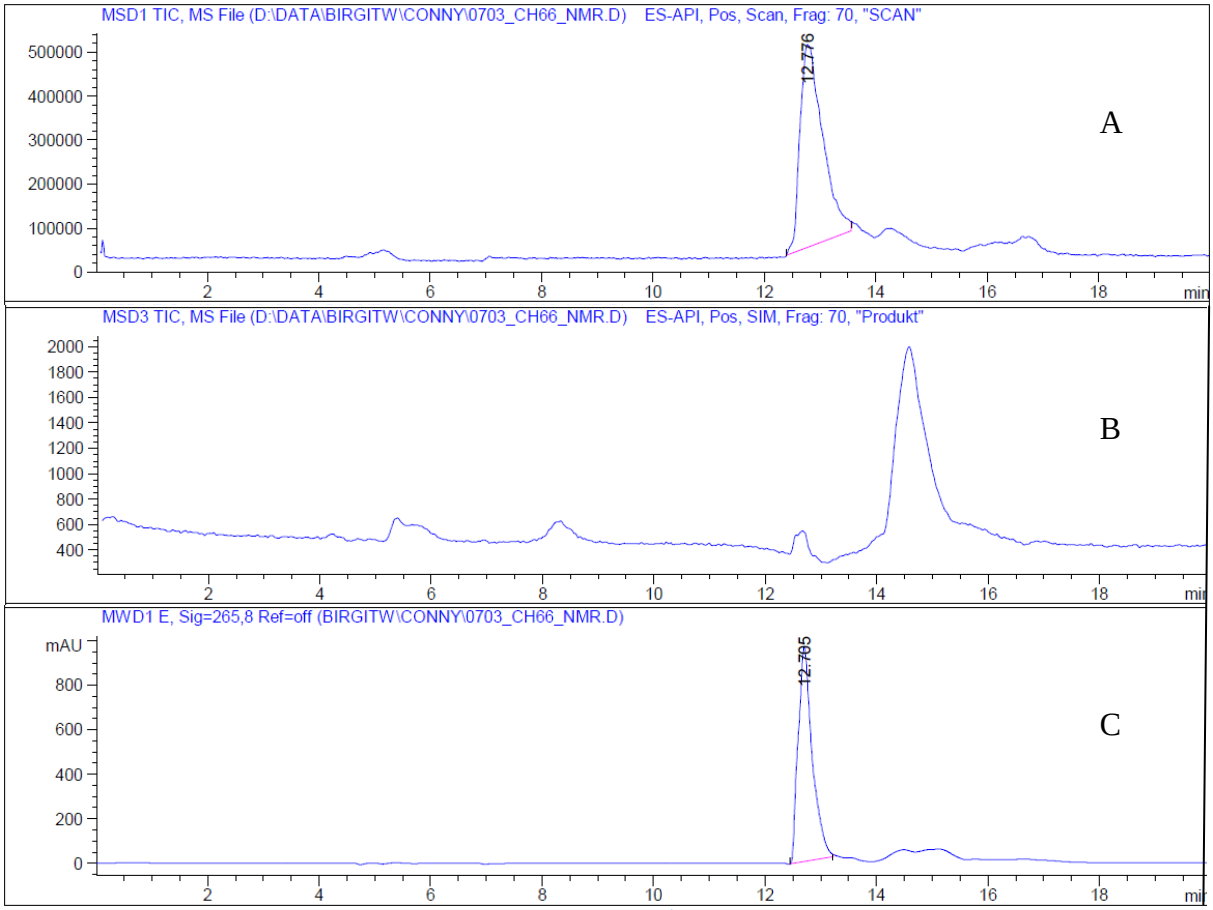
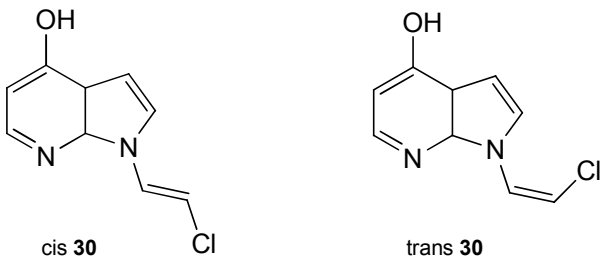


Figure 20: HPLC measurement of compound 29: A: Scan-mode (MH^+ = 135.1), B: Sim-mode, C: UV signal at 265 nm

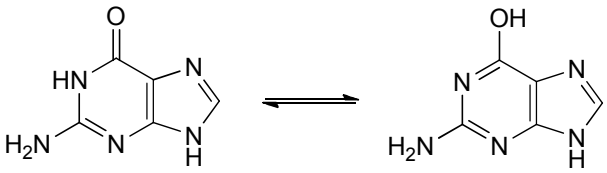
The main product was successfully identified as 1-substituted azaindole **30** by ^{1}H, ^{13}C and HSQC NMR spectroscopy. This product was formed by condensation reaction of a second equivalent of chloroacetaldehyde to the amine group of the starting material **28**. NMR spectroscopy demonstrated compound **30** was formed in both, *cis*- and *trans*- configuration (Scheme 33).



Scheme 33: *cis* and *trans* compound 30

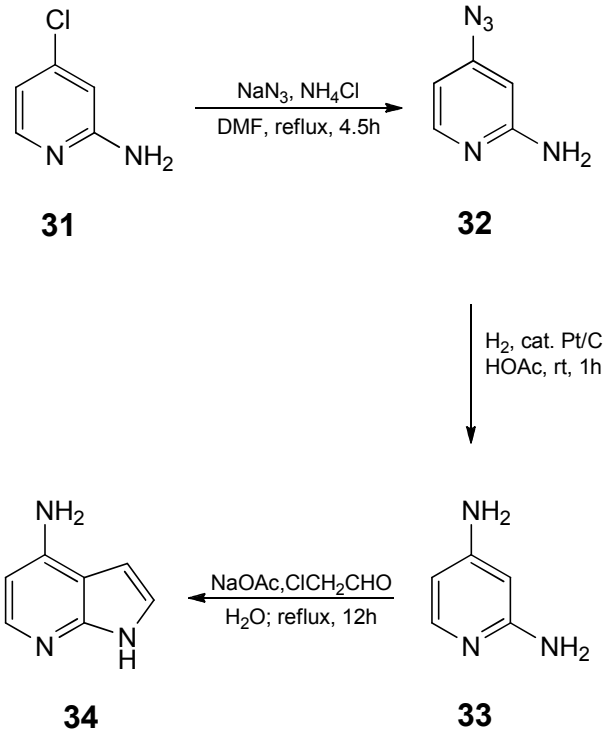
This type of condensation reaction has not been discussed for pyrrolopyridines in literature, but only for pyrrolopyrimidines. In contrast to the pyridine starting material used in the synthesis of compound **30**, pyrimidine starting materials show a lactim-lactam tautomerism. Position 5 in the pyrimidine ring is better activated in its lactam form and therefore better accessible by

chloroacetaldehyde. However, successful preparation of compound **30** proved, that the tautomerism is not essential to the formation of the bicyclic ring system.[9]



Scheme 34: Lactam-lactim tautomerism of guanine

In the next approach it was investigated if the keto functionality in position 4 is essential for the cyclization step or if it could be replaced by an amino group, as shown in Scheme 35.



Scheme 35: Synthetic route to compound 34

Compound **34** was synthesised starting from 2-amino-4-chloropyridine **31** by treating with ammonium chloride and sodium azide in dimethylformamide under nitrogen atmosphere, thus replacing the chloride in position 4 by an azido group. The reaction mixture was refluxed and stirred for 4.5 hours. After quenching the reaction with saturated sodium carbonate-solution various ammonia-salts precipitated and were separated by filtration. When adding insufficient amounts of sodium carbonate, the ammonia-salts did not precipitate which made separation difficult and lowered the yield. The product was obtained in 67% yield and was characterised by HPLC-MS and NMR spectroscopy. Both proved formation of compound **32**. Afterwards the azide was reduced to an

amine group. Two different reducing methods were investigated. The desired product **33** could be achieved by reduction of the azide with sodium borohydride in water and dioxane. However, due to the increased polarity of the diamino product **33**, separation from inorganic carbonates was difficult. Product formation was proven by HPLC-MS.

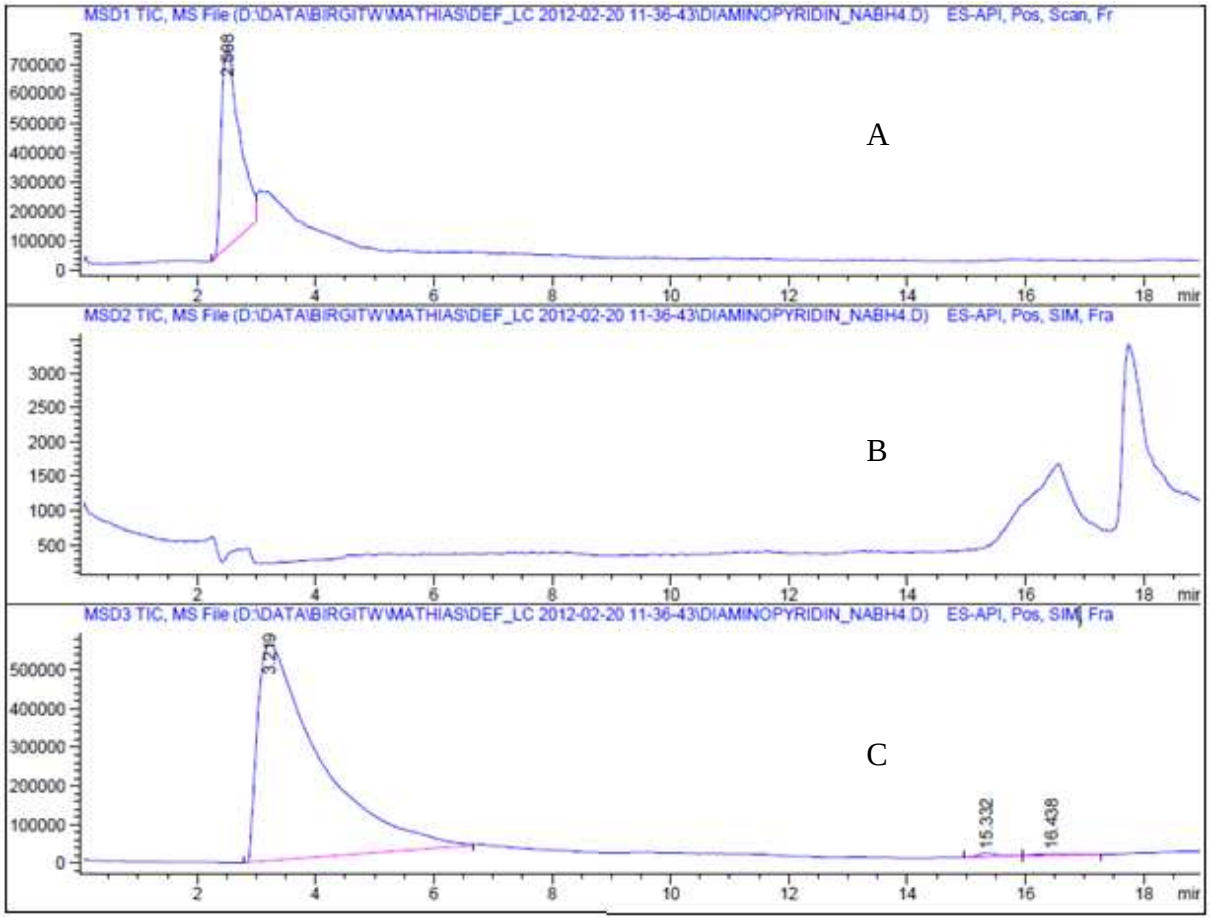


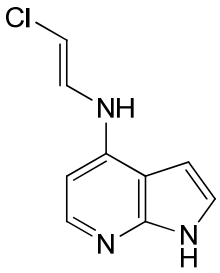
Figure 21: HPLC measurement of compound 33: A: Scan-mode (MH^+ = 136.1), B: Sim-mode 32, C: Sim-mode 33 (MH^+ = 110.1)

The azide functionality was also successfully reduced to the amine in a hydrogenation reaction using a platinum catalyst on charcoal. Product 24 was obtained in 114% yield, and characterized by HPLC-MS and NMR spectroscopy, however, residual solvents, i.e. acetic acid and dimethyl formamide has still found. Compared to the reduction using sodium borohydride, product isolation was significantly easier in the case of hydrogenation reaction.

Compound **33** was then used for the following cyclisation reaction without further purification. The reaction was performed with sodium acetate in deionised water. The reaction was carried out with different amounts of chloroacetaldehyde and the reaction progress was followed by HPLC-MS. Reaction conditions and products formed are summarized in Table 11.

Table 11: Reaction conditions and progress of the cyclisation reaction

Reaction time [min]	Chloroacetaldehyde [ml]	Temperature [°C]	Reagent 33 [%]	Product 34 [%]	Byproduct 35 [%]
30	0.13	90	67	18	15
60	0.25	90	52	22	26
90	0.38	90	36	21	43
120	0.50	rt	31	17	52



35

Scheme 36: Byproduct 35 of the synthesis of compound 34

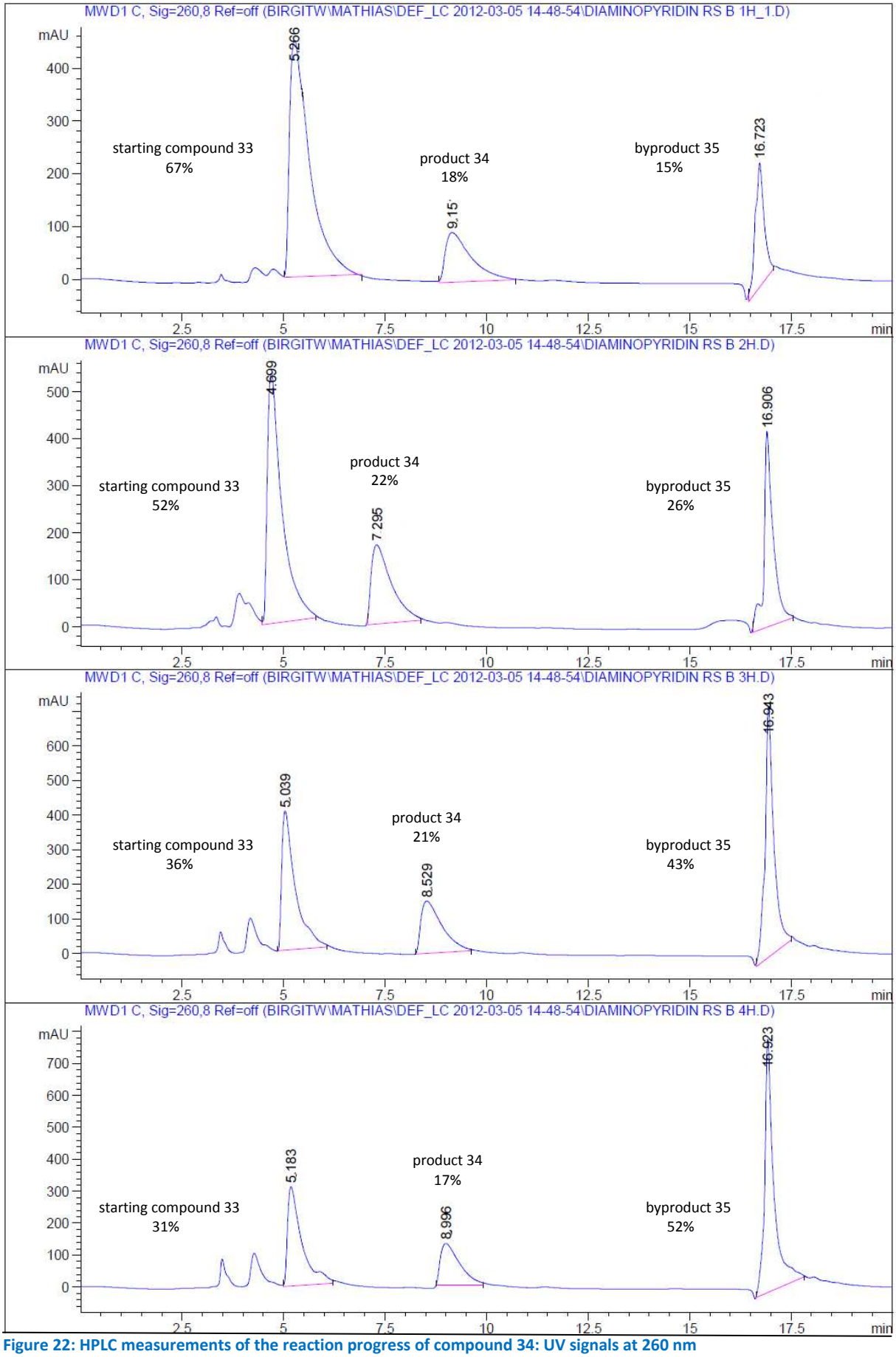


Figure 22: HPLC measurements of the reaction progress of compound 34: UV signals at 260 nm

The chromatograms reveal that the conversion of substrate **34** depends on reaction time, stoichometric ratio of chloroacetaldehyde and possibly reaction temperature. After a reaction time of one hour and addition of 0.25 mL chloroacetaldehyde 22% of the corresponding 4-aminopyrrolo[2,3-*b*]pyridine **34** was obtained. The longer the reaction time the higher was the amount of byproduct **35**, whereas the amount of product **34** stayed unaffected. The reaction was stopped after four hours, at which point 52% of byproduct **35** and 20% of product **34** were found in the reaction mixture. The yield of compound **35** could be further increased by longer reaction times, since about one third of starting material **34** was still available in the reaction mixture after a reaction time of four hours.

Compounds **34** and **35** were seperated by column chromatography using dichloromethane/methanol as solvent in a ratio of 5:1. Only a small part of purified byproduct **35** was isolated. Consequently, a less polar solvent was chosen for the purification step, a gradient of dichloromethane to dichloromethane/methanol 5:1. Neither byproduct **35** nor product **34** could be eluted with unpolar solvents, using dichloromethane/methanol 10:1 both compounds were eluted simultaneously, as shown in Figure 23.

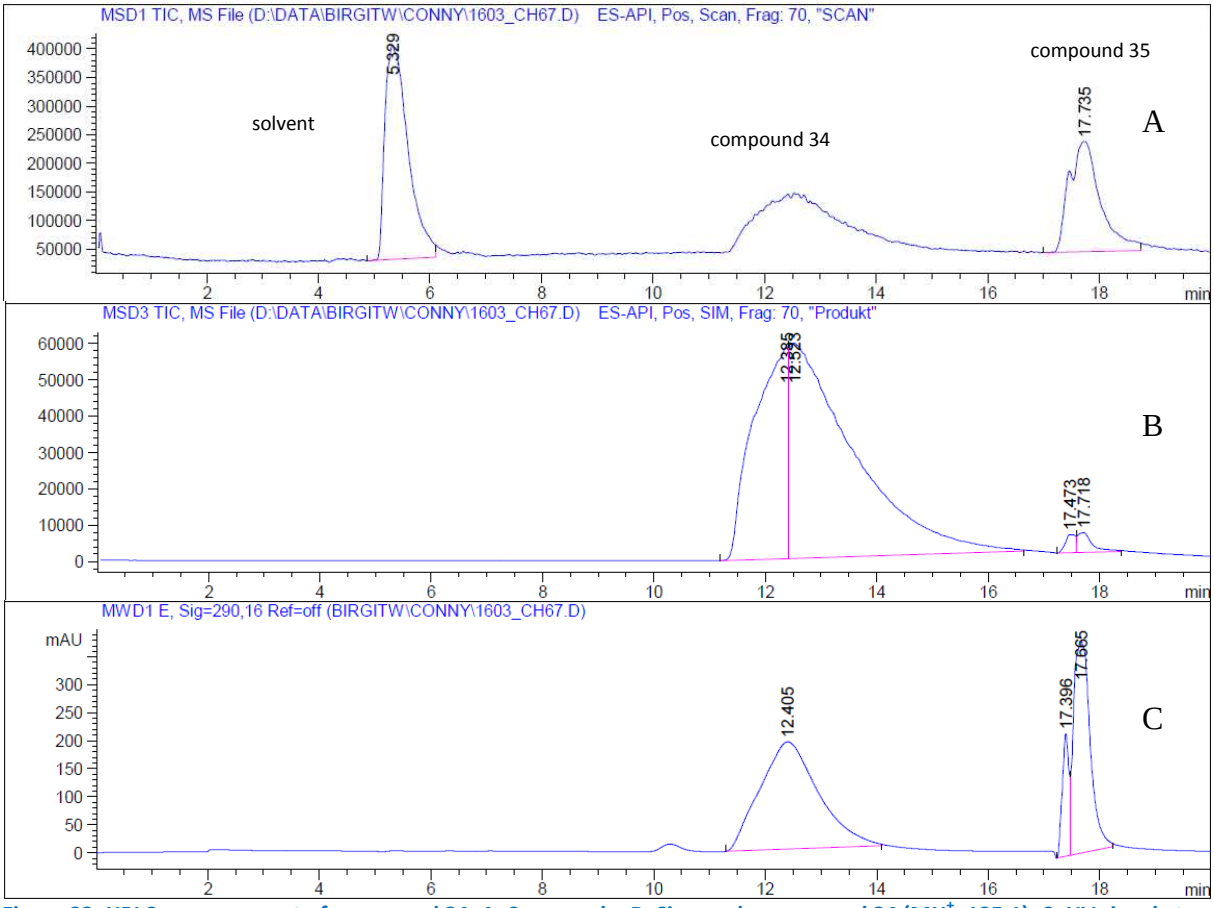
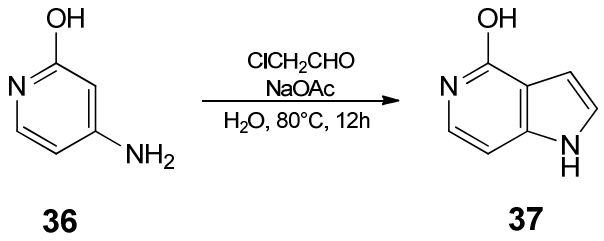


Figure 23: HPLC measurement of compound 34: A: Scan-mode, B: Sim mode compound 34 (MH^+=135.1), C: UV signal at 290 nm

3.2.2 Synthesis of 1H-pyrrolo[3,2-*c*]pyridine (5-azaindole)

5-azaindole **37** was synthesised starting from a pyridine precursor as depicted in Scheme 37.



36 **37**

Scheme 37: Synthesis of compound 37

4-Amino-2-hydroxypyridine **36** was suspended in a solution of sodium acetate in deionised water and heated to 80°C. Afterwards, chloroacetaldehyde was added dropwise and the reaction mixture was stirred at 80°C overnight. Extraction with ethyl acetate could not eliminate the impurities, so purification was carried out by column chromatography using dichloromethane/methanol 20:1 as eluent. HPLC-MS confirmed formation of compound **37**.

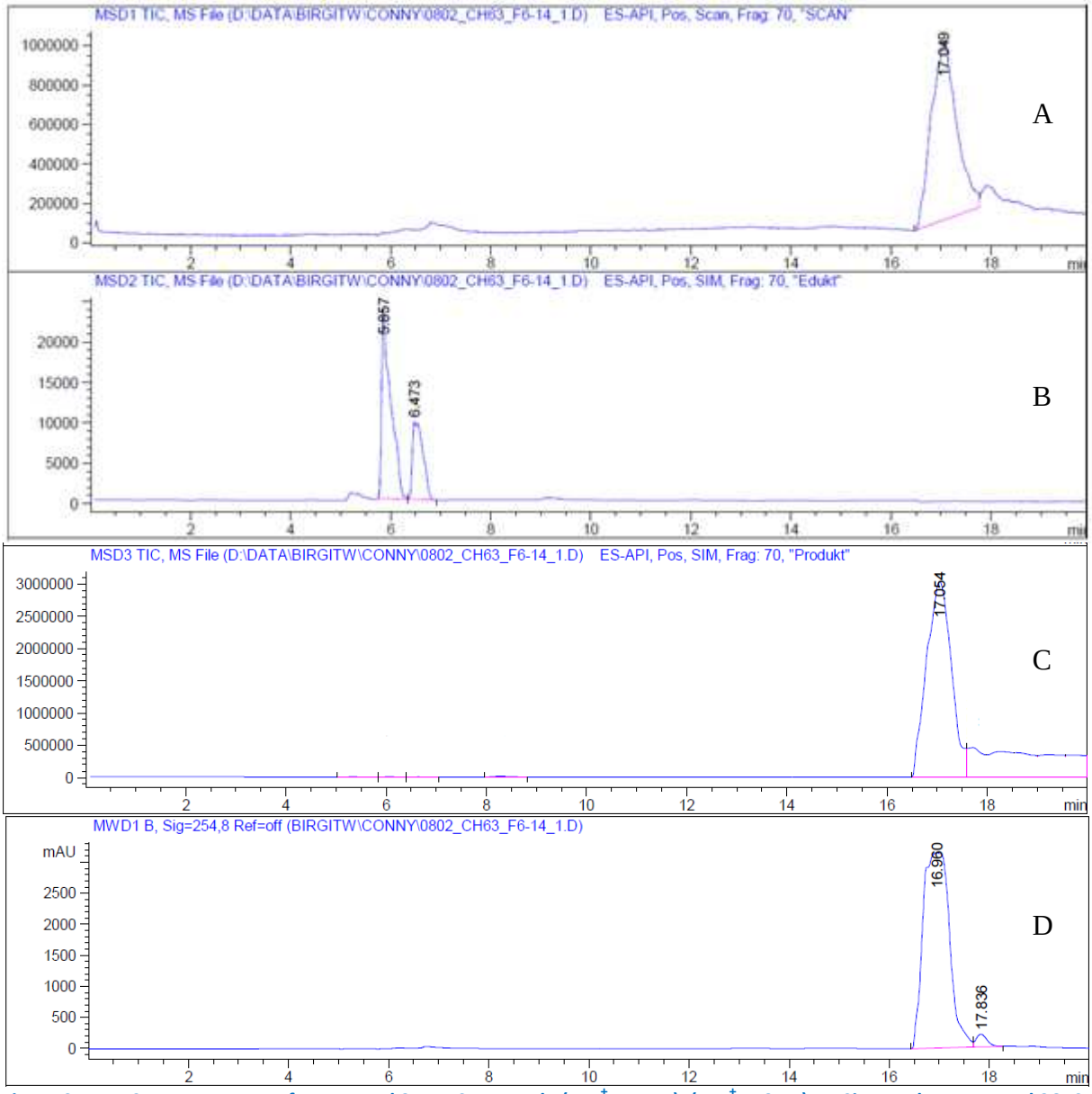
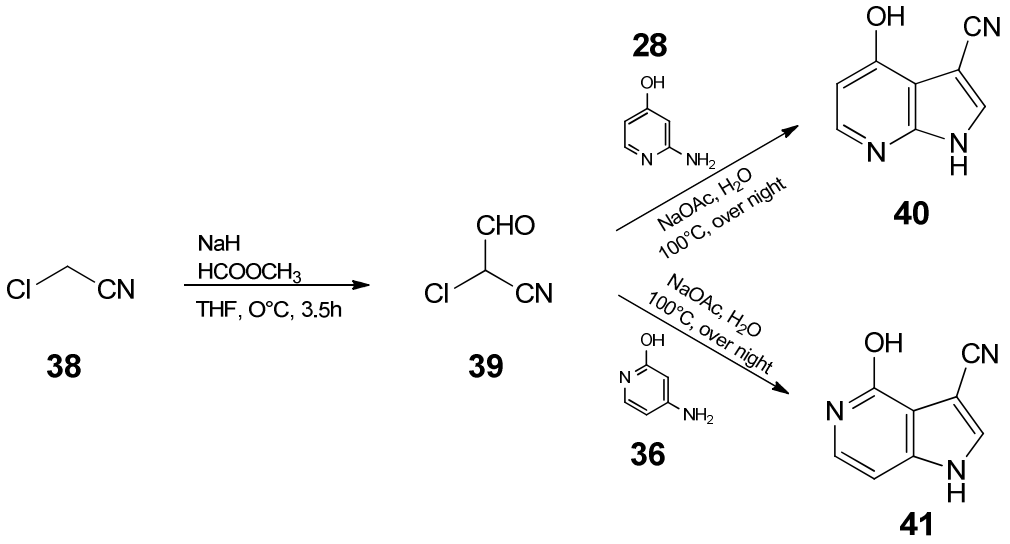


Figure 24: HPLC measurement of compound 37: A: Scan-mode (MH^+= 111.1), (MH^+= 135.1), B: Sim-mode compound 36, C: Sim-mode compound 37, D: UV signal at 254 nm

Compound **37** was also characterized by ^{1}H- and ^{13}C NMR spectroscopy. However, the product contained acetic acid as impurity. To eliminate acetic acid the sample was treated with toluene at reflux generating an azeotrop. Most of the acetic acid was removed yielding compound **37** as brown solid in satisfying purity.

3.2.2.1 Introduction of a cyanide functionality in position 3 in 5- and 7-azaindoles

The next synthetic step was the introduction of a cyano group in position 3 of the azaindole ringsystem. This could be achieved by formylation followed by conversion of the aldehyde-functionality into an oxime and subsequent dehydration to the nitrile. This approach includes three steps, however the formylation reaction with DMF and $POCl_3$ (Vilsmeier reaction) already created various difficulties, as described in chapter 3.1.2.4. Gangjee *et al.*[6] reported a method preparing 2-amino-4-oxo-5-cyanopyrrolo[2,3-*d*]pyrimidine by condensation of chloro(formyl)acetonitrile starting from the corresponding 2-diamino-6-hydroxypyrimidine. In this work, this method was applied to the prepartion of 3-cyanoazaindoles, allowing the preparation of the 3-cyano substituted azaindoles from pyridines in only two steps, as depicted in Scheme 38.



Scheme 38: Synthetic route to compounds 40 and 41

Compound **39** was prepared by treating sodium hydride with 1.1 equivalents of methyl formate and chloracetonitrile in tetrahydrofuran for 3.5 hours at 0°C. The dark brown reaction mixture was slowly quenched with deionised water and extracted with diethyl ether. The aqueous layer was poured onto ice and the pH value was adjusted with 5 N hydrochloric acid to pH 4 and was then extracted again with diethyl ether. The organic layer was then dried over sodium sulfate and concentrated under reduced pressure. The solvent was reduced at room temperature and precursor **39** was immediately used for the next synthetic step, as the compound is known to be unstable. Compound **39** was used without further purification for the condensation reaction with 2-amino-4-hydroxypyridine **28** yielding 4-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile **40** or with 4-amino-2-hydroxypyridine **36** producing 4-hydroxy-1*H*-pyrrolo[3,2-*c*]pyridine-3-carbonitrile **41**. These reactions were carried out with 2 equivalents of sodium acetate in deionised water at 100°C and were stirred

overnight. After work up with aqueous ammonia-solution (pH 7.5) a brown precipitate formed, but it was too fine to filter it off, so the aqueous layer was extracted with ethyl acetate. The product was then purified by elution from a silica gel frit with dichloromethane/ methanol 5:1. The ^{1}H-NMR spectra of both substrates, **40** and **41**, did not allow unambiguous identification, as the samples contained major amounts of impurities. While product formation of both products, **40** and **41**, was proven by HPLC-MS, only a small amount of the desired product was formed in both reactions.

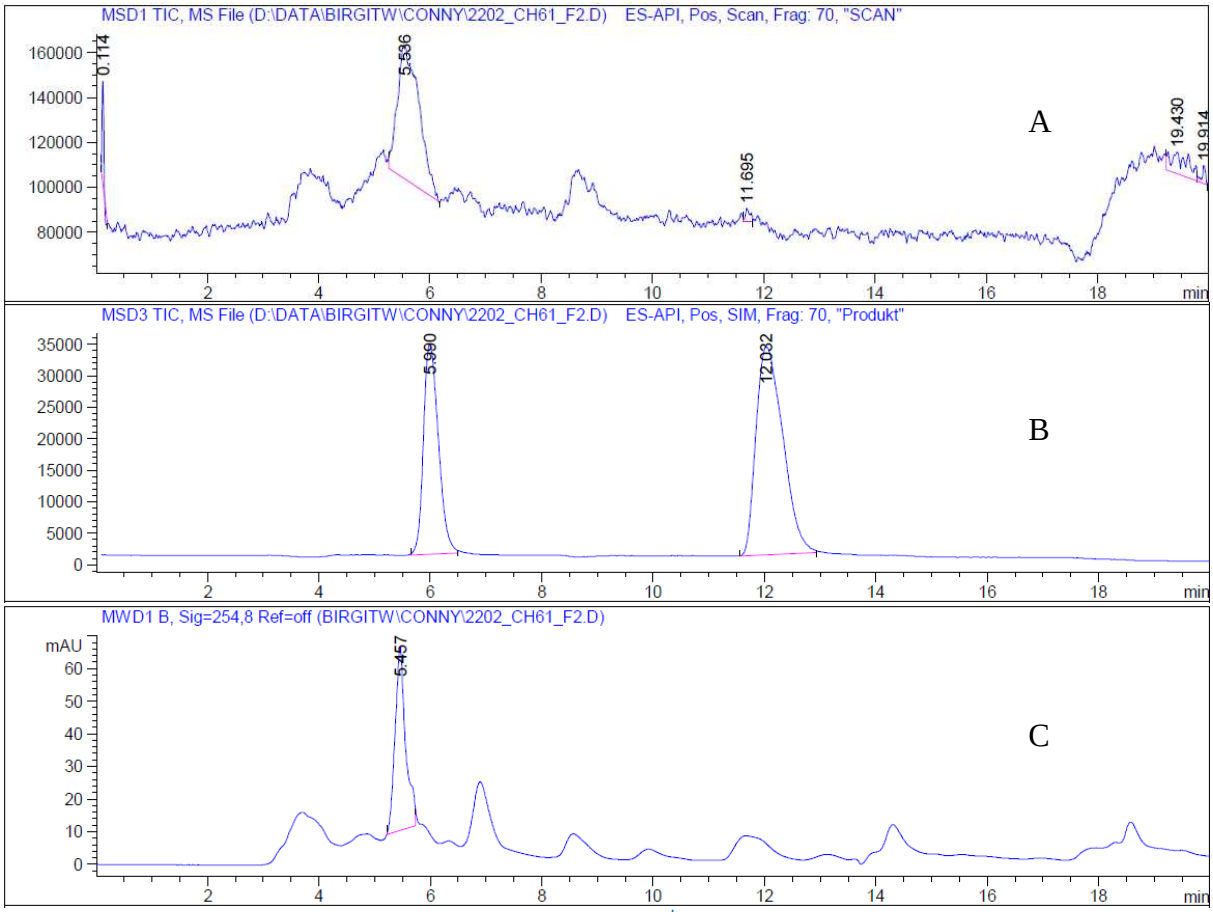


Figure 25: HPLC measurements of compound 40: A: Scan-mode MH^+ (5.54 min)= 160.1, B: Sim-mode compound 40, C: UV signal at 254 nm

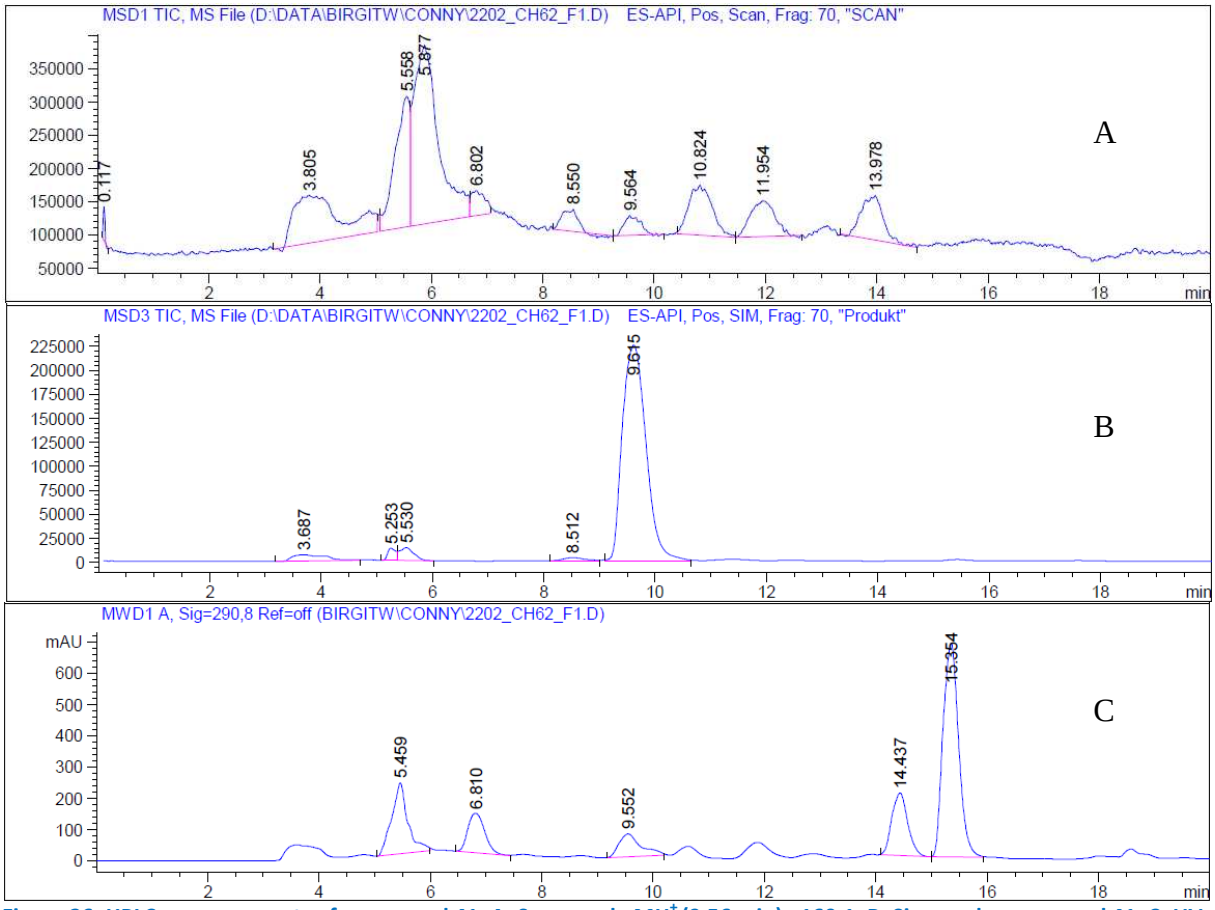


Figure 26: HPLC measurements of compound 41: A: Scan-mode MH^+ (9.56 min)= 160.1, B: Sim-mode compound 41, C: UV signal at 290 nm

Low conversions might be explained by degradation of the precursor **39**, since this compound is not stable over a longer period and at high temperature. Reducing the solvent in vacuum could have taken too long or the reaction temperature for the cyclization step (100°C) was too high. Fragments from the decomposition of **39** might have reacted with other reagents producing various compounds in different side reactions which were not identified in this project. Optimization of the reaction conditions regarding temperature, reaction time or purification could possibly increase the yield of compounds **40** and **41**.

4 Conclusion and Outlook

During this master thesis the synthesis of substituted pyrrolo[2,3-*b*]pyridines as well as substituted pyrrolo[3,2-*c*]pyridines were investigated by using two different synthetic strategies: the synthesis of the bicyclic ring systems starting from a pyrrole (Figure 27) as well as from a pyridine (Figure 28) precursor.

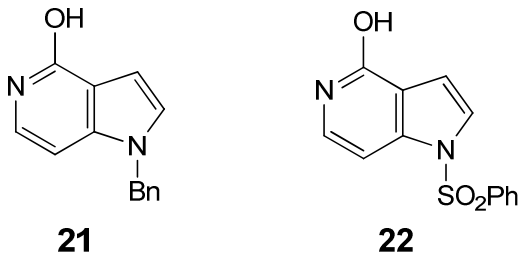


Figure 27: Compounds prepared starting from pyrrole as precursor

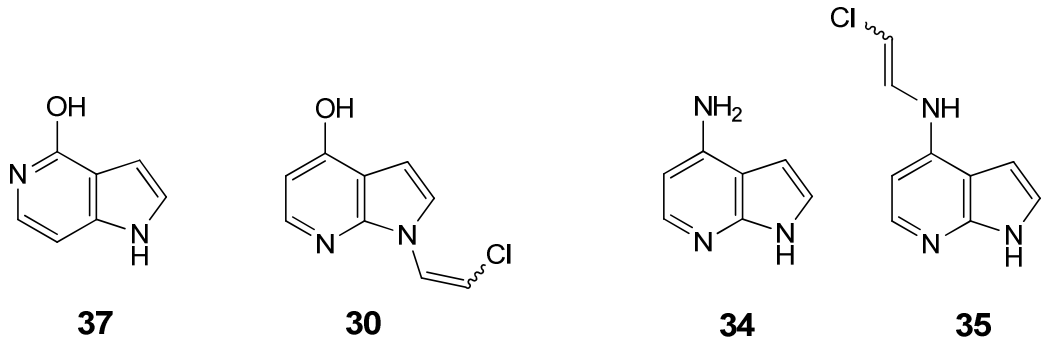


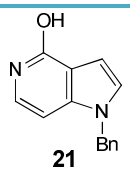
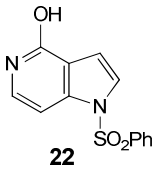
Figure 28: Compounds prepared starting from pyridine as precursor

Substituted 5-azaindoles could be successfully prepared starting from pyrrolo-2-carboxaldehyde. The conversion of the aldehyde functionality into a carboxylic acid by Knoevenagel condensation proved to be an efficient reaction with good yields. Nevertheless, the choice of the appropriate base and solvent mixture was essential for the formation of this unsaturated condensation product. The Doebner modification of the Knoevenagel condensation proved to be successful and the desired product was obtained in 41% yield. To improve the solubility of the starting material, pyridine was used as a solvent instead of ethanol, and piperidine acted as catalyst. Limitations in solubility of the highly polar condensation product were circumvented by introducing a *N*-1 protection group. Benzyl-protection was chosen due to its prevalence in literature. However, drastic cleavage conditions pose a disadvantage of the benzyl-protecting group. Alternatively, phenylsulfonyl protection was chosen. This demonstrated that protecting group chemistry efficiently solved solubility issues.

The subsequent Knoevenagel reaction was optimized seperately for the differently protected pyrrole compounds. In the case of the benzyl protected compound aniline in ethanol yielded the desired product in 60% yield, while for phenylsulfonyl protected starting material similar reaction conditions let to the corresponding imine. The desired product was achieved in 82% yield, applying the reaction conditions of the Doebner modification, namely malonic acid with piperidine as base in pyridine as solvent. The conversion of the carboxylic acid group into an azide functionality and subsequent Curtius rearrangement yielding *N*-1 protected 5-azaindoles was achieved under the same reaction conditions for both, the benzyl protected as well as the phenylsulfonyl protected pyrrole compound. Product formation was proven by HPLC-MS, as characterization by NMR spectroscopy was not possible due to residual diphenyl ether in the product.

The efficiency of this synthetic route starting from pyrrole could be increased by using a different solvent for the Curtius rearrangement in the last step. In this reaction a high boiling solvent is necessary to initiate cyclisation to azaindole compounds. Diphenyl ether is generally used in literature. Alternatively, other high boiling solvents, for example diethylene glycol, dimethyl formamide or dimethylsulfoxide, could be considered for this reaction step.

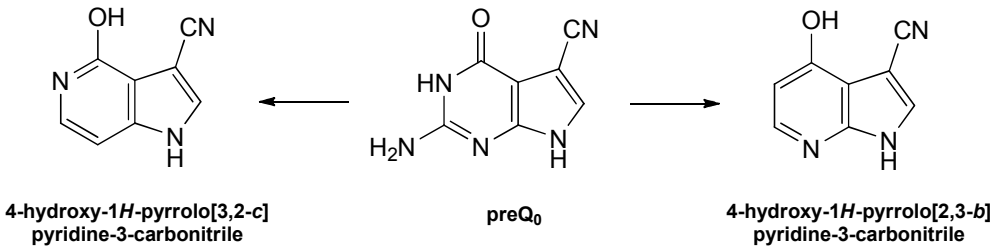
Table 12: HPLC-MS measurements of product 21 and 22

	Retention time [min]	MH^+
 **21**	9.24	225.1
 **22**	16.70	275.1

During this work, a novel synthetic route for the preparation of 5- and 7-azaindoles was established using 2- or 4-substiututed hydroxypyridine as starting material. Azaindoles were achieved in only one step, in condensation reactions of pyridine precursors with chloroacetaldehyde, albeit in moderate yields. Starting from commercially available 4-amino-2-hydroxypyridine, 2-hydroxypyrrolo[3,2-*c*]pyridine (**37**) was obtained in 47% yield after purification by column chromatography. In the case of pyrrolo[2,3-*b*]pyridine, the *N*-1 position reacted with chloroacetaldehyde introducing a chlorovinyl functionality in this position. Consequently, *N*-1 substituted pyrrolo[2,3-*b*]pyridine (**30**) could be prepared in *cis*- and *trans*- configuration in 47% yield. 4-Aminopyrrolo[2,3-*b*]pyridine was synthesised in a condensation reaction of 2,4-diaminopyridine with chloroacetaldehyde, however, reaction

byproducts **35** were detected by HPLC-MS. Formation of the substituted byproduct **35** was increased when longer reaction times and higher amount of chloroacetaldehyde were used.

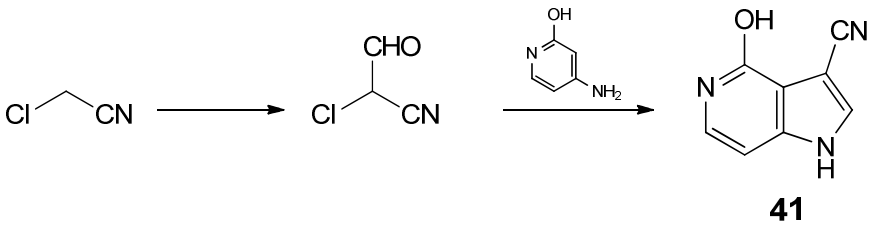
For investigations of these compounds as substrates for the novel enzyme nitrile reducatese queF, a cyanide group in position 3 of the azaindole system is prerequisite.



4-hydroxy-1*H*-pyrrolo[3,2-*c*] pyridine-3-carbonitrile | **preQ$_0$** | **4-hydroxy-1*H*-pyrrolo[2,3-*b*] pyridine-3-carbonitrile**

Figure 29: preQ$_0$ and pyrrolopyridine analoga

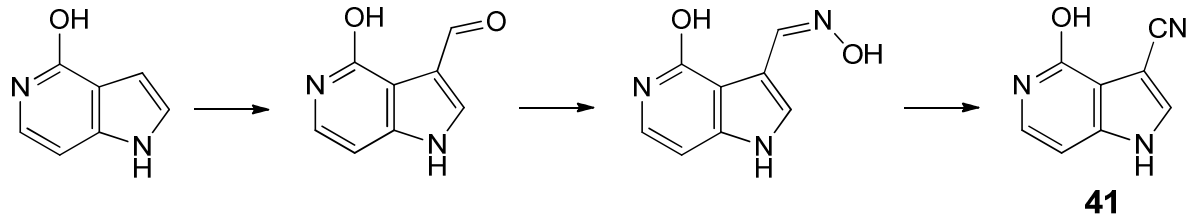
Two different synthetic strategies of introducing a cyanide functionality in position 3 of the pyrrolopyridine ringsystem were investigated in this work. Condensation of chloro(formyl)acetonitrile with the corresponding 2- or 4-substituted hydroxypyridine allows the synthesis of an cyano-substituted azaindole from an appropriately substituted pyridine precursor in only two steps, as depicted in Scheme 39. However, this synthesis yielded only small amounts of the desired product.



41

Scheme 39: Introducing a cyanide group in position 3 of azaindole compounds

Another possibility of introducing a cyanide functionality is formylation of azaindoles in position 3 followed by the conversion of the aldehyde into an oxime and subsequent dehydratisation to the nitrile. This approach includes three steps to the cyano compound (Scheme 40).



Scheme 40: Introducing a cyanide group in position 3 of azaindole compounds

Introduction of a cyano group leaves many questions unanswered, and is therefore the goal for further investigations.

5 Experimental section

5.1 List of chemical used

Table 13: Chemicals used for synthesis (I)

Chemicals	CAS-no.	company
Acetic acid	64-19-7	Sigma-Aldrich
Acetonitrile	75-05-8	Acros Organics
2-Amino-4-hydroxypyridine	33631-05-9	SynChem OHG
4-Amino-2-hydroxypyridine	38767-72-5	SynChem OHG
Aniline	62-53-3	Sigma-Aldrich
Aqueous Ammonia	1336-21-6	Fisher Scientific
Benzenesulfonyl chloride	98-09-9	Fluka
Benzyl bromide	100-39-0	Sigma-Aldrich
Benzylamine	100-46-9	Fluka
Boron tribromide solution in DCM	10294-33-4	Sigma-Aldrich
Celite	61790-53-2	Sigma-Aldrich
Chloroacetaldeyde	107-20-0	Sigma-Aldrich
Cyclohexane	110-82-7	VWR International
Dichloromethane	75-09-2	Fisher Scientific
Diethyl ether	60-29-7	Acros Organics
Diethyl malonate	105-53-3	Sigma-Aldrich
Dimethyl formamide	68-12-2	Roth
Dimethyl sulfoxide	67-68-5	Sigma-Aldrich
Dimethyl sulfoxide-d_6	2206-27-1	Sigma-Aldrich
Diphenyl ether	101-84-8	Sigma-Aldrich
Ethanol	64-17-5	Carl Roth
Ethyl acetate	141-78-6	VWR International
Ethyl chloroformate	541-41-3	Sigma-Aldrich
Hydrochloric acid	32862-91-2	Fisher Scientific
Malonic acid	141-82-2	Sigma-Aldrich
Methanol	67-56-1	Fisher Scientific
4-Methoxypyridine *N*-oxide hydrate	207511-18-0	Sigma-Aldrich
Methyl formate	107-31-3	Sigma-Aldrich
Phosphorus(V)oxychloride	10025-87-3	Sigma-Aldrich
Piperidine	110-89-4	Sigma-Aldrich
Potassium hydride	7693-26-7	Sigma-Aldrich
Potassium hydroxide	1310-58-3	Roth
Potassium *tert*-butoxide	865-47-4	Acros Organics
p-Toluenesulfonic anhydride	4124-41-8	Sigma-Aldrich
p-Toluenesulfonyl chloride	98-59-9	Acros Organics
Pyridine	110-86-1	Sigma-Aldrich
Pyrrole-2-carboxaldehyde	1003-29-8	Acros Organics
Sand 50-70 mesh	14808-60-7	Sigma-Aldrich
Silica gel	7631-86-9	Merck Chemicals
Sodium acetate	127-09-3	Merck Chemicals
Sodium azide	26628-22-8	Sigma-Aldrich
Sodium bicarbonate	144-55-8	Fluka

Table 13 continued: Chemicals used for synthesis (II)

Chemicals	CAS-no.	company
Sodium chloride	7647-15-5	VWR International
Sodium hydride	7646-69-7	Sigma-Aldrich
Sodium hydroxide	1310-73-2	Roth
Succinonitrile	110-61-2	Sigma-Aldrich
tert-Butanol	75-65-0	Acros Organics
tert-Butylamine	75-64-9	Sigma-Aldrich
Tetrahydrofuran	109-99-9	Sigma-Aldrich
Toluene	108-88-3	Sigma-Aldrich
Tributylamine	102-82-9	Sigma-Aldrich
Triethyl phosphonoacetate	867-13-0	Sigma-Aldrich
Triethylamine	121-44-8	Acros Organics
Trifluoroacetic acid	76-05-1	Sigma-Aldrich
α,α,α-Trifluorotoluene	98-08-8	Sigma-Aldrich

All reagents and starting materials used were analytical grade chemicals and were used without further pretreatment.

5.2 General methods

All syntheses were carried out under air, except explicitly noted. Experiments with air- /moisture sensitive materials were performed under inert atmosphere using a dual vacuum/nitrogen line and standard Schlenk techniques. Flasks needed were heated in vacuum and ventilated with inert gas. The addition of reagents occurred by application of Schlenk techniques in N_2-counter flow.

5.2.1 Thin-layer chromatography

For analytical thin layer chromatography Merck precoated aluminum silica gel 60 F254 plates were applied. Signal detection was carried out under UV-light at a wave length of 254 nm and/or by staining with an ammonium molybdate- cerium sulfate-solution (100 g $(NH_4)_6Mo_7O_{24}.4H_2O$, 8 g $Ce(SO_4)_2$ in 1000 mL 10% H_2SO_4).

5.2.2 Column chromatography

This purification method was carried out with Merck Silica Gel 60 (0.040-0.063 mm). For good separation the thirtyfold to fiftyfold amount of the adsorption agent was employed and light excess pressure was applied.

5.2.3 Gas chromatography with mass selective detector

For analytical gas chromatography an Agilent Technologies 7890A GC System with an Agilent Technologies 7683B Series Injector and an Agilent Technologies 7683 Series Auto sampler were used. The insertion of the sample was carried out with split-mode and helium was used as carrier gas. Samples were separated according to their polarity and boiling point on a polar HP-5MS capillary column (length: 30 m, diameter: 0.25 mm, layer thickness: 0.25 µm). After ionization by an EI-ionization source with a potential of E = 70 eV the registration took place by dint of a mass selective detector Agilent Technologies 5975C inert MD with Triple-Axis Detector.

ML_50_S: 50°C 1 minute, ramp 40 °C/min. linear until 300 °C, 300 °C, 5 minutes

5.2.4 High Performance Liquid chromatography

HPLC-MS analyses were done using an Agilent Technologies 1200 Series. Two different columns were used: phenomenix Gemini-NX 3 C18 110A (150 x 2.0 mm) column and Merck LiChroCART® 250-4 Purospher STAR RP-18e (5 µm) column, respectively. An Agilent Technologies 1200 Series MWD SL detector at wave lengths of λ = 220, 240, 254 and 262 nm was used for UV signal detection, and an Agilent Technologies 6120 Quadrupole LC/MS for MS signal detection. 0.1 % HOAc in water (eluent 1) or 20 mM ammonium acetate in water (eluent 2) and acetonitrile were used as eluents.

Method_1: Merck LiChroCART® 250-4 Purospher®STAR RP-18e (5 µm)

Stepwise gradient from 20% – 40 % acetonitrile over a period of 5 minutes with eluent 1, hold for 2 minutes, increase to 50 % acetonitrile over a period of 3 minutes, hold for 2 minutes, increase to 80 % acetonitrile in 2 minutes, hold for 1 minute and decrease to 20 % acetonitrile in 2 minutes; 0.8 mL/min; 30 °C column temperature

Method_2: Merck LiChroCART® 250-4 Purospher®STAR RP-18e (5 µm)

Stepwise gradient from 20% – 40 % acetonitrile over a period of 5 minutes with eluent 1, hold for 2 minutes, increase to 50 % acetonitrile over a period of 3 minutes, hold for 2 minutes and decrease to 20 % acetonitrile in 1 minute; 0.8 mL/min; 30 °C column temperature

Method_3: Phenomenix Gemini-NX 3 C18 110A (150 x 2.0 mm)

Stepwise gradient from 20% – 40 % acetonitrile over a period of 5 minutes with eluent 2, hold for 3 minutes, increase to 50 % acetonitrile over a period of 3 minutes, hold for 3 minutes and decrease to 20 % acetonitrile in 2 minutes; 0.19 mL/min; 30 °C column temperature

Method_4: Merck LiChroCART® 250-4 Purospher®STAR RP-18e (5 µm)

Start with 5 % acetonitrile and eluent 2, hold for 13 min, increase to 40 % acetonitrile over a period of 2 min, hold for 1 min and decrease to 5 % acetonitrile in 1 min; 0.5 $mL.min^{-1}$; 20 °C column temperature

Method_5: Merck LiChroCART® 250-4 Purospher®STAR RP-18e (5 µm)

Start with 5 % acetonitrile and eluent 2, hold for 5 minutes, increase to 30 % acetonitrile over a period of 1 minute., hold for 5 minutes, increase to 60 % acetonitrile in 1 minute, hold for 6 minutes and decrease to 5 % acetonitirle in 1 minute; 0,5 mL/min, 20 °C column temperature

Method_6: Phenomenix Gemini-NX 3 C18 110A (150 x 2.0 mm)

Start with 10 % acetonitrile and eluent 2, hold for 7 minutes, increase to 40 % acetonitrile over a period of 5 minutes, hold for 2 minutes and decrease to 10 % acetonitrile in 1 minute; 0,19 mL/min, 20 °C column temperature

Method_7: Phenomenix Gemini-NX 3 C18 110A (150 x 2.0 mm)

Start with 5 % acetonitrile and eluent 2, hold for 7 minutes, increase to 30 % acetonitrile over a period of 5 minutes, increase to 60 % acetonitrile over a period of 2 minutes and decrease to 10 % acetonitrile in 1 minute; 0,19 mL/min, 20 °C column temperature

Method_8: Merck LiChroCART® 250-4 Purospher®STAR RP-18e (5 µm)

Start with 5 % acetonitrile and eluent 2, hold for 10 minutes, incrase to 50 % acetonitrile over a period of 2 minutes, hold for 3 minutes and decrease to 5 % acetonitrile in 1 minute; 0,5 mL/min, 20 °C column temperature

Preliminary experiments for the separation of substance mixtures on a semi preparative HPLC system were accomplished with an Agilent 1100 Series-HPLC system with an Agient 1100 Series DAD-Diode-Array detector. The separation was carried out with a C-18-Reversed-Phase column of the type Nucleodure® 100-5 C18 ec, 4.0 x 150 mm. 5.0 µm from Macherey-Nagel.

Method A: methanol/water 40/60 isocratic for 15 min with a flow rate of 0.7 mL/min; 30 °C; 412 bar

For the semi preparative separation of substance mixtures a Knauer Smartline-HPLC system was used with a C-18-Reversed-Phase column of the type Nucleodure® 100-5 C18 ec, 21.0 x 125 mm. 5.0 µm from Macherey-Nagel. Fractions were collected with a Foxy Jr.- fraction collector in 8 mL test tubes.

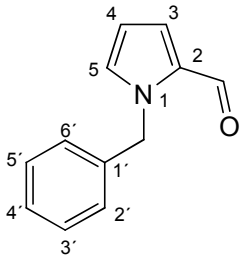
Method B: methanol/water 50/50 isocratic; 16 mL/min; 130 bar

5.2.5 Nuclear magnetic resonance spectrometry

^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AVANCE III spectrometer with autosampler (^{1}H-NMR: 300.36 MHz, ^{13}C-NMR: 75.53 MHz). Signal multiplicities were assigned with the subsequent abbreviations: s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), dd (doublet of a doublet), t (triplet), q (quartet) and m (multiplet). Chemical shifts δ are given in ppm, coupling constant J in Hz. Depending on the solubility of the substances deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$) were used as solvents.

5.3 Syntheses of pyrrolo[3,2-*c*]pyridines (5-azainoles)

1*N*-benzyl-1*H*-pyrrole-2-carboxaldehyde (15)



1*N*-benzyl-1*H*-pyrrole-2-carboxaldehyde was prepared according to a modified literature procedure.[63]

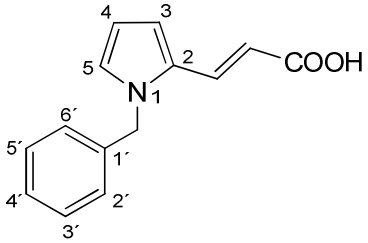
1*H*-pyrrole-2-carboxaldehyde (1.9 g, 21 mmol) was dissolved in 8.0 mL acetonitrile under nitrogen. NaH (0.76 g, 32 mmol) was washed twice with cyclohexane and once with acetonitrile, was added to the solution and stirred for half an hour. Benzyl bromide (3.8 mL, 32 mmol) was added dropwise *via* syringe and upon addition a solid precipitated. The reaction mixture was stirred for 24 hours and then quenched with deionised water, which dissolved the precipitate. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (Cy/EE 4:1) to give 2.6 g (66%) of the desired product as yellow oil.

TLC: cyclohexane/ethyl acetate 4:1; R_f: 0.64

^{1}H NMR ($CDCl_3$) δ	5.48 (s, 2H, CH2), 6.19 (t, J = 6.5 Hz, 3.2 Hz, 1H, H-4), 6.89 (d, J = 3.5 Hz, 2H, H-2´,H-6´), 7.06 (br d, J = 6.4 Hz, 2H, H-3´,H-5´), 7.28-7.13 (m, 3H, H-3, H-5, H-4´), 9.48 (s, 1H, -C*H*O)
^{13}C NMR ($CDCl_3$) δ	50.9 (C-7), 109.11 (C-4), 123.8 (C-3), 126.25 (C-4´), 126.7 (C-2´, C-6´), 127.7 (C-3´, C-5´), 130.4 (C-2), 130.52 (C-5), 136.5 (C-1´), 178.5 (*C*HO)

The NMR data is in accordance with literature.[64]

3-(1*N*-benzyl pyrrol-2-yl)acrylic acid (17)



3-(1*N*-benzyl-1-pyrrolyl-2)acrylic acid was prepared according to a literature procedure.[5]

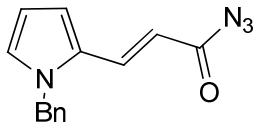
Malonic acid (3.4 g, 32 mmol) and aniline (2.8 mL, 32mmol) were dissolved in 25 ml EtOH under nitrogen and boiled under reflux. After half an hour 1*N*-benzyl-1*H*-pyrrole-2-carboxaldehyde (5.6 g, 30 mmol) was added at once and the solution was stirred at reflux for further 1.5 hours. The reaction mixture was then poured on ice water which led to a solid precipitating from the mixture, which was filtered off. 4.1 g (60%) of the product were obtained after recrystallization from toluene as brown solid.

TLC: cyclohexane/ethyl acetate 1:3; R_f: 0.5

^{1}H NMR (DMSO-d_6) δ	5.35 (s, 1H, CH2), 6.10 (d, J = 15.7 Hz, 1H, -CH=C*H*-), 6.22 (t, J = 6.2 Hz, 2.9 Hz, 1H, H-4), 6.84 (d, J = 2.5 Hz, 1H, H-3), 7.04 (d, J = 7.1 Hz, H-2´, H-6´), 7.39-7.14 (m, H-5, H-4´, H-4´, H-5´), 7.44 (d, J = 15.7 Hz, 1H, -C*H*=CH-), 12.0 (s, 1H, -COO*H*)
^{13}C NMR (DMSO-d_6) δ	49.6 (C-9), 109.43 (C-4), 111.9 (C-3), 113.3 (-CH=*C*H-), 126.1 (C-2´, C-6´), 127.2 (C-2), 127.32 (C-4´), 128.2 (C-5), 132.1 (C-1´), 138.5 (-*C*H=CH-), 167.9 (C-8)

No NMR reference data was available for this compound.

(2*E*)-3-(1*N*-benzyl-1*H*-pyrrol-2-yl)acryl azide (19)

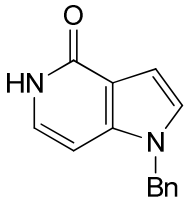


(2*E*)-3-(1*N*-benzyl-1*H*-pyrrol-2-yl)acryl azide was prepared according to a modified literature procedure.[54]

3-(1*N*-benzyl-1-pyrrolyl-2)acrylic acid (4.1 g, 18 mmol) was dissolved in 30 ml acetone and triethylamine (3.0 mL, 22 mmol) in 5.0 mL acetone was added dropwise. The reaction mixture was cooled to -10 °C with an ice/NaCl bath. Ethyl chloroformate (2.3 mL, 54 mmol) dissolved in 5.0 mL acetone was added slowly to the mixture. After stirring the mixture for an hour, a solution of NaN_3 (1.8 g, 28 mmol) in 9.5 mL deionised water was added dropwise. The reaction mixture was stirred for further 2 hours and then poured on ice water. The aqueous mixture was extracted three times with

cold DCM. The combined organic layers were dried over Na_2SO_4, and filtered. The organic layer was used for the next synthetic step without further purification.

1*N*-benzyl pyrrolo[3,2-*c*]pyridin-4-one (21)

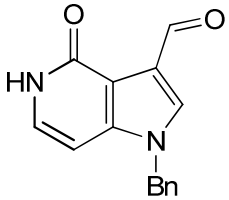


1*N*-benzyl pyrrolo[3,2-*c*]pyridin-4-one was prepared according to a literature procedure.[54]
The DCM-solution which contained (2*E*)-3-(1*N*-benzyl-1*H*-pyrrol-2-yl)acryl azide was added dropwise to a heated reflux solution of 200 mL diphenylether and 1.5 mL tributylamine. After completed addition the solution was stirred for one hour at reflux and then at room temperature over night. The solvents were reduced by distillation. The product was precipitated with diethyl ether and obtained as a brown solid in 20% (0.12 g) yield. It was used for the next synthetic step without further purification. Analysis was carried out with HPLC-MS.

TLC: dichloromethane/methanol 10:1; R_f: 0.84

HPLC-MS: method 2; retention time: 9.24 min; MH^+ (225.1)

1*N*-benzyl-3-formyl-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine (23)

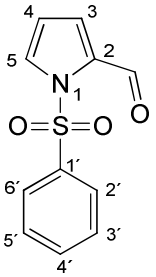


1*N*-benzyl-3-formyl-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine was prepared according to a modified literature procedure.[49 (c)]
1*N*-benzyl pyrrolo[3,2-*c*]pyridin-4-one (0.15 g, 0.63 mmol) was dissolved in DMF (0.15 mL; 1.9 mmol). Afterwards $POCl_3$ (60 µL, 0.63 mmol) was added dropwise and the reaction mixture was stirred for one hour at room temperature, then heated at 50 °C and stirred over night. The reaction was quenched with ice water and the pH of the solution was adjusted to pH 6 with 5 N aqueous sodium hydroxide solution. The aqueous layer was extracted three times with DCM. The combined organic

layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated and analyzed with HPLC-MS.

HPLC-MS: method 2; retention time: 8. 42 min; MH^+ (253.1)

1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-carboxaldehyde (16)



1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-carboxaldehyde was prepared according to a modified literature procedure.[65]

1*H*-pyrrole-2-carboxaldehyde (5.0 g, 53 mmol) was added to a vigorously stirred suspension of NaOH (6.3 g, 158 mmol) in 40 mL DCM. The mixture was cooled to 0 °C and stirred for 10 min. A solution of *p*-toluenesulfonyl chloride (8.0 mL, 63 mmol) in 7.0 mL DCM was added dropwise and then the reaction was heated to reflux (50 °C) overnight. The reaction was quenched with deionised H_2O, and extracted three times with DCM . The combined organic layers were dried over Na_2SO_4, concentrated and purified with silica gel column chromatography ($CHCl_3$ with a few drops aq. NH_3) to give 2.5 g (20 %) of the desired product as a yellow solid.

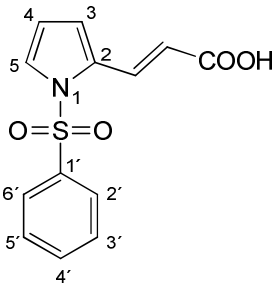
TLC: chloroform/a few drops of aq. ammonia; R_f: 0.58

^{1}H NMR ($CDCl_3$) δ	6.35 (t, J = 6.8 Hz, 3.5 Hz, 1H, H-4), 7.10 (dd, J = 3.8 Hz, 1.7 Hz, 1H, H-3), 7.63-7.41 (m, 4H, H-2´, H-3´, H-5´, H-6´), 7.92-7.81 (m, 2H, H-5, H-4´), 9.88 (s, 1H, -C*H*O)
^{13}C NMR ($CDCl_3$) δ	111.5 (C-4), 123.82 (C-3), 126.4 (C-2´, C-6´), 128.5 (C-3´, C-5´), 132.6 (C-2), 133.5 (C-5), 137.2 (C-1´), 177.8 (**C**HO)

The NMR data is in accordance with literature.[66]

HPLC-MS: method 1; retention time: 15.70 min; MH^+ (236.1)

(*E*)-3-(1*N*-phenylsulfonyl)-1*H*-pyrrol-2-yl) acrylic acid (18)



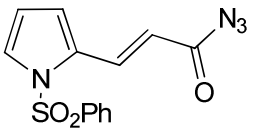
(*E*)-3-(1*N*-phenylsulfonyl)-1*H*-pyrrol-2-yl) acrylic acid was prepared according to a modified literature procedure.[49 (c)]

malonic acid (3.7 g, 35 mmol) was dissolved in 7 mL pyridine. Afterwards 1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-carboxaldehyde (6.9 g, 29 mmol) and piperidine (0.29 mL, 2.9 mmol) were added and the reaction mixture heated to reflux (bath temperature 80 °C) overnight. The solution was poured on 2 N HCl and a brown precipitated, which was subsequently filtered off and dried in vacuum to give 6.7 g (82 %) of the desired product.

^{1}H NMR (DMSO-d_6) δ	6.30 (d, J = 15.8 Hz, 1H, -CH=C*H*-), 6.49 (t, J = 6.9 Hz, 3.6 Hz, 1H, H-4), 7.11 (dd; J = 3.4 Hz, 0.9 Hz, 1H, H-3), 7.89-7.56 (m, 6H, H-5, H-2´, H-3´, H-4´, H-5´, H-6´), 7.93 (d, J = 15.8, 1H, -C*H*=CH-), 12.43 (br s, 1H, -COO*H*)
^{13}C NMR (DMSO-d_6) δ	113.7 (C-4), 116.74 (C-3), 118.9 (C-2), 126.4 (C-2´, C-6´, -CH=*C*H-), 130.1 (C-3´, C-5´), 130.2 (C-4´), 130.59 (C-5), 134.9 (C-1´), 137.7 (-*C*H=CH-), 167.3 (-*C*OOH)

No NMR reference data was available for this compound.

(*E*)-3-(1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-yl)acryl azide (20)

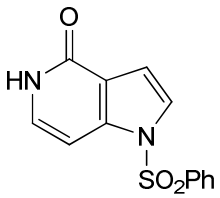


(*E*)-3-(1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-yl)acryl azide was prepared according to a modified literature procedure.[54]

(*E*)-3-(1*N*-phenylsulfonyl)-1*H*-pyrrol-2-yl)acrylic acid (0.39 g, 1.4 mmol) was dissolved in 2.0 mL acetone and triethylamine (0.23 mL, 1.7 mmol) in 1.0 mL acetone was added dropwise. Afterwards the reaction mixture was cooled to -10 °C with an ice/NaCl bath and ethyl chloroformate (0.18 mL, 1.9 mmol) in 2.0 mL acetone was added slowly. After stirring the mixture for one hour, NaN_3 (0.14 g, 2.2 mmol) dissolved in 0.70 mL deionised H_2O was added dropwise. The reaction mixture was stirred for further four hours at -10 °C and then poured on ice. A precipitate occurred and the mixture was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and

the dried DCM-layer, which contained the product (*E*)-3-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)acryloyl azide was then used for the next synthetic step without further purification.

1*N*-(phenylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-4-one (22)



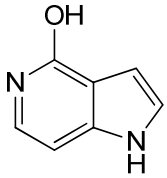
1*N*-(phenylsulfonyl)-1*H*-pyrrolo[2,3-c]pyridin-4-one was prepared according to a modified literature procedure.[49 (c)]

The DCM-solution which contained (*E*)-3-(1*N*-(phenylsulfonyl)-1*H*-pyrrol-2-yl)acryloyl azide was added very slowly to a heated flask (160 °C bath temperature) and was stirred overnight. The reaction mixture was washed with 1N HCl. The organic layer was dried over Na_2SO_4, the solvent was removed under pressure and the product was recrystallized from toluene to obtained 20% (80 mg) of the desired product as a brown solid.

TLC: dichloromethane/methanol 10:1; R_f: 0.9

HPLC-MS: method: 3; retention time: 16.70 min; MH^+ (275.1)

1*H*-pyrrolo[3,2-*c*]pyridin-4-one (37)



1*H*-pyrrolo[3,2-*c*]pyridin-4-one was prepared analogously to a literature procedure for pyrrolopyrimidines.[6]

NaOAc*3H_2O (0.87 g, 6.4 mmol) was dissolved in 9.0 mL deionised H_2O. 4-Amino-2-hydroxypyridine (0.20 g, 1.8 mmol) was added and the mixture was heated to 80 °C. Chloroacetaldehyde (50% solution in water; 0.28 mL, 4.2 mmol) in 3.0 mL of deionised H_2O was added dropwise. The reaction mixture was refluxed for 24 hours and then the pH of the solution was adjusted to pH 7.5 with diluted aqueous ammonia solution. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was

purified by silica gel column chromatography (DCM/MeOH 20:1). The desired product was obtained as a brown solid in 47% yield.

TLC: dichloromethane/methanol 10:1; R_f = 0.6

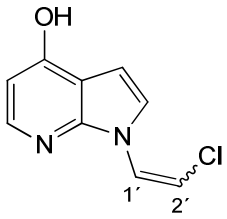
^{1}H NMR (DMSO-d_6) δ	6.40 (d, J = 5.6 Hz, 1H, H-3), 6.62 (s, 1H, OH), 7.03 (d; J = 2.4 Hz, 1H, H-7), 7.72 (d, J = 2.4 Hz, 1H, H-6), 7.79 (d, J = 5.6 Hz, 1H, H-2)
^{13}C NMR (DMSO-d_6) δ	103.3 (C-3), 104.3 (C-7), 104.4 (C-3a), 140.6 (C-2), 144.6 (C-7a), 149.8 (C-6), 163.4 (C-4)

No NMR reference data was available for this compound.

HPLC-MS: method: 3; retention time: 16.88 min; MH^+ (135.1)

5.4 Syntheses of pyrrolo[2,3-*b*]pyridines (7-azainoles)

1*N*-(2-chlorovinyl)-4-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine (30)



1*N*-(2-chlorovinyl)-4-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridine was prepared analogously to a literature procedure for pyrrolopyrimidines.[6]

NaOAc*3H_2O (0.87 g, 6.4 mmol) was dissolved in 9.0 mL deionised H_2O. 2-Amino-4-hydroxypyridine (0.20 g, 1.8 mmol) was added and the mixture was heated to 80 °C. Chloroacetaldehyde (50% solution in water; 0.28 mL, 4.2 mmol) in 3.0 mL of deionised H_2O was added dropwise. The reaction mixture was refluxed for 24 hours and then the pH of the solution was adjusted to pH 7.5 with a diluted aqueous ammonia solution. The aqueous layer was extracted three times with ethyl acetate and the combined organic layer was dried over Na_2SO_4, filtered and concentrated. The product was purified by with silica gel column chromatography (DCM/MeOH 20:1). The desired product was obtained as a yellow solid in 47% yield.

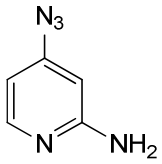
TLC: dichloromethane/methanol 10:1; R_f = 0.4

^{1}H NMR (DMSO-d_6) δ	4.48 (dd, J = 10.4 Hz, 2.1 Hz, 1H, trans H-2´), 4.71 (dd, J = 10.4 Hz, 6.9 Hz, 1H, cis H-2´), 5.64 (d, J = 5.0 Hz, 1H, H-1´), 6.84 (d, J = 7.3 Hz, 1H, H-5), 7.49 (d, J = 0.9 Hz, 1H, H-3), 7.92 (d, J = 1.1 Hz, 1H, H-2), 8.6 (d, J = 7.3 Hz, 1H, H-6)
^{13}C NMR (DMSO-d_6) δ	69.2 (C-1´), 80.3 (C-2´), 100.9 (C-3), 111.0 (C-3a), 112.7 (C-5), 129.2 (C-2), 132.1 (C-6), 142.9 (C-7a), 157.8 (C-4)

No NMR reference data was available for this compound.

HPLC: method: 5; retention time: 12.77 min; MH^+ (177.1)

2-amino-4-azidopyridine (32)



2-amino-4-azidopyridine was prepared according to a literature procedure.[67]

To a solution of 2-amino-4-chloropyridine (0.50 g, 3.9 mmol) in 11 mL DMF under nitrogen was added 0.49 g NH_4Cl (8.7 mmol) and 0.53 g NaN_3 (8.1 mmol). The reaction mixture was heated to reflux and stirred for 4.5 hours and then quenched with saturated $NaCO_3$-solution where a white precipitate was formed. The solid was filtered off and the filtrate was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 0.35 g of 2-amino-4-azidopyridine (2.6 mmol) as a brown solid in 67 % yield.

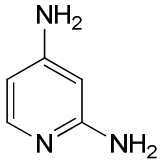
TLC: dichloromethane/methanol 10:1; R_f = 0.5

^{1}H NMR (DMSO-d_6) δ	6.13 (s, 2H, NH2), 6.14 (d, J =1.9 Hz, 1H, H-3), 6.35 (dd, J =5.5 Hz, 1.9 Hz , 1H, H-5), 7.86 (d, J =5.5 Hz, 1H, H-6)
^{13}C NMR (DMSO-d_6) δ	96.5 (C-3), 103.1 (C-5), 148.4 (C-4), 149.6 (C-6), 161.1 (C-2)

HPLC-MS: method: 6; retention time: 13.82 min; MH^+ (136.1)

No NMR reference data was available for this compound.

2,4-diaminopyridine (33)



2-amino-4-azidopyridine (0.10 g, 0.74 mmol) was suspended in 10 mL acetic acid. A catalytic amount of platinum on charcoal catalyst was added and the suspension was stirred for one hour at room temperature under hydrogen. The catalyst was removed by filtration over celite and washed with deionised H_2O and then with MeOH. The filtrates were reduced in vacuum until dryness. 88 mg (114 %) of 2,4-diaminopyridine was obtained as black solid.

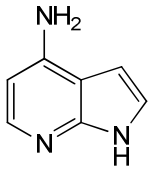
TLC: dichloromethane/methanol 3:1; R_f = 0.1

^{1}H NMR (DMSO-d_6) δ	5.39(s, 2H, NH_2), 5.69 (s, 2H, NH_2), 6.22 (s, 1H, H-3), 6.91 (s, 1H, H-5), 7.12 (s, 1H, H-6)
^{13}C NMR (DMSO-d_6) δ	89.9 (C-3), 101.5 (C-5), 140.2 (C-4), 157.2 (C-6), 175.3 (C-2)

HPLC-MS: method: 7; retention time: 3.12 min; MH^+ (110.1)

The NMR data is in accordance with literature.[68]

4-aminopyrrolo[2,3-*b*]pyridine (34)



4-aminopyrrolo[2,3-*b*]pyridine was prepared analogously to a literature procedure for pyrrolopyrimidines.[6]

$NaOAc*3H_2O$ (0.86 g, 6.3 mmol) was dissolved in 10 mL deionised H_2O. 2,4-diaminopyridine (0.35 g, 3.2 mmol) was added and the mixture was heated to reflux, at which time chloroacetaldehyde (50% solution in water; 0.50 mL, 7.8 mmol) was added dropwise. The reaction mixture was stirred at 100 °C over night. The black precipitate was filtered off and the filtrate was reduced in vacuum to dryness. The crude product was obtained in 71 % yield and was purified with silica gel column chromatography (DCM/MeOH 5:1) to give 4-aminopyrrolo[2,3-*b*]pyridine as a yellow oil.

TLC: dichloromethane/methanol 3:1; R_f = 0.5

HPLC-MS: method: 8; retention time: 12.41 min; MH^+ (134.1)

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7 Appendix

7.1 Abbreviations

AcCl	Acetyl chloride
Bn	Benzyl
BuLi	Buthyllithium
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Equiv.	Equivalents
Et_3N	Triethylamine
EtOH	Ethanol
H_2SO_4	sulphuric acid
HCl	Hydrochloric acid
HOAc	Acetic acid
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear single quantum coherence spectroscopy
MeCN	Acetonitrile
MeOH	Methanol
MeONa	Sodium methanolate
MS	Mass spectroscopy
Na_2SO_4	Sodium sulphate
NaH	Sodium hydride
NaN_3	Sodium azide
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NH_4Cl	Ammonium chloride
NMR	Nuclear magnetic resonance
$PhSO_2Cl$	*p*-Toluenesulfonyl chloride
$POCl_3$	Phosphorus(V)oxychloride
ppm	Parts per million
R_f	Retardation factor
TLC	Thin layer chromatography
TsCl	tosylchloride
TsO	Tosylate
Ts_2O	*p*-Toluenesulfonic anhydride
UV	Ultraviolet

7.2 List of Figures

7.3 List of Schemes

7.4 List of Tables