Jarle Holt

Nitropyridine carbamates, amides and carboxylates in heterocyclic chemistry

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Norwegian University of Science and Technology
Faculty of Natural Sciences and Technology
Department of Chemistry

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Innovation and Creativity

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Summary

Based on new methodology for nitration of pyridine and pyridine derivatives developed at our department by Professor Jan Bakke and coworkers at NTNU, a whole range of substituted nitropyridines are now readily available. The method provides new possibilities in heterocyclic chemistry for the preparation of new materials. Due to the importance and useful properties of many pyridine-based compounds, the chemistry of nitropyridine derivatives is being investigated by our group at NTNU and results for nitropyridine carbamates, amides and carboxylates are presented in this thesis. These nitropyridine derivatives have been used as substrates for the formation of new bis-heterocyclic compounds and pyridine derivatives. New synthetic routes to fused heterocycles have been developed.

Chapter 2 and Paper I presents the preparation, stability and reactivity of nitropyridine isocyanates (**13**, **23**), a new class of compounds in organic chemistry. The introduction of an electronegative substituent represented by the nitro group was expected to reduce the basisity of the pyridine nitrogen, hence decrease the rate of dimerisation and increase the reactivity of the isocyanate carbon towards a nucleophile. The preparation of nitropyridine isocyanates (**13**, **23**) are reported.

Isocyanates constitute an important class of compounds in organic chemistry and undergo a series of reactions to yield a variety of interesting products including heterocyclic derivatives. Heterocyclic isocyanates, however, have not received the same attention as the respective aromatic compounds in synthesis and reactivity studies because of their instability and high reactivity. 2-Pyridine isocyanate dimerises while the 4-isomer trimerises to form the trimer.

Chapter 3 and Paper I presents the preparation, stability and reactivity of the isocyanate dimer and trimer. The isocyanate dimer (**28**) was formed in high yield from the reactive 5-nitro-2-pyridine isocyanate (**23**) by a [2+4]-cycloaddition reaction. Another byproduct in the preparation of the isocyanate using oxalyl chloride was the tetrone (**26**).

The isocyanate trimer was formed from the unstable 4-pyridine isocyanate for reference purposes. The trimer proved to be less stable than previously reported and afforded 4-aminopyridine and methyl 4-pyridine carbamate as decomposition products in the presence of moisture and alcohols, respectively. This demonstrates that the reactive trimer can be used as a protected version of the isocyanate for synthetic purposes.

Chapter 4 and Paper II presents studies of the nitropyridine isocyanates in cycloaddition reactions. The reactivity of the nitropyridine isocyanates in 1,3-dipolar cycloaddition reactions with trimethylsilylazide and 3,5-dimethylpyridine *N*-oxide to afford tetrazolinones (**41**, **43**) and substituted amines (**52**, **55**) was investigated. A [2+4]-cycloaddition reaction of nitropyridine isocyanate with diphenylketene was also studied. The cycloadduct (**59**) was formed. These results demonstrate the potential of the nitropyridine isocyanates to undergo cycloaddition reactions.

Application of nitropyridine carbamates, amides and carboxylates in the formation of new heterocyclic compounds have been investigated and discussed in Chapter 5-7.

Chapter 5 and Paper III presents the aromatic nucleophilic substitution reaction of the nitro group of methyl 3-nitro-4-pyridine carboxylate. The nitro group was successfully replaced by nitrogen, oxygen and sulfur nucleophiles to afford the substitution products (**16a-d**) in moderate yields.

Chapter 6 and Paper IV presents the cyclization reaction of nitropyridine carbamates for the formation of 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one (**79a-b**), a biologically active compound. A facile acid-catalysed cyclization method for the preparation of the cyclic urea by traditional heating and the corresponding microwave-promoted reaction were developed. Both methods afforded the cyclic urea in high yield and represent a "green method" for the preparation of this compound.

Chapter 7 and Paper V presents the preparation of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine (**86**) and *N*-acyl and *N*-alkoxycarbonyl triazolo[4,5-*c*]pyridine derivatives (**96a-e**, **98a-e**). The triazolopyridine derivatives were readily formed by diazotization and cyclization of the respective nitropyridine carbamates and amides in high yields. The application of triazolo[4,5-*c*]pyridine derivatives (**98a-e**) in the acylation of amines and amino acids was investigated. They proved to be more effective than the commercially available benzotriazole and afforded the protected amines in high yields under mild conditions.
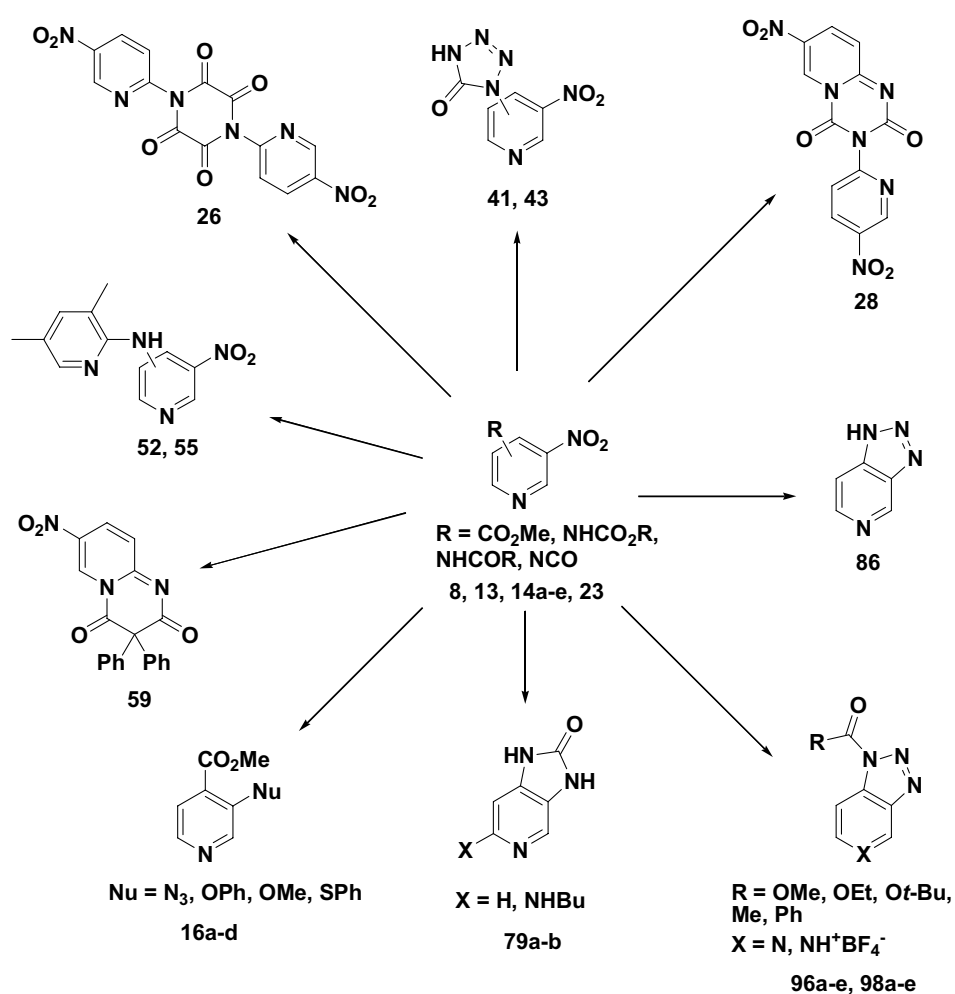
Scheme 1 Synthesis of bis-heterocyclic compounds, fused heterocyclic compounds and methyl 4-pyridine carboxylate derivatives from 3-nitropyridine derivatives

Acknowledgements

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Jarle Holt

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Abbreviations and symbols

N_2O_5	Dinitrogen pentoxide
DPPA	Diphenylphosphoryl azide
FVT	Flash vacuum thermolysis
INH	Isonicotinic acid hydrazide
FMO	Frontier molecular orbital
LUMO	Lowest unoccupied molecular orbital
HOMO	Highest occupied molecular orbital
TMSA	Trimethylsilylazide
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
THF	Tetrahydrofuran
MCPBA	*Meta*-Chloroperoxybenzoic acid
MAOS	Microwave-assisted organic synthesis
MW	Microwave irradiation
H_2SO_4	Sulfuric acid
HBF_4	Tetrafluoroboric acid
Bn	Benzyl
i-Pr	*iso*-Propyl
Boc	*tert*-Butyl carbamate
NMR	Nuclear magnetic resonance spectroscopy
IR	Infrared spectroscopy
FT-IR	Fourier-transformed infrared spectroscopy
MS	Mass spectrometry
HRMS	High resolution mass spectrometry
TMS	Tetramethylsilane
ppm	Parts per million
mp	Melting point
et al.	*et alii*, and others
Hz	Hertz

EI	Electronic ionization
eV	Electron volt
^{o}C	Degrees Celcius
J	Coupling constant

List of papers

Paper I

Holt, Jarle, Andreassen, Trygve, Bakke, Jan M. and Fiksdahl, Nitropyridyl isocyanates, *J. Heterocyclic Chem.*, **42**, 259-264 (2005)

Paper II

Holt, Jarle and Fiksdahl, Anne, Study of nitropyridyl isocyanates in 1,3-dipolar cycloaddition reactions, *J. Heterocyclic Chem.*, manuscript to be submitted

Paper III

Holt, Jarle, Tjosås, Freddy, Bakke, Jan M. and Fiksdahl, Anne, Nucleophilic aromatic substitution of methyl 3-nitropyridine-4-carboxylate, *J. Heterocyclic Chem.*, **41**, 987-989 (2004)

Paper IV

Holt, Jarle, Bakke, Jan M. and Fiksdahl, Anne, 1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one, *J. Heterocyclic Chem.*, **43**, (2006), in press

Paper V

Holt, Jarle and Fiksdahl, Anne, *N*-Acyl- and *N*-alkoxycarbonyl derivatives of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine; preparation and application, *J. Heterocyclic Chem.*, **43**, (2006), in press

Papers I-V are given as appendices to this thesis.

Chapter 1: Introduction

1.1 Nitration of pyridines

The pyridine ring system occurs in the structures of many natural products, pharmaceutical and agrochemical compounds and other commercial substances. A wide range of synthetic methods, therefore, have been developed for construction of the pyridine ring and formation of pyridine derivatives [1].

Unfortunately, one of the most important classes of aromatic substitution reactions, electrophilic aromatic substitution, takes place with great difficulty under vigorous conditions [1]. This is due to the electron-deficient character of the pyridine ring. This is typical for the nitration of pyridine and pyridine derivatives. The partial rate factor for an electrophilic aromatic substitution of pyridine has been estimated to be 10^{-6} and for the pyridinium ion, in most cases formed under standard conditions for this type of reaction, to be 10^{-22} [2]. Typically, nitration of pyridine at 350°C afforded 12 % yield of 3-nitropyridine (**2**). This could not even be reproduced by den Hertog *et al.* who obtained 6 % yield under the same conditions [3].

In the 1980s and 1990s Bakke *et al.* were investigating the nitration of aromatic compounds by dinitrogen pentoxide (N_2O_5) in liquid SO_2 [4-6]. This proved to be an especially powerful nitrating system. A few pyridines were nitrated using this method, and the yields were better than those reported from nitration with HNO_3/H_2SO_4.

3-Nitropyridine (**2**) was obtained in 56 % yield. Using an organic solvent together with an aqueous solution of SO_2/HSO_3^- afforded compound (**2**) in 77 % yield (Scheme 1.1) [4].

Preliminary results indicated that the N_2O_5/SO_2 nitration was not an electrophillic aromatic substitution. Later experiments showed that the reaction was intramolecular with respect to the pyridine compound. Several modes appeared possible for the migration of the nitro group. Mechanistic studies showed that the reaction took place by a [1,5]-sigmatropic shift of the nitro group from the 1-position to the 3-position [4].
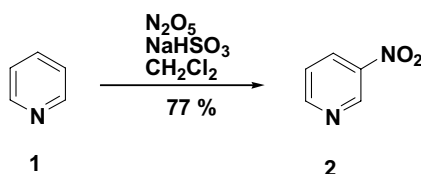
Scheme 1.1 Nitration of pyridine (**1**)

The method is general for the nitration in the 3-position of many pyridine compounds. A number of pyridine derivatives have been nitrated using this protocol to afford 3-nitropyridine derivatives in acceptable to excellent yields [4-6].

Recently, Katritzky *et al.* have developed a procedure for the direct nitration of pyridine [7]. They searched for a method to readily generate N_2O_5 *in situ* under conditions where it would react immediately with pyridine. An equilibrium concentration of N_2O_5 has been proposed to exist in a system containing nitric acid and acetic anhydride. The nitric acid-trifluoroacetic anhydride system is cheap and readily available, in contrast to N_2O_5 which is difficult to prepare. The yields of 3-nitropyridines using this protocol were generally higher than those using N_2O_5 [7].

This project has focused on the application of nitropyridine carbamates, amides and carboxylic acids for the preparation of nitropyridyl isocyanates, pyridine derivatives and bis-heterocyclic compounds.

1.2 Isocyanates in organic synthesis

Isocyanates constitute an important class of compounds in organic chemistry and undergo a series of reactions to yield a variety of interesting products including heterocyclic derivatives [8]. Isocyanates are prepared on a large scale in the polymer industry for the manufacture of polyurethanes. The isocyanates have also found application in the synthesis of agrochemicals and pharmaceutical drugs.

Heterocyclic isocyanates, however, have not received the same attention as the respective aromatic compounds in synthesis and reactivity studies. A reason for this is their instability and high reactivity.
The tendency of many heterocyclic isocyanates to oligomerise results from autocatalysis by the heterocycle. In this respect, they are comparable with their aliphatic and aromatic analogues. One example reported by Richter and Ulrich in 1975 is the stable benzyl isocyanate [8]. It can be dimerised to a 1,3-diazetidine or trimerised to the trimer under the influence of 1,2-dimethylimidazole at room temperature.

In 1967, the first pyridine isocyanate, 3-pyridine isocyanate (**4**) was isolated and characterised [9]. Of the three possible isocyanates (Figure 1.1), the 3-isomer (**4**) was successfully isolated after a Curtius rearrangement of the corresponding acyl azide. Attempts to generate 2-pyridine isocyanate (**3**) led to the formation of the dimer (**6**). Similarly, the 4-isomer (**5**) trimerised into the trimer (**7**) (Figure 1.1) [10].
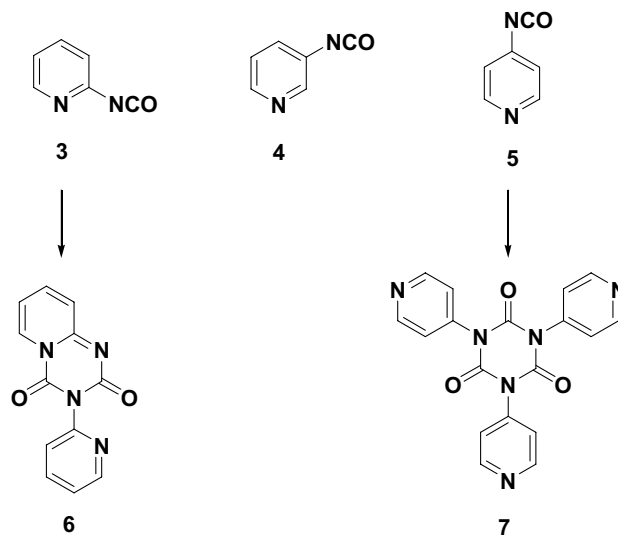
Figure 1.1 Three isomers of pyridine isocyanate

The introduction of electronegative substituents are expected to influence the chemical reactivity of the pyridine isocyanates in two ways. First, they reduce the basisity of the pyridine nitrogen, and thereby slow down the rate of dimerisation. Secondly, they increase the reactivity of the isocyanate carbon atom towards a nucleophile. The last point has been illustrated by von Gizycki, who prepared the highly chlorinated isocyanate (**8**) (Figure 1.2) [11].
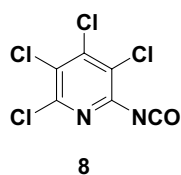
Figure 1.2 A highly chlorinated pyridine isocyanate (**8**) [11]

Chapter 2 and Paper I presents the preparation, stability and reactivity of nitropyridine isocyanates, a new class of compounds in organic chemistry. The introduction of an electronegative substituent represented by the nitro group was expected to reduce the basisity of the pyridine nitrogen, hence decrease the rate of dimerisation and increase the reactivity of the isocyanate carbon towards a nucleophile.

Chapter 3 and Paper I presents the preparation, stability and reactivity of the isocyanate dimer and trimer. The isocyanate dimer was formed in high yield from the reactive 5-nitro-2-pyridine isocyanate by a [2+4]-cycloaddition reaction. Another byproduct in the preparation of the isocyanate using oxalyl chloride was the tetrone. The isocyanate trimer was formed from the unstable 4-pyridine isocyanate for reference purposes. The trimer proved to be less stable than previously reported and afforded 4-aminopyridine and methyl 4-pyridine carbamate as decomposition products in the presence of moisture and alcohols, respectively. This demonstrates that the reactive trimer can be used as a protected version of the isocyanate for synthetic purposes.

Chapter 4 and Paper II presents studies of the nitropyridine isocyanates in cycloaddition reactions. The reactivity of the nitropyridine isocyanates in 1,3-dipolar cycloaddition reactions with trimethylsilylazide and 3,5-dimethylpyridine *N*-oxide to afford tetrazolinones and substituted amines was investigated. A [2+4]-cycloaddition reaction of nitropyridine isocyanate with diphenylketene was also studied. The corresponding cycloadduct was formed. These results demonstrate the potential of the nitropyridine isocyanates to undergo cycloaddition reactions, in contrast to their non-nitro analogues.

1.3 Application of nitropyridine carbamates, amides and carboxylates

Application of nitropyridine carbamates, amides and carboxylates in the formation of new heterocyclic compounds have been investigated.

Chapter 5 and Paper III presents the aromatic nucleophilic substitution reaction of the nitro group of methyl 3-nitro-4-pyridine carboxylate. The nitro group was successfully replaced by nitrogen, oxygen and sulfur nucleophiles to afford the substitution products in moderate yields. The methyl ester *ortho* to the nitro group and the nitrogen atom makes the pyridine ring electron-deficient and the nitro group to a particularly good leaving group.

Chapter 6 and Paper IV presents the cyclization reaction of nitropyridine carbamates for the formation of 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one, a biologically active compound present in many pharmaceuticals. A facile acid-catalysed cyclization method for preparation of the cyclic urea by traditional heating and a corresponding microwave-promoted reaction were developed. Both methods afforded the cyclic urea in quantitative yield, under milder conditions than previously reported.

Chapter 7 and Paper V presents the preparation of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine and *N*-acyl and *N*-alkoxycarbonyl triazolo[4,5-*c*]pyridine derivatives. The triazolopyridine derivatives were readily formed by diazotization and cyclization of the respective nitropyridine carbamates and amides in high yields. The application in the acylation of amines and amino acids was investigated. They proved to be more effective than the commercially available benzotriazole and afforded the protected amines and amino acids in high yields under mild conditions.

The results of these projects are presented in Chapter 2-7 and the relevant background and theory on which they are based, will be discussed in further detail.

Chapter 2: Nitropyridyl isocyanates

Based on previous substituent effect investigations of pyridine isocyanates [11], the introduction of an electronegative substituent represented by the nitro group was expected to reduce the basisity of the pyridine nitrogen, hence retard the di- or trimerisation, but also increase the reactivity of the isocyanate carbon towards a nucleophile. The preparation, stability and reactivity of nitropyridyl isocyanates was therefore studied.

A number of substituted 3-nitropyridine derivatives have now become readily available through the improved nitration protocols developed by Bakke *et al.* [4-6] and Katritzky *et al.* [7]. Some of these derivatives are suitable substrates for the preparation of 3-nitropyridyl isocyanates.

Isocyanates constitute an important class of compounds in organic chemistry and undergo a series of reactions such as nucleophilic addition reactions, Diels-Alder reactions, cycloaddition reactions to unsaturated systems and reactions with bifunctional compounds to yield a variety of interesting products including heterocyclic derivatives [8].

Isocyanates are prepared on a large scale in the polymer industry for the manufacture of polyurethanes. The isocyanates have also found application in the synthesis of agrochemicals and pharmaceutical drugs, among many other compounds.

Heterocyclic isocyanates, however, have not received the same attention as the respective aromatic compounds in synthesis and reactivity studies. A reason for this is their instability and high reactivity.

Some of these derivatives have been generated *in situ* and trapped with alcohols or other reagents. Other isocyanates undergo spontaneous di- or trimerisation during their preparation. Only a few have been isolated and characterised in the monomeric form.

The tendency of many heterocyclic isocyanates to oligomerise results from autocatalysis by the heterocycle. In this respect, they are comparable with their aliphatic and aromatic analogues. They di- and/or trimerise in the presence of bases such as tertiary amines, phosphines, alkoxides, pyridine, azoles and many others.

One example reported by Richter and Ulrich in 1975 is the stable benzyl isocyanate [8]. It can be dimerised to a 1,3-diazetidine or trimerised to the trimer under the influence of 1,2-dimethylimidazole at room temperature. This knowledge is important in understanding the lability of heterocyclic isocyanates.

Although other heterocyclic isocyanates such as 2-furyl isocyanate and pyrazine-2,5-diisocyanate had been isolated, there were no published protocols describing the isolation and characterisation of pyridine isocyanates until the late 1960s [9]. This was surprising, since their precursors such as nicotinyl azide and 2,6-dipicolinic acyl azide, had been known for more than the previous fifty years. Other compounds such as ethyl 3-pyridyl carbamate and diethyl 2,6-pyridyl dicarbamate had been prepared from their respective acyl azides with ethanol, or from their amines by reaction with ethyl chloroformate [9].

In 1967, the first pyridine isocyanate, 3-pyridine isocyanate (**4**) was isolated and characterised [9]. Of the three possible isocyanates, the 3-isomer (**4**) was successfully isolated after a Curtius rearrangement of the corresponding acyl azide. However, it was extremely reactive and in the presence of atmospheric moisture it was rapidly converted into a dipyridylurea. This was, as noted earlier, most likely due to an autocatalytic rate enhancement by the pyridine ring.

Attempts to generate 2-pyridine isocyanate (**3**) led to the formation of the dimer (**6**). Similarly, the 4-isomer (**5**) trimerised into the trimer (**7**) [10].

The introduction of electronegative substituents are expected to influence the chemical reactivity of the pyridine isocyanates in two ways. First, they reduce the basisity of the pyridine nitrogen, and thereby slow down the rate of dimerisation. Secondly, they increase the reactivity of the isocyanate carbon atom towards a nucleophile. The last point has been illustrated by von Gizycki, who prepared the highly chlorinated isocyanate (**8**) [11].

In many experiments, the pyridine isocyanates have been used as transient intermediates in heterocyclic synthesis. These include cyclization reactions with adjacent substituents (such as acyl azides with amines), intramolecular aromatic substitution (acyl azides react to form new heterocyclic rings), Diels-Alder reactions (with ketenes, isocyanates and imines) and cycloaddition reactions (with isonitriles) [8].

The results discussed in this chapter are presented in Paper I.

2.1 Synthesis of 3-nitro-4-pyridyl isocyanate
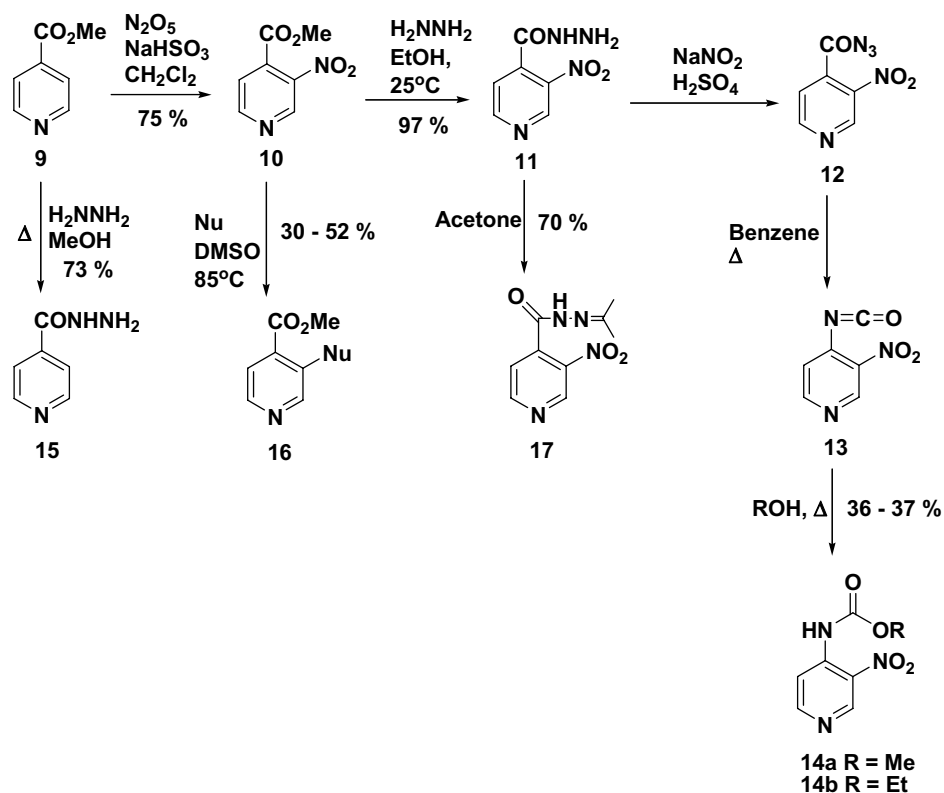
Scheme 2.1 Preparation of 3-nitro-4-pyridyl isocyanate (**13**)

The synthesis of 3-nitro-4-pyridyl isocyanate (**13**), starting from methyl 4-pyridinecarboxylate (**9**), was carried out by a four-step procedure (Scheme 2.1).

The nitropyridine substrate (**10**) was generated by nitration [5, 6] of the methyl ester (**9**) with N_2O_5 in 75 % yield. By treatment of the nitropyridine methyl ester (**10**) with sodium azide in DMSO to afford the acyl azide (**12**), the substitution product (**16**) was isolated. The nitro group had been substituted by the azide ion. This led to further studies of aromatic nucleophilic substitution reactions and will be discussed in more detail in Chapter 5.

In contrast to the formation of the hydrazide (**15**) in 73 % yield from compound (**9**), the preparation of the hydrazide (**11**) from product (**10**) had to be carried out at room temperature since heating of the hydrazine reaction mixture yielded several byproducts [50]. Methanol had to be avoided as solvent for the reaction, in the workup and as eluant in the flash column chromatography since two unidentified di-*N*-methylated byproducts were easily formed, as shown by MS and ^{1}H NMR. This method afforded the hydrazide (**11**) in 97 % yield.

The acetone hydrazone derivative (**17**) was formed in 70 % yield by addition of acetone to the 3-nitropyridine-4-carbonylhydrazide reaction mixture. The hydrazone (**17**) was characterised as a 70:30 mixture of two tautomers, as shown by ^{1}H and ^{13}C NMR.

The acyl azide (**12**) was prepared by diazotization of hydrazide (**11**). The acyl azide easily decomposed in MS and by the Curtius rearrangement in solution to isocyanate (**13**). The exact yield of the acyl azide (**12**) was not measured since this potential unstable product was always kept in dry diethyl ether and stored in the freezer.

A Curtius rearrangement of acyl azide (**12**) carried out in refluxing benzene until nitrogen gas evolution ceased, afforded isocyanate (**13**). The Curtius rearrangement involves the pyrolysis of acyl azides to yield isocyanates. The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction can be carried out in water or alcohol, in which case the products are amines, carbamates or acylureas. The reaction mechanism of the Curtius rearrangement (Scheme 2.2) is similar to that in the Hofmann rearrangement. It is also the exact analogy between this reaction and the Wolff rearrangement. In this case, however, there is no evidence for a free nitrene (**18**) and it is probable that the steps are concerted [12].

The reaction was followed frequently by ^{1}H NMR, indicating a gradual conversion of acyl azide (**12**) into isocyanate (**13**), demonstrated by the increased shielding effect and lower frequency shift values, especially of the proton in the 5-position.

More than 93 % conversion of acyl azide (**12**), and respectively 93 % purity and yield of isocyanate (**13**) was obtained after 15 minutes. No trimerisation into the isocyanate trimer or other byproducts could be observed. Isocyanate (**13**) was stored in dry benzene. It was stable at room temperature for several weeks.
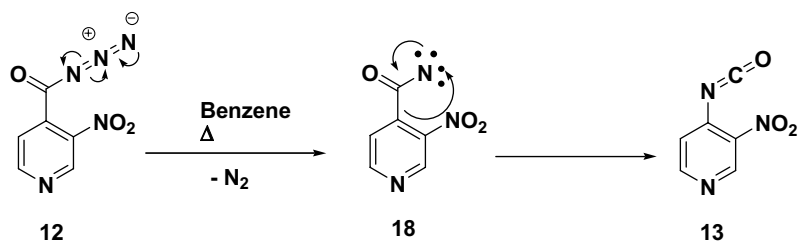
Scheme 2.2 The Curtius rearrangement

The carbamates (**14a-b**) were prepared directly from acyl azide (**12**) in the presence of methanol or ethanol via isocyanate (**13**) by reflux, in 36-37 % yield [13, 104].

2.2 Synthesis of 5-nitro-2-pyridyl isocyanate

5-Nitro-2-pyridyl isocyanate (**23**) was also prepared through a four-step procedure (Scheme 2.3). Nitration [14, 105] of the readily available 2-picoline (**19**) afforded 5-nitro-2-picoline (**20**) in 35 % yield. Oxidation of the methyl group afforded 5-nitro-2-picolinic acid (**21**) in 48 % yield. Diphenylphosphorylazide (DPPA) is a reagent that transforms carboxylic acids directly and conveniently into acyl azides in high yields [15]. This was demonstrated for acyl azide (**22**), which was prepared in 87 % yield. Finally, isocyanate (**23**) was prepared by a Curtius rearrangement of acyl azide (**22**).

However, isocyanate (**23**) proved to be less stable than the isocyanate (**13**) and had to be used immediately for synthetic purposes. The presence of isocyanate (**23**) was confirmed by trapping with ethanol to afford the ethyl carbamate (**24**) in 83 % yield from acyl azide (**22**). This demonstrated the ability of 5-nitro-2-pyridyl isocyanate (**23**) to be trapped, despite its instability.
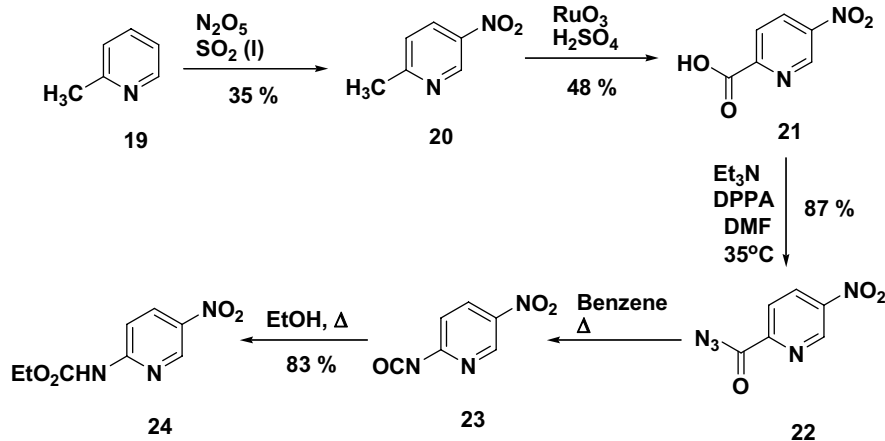
Scheme 2.3 Preparation of 5-nitro-2-pyridyl isocyanate (**23**)

A standard phosgene reaction or oxalyl chloride reaction [11] of 2-amino-5-nitropyridine (**25**) to afford isocyanate (**23**) proved to be unsuccessful (Scheme 2.4).

Compound (**25**) was generated in two steps. Nitration of pyridine (**1**) afforded 3-nitropyridine (**2**) in 77 % yield [4-6]. Amination using hydroxylamine, zinc chloride and potassium hydroxide afforded 2-amino-5-nitropyridine (**25**) in 54 % yield [16].

The reactions yielded several products depending on the reagent used (Scheme 2.4). The phosgene reaction afforded mainly the isocyanate dimer (**28**) and minor amounts of the urea compound (**29**).
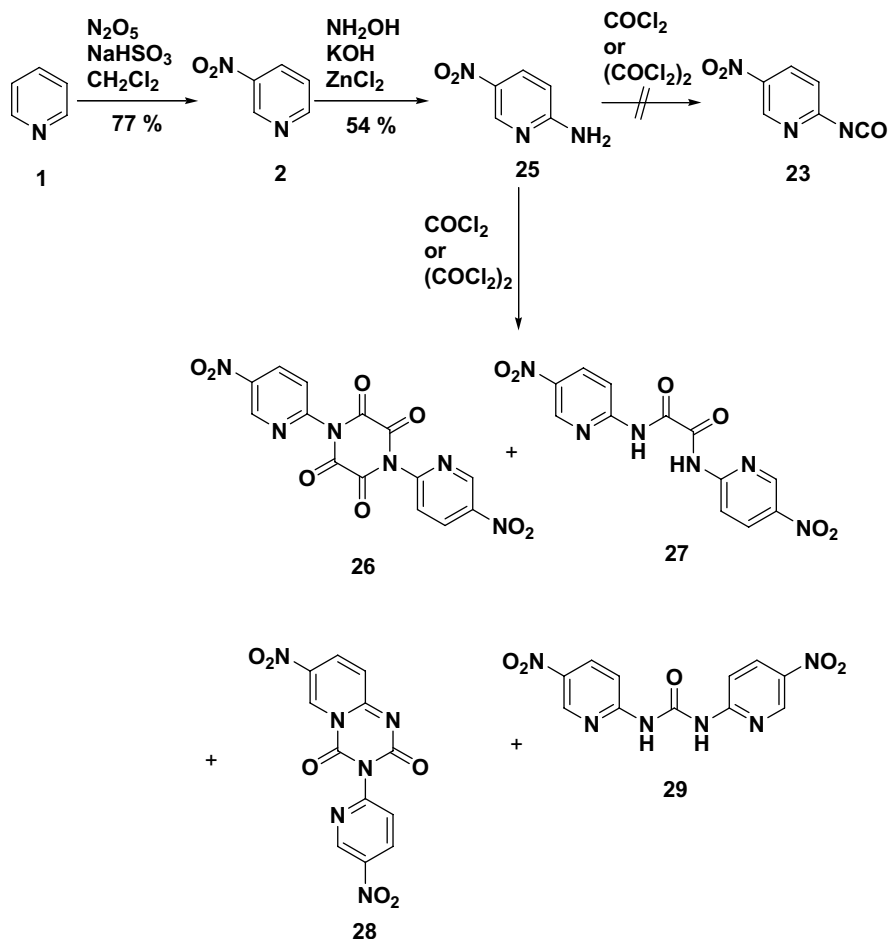
Scheme 2.4 The phosgene/oxalylchloride pathway to 5-nitro-2-pyridyl isocyanate (**23**)

The tetrone (**26**) was isolated and characterised after reaction with oxalyl chloride. This reaction seemed to proceed via the *N,N'*-dipyridylethanediamide (**27**). Indications of compound (**27**) and the urea compound (**29**) were only based on a limited amount of spectroscopic data (IR, ^{1}H and ^{13}C NMR).

The fact that no carbamate could be isolated from the reaction mixtures after addition of ethanol, also demonstrated the absence of isocyanate (**23**).

2.3 Summary

3-Nitro-4-pyridyl isocyanate (**13**) and 5-nitro-2-pyridyl isocyanate (**23**) have been prepared from methyl 4-pyridinecarboxylate (**9**) and 2-picoline (**19**), respectively, through a four-step protocol. The key step in both protocols is the Curtius rearrangement of the acyl azides (**12**, **22**).

3-Nitro-4-pyridyl isocyanate (**13**) proved to be stable in dry benzene at room temperature for several weeks. 5-Nitro-2-pyridyl isocyanate (**23**) was less stable and had to be used for synthetic purposes immediately. It was spectroscopically characterised before trapped as either the dimer (**28**) or carbamate (**24**). Treatment of both isocyanates (**13**, **23**) with methanol or ethanol afforded the corresponding carbamates (**14a-b**, **24**).

The results demonstrate that the introduction of the nitro group in the pyridine ring stabilises heterocyclic isocyanates. Nitropyridyl isocyanates have now become available as a new and interesting class of compounds, similar to the aromatic isocyanates.

Investigation of the nitropyridyl isocyanates as substrates for the synthesis of new heterocyclic compounds will be discussed in Chapters 3 and 4.

Chapter 2 Nitropyridyl isocyanates

Chapter 3: Synthesis of pyridine isocyanate dimer and trimer

The results discussed in this chapter are presented in Chapter 1.

3.1 Synthesis of pyridine isocyanate dimer

The first attempt to synthesise 2-pyridyl isocyanate (**3**) was performed in 1975 [10]. The method of refluxing the acyl azide (**30**) in benzene resulted only in the formation of the isocyanate dimer (**6**) (Scheme 3.1). IR-Spectroscopy only showed a weak band owing to 2-pyridyl isocyanate (**3**).
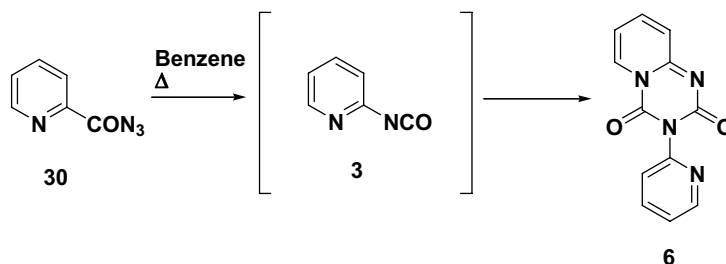
Scheme 3.1 Synthesis of the isocyanate dimer (**6**) from 2-pyridine isocyanate (**3**)

Previous experience with the preparation, reactivity and instability of the isocyanate (**3**) is based on a study [49, 50] of preparation and thermal cycloreversion/decomposition of the isocyanate dimer (**6**) of isocyanate (**3**), and the cycloaddition products of isocyanate (**3**) with ketenes. The latter reaction will be further discussed in Chapter 4. The decomposition products were characterised by an IR/Ar matrix after sublimation, flash vacuum thermolysis (FVT) and argon matrix deposition.

When 5-nitro-2-pyridyl isocyanate (**23**) was generated from acyl azide (**22**) in the absence of a trapping agent, the isocyanate dimer (**28**) was formed in 77 % yield after refluxing for two hours, based on ^{1}H NMR of the reaction mixture (Scheme 3.2).
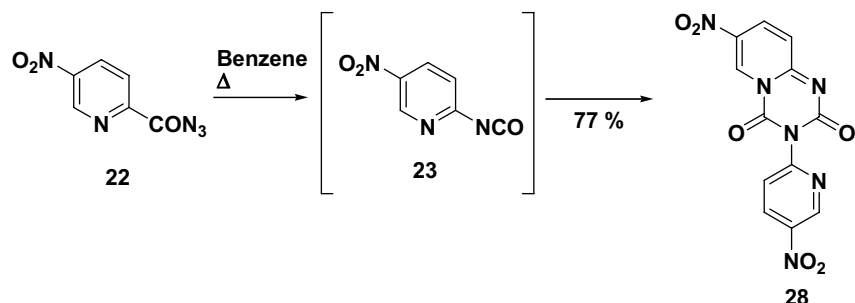
Scheme 3.2 Synthesis of the isocyanate dimer (**28**) from 5-nitro-2-pyridyl isocyanate (**23**)

3.2 Synthesis of pyridine isocyanate trimer

Isocyanurates are intermediates for the industrial production of polymers from polyisocyanates [8].

The decomposition of isonicotinoyl azide (**32**) in refluxing benzene has been studied [10, 17]. The orange precipitate obtained was believed to be the isocyanate trimer (**7**). It undergoes hydrolysis in aqueous solution to yield the urea compound (**29**) and 4-aminopyridine (**36**) as decomposition products.

The isocyanate trimer (**7**) of the unstable pyridine isocyanate (**5**) was synthesised for reference purposes. The acyl azide precursor (**32**) was obtained in 80 % yield after reaction of 4-picolinic acid (**31**) with DPPA. In accordance with literature [10, 17] characteristic orange crystals were obtained in quantitative yield through a Curtius rearrangement of acyl azide (**32**) (Scheme 3.3).
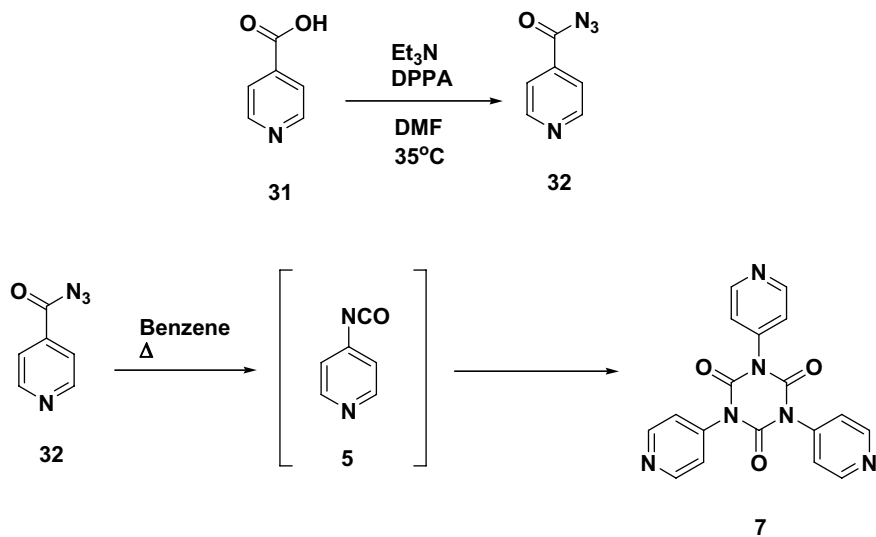
Scheme 3.3 Synthesis of the isocyanate trimer (**7**) from 4-pyridine isocyanate (**5**)

The mechanism for preparation of acyl azide (**32**) with DPPA is shown in Scheme 3.4. The six-membered cyclic complex (**34**) is formed as an intermediate [15].
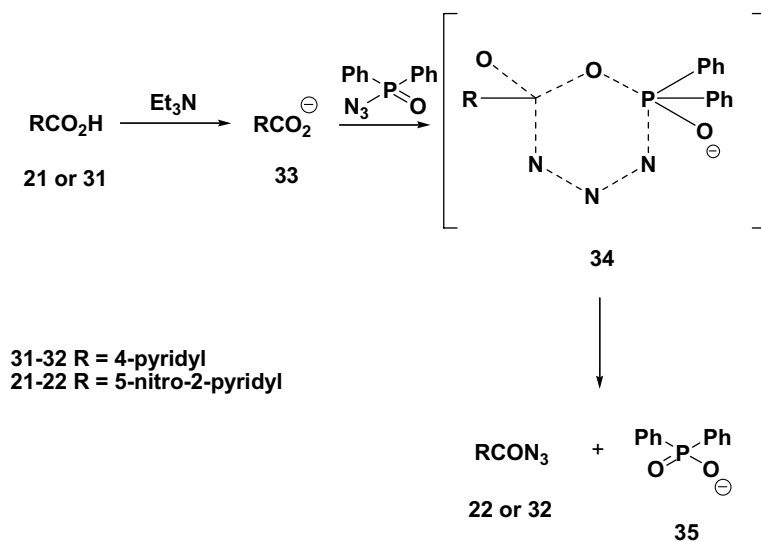
Scheme 3.4 The mechanism for the reaction of carboxylic acids with DPPA [15]

The isocyanate trimer (**7**) proved to be less stable than previously reported [10, 17]. The amine or carbamate decomposition products were observed in the presence of moisture or alcohols (Scheme 3.5). Quantitative yield of the methyl carbamate (**37**) was isolated after reflux in methanol. Correspondingly, the trimer (**7**) decomposed by flash column chromatography or thin layer chromatography to yield 4-aminopyridine (**36**). The urea compound (**29**) has been reported in the literature [10] as decomposition product, but was not observed here.
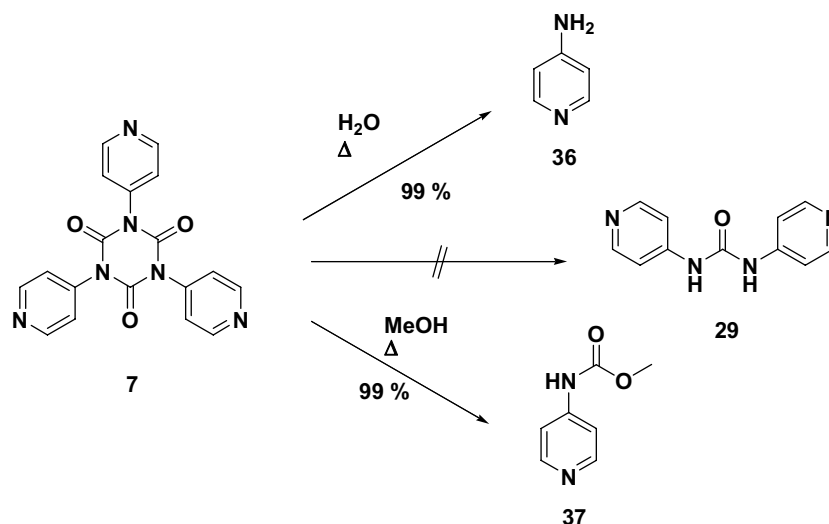
Scheme 3.5 Decomposition of the isocyanate trimer (**7**)

The observed reactivity of the trimer (**7**) towards nucleophiles such as methanol and moisture, demonstrates the potential of the trimer (**7**) as a stable and protected derivative of the unstable pyridine isocyanate (**5**) for synthetic purposes.

The isocyanate trimer (**7**) has a threefold symmetry and may have nonlinear optical properties, since it promises strong first hyperpolarisabilities. This is a measure of the molecular capability to double the frequency of incoming light such as laser-light. Other properties might change the refractive index of materials with an applied electric field.

Isocyanate (**13**) was stable in dry benzene for up to several weeks at room temperature and did not undergo trimerisation to the corresponding trimer (**38**) (Scheme 3.6), as the non-nitro analogue (**5**).
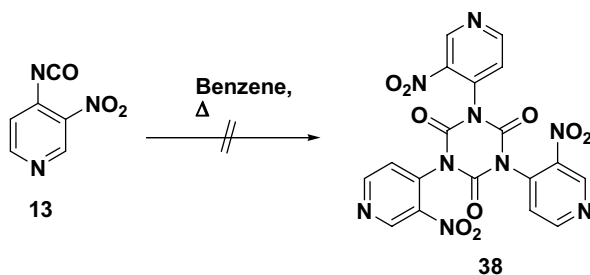
Scheme 3.6 Trimerisation of 3-nitro-4-pyridyl isocyanate (**13**)

3.3 Summary

The isocyanate dimer (**28**) was formed in 77 % yield in two steps from acyl azide (**22**) via a Curtius rearrangement to isocyanate (**23**). This shows that isocyanate (**23**) is less stable than isocyanate (**13**), which is stable in dry benzene for up to several weeks. Isocyanate (**23**) must be used immediately for synthetic purposes or trapped with ethanol to yield the ethyl carbamate (**24**). The absence of a trapping agent in the reaction mixture however, afforded the dimer (**28**).

The isocyanate trimer (**7**) was made for reference purposes according to a literature procedure. The trimer (**7**) proved, however, to be more reactive than described, and was readily converted to 4-aminopyridine (**36**) or methyl carbamate (**37**) in the presence of moisture or methanol, respectively. This shows the potential of the trimer (**7**) as a stable and protected derivative of the unstable pyridine isocyanate (**5**) for synthetic purposes. It remains to be seen whether the trimer (**7**) may have nonlinear optical properties.

Chapter 3 Synthesis of isocyanate dimer and trimer

Chapter 4: Nitropyridyl isocyanates in cycloaddition reactions

The results from the 1,3-dipolar cycloaddition reactions discussed in this chapter are presented in Paper II.

Cycloaddition reactions provide useful synthetic routes to a wide range of heterocyclic compounds, especially those containing four, five or six atoms in the ring. 1,3-Dipolar cycloaddition provides an excellent method for constructing five-membered rings (Scheme 4.1) because a wide variety of 1,3-dipoles are available and these undergo addition to carbon-carbon multiple bonds or to multiple bonds containing heteroatoms [18].
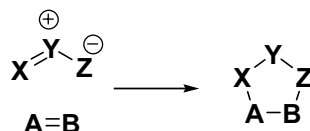
Scheme 4.1 1,3-Dipolar cycloaddition reaction

A 1,3-dipole is a three-atom π-electron system with four π-electrons delocalized over the three atoms. 1,3-Dipolar compounds can be divided into two main types (Figure 4.1). Type 1 is where the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom. Azides, diazo compounds, nitrile oxides, nitrile imides, nitrile sulfides and nitrile ylides are examples of this type. Type 2 is where the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond. Nitrones, azomethine imides, azomethine ylides, carbonyl ylides and thiocarbonyl ylides are classified as type 2 [19].

Type 1:

$$\overset{\ominus}{X}-\overset{\oplus}{Y}=Z- \quad \longleftrightarrow \quad \overset{\ominus}{X}-\overset{\oplus}{Y}\equiv Z- \qquad \begin{array}{l} X = C, N, O \\ Y = N \\ Z = C, N \end{array}$$

Type 2:

$$\overset{\ominus}{X}-\overset{\oplus}{Y}-Z- \quad \longleftrightarrow \quad \overset{\ominus}{X}-\overset{\oplus}{Y}=Z- \qquad \begin{array}{l} X = C, N, O \\ Y = N, O \\ Z = C, N, O \end{array}$$
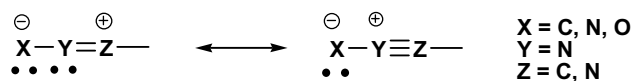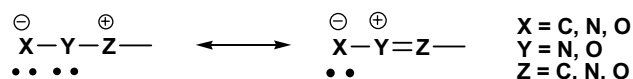
Figure 4.1 Two types of 1,3-dipoles in cycloaddition reactions [19]

Compounds that can react with these species in cycloaddition reactions are called dipolarophiles and contain unsaturated functional groups such as C=C, C=N, C=O and C=S. There are thus many possible combinations of 1,3-dipoles and dipolarophiles.

The reactions can be represented as proceeding through a transition state where the 4π-electron system of the dipole interacts with the 2π-electron system of the dipolarophile. This is a thermally allowed process on the basis of the Woodward-Hoffmann rules. The reactivity of 1,3-dipoles towards different dipolarophiles often varies considerably. The orbitals must be of the correct phase to interact, the interaction must be sterically feasible and the interaction is stronger the closer in energy the orbitals are (Figure 4.2). Reactions are therefore favoured if one component is strongly nucleophilic and the other strongly electrophilic. The more electrophilic dipolarophiles have lower energy LUMO values whereas the more nucleophilic species have higher energy HOMO values [18].
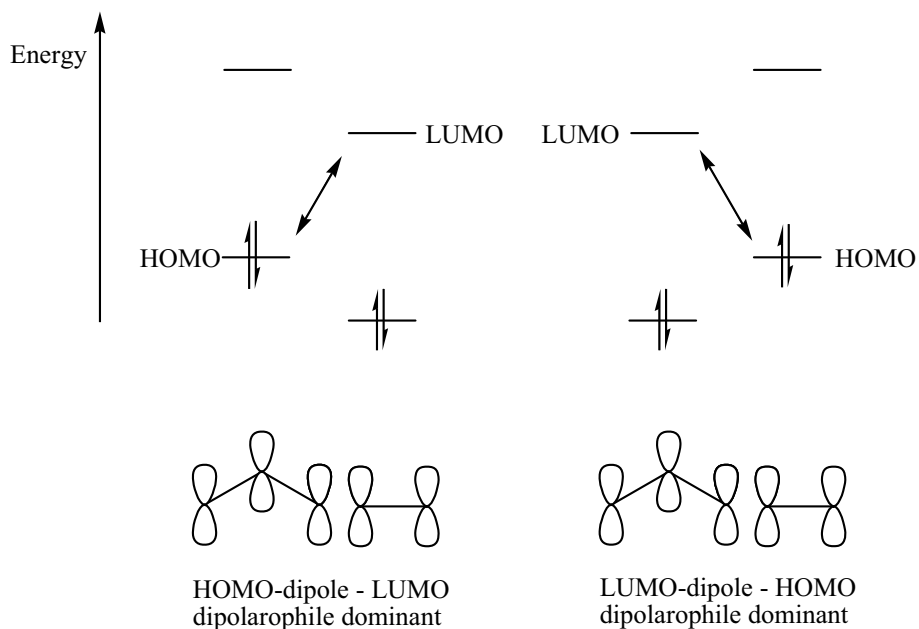
Figure 4.2 Frontier-orbital combinations in 1,3-dipolar cycloaddition reactions [18]

4.1 1,3-Dipolar cycloaddition reaction with azides

Only a few cycloaddition reactions of isocyanates with organic azides have been reported. The reason for this is probably because alkyl and aryl isocyanates can be prepared from their corresponding acyl azides through the Curtius rearrangement. Acyl azides do not normally react with the resulting isocyanate products in the Curtius rearrangement [20]. Reaction with other organic azides, however, affords the 1,3-dipolar cycloadducts [20-22].

Phenyl isocyanate (**39**) has been reported to react with either sodium azide [23, 24] or trimethylsilylazide (TMSA) [25, 26] to form 1-phenyl-5(4*H*)-tetrazolinones (**40**) (Scheme 4.2).

TMSA is known to be a versatile reagent in organic synthesis and behaves as a 1,3-dipole in analogy to organic azides towards acetylenes [27], olefins [21, 22, 28] and nitriles [28, 29]. The corresponding cycloadducts are formed. Reaction with acid chlorides [30, 31], anhydrides [31-34], imides [33], esters and lactones [35] yields a variety of isocyanates. In some cases the isocyanates are cyclized directly to heterocyclic compounds such as uracils [33], pyridones [31], dihydropyridines [22], triazoles [29] and aziridines [21]. TMSA also reacts with aldehydes to afford the corresponding amides [33]. The reaction of TMSA with heterocumulenes, like isocyanates, isothiocyanates, carbodiimides and diphenylketene has received little attention.
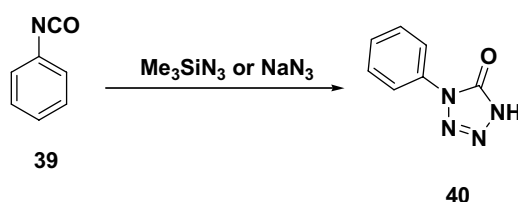
Scheme 4.2 1,3-Dipolar cycloaddition of phenyl isocyanate (**39**) with azides

The 1,3-dipolar cycloaddition of phenyl isocyanate (**39**) with TMSA affords the desired 1-phenyl-5(4*H*)-tetrazolinone (**40**) in variable yields, depending on the reaction conditions. Equimolar amounts of TMSA yields 1,3-diphenylurea and phenylcarbamoylazide as byproducts in the reaction. However, using an excess of TMSA (two equivalents) afforded the desired 1-phenyl-5(4*H*)-tetrazolinone (**40**) in quantitative yield [25, 26].

Compounds which have incorporated the tetrazolinone structure are used as herbicides [36, 37], pesticides [38] and short-acting narcotic analgesics [39]. The tetrazolinones are either monosubstituted in the 1- or 4-position, or disubstituted.

3-Nitro-4-pyridyl isocyanate (**13**) was made *in situ* in dry benzene from the corresponding acyl azide through a Curtius rearrangement. The acyl azide was made in dry diethyl ether through diazotization of the corresponding carbonyl hydrazide. For our purpose the 1,3-dipolar cycloaddition with TMSA was performed in dry benzene, since the isocyanate was generated in this solvent, in contrast to the cycloaddition with phenyl isocyanate (**39**) which could be run without solvent [25].

An excess of TMSA (2 equivalents) was used [25, 26]. Reflux overnight afforded 1-(3-nitro-4-pyridyl)-1*H*-tetrazol-5(4*H*)-one (**41**) in 50 % yield (Scheme 4.3).
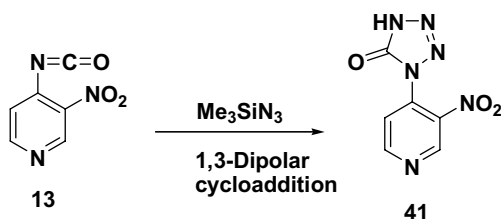
Scheme 4.3 Synthesis of tetrazolinone (**41**)

It was discovered that the tetrazolinone (**41**) underwent cycloreversion, hydrolysis of the isocyanate (**13**) and decarboxylation in accordance with previous reports [20]. Left in solution in the presence of moisture 4-amino-3-nitropyridine (**42**) was gradually formed after a period of four weeks (Scheme 4.4). The reverse process could be followed by ^{1}H NMR.
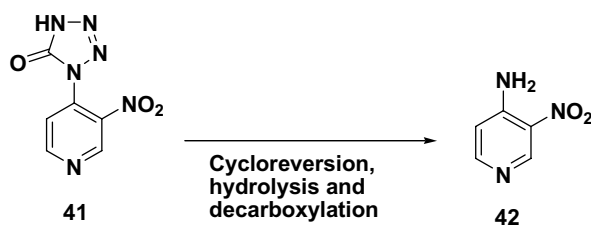
Scheme 4.4 Cycloreversion, hydrolysis and decarboxylation of tetrazolinone (**41**)

Although retro Diels-Alder reactions are well known in the literature, a few cycloreversions of 1,3-dipole adducts have been reported. Azides have been described in only one [20]. In contrast to previous reports the reverse reaction took place at room temperature.

1-(5-Nitro-2-pyridyl)-1*H*-tetrazol-5(4*H*)-one (**43**) was formed in a similar manner (Scheme 4.5), starting from the acyl azide which was converted to isocyanate (**23**) *in situ*. The product (**43**) was isolated in 64 % yield. No purification could be performed, as it decomposed in solution. This will be discussed in the following.
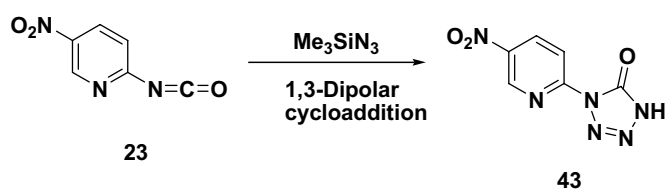
Scheme 4.5 Synthesis of tetrazolinone (**43**)

Tetrazolinone (**43**) also underwent cycloreversion, hydrolysis and decarboxylation (Scheme 4.6) in solution in the presence of moisture. The urea compound (**29**) was initially formed together with 5-amino-2-nitropyridine (**25**), as shown by ^{1}H NMR.
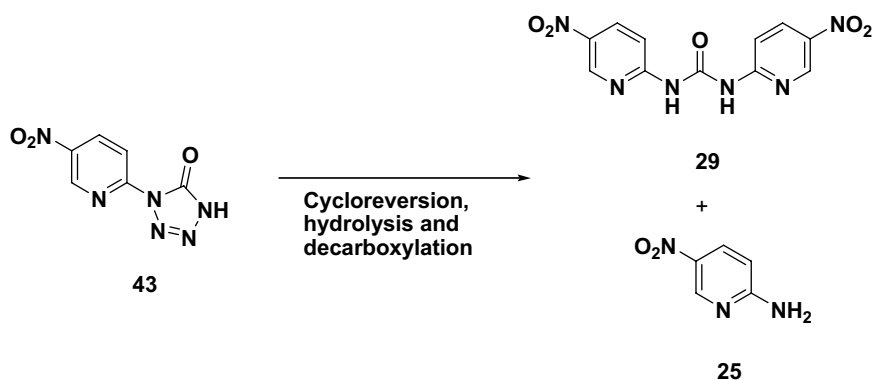
Scheme 4.6 Cycloreversion, hydrolysis and decarboxylation of tetrazolinone (**43**)

4.2 1,3-Dipolar cycloaddition reaction with pyridine *N*-oxides

One of the most important recent theoretical developments in connection with cycloaddition has been the application of the frontier molecular orbital (FMO) approach. This method has been used successfully to account for the cycloaddition characteristics (reactivity and peri- and regioselectivities) by considering the interaction of the highest occupied molecular orbital (HOMO) of the donor and the lowest unoccupied molecular orbital (LUMO) of the acceptor.

On the other hand, in a recent rationalization of reactivity and mechanistic phenomena observed in cycloadditions, it has been proposed that charge transfer is of importance in stabilizing the transition states of cycloadditions, and the FMO theory has been used successfully in explaining the formation of charge-transfer complexes [40].

The 1,3-dipolar cycloaddition of isocyanates (**45**) with pyridine *N*-oxides (**44**) is a well known reaction (Scheme 4.7) [40-48]. It has been studied since the early 1980s and considered as a 1,3-dipolar cycloaddition to the nitrone function, followed by rearomatization by decarboxylation. Based on the stereoselectivity, lack of solvent dependence, the low activation enthalpy and the strong negative activation entropy it was later shown that this reaction proceeds by a concerted mechanism.

R$_1$, R$_2$, R$_3$ = H, Me, Cl, Br

R$_4$ = H, Br
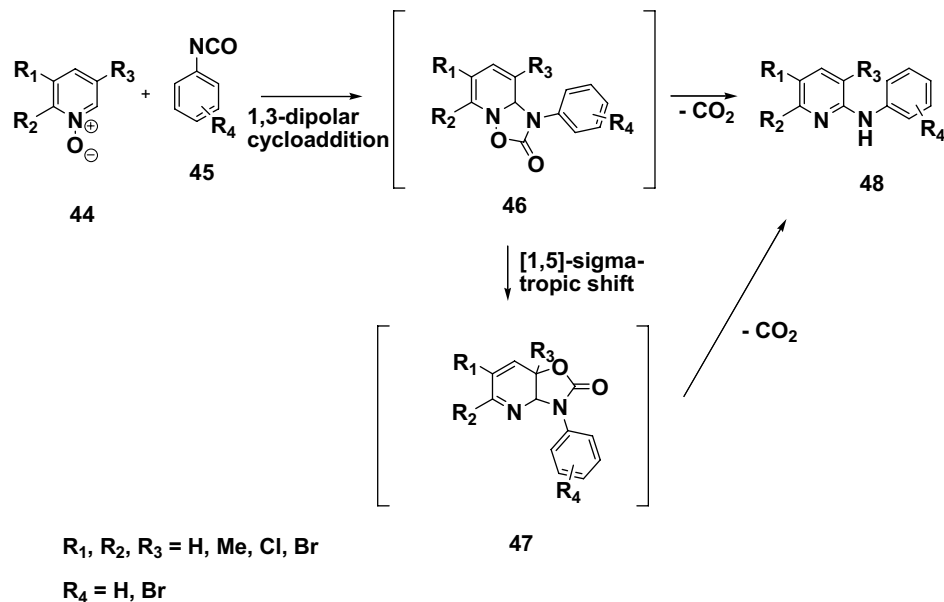
Scheme 4.7 1,3-Dipolar cycloaddition of substituted phenyl isocyanates (**45**) with substituted pyridine *N*-oxides (**44**)

It has been suggested that the reaction falls into the category of a neutral-type reaction in Sustmann's classification for cycloadditions [49]. The reactivity may result from both the FMO interaction and the relatively high degree of coulombic attraction arising from the highly polarized structures of both addends. The aromaticity of pyridine *N*-oxides may play a major role in determination of reactivity. The rates of the cycloadditions of pyridine *N*-oxides with phenyl isocyanate were not affected by change in the polarity of the solvents, ruling out an intermediate involving a significant degree of charge separation. The charge-transfer complexes do not have a random structure but a highly ordered one resembling crystal structure, in which the molecules are stacked in parallel planes.

Molecular-orbital theory suggests that electrons from one of the two original molecules jump into higher vacant orbitals of the other, and the electron transfers leading to charge-transfer complex formation and to transition-state intermediate formation in cycloaddition reactions very probably require similar structural arrangements, in which the two interacting molecules lie in planes. The transition state of 1,3-dipolar cycloaddition might be stabilized by the secondary orbital interaction. In the early stages of the reaction, coulombic attractions are operative rather than FMO interactions, as reflected by the highly polarized structure of the addends, and the resultant molecular complexes may be further stabilized by FMO interaction involving the secondary orbital interaction, resulting in the formation of a highly ordered complex.

These results suggest that whether the cycloaddition does occur or not depends upon the relative stabilities of the ground state and transition state [40].

Both the energy and the form of the HOMO are affected to a smaller extent than those of the LUMO because the former has a node close to the C_3 and C_5 atoms. The LUMO orbital is localized at the positions of the C_3 and C_5 atoms, and consequently substitution by donor groups at positions 3 and 5 destabilizes the LUMO orbital. In some cases the steric effect can be overpowered by the FMO controlling effects [44].

The 1,2-dihydro intermediates (**46**) are too unstable to be neither seen during the reaction nor isolated from the reaction mixtures. The 2,3-dihydro intermediates (**47**) formed from the intermediates (**46**) through a [1,5]-sigmatropic shift are more stable [40-48]. They have been isolated and characterised. This is in agreement with calculations performed which indicated that the heat of formation of the rearranged compound is lower in energy than that of the primary one, indicating the primary adduct to be thermodynamically less stable [44]. After re-aromatization by decarboxylation, the substituted amines (**48**) are formed.

3,5-Dimethyl-*N*-(3-nitro-4-pyridyl)pyridin-2-amine (**52**) was formed through a 1,3-dipolar cycloaddition of 3-nitro-4-pyridyl isocyanate (**13**) to 3,5-dimethylpyridine *N*-oxide (**49**) (Scheme 4.8). 3-Nitro-4-pyridyl isocyanate (**13**) was formed *in situ* in dry benzene from the corresponding acyl azide through a Curtius rearrangement. The acyl azide was made in dry diethyl ether from the corresponding carbonyl hydrazide. Isocyanate (**13**) was added to a solution of 3,5-dimethylpyridine *N*-oxide (**49**) in dry toluene and refluxed for five days. The reaction proceeded according to previous reports (Scheme 4.8) [41]. The 1,2-dihydro intermediate (**50**) was never observed by ^{1}H NMR or isolated from the reaction mixture. 3,5-Dimethyl-*N*-(3-nitro-4-pyridyl)pyridin-2-amine (**52**) was isolated in 65 % yield after purification. The crude product showed a mixture of the substituted amine (**52**) and 20 % of the 2,3-dihydro intermediate (**51**). The 2,3-dihydro intermediate (**51**) formed through a [1,5]-sigmatropic shift is more stable than the 1,2-dihydro intermediate (**50**) (Scheme 4.8) [40-48]. The 2,3-dihydro intermediate (**51**) undergoes re-aromatization by decarboxylation to afford the substituted amine (**52**).
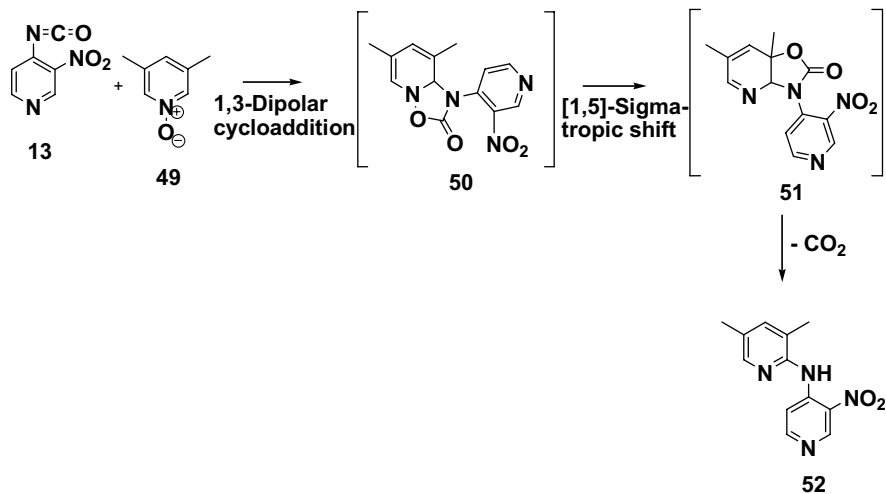
Scheme 4.8 Synthesis of 3,5-dimethyl-*N*-(3-nitro-4-pyridyl)pyridin-2-amine (**52**)

The aromatic character of the pyridine *N*-oxide reflects its reactivity. 3,5-Dimethylpyridine *N*-oxide (**49**) was used because it is less aromatic than pyridine *N*-oxide and more sterically congested with its two electron-donating methyl groups [46]. It is therefore believed to be more reactive than pyridine *N*-oxide.

3,5-Dimethyl-*N*-(5-nitro-2-pyridyl)pyridin-2-amine (**55**) was formed through a 1,3-dipolar cycloaddition reaction in a similar manner (Scheme 4.9) [41]. 5-Nitro-2-pyridyl isocyanate (**23**) was formed *in situ* in dry benzene from the corresponding acyl azide. It was added to a solution of 3,5-dimethylpyridine *N*-oxide (**49**) in dry toluene and refluxed for four days. 3,5-Dimethyl-*N*-(5-nitro-2-pyridyl)pyridin-2-amine (**55**) was isolated in 67 % yield after purification. In this reaction, however, the 2,3-dihydro intermediate (**54**) could not be observed in the crude product, as shown by ^{1}H NMR. The less stable 1,2-dihydro intermediate (**53**) could not be observed in the ^{1}H NMR spectrum of the crude product or isolated, as was also the case for intermediate (**50**).
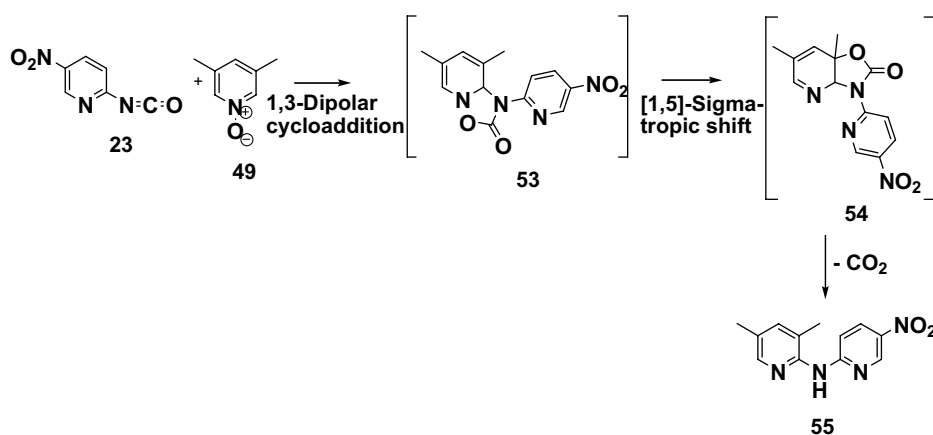
Scheme 4.9 Synthesis of 3,5-dimethyl-*N*-(5-nitro-2-pyridyl)pyridin-2-amine (**55**)

4.3 [2+4]-Cycloaddition reaction with diphenylketene

4*H*-Pyrido[1,2-*a*]pyrimidine-2,4-diones, also known as the Chichibabin derivatives, have previously been formed by two routes in high yields.

In the original route substituted dialkylmalonates are condensed with substituted 2-aminopyridines by heating at 160-200°C for several hours with continuous removal of the alcohol [50, 51].

More reactive chloroarylmalonate esters are used in the second route, and condensed with substituted 2-aminopyridines. This condensation reaction proceeds more rapidly at modest temperatures [50].

Both of these routes are feasible when the 2-aminopyridines are substituted with electron-donating groups such as methyl. With electron-withdrawing groups represented by the nitro group the reaction does not take place. This has been reported for 5-nitro-2-aminopyridine (**25**) [52].

Based on previous work performed by Fiksdahl and Wentrup [53, 54] concerning the cycloaddition reaction of 2-pyridyl isocyanate (**3**) with ketenes, the cycloaddition reaction of 5-nitro-2-pyridyl isocyanate (**23**) with diphenylketene was investigated. The expected [2+4]-cycloadduct would be pyridopyrimidinone (**57**). Isocyanate (**23**) has not been tested as a diene, but many similar compounds such as azomethines have previously yielded promising results [55].
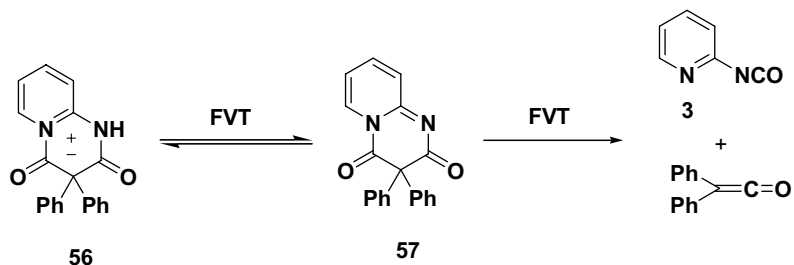
Scheme 4.10 Flash vacuum thermolysis of pyridopyrimidinone (**57**) to 2-pyridine isocyanate (**3**) and diphenylketene

FVT of the non-nitrated pyridopyrimidinone (**57**) showed cycloreversion back to the ketene and pyridine isocyanate (**3**) (Scheme 4.10) [53, 54]. Attempts to prepare pyridopyrimidinone (**57**) through cycloaddition of isocyanate (**3**) with diphenylketene have so far been unsuccessful. The main product of the reaction appeared unexpectedly to be the 3-substituted pyrido[1,2-*a*][1,3,5]triazine-2,4-dione (**58**) (Scheme 4.11) [54]. The mechanism for the formation of compound (**58**) is not known.
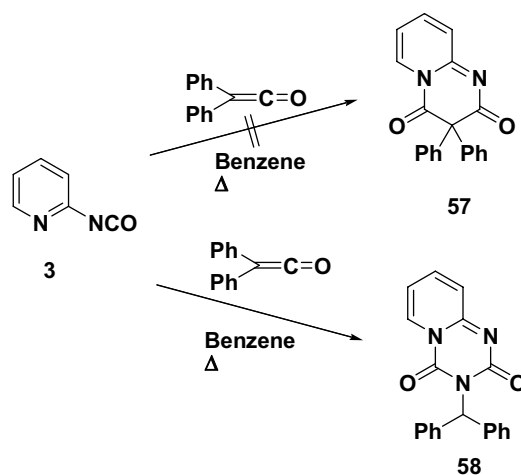
Scheme 4.11 Cycloaddition of 2-pyridine isocyanate (**3**) with diphenylketene [54]

35

The introduction of a nitro group in the isocyanate will possibly stabilise to prevent dimerisation and promote the desired [2+4]-cycloaddition.

Diphenylketene was prepared according to the literature by dehydrohalogenation of diphenylacetylchloride with triethylamine [56]. Diphenylketene was distilled and stable in pure form. Diphenylketene was reacted with isocyanate (**23**) generated *in situ* from acyl azide (**22**). The compound pyridopyrimidinone (**59**) was formed, as shown by ^{1}H NMR (Scheme 4.12).
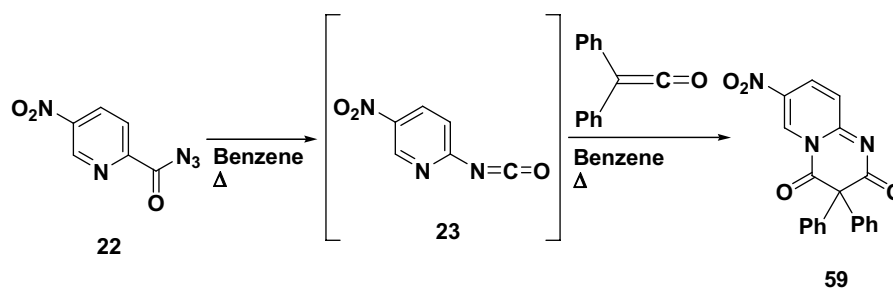
Scheme 4.12 Cycloaddition of 5-nitro-2-pyridyl isocyanate (**23**) with diphenylketene

Attempts were made to isolate product (**59**) as it readily decomposed to 5-nitro-2-pyridyl benzeneacetamide (**60**) (Scheme 4.13). Several methods were tested, all yielding the same negative result.

The reason why the cycloadduct (**59**) is unstable might be due to the two phenyl groups attached to the carbon between the two carbonyl groups. The phenyl groups are large and planar and might promote some sterical hindrance between each other and the neighbouring carbonyl groups on the cycloadduct. Other pyridopyrimidinones reported in the literature [50-52, 57] are monosubstituted or not substituted at all with respect to the carbon between the two carbonyl groups. These compounds have been reported to undergo enolization since there are one or two hydrogens available to afford aromatic structures [50-52, 57]. In the cycloadduct (**59**) there are no hydrogens and enolization can not take place. The driving force will then be re-aromatization of the pyridine ring by nucleophilic attack at one of the carbonyl groups [55].
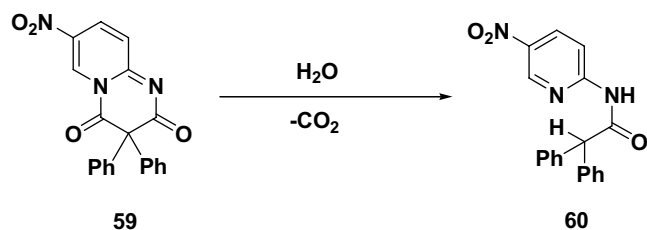
Scheme 4.13 Decomposition of pyridopyrimidinone (**59**)

Three other ketenes, monophenylketene, monochloroketene and dichloroketene, were also tested. They were all unstable compared to diphenylketene, which could be added at the start of the reaction. The ketenes were made *in situ* and slowly added to keep the ketene concentration low, and thus avoid polymerisation. None of them afforded the desired cycloadduct. However, 5-nitro-2-pyridyl carboxamide (**61**) was formed, apparently through a reduction of acyl azide (**22**) (Scheme 4.14).
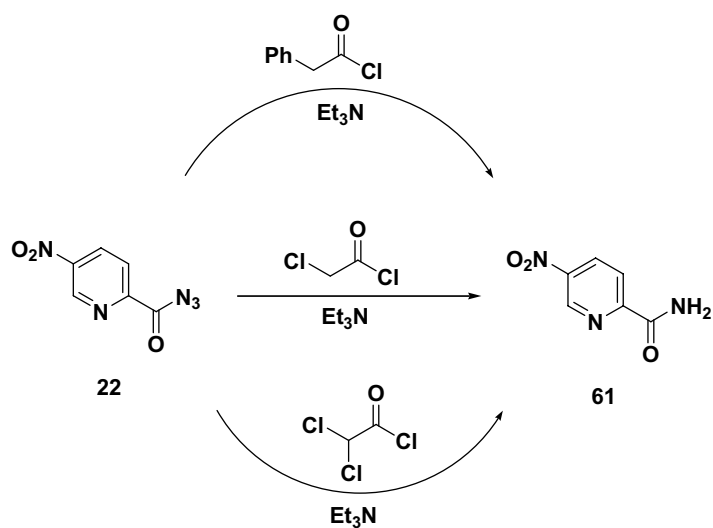
Scheme 4.14 Cycloaddition of acyl azide (**22**) with other ketenes

4.4 Summary

1,3-Dipolar cycloaddition reactions of isocyanates (**13**, **23**) with azides and pyridine *N*-oxides have been studied.

The tetrazolinones 1-(3-nitro-4-pyridyl)-1*H*-5(4*H*)one (**41**) and 1-(5-nitro-2-pyridyl)-1*H*-5(4*H*)one (**43**) were synthesised through a 1,3-dipolar cycloaddition of isocyanates (**13**, **23)** with TMSA in 50 % and 64 % yield, respectively. Both of the products underwent cycloreversion, hydrolysis and decarboxylation in solution in the presence of moisture to yield 4-amino-3-nitropyridine (**42**), 5-amino-2-nitropyridine (**25**) and urea (**29**) as decomposition products.

The substituted amines 3,5-dimethyl-*N*-(3-nitro-4-pyridyl)pyridin-2-amine (**52**) and 3,5-dimethyl-*N*-(5-nitro-2-pyridyl)pyridin-2-amine (**55**) were formed through a 1,3-dipolar cycloaddition reaction of isocyanates (**13**, **23**) with 3,5-dimethylpyridine *N*-oxide (**49**). The yields were 65 % and 67 %, respectively. The 1,2-dihydro intermediates (**50**, **53**) were unstable and could never be observed or isolated. In the reaction with 3-nitro-4-pyridyl isocyanate (**13**) the more stable 2,3-dihydro intermediate (**51**) was present in the crude product in 20 % yield. In the reaction with 5-nitro-2-pyridyl isocyanate (**23**) the 2,3-dihydro intermediate (**54**) could not be observed.

A [2+4]-cycloaddition reaction between diphenylketene and isocyanate (**23**) afforded the cycloadduct (**59**), as shown by ^{1}H NMR. The product proved, however, to be unstable. During any kind of workup it decomposed to 5-nitro-2-pyridyl benzeneacetamide (**60**). When kept in a dry solution in the freezer, it was stable for several weeks. Other unstable ketenes were also tested. In these cases, no cycloadduct could be observed. Instead 5-nitro-2-pyridyl carboxamide (**61**) was formed, apparently through reduction of acyl azide (**22**).

The results show that nitropyridyl isocyanates are able to undergo cycloaddition reactions, in contrast to their non-nitro analogues.

Chapter 5: Aromatic nucleophilic substitution

The results discussed in this chapter are presented in Paper III. *Cand. scient* Freddy Tjosås is acknowledged for optimizing the yields and preparing the methoxysubstituted compound (**16d**).

5.1 General remarks

Aromatic nucleophilic substitution is not a very common reaction. Pyridines, however, are an exception. Substitution at the 2- and 4-position takes place more easy due to activation by the nitrogen atom. The reaction proceeds by an addition-elimination mechanism and the leaving group is displaced by a nucleophile. *N*-Alkylpyridinium salts are even more activated for substitution.

There are four principal mechanisms for aromatic nucleophilic substitution. Each of them is similar to one of the corresponding aliphatic nucleophilic substitution mechanisms [58].

The most important mechanism for aromatic nucleophilic substitution is outlined in Scheme 5.1, shown for compound (**9**).
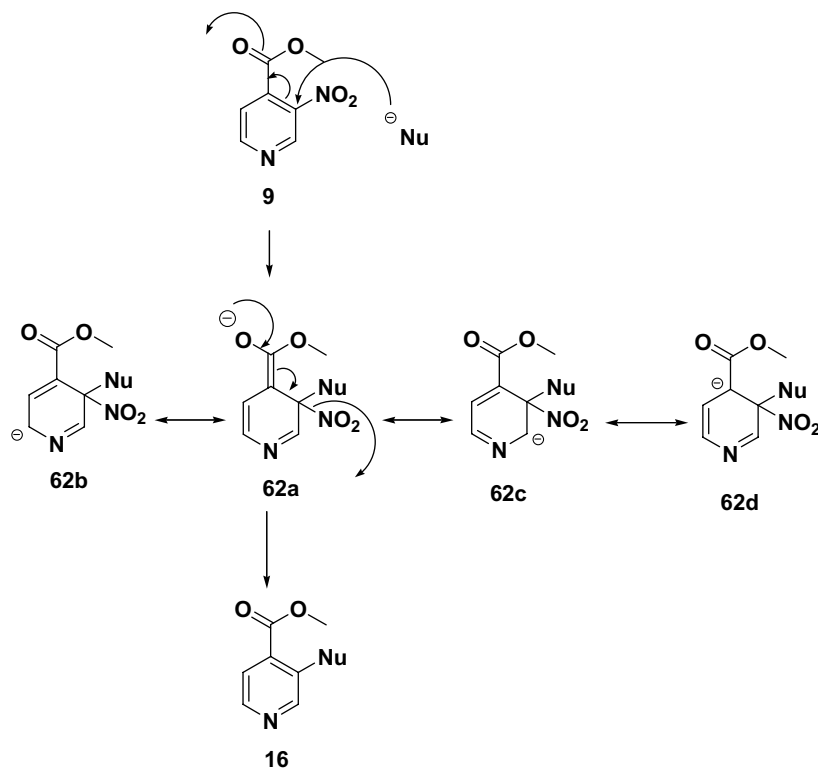
Scheme 5.1 The mechanism for aromatic nucleophilic substitution of the nitro group in compound (**9**) [58]

The first step is usually the rate-determining step. The nucleophile forms a bond with the substrate to give an intermediate and the leaving group departs. In general, aromatic substrates are extremely unreactive towards nucleophilic substitution. The mechanism is referred to as a $S_N Ar$ mechanism, and is generally found where there are activating groups present in the *ortho* and *para* positions on the ring [58]. Furthermore, reactions following this mechanism are accelerated by electron-withdrawing groups, especially in the *ortho* or *para* positions to the leaving group. Electron-donating groups have the opposite effect. Hetero atoms in the ring such as nitrogen are also strongly activating, especially when they are quarternised.

The nitro group is generally not displaced in aliphatic systems, but proves to be a particularly good leaving group in aromatic nucleophilic substitution [59, 60].

5.2 Aromatic nucleophilic substitution of the nitro group by nitrogen, oxygen and sulfur nucleophiles

These effects and the synthetic potential for the replacement of a nitro group on a pyridine ring have been demonstrated by the aromatic nucleophilic substitution of the nitro group in compound (**9**). Different nucleophiles have been tested to yield new substitution products. The results are discussed below.

An aromatic nucleophilic substitution of the nitro group by azide has been observed for 4-cyano-3-nitropyridine (**63**), affording 3-azido-4-cyanopyridine (**64**) in high yield (Scheme 5.2) [61].
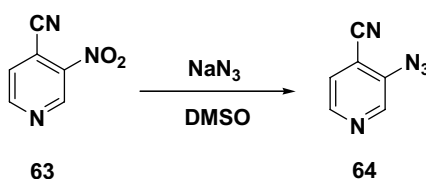
Scheme 5.2 Aromatic nucleophilic substitution of 4-cyano-3-nitropyridine (**63**) by azide [61]

The azido, phenoxy, methoxy and thiophenoxy substitution products (**16a-d**) were correspondingly prepared in a similar manner (Scheme 5.3).

The azide ion easily replaced the nitro group in compound (**9**) to afford the 3-azido substitution product (**16a**) in 50 % yield (Scheme 5.3). Infrared spectroscopy confirmed the absence of the nitro frequencies at 1344 and 1528 cm^{-1} of methyl ester (**9**) and the presence of the characteristic strong azide frequency at 2110 cm^{-1}.

The phenoxy substitution product (**16b**) was prepared by treating compound (**9**) with phenol and sodium hydride in DMSO [62]. ^{1}H NMR showed complete conversion of compound (**9**) into product (**16b**) after heating at approximately 80°C for 20 minutes. After purification the phenoxy substituted compound (**16b**) was afforded in 32 % yield.
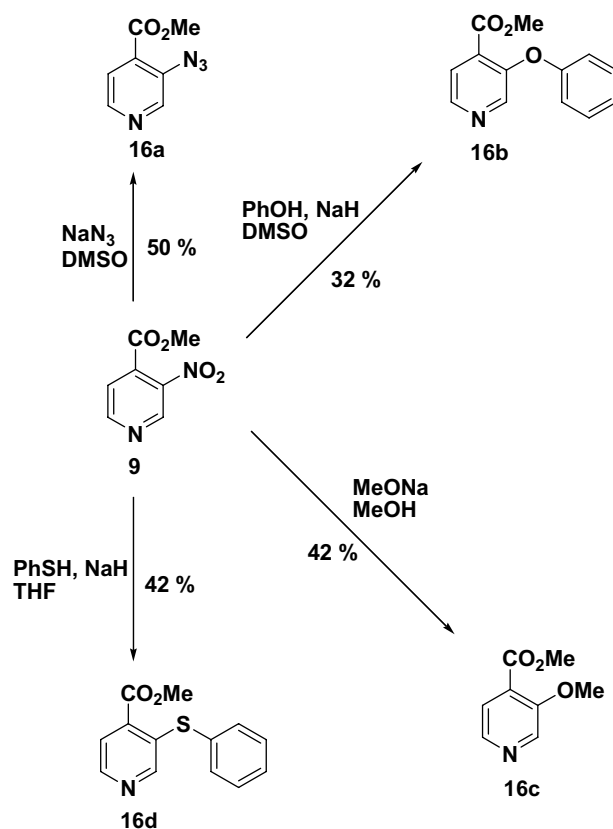
Scheme 5.3 Aromatic nucleophilic substitution of the nitro group of compound (**9**)

The methoxy substituted compound (**16c**) has previous been prepared through aromatic nucleophilic substitution of the 3-bromo-analogue with sodium methoxide [63], and later by a photochemical methoxylation at the 3-position of methyl ester (**8**) in methanol under oxygen in the presence of sulfuric acid [64, 65].

^{1}H NMR showed complete conversion of compound (**9**) into product (**16c**) after reflux with sodium methoxide in methanol. The methoxy substitution product (**16c**) was obtained in 42 % yield after purification. The methyl ester (**9**) was extremely sensitive to moisture under these conditions, and an immediate hydrolysis of compound (**9**) into 3-nitro-4-pyridyl carboxylic acid was observed when traces of water were present.

The thiophenoxy substituted compound (**16d**) was prepared in 42 % yield in the same manner, exchanging phenol with thiophenol [62]. THF proved to be a better solvent than DMSO in this case.
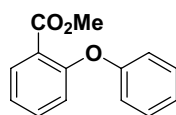
65

Figure 5.1 Methyl *o*-phenoxybenzoate (**65**)

To our knowledge, the phenoxy and thiophenoxy substitution products (**16b**) and (**16d**) have not previously been described. The phenoxy analogue, methyl *o*-phenoxybenzoate (**65**) (Figure 5.1), however, is an herbicide agent [66] and has shown fungicidal activity [67].

The aromatic nucleophilic substitution of the electronegative nitro group with nitrogen, oxygen and sulfur nucleophiles can easily be followed by ^{1}H NMR. Especially the protons in the 2- and 6-position of the pyridine ring affords characteristic low frequency shift values and an increased shielding effect of the respective protons of the appearing substitution products (**16a-d**).

This direct aromatic nucleophilic substitution of the nitro group may be a more convenient and rapid pathway to these substituted compounds compared to the traditional three-step procedure (Scheme 5.4) This protocol proceeds through reduction of the nitro group, diazotization, and then nucleophilic substitution.
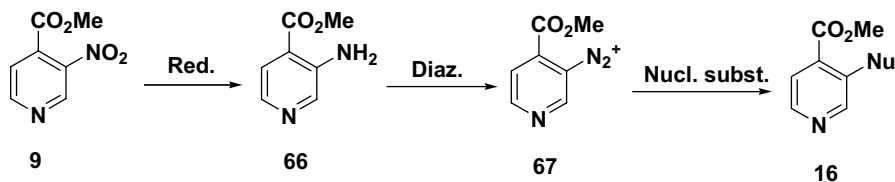
Scheme 5.4 The traditional diazotization pathway to compound (**16**)

Several unsuccessful attempts were made to substitute the nitro group by carbon nucleophiles. Carbon nucleophiles such as phenylacetylene, sodium cyanide, acetylacetone and diethyl malonate were tried, along with suitable bases such as sodium hydride or butyllithium under different conditions (temperature, reaction time and mixing of the reagents prior to addition of compound (**9**) or in a one-pot procedure). Halogen nucleophiles (hydrogen chloride, hydrogen bromide, ammonium chloride, ammonium bromide, potassium chloride, potassium bromide, copper iodide, copper fluoride and phosphorus pentachloride) were correspondingly tested in a similar manner, yielding the same negative result. No substitution products (**16e-j**) were observed, as shown by ^{1}H NMR (Scheme 5.5).

The aromatic nucleophilic substitution of the nitro group with dimethyl malonate [68] and fluorine [69] has later been successful, and further study on the preparation of pyridylmalonates are now in progress.
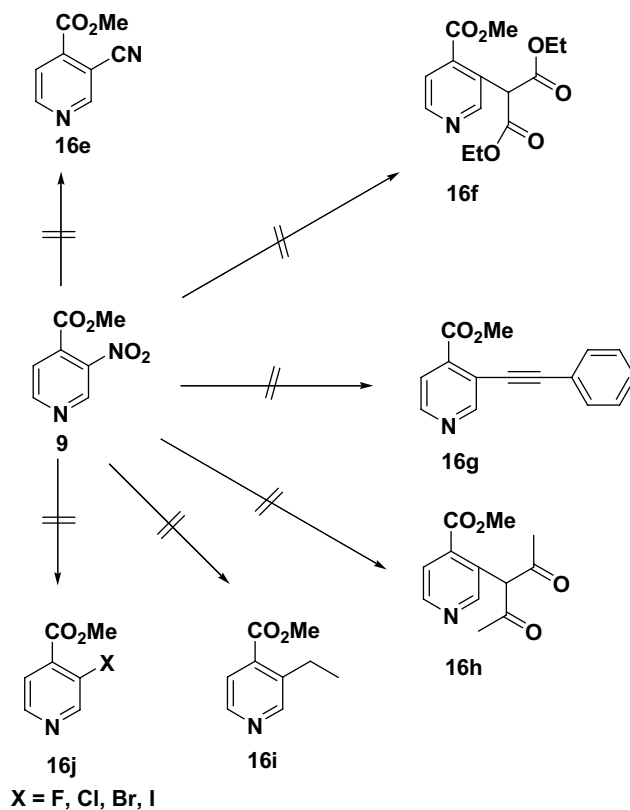
Scheme 5.5 Aromatic nucleophilic substitution of the nitro group of compound (**9**) with carbon and halogen nucleophiles

5.3 Attempt of an intramolecular aromatic nucleophilic substitution of the nitro group; Synthesis of 1*H*-pyrazolo[3,4-c]pyridin-3(2*H*)one (71)

It has been reported that *N'*-alkyl derivatives of isonicotinic acid hydrazide (INH) were more active against tubercle bacili than the acyl derivative containing the same number of carbon atoms. Later it was reported that pyrido[2,3-*d*]pyridazine was closely related to the acyl derivative of INH. In this compound the terminal carbonyl group was cyclized to the pyridine ring. This difference was crucial, and therefore these derivatives showed no effect against tubercle bacili [70].

Pyrazolopyridinone, however, which is similar to the alkyl derivatives of INH proved to be more effective against tubercle bacili. Four derivatives of pyrazolopyridinone have previously been synthesised (Figure 5.2). The activity of these compounds against the human tubercle bacillus (strain 1137 Rv) was about 1/30 that of INH, in the same microbiological *in vitro* tests. Compound (**71**) with the carbonyl group in the γ position of the pyridine ring showed the best activity (50 γ/mL), followed by compound (**68**) with the carbonyl in the α position (100 γ/mL). The two other compounds (**69**) and (**70**) were not effective [70]. Other derivatives have shown to be active as tumour inhibitors [71].
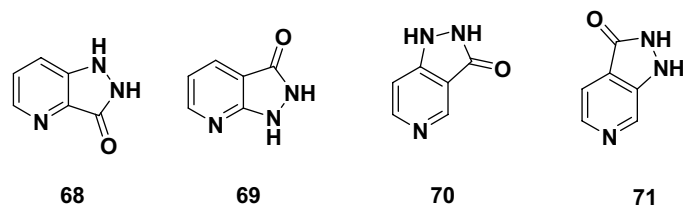
Figure 5.2 Pyrazolopyridinone derivatives (**68**-**71**) [70]

The methodology of nitro group substitution was applied to the synthesis of 1*H*-pyrazolo[3,4-*c*]pyridin-3(2*H*)one (**71**) (Scheme 5.6). An attempt to substitute the nitro group with hydrazine was made. Refluxing would presumably yield 1*H*-pyrazolo[3,4-*c*]pyridin-3(2*H*)-one (**71**) in a one-pot procedure. As expected, -NH_2 is a weaker nucleophile than ArO⁻ [58]. Hydrazine proved to be a less effective nucleophile than the previously and yielded only a complex mixture of compounds under the same conditions. The reaction of compound (**9**) only afforded hydrazide (**10**).
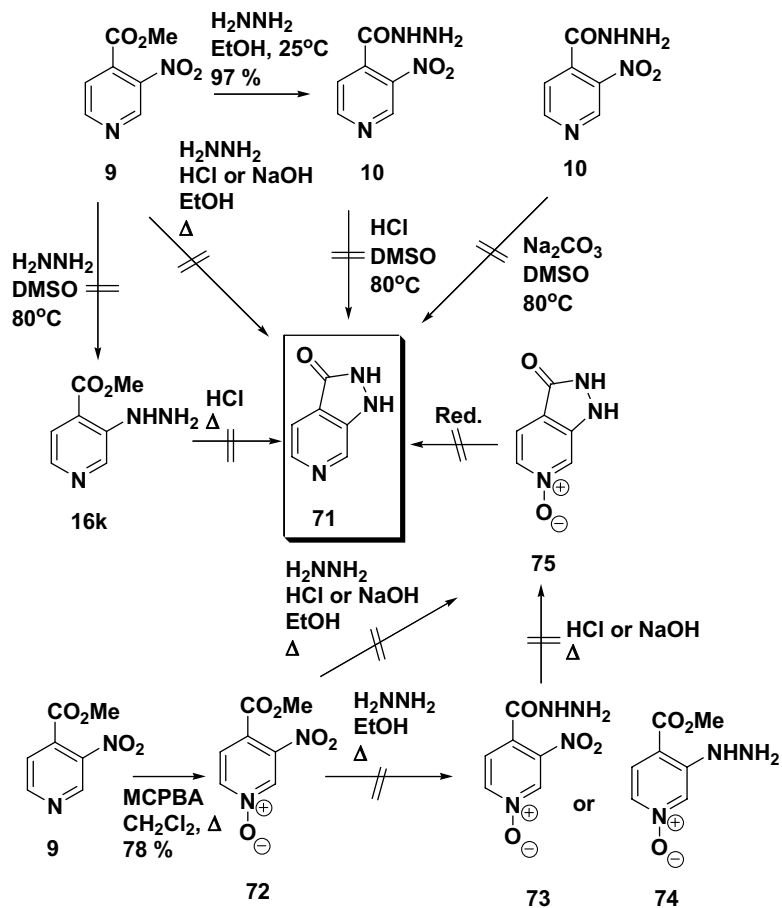
Scheme 5.6 Different synthetic pathways to 1*H*-pyrazolo[3,4-*c*]pyridin-3(2*H*)-one (**71**) [70-74]

An alternative approach involved either acid or base treatment [70-73] of hydrazide (**10**) by heating, attempting an intramolecular substitution of the nitro group to afford 1*H*-pyrazolo[3,4-*c*]pyridin-3(2*H*)-one (**71**).

Alternatively, pyridine *N*-oxides or *N*-alkylpyridinium salts would activate the nitro group towards nucleophilic substitution. *N*-Alkylpyridinium salts are usually more reactive than the corresponding pyridine *N*-oxides.

4-(Methoxycarbonyl)-3-nitropyridine 1-oxide (**72**) was prepared by oxidation with MCPBA. An excess of ten equivalents was necessary for complete conversion of compound (**9**) to afford 4-(methoxycarbonyl)-3-nitropyridine 1-oxide (**72**) in 78 % yield. *N*-Alkylation of compound (**9**) with methyl iodide yielded only a complex mixture of compounds, as shown by ^{1}H NMR. 4-(Methoxycarbonyl)-1-methyl-3-nitropyridinium iodide (**76**) was not observed (Scheme 5.7) [74].
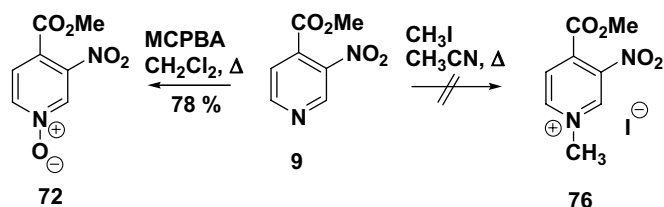
Scheme 5.7 *N*-Oxidization and *N*-alkylation of compound (**9**) [74]

4-(Methoxycarbonyl)-3-nitropyridine 1-oxide (**72**) was subjected to the same reaction conditions as the non-oxidised pyridine. The addition of hydrazine and either acid or base under reflux yielded only complex mixtures of compounds, as shown by ^{1}H NMR. Neither 4-(hydrazinecarbonyl)-3-nitropyridine 1-oxide (**73**) nor 3-hydrazinyl-4-(methoxycarbonyl)pyridine 1-oxide (**74**) were observed (Scheme 5.6).

5.4 Summary

The nitro group in compound (**9**) was readily replaced through aromatic nucleophilic substitution by nitrogen (azide), oxygen (methoxy and phenoxy) and sulfur (thiophenoxy) nucleophiles, affording the corresponding substitution products (**16a-d**) in moderate yields (30-52 %). The heteroatom in the pyridine ring and the ester group *ortho* to the nitro group make the pyridine ring electron-deficient and the nitro group to a particularly good leaving group in aromatic nucleophilic substitutions.

Attempts to synthesise the antituberculosis compound (**71**) using the nitro group substitution methodology were performed. The preparation of pyrazolopyridinone (**71**) was not successful, most likely due to the poor nucleophilic character of hydrazine. Hydrazine proved to be a less effective nitrogen nucleophile compared to sodium azide, sodium methoxide, sodium phenoxide and sodium thiophenoxide in the aromatic nucleophilic substitution of the nitro group in compound (**9**). Activation of the pyridine ring through *N*-oxidization or *N*-alkylation was not adequate to promote the desired reaction.

Chapter 6: Synthesis of 1,3-dihydro-2*H*-imidazo-[4,5-*c*]pyridin-2-one

The results discussed in this chapter are presented in paper IV.

6.1 General remarks

The imidazo[4,5-*c*]pyridin-2-one ring system is incorporated into a number of biologically active compounds [75, 76], like a retroviral protease inhibitor for HIV/AIDS treatment and various cephalosporin derivatives.
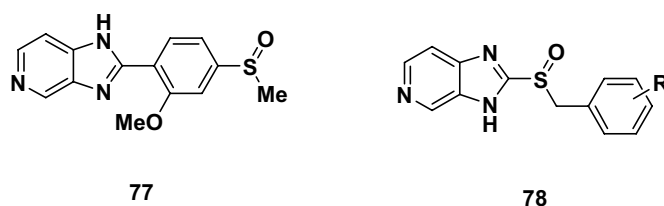
Figure 6.1 Isomazole (**77**) [77] and the potentially antiosteoporotic agent 2-[(aryl)methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine (**78**) [78]

Isomazole (**77**) [77], an analogue of the inotropic agent sulmazole, used in the treatment of heart failure, and the potentially antiosteoporotic agent 2-[(aryl)methyl]sulfinyl-1*H*-imidazo[4,5-*c*]pyridine (**78**) [78] (Figure 6.1) are two examples. Due to its importance in pharmaceutical drugs, many synthetic routes to this ring system have been reported.
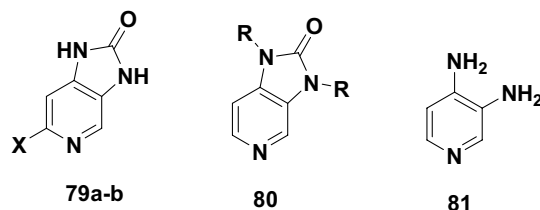
Figure 6.2 1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one derivatives (**79a-b**) and (**80**), and 3,4-diaminopyridine (**81**)

1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one (**79a**) has been prepared from 3,4-diaminopyridine (**81**) [79] (Figure 6.2), which is also biologically active, using various reagents such as urea [80, 81], carbonylimidazole [82] and selenium assisted carbon monoxide incorporation [83]. Another approach has utilised 3-amino-4-pyridyl carbonyl azide, prepared from 3-amino isonicotinic acid, which was transformed into the cyclic urea (**79a**) [84, 85]. In addition, a number of mono- and di-*N*-substituted imidazo[4,5-*c*]pyridin-2-ones (**80**) have been reported (Figure 6.2) [80, 86-95]. These compounds are obtained from the cyclic urea (**79a**) [92, 93] or mono- and di-*N*-substituted 3,4-diaminopyridines, which are treated in the same manner using appropriate carbonylating reagents [86-87, 90-91, 94-95].

Only a few examples where the cyclic urea (**79a**) is substituted on the pyridine ring and where product (**79a**) is part of a larger polycyclic skeleton, such as quinolines and ?-carbolines, are reported in the literature [96, 97]. Various substituted 4-hydroxy-3-nitropyridin-2-ones made through cycloaddition of nitromalonesters and ketimines have also been utilised as substrates for synthesis of the cyclic urea (**79a**) [98-102].

4,6-Disubstituted imidazo[4,5-*c*]pyridin-2-ones have also been prepared using this intermediate. In this case, however, the nitro group was incorporated through nitration [103]. Recently, a method for preparing imidazo[4,5-*c*]pyridin-2-ones (**79b**) with various types of substituents in the 6-position of the pyridine ring has been reported [104].

6.2 Improved synthetic protocol
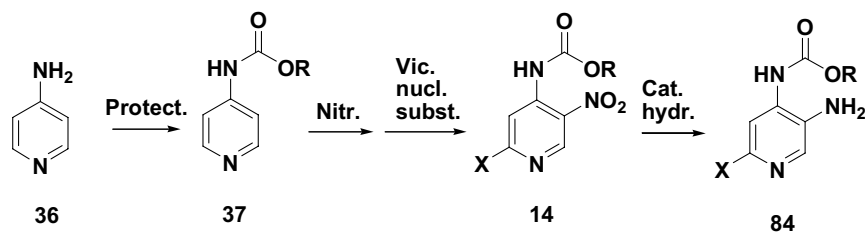
Scheme 6.1 Synthetic pathway to 3-amino-4-pyridyl carbamates (**84**) from 4-aminopyridine (**36**) [79, 104-105]

The 3-amino-4-pyridyl carbamates (**84**) were prepared in three or four steps from 4-aminopyridine (**36**) (Scheme 6.1) [79, 104-105]. Nitration of the pyridine ring was done after protection of the amino group as alkoxycarbonyl groups to give product (**37**). The methyl and ethyl carbamates (**14a-b**) have also been prepared by nitration of compound (**8**) followed by hydrazide formation, diazotization to the acyl azide and Curtius rearrangement followed by reflux in methanol or ethanol. Selective reduction of the nitro group by catalytic hydrogenation gave compound (**84**) in quantitative yield. 3,4-Diaminopyridine (**81**), which is also a suitable substrate for the preparation of the cyclic urea (**79a**), as discussed earlier, has been prepared based on the improved nitration method [79, 105] in higher yield compared to previous reports.

Previous methods [104] developed for this cyclization reaction afforded product (**79a**) and the 6-substituted derivative (**79b**) in 74 % and 55 %, respectively by refluxing in diglyme for 24 hours. It was discovered that heating product (**84a**) in 2 % sulfuric acid yielded compound (**79a**). However, the cyclization was also successful at lower concentrations of sulfuric acid (Scheme 6.2 and Table 1). Full conversion of compound (**84**) to the cyclic urea (**79a**) was obtained after a period of ten minutes to three hours by heating at 90°C, even with 0.1 % sulfuric acid. Cyclization of the *tert*-butyl carbamate (**84c**) proved to be faster than the methyl and ethyl carbamates (**84a-b**).

A prolonged reaction time (three hours) was required for larger batches (100 mg). The same was also evident when the reaction temperature was lowered to 40°C.

The cyclization reaction was also investigated under milder conditions. Sulfuric acid, a very strong acid ($pK_a = -9$), was replaced by aqueous tetrafluoroboric acid ($pK_a = 1$-3). All of the methyl, ethyl and *tert*-butyl carbamates (**84a-c**) underwent complete cyclization using 3.5 equivalents of aqueous tetrafluoroboric acid. Prolonged reaction times were necessary when the number of equivalents (0.65 equivalents) were reduced. When the reaction temperature was lowered to 40°C, no cyclization took place, even with longer reaction times (8 hours) and an increased number of equivalents of tetrafluoroboric acid (7.0 equivalents).

A one-pot procedure combining the catalytic hydrogenation of compound (**14**) and the cyclization reaction of product (**84**) also proved to be successful and afforded the cyclic urea (**79a**) in 95 % yield from methyl carbamate (**84a**). This would be the preferred method for the synthesis of the cyclic urea (**79a**).

84a R = Me, X = H
84b R = Et, X = H
84c R = *t*-Bu, X = H
84d R = *i*-Pr, X = NHBu
79a X = H
79b X = NHBu

84a-d → **79a-b**
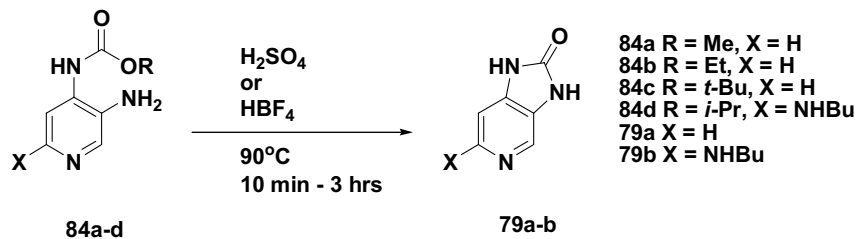
Table 1: Cyclization of (84a-d) to (79a-b)

Catalyst	Amount	Temp.	Time	Conversion[a]	Yield[b]
H_2SO_4	0.1 %	90°C	10-30 min (5 mg)[c]	99 %	> 95 %
H_2SO_4	0.1 %	90°C	3 hrs (100 mg)[d]	99 %	> 95 %
H_2SO_4	0.1 %	40°C	8 hrs (5 mg)[c]	40 %	
HBF_4	3.5 eqv.	90°C	10-30 min (5 mg)[c]	99 %	> 95 %
HBF_4	3.5 eqv.	90°C	1-3 hrs (100 mg)[d]	99 %	> 95 %
HBF_4	0.65 eqv.	90°C	5 hrs (5 mg)[c]	99 %	> 95 %
HBF_4	7.0 eqv.	40°C	8 hrs (5 mg)[c]	0 %	

a. Conversion was based on ^{1}H NMR of crude product
b. Yield after work-up
c. All substrates, (**84a-d**)
d. Substrate (**84a**)

6.3 Microwave-assisted cyclization

Microwave-assisted organic synthesis (MAOS) is a subfield within organic chemistry that has grown rapidly since its introduction in the mid eighties. The greatest advantage of this method is clearly the enhancement of reaction rates. Other benefits are that the products often may be produced in both higher yields and purity compared to traditional methods.

The microwave-assisted method was tested on the cyclization reaction based on previous successful experiments for a number of other reactions [68]. Full conversion of the carbamates (**84a-c**) to the cyclic urea (**79a**) were obtained within two to six minutes under MW irradiation (Scheme 6.3 and Table 2). A difference in rate of the reactions was observed between the different carbamates. The *tert*-butyl carbamate (**84c**) proved to be the most reactive, followed by the methyl and ethyl carbamates (**84a-b**). These observations correlated well with the previous results obtained by traditional methods. Reactions using sulfuric acid as catalyst were more rapid than with aqueous tetrafluoroboric acid as catalyst. An important observation with the microwave-assisted protocol was that larger batches (100 mg) showed complete conversion in the same reaction time as the small batches (5 mg). Cyclization of the 6-substituted derivative (**84d**) was also carried out using the microwave-assisted protocol. The 6-substituted cyclic urea (**79b**) was obtained in a similar manner and full conversion was observed after two to six minutes. Due to the low solubility of the substrate (**84d**), water was replaced by DMSO. A one-pot procedure including the previous hydrogenation step and the cyclization step by MW irradiation was also performed. A prolonged reaction time was necessary to achieve complete conversion of the precursor (**84d**), most likely due to the solid-liquid interaction caused by the presence of palladium on carbon used in the hydrogenation step. However, it is still advantageous since two steps are combined and less workup is needed.

84a R = Me, X = H
84b R = Et, X = H
84c R = t-Bu, X = H
84d R = i-Pr, X = NHBu
79a X = H
79b X = NHBu
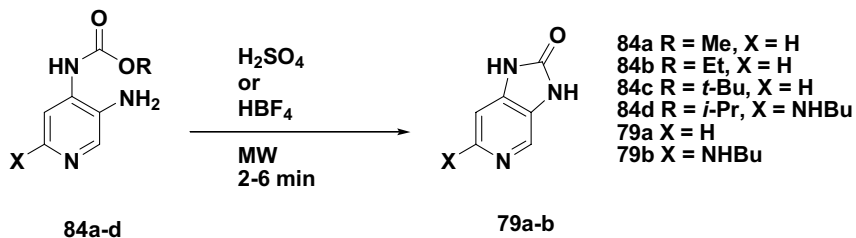
Table 2: Cyclization of (84a-d) to (79a-b) by MW irradiation

Substrate	Catalyst	Amount	Time	Conversion[a]
(**84a**), R = Me	H_2SO_4	0.1 %	4 min (5 mg)	99 %
(**84b**), R = Et	H_2SO_4	0.1 %	4 min (5 mg)	99 %
(**84c**), R = t-Bu	H_2SO_4	0.1 %	2 min (5 mg)	99 %
(**84d**), R = i-Pr, X = NHBu	H_2SO_4	0.1 %	2 min (5 mg)	99 %
(**84a**), R = Me	HBF_4	3.5 eqv.	6 min (5 mg)	99 %
(**84b**), R = Et	HBF_4	3.5 eqv.	6 min (5 mg)	99 %
(**84c**), R = t-Bu	HBF_4	3.5 eqv.	2 min (5 mg)	99 %
(**84c**), R = t-Bu	HBF_4	3.5 eqv.	2 min (100 mg)	99 %[b]
(**84c**), R = t-Bu	HBF_4	0.65 eqv.	2 min (5 mg)	99 %
(**84c**), R = t-Bu	HBF_4	0.65 eqv.	3 min (100 mg)	99 %[b]
(**84c**), R = t-Bu	HBF_4	0.2 eqv.	8 min (5 mg)	99 %
(**84d**), R = i-Pr, X = NHBu	HBF_4	3.5 eqv.	6 min (5 mg)	99 %

a. Conversion was based on ^{1}H NMR of crude product
b. > 95 % yield after work-up

The pH of the aqueous solution during workup by extraction proved to be crucial for the yield of product (**79a**). Due to the urea part of the molecule, only moderate yields were obtained by extracting under basic conditions, at pH 9-12. Changing to neutral conditions, pH 7, quantitative yields of the cyclic urea were obtained by extraction with ethyl acetate. Recrystallization generally afforded the product in > 95 % yield. Adjusting to pH 7 afforded a spontaneous and quantitative precipitation of product (**79a**) (pure by melting point and ^{1}H NMR). This was observed when the precursor (**84a**) was cyclized to compound (**79a**). This proved to be an even simpler method of workup and completed the facile "green" protocol for preparing compound (**79a**) under solvent-free conditions.

6.4 Summary

The biologically active compound (**79a**) has been prepared in ??95 % yield through an acid-catalysed cyclization reaction by heating 3-amino-4-pyridyl carbamates (**84a-c**) in sulfuric acid (0.1 %) or aqueous HBF$_4$ (3.5 equivalents) at 90°C for ten minutes to three hours.

Correspondingly, the MW-assisted reactions afforded pure cyclic urea (**79a**) in quantitative yield within a few minutes. A derivative of product (**79a**), the 6-butylamino-substituted cyclic urea (**79b**), was prepared in a similar manner by cyclization of the precursor (**84d**). Both conventional heating and MW irradiation afforded the cyclic urea (**79b**) in quantitative yield.

Quantitative yield of product (**79a**) was obtained through accurate adjustment of pH of the reaction mixture, which proved to be excellent and facile. The cyclic urea (**79a**) was obtained through less vigorous reaction conditions and in higher yield compared to previous methods. This protocol represents a solvent-free and "green" method for the preparation of compound (**79a**).

Chapter 7: Triazolopyridine derivatives; synthesis and application

The results discussed in this chapter are presented in Paper V.

7.1 Synthesis of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine (87)

The diazotization and cyclization sequence of methyl 3-amino-4-pyridyl carbamate (**84a**) for the formation of pyridoxazolidinone (**88**) was investigated (Scheme 7.1). Compound (**84a**) was formed as previously discussed by catalytic hydrogenation of the nitro group in product (**14**). Diazotization in an aqueous solution may afford the phenolic intermediate (**87**) which may yield the product (**88**) through an acid-catalysed cyclization.
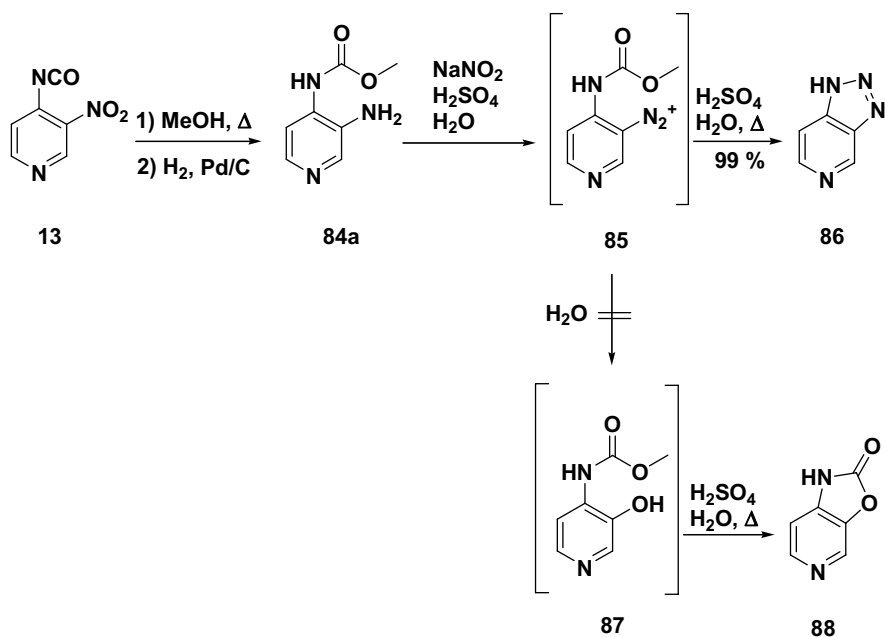
Scheme 7.1 Synthetic pathway to triazolopyridine (**86**) and pyridoxazolidinone (**88**)

The proposed reaction sequence did not take place and product (**88**) was not obtained. However, 1*H*-1,2,3-triazolo[4,5-*c*]pyridine (**86**) was obtained in quantitative yield due to the fact that substitution of the diazonium salt (**85**) by the hydroxy group was unsuccessful. This is the most difficult substitution to perform on diazonium salts. The carbamate group in the *ortho* position of the pyridine ring might play a significant role. It is only a moderately activating group, and thus not strong enough for this purpose. The diazonium salt (**85**) did not precipitate from the reaction mixture and could not be isolated. This can be due to the fact that methyl carbamate (**84a**) contains several nitrogens that can be protonated and prevent the diazonium salt (**85**) from precipitating.

Triazolopyridine (**86**) is commercially available but only made on a milligram scale and thus very expensive. Some substituted 1,2,3-triazolopyridines are analgesic, antipyretic, antiasthmatic or useful as inflammation inhibitors [106, 107] while others have been patented for their anxiolytic antidepressant properties [108], herbicidal activity [109], antibiotic properties [110] and activity against HIV-1 [111]. Substituted 1,2,3-triazolopyridines have previously been prepared by amine substitution of a chloroaminopyridine followed by diazotization and cyclization [106, 112]. Diazotization of ethyl 2-aminopyridyl-3-carbamate with *iso*-amyl nitrite in acetic acid has been reported to give the ethyl 3-carbamate derivative of 1,2,3-triazolo[4,5-*b*]pyridine [113] while benzotriazole (**89**) has been synthesised in high yields by diazotization of *o*-phenylenediamine with sodium nitrite in acetic acid followed by cyclization [114-117].

7.2 1*H*-1,2,3-Benzotriazole, a well known acylating agent in organic chemistry

Benzotriazole (**89**) is a readily available synthetic auxiliary with benign biological (nontoxic and odorless) and physical (crystalline, nonvolatile and stable) properties that offers many advantages. A benzotriazole group is easily introduced and activates molecules towards various transformations. At the end of the reaction sequence, it can be easily removed.

A benzotriazole group activates the carbon atom to which it is attached by behaving as a leaving group, enabling deprotonation, acting as an electron donor and being capable of reductive elimination to provide either a radical or a carbanion. In allylic systems, the benzotriazolyl moiety behaves as an ambient anion-directing group. All of these properties of benzotriazole facilitate a broad range of synthetic transformations. The chemistry of benzotriazole is usually simple and easy to understand. The main advantage is that rather common transformations can be performed efficiently, quickly and inexpensively [118].
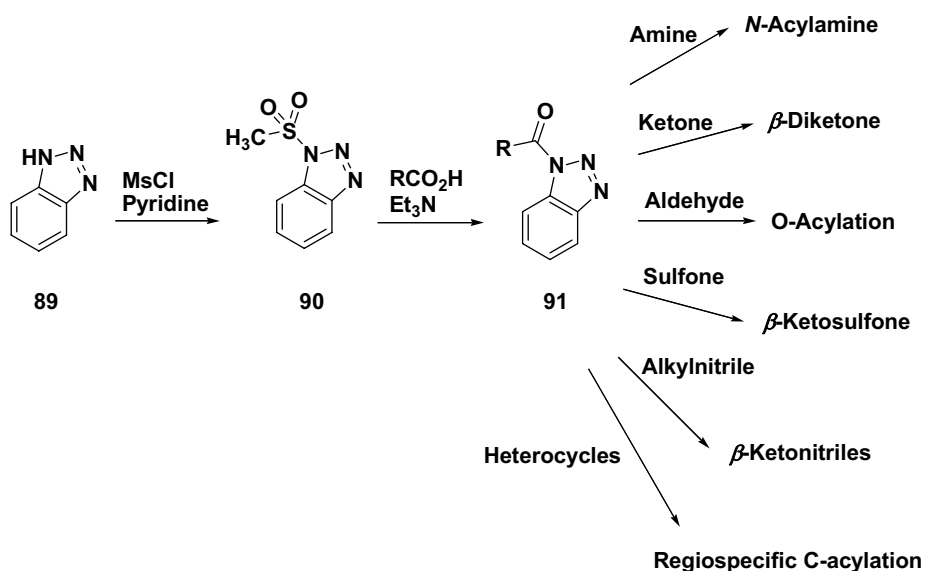
Scheme 7.2 Synthetic applications of benzotriazole (**89**) [118-123]

Katritzky *et al.* have demonstrated the use of benzotriazole (**89**) as a synthetic auxiliary in synthetic transformations such as O-acylation of aldehydes [118], *N*-acylation of amines [119], synthesis of β-dicarbonyl compounds [120], C-acylation of sulfones in the preparation of β-ketosulfones [121], alkyl cyanides to α-substituted β-ketonitriles [122] and regiospecific C-acylation of heterocycles [123] (Scheme 7.2).

The mechanism for the formation of *N*-acylbenzotriazole (**91**) is shown in Scheme 7.3 [119]. In this reaction there is no leaving group, in contrast to acylation with acid chlorides or imidazoles. The carboxylic acid is actually the reactant under these conditions. The carboxylate formed in the presence of triethylamine attacks the sulfur atom of the mesylated benzotriazole (**90**), followed by departure of the benzotriazole anion. The intermediate (**93**) is formed. Addition of the benzotriazole anion to the carbonyl carbon of this intermediate with subsequent elimination of methyl sulfonate (**94**) yields the *N*-acylbenzotriazole (**91**).

The high reactivity of these acylating agents is caused by the relative weakness of the "amide" bond. The aromatic character of the heterocycle makes the -N-C=O bond less delocalised and thus less stabilised compared to regular amides. Triazolopyridine (**86**) is expected to be an even better leaving group than benzotriazole (**89**), due to the electron-deficient character of the pyridine moiety.
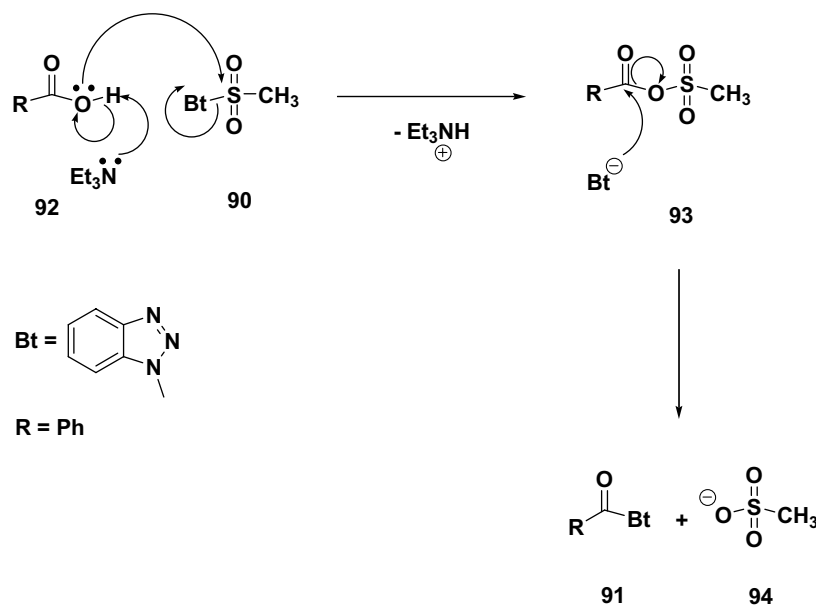
Scheme 7.3 Mechanism for the formation of *N*-acyl benzotriazole (**91**) from mesyl benzotriazole (**90**) [119]

7.3 1*H*-1,2,3-Triazolo[4,5-*c*]pyridine, an acylating agent in organic chemistry

The respective properties of triazolopyridine (**86**) were studied based on those of benzotriazole (**89**). Triazolopyridine (**86**) was subjected to the Katritzky methodology developed for benzotriazole (**89**) [118-123] (Scheme 7.4). The mesylated compound (**90**) was first made by treatment with mesyl chloride and pyridine. The *N*-acylbenzotriazole (**91**) was made upon reaction with benzoic acid (**92**) and triethylamine. Product (**91**) can be used as acylating reagent of many different types of compounds. An interesting field is the acylation of amines. The *N*-acylbenzotriazoles have been used in the preparation of a wide range of primary, secondary and tertiary amides in high yields and represent a milder method compared to the traditional acid chlorides and imidazoles [119].
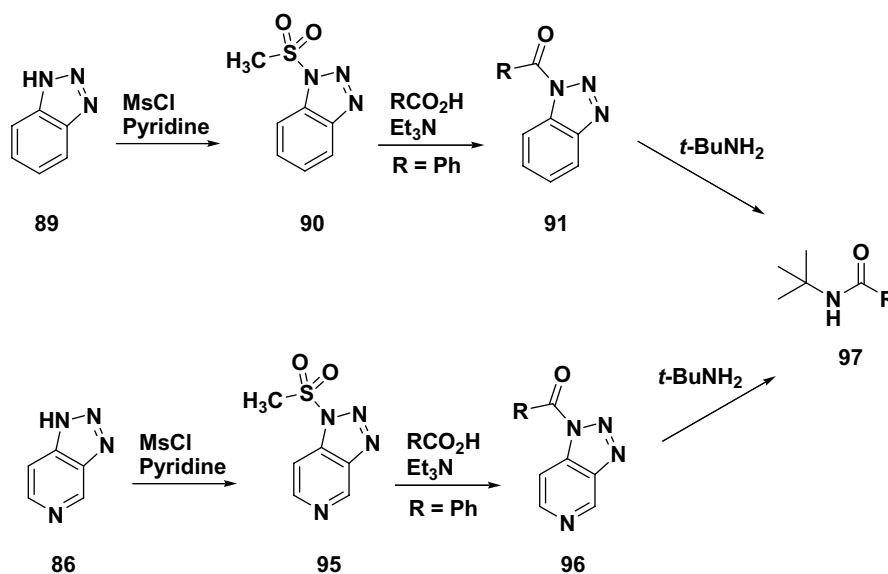
Scheme 7.4 Comparison of the reactivity of triazolopyridine (**86**) and benzotriazole (**89**) in the acylation of amines

The mesylated triazolopyridine (**95**) was made in a similar manner in good yield. It proved to be unstable upon workup and decomposed when subjected to either column chromatography or recrystallization.

Thus, due to the high reactivity compound (**95**) was used directly for the preparation of *N*-acyltriazolopyridine (**96**). Compound (**96**), however, was unstable and decomposed shortly after generation and was never isolated in pure form. Protection of amines could therefore not be performed with this protocol. Other methods to generate compound (**96**) were thus investigated.

7.4 Synthesis of *N*-acyl and *N*-alkoxycarbonyl derivatives of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine

The *N*-acyl and *N*-alkoxycarbonyl triazolopyridines (**96a-e**) were readily available from 4-aminopyridine (**36**) in four steps (Scheme 7.5). Nitration [4-6, 78, 124] of the pyridine ring was carried out after protection of the 4-amino group by acyl or alkoxycarbonyl groups [79] to afford the acyl products (**37d-e**) or the alkoxycarbonyl products (**37a-c**), respectively. The amides (**84e-f**) and carbamates (**84a-c**) were obtained by selective reduction of the nitro group in quantitative yield [79]. Diazotization of the methyl carbamate (**84a**) with sodium nitrite and sulfuric acid in water, followed by reflux afforded triazolopyridine (**86**). Milder conditions, *iso*-amyl nitrite and acetic acid in refluxing THF, afforded the alkoxycarbonyl triazolopyridines (**96a-c**) in high yields [113]. The acyl triazolopyridines (**96d-e**), however, were unstable and decomposed upon workup.

Scheme 7.5 Synthesis of *N*-acyl and *N*-alkoxycarbonyl triazolopyridine derivatives
(96a-e) from 4-aminopyridine (**36**) [4-6, 78-79, 113, 124]

Less vigorous conditions, *iso*-amyl nitrite and tetrafluoroboric acid in ethanol, or
nitrosonium tetrafluoroborate in acetonitrile (Scheme 7.6) afforded the alkoxycarbonyl
triazolopyridines (**96a-c**) (X = OMe, OEt, O*t*-Bu) spontaneously and quantitatively, as
shown by ^{1}H NMR. The products were isolated as their corresponding tetrafluoroborate
salts (**98a-c**), as shown by ^{19}F NMR in > 95 % yield. Hydrolysis of product (**98a**) by
reflux in 2 % sulfuric acid yielded triazolopyridine (**86**).

From previous experiments, the acyl triazolopyridines (**96d-e**) (X = Me, Ph) proved to be unstable due to the presence of moisture. Unsuccessful attempts were made to isolate the acyl derivatives (**96d-e**) as their respective tetrafluoroborate salts (**98d-e**). However, the acyl derivatives (**98d-e**) proved to be stable in solution after *in situ* preparation for a limited amount of time. Thus, the nitrosonium tetrafluoroborate protocol was preferred compared to the aqueous tetrafluoroboric acid method. The derivatives (**98a-b**) (X = OMe, OEt) were purified by flash column chromatography and the crystalline salts were stable at room temperature for weeks. The derivatives (**98c-e**) (X = O*t*-Bu, Me, Ph) however, were unstable, and could not be purified or stored.
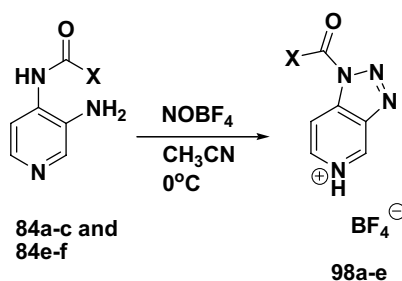
Scheme 7.6 Synthesis of the tetrafluoroborate salts (**98a-e**) from 3-amino-4-pyridyl carbamates (**84a-c**) and amides (**84e-f**)

7.5 *N*-Acylation and *N*-alkoxycarbonylation of amines

In the literature, the preparation of 1- and 3-alkoxycarbonyl-*v*-triazolo[4,5-*b*]pyridines (**99a-b**) and the corresponding acyl compounds (**100a-b**) (Figure 7.1) have been reported [113]. Experiments shown their acylating properties. The different reactivity of the alkoxycarbonyl derivatives (**99a-b**) and the acyl derivatives (**100a-b**) towards primary amines has been studied. The amines *iso*-propyl amine and benzyl amine have been protected by alkoxycarbonyl derivatives (**99a-b**) and acyl derivatives (**100a-b**) in good to high yields in 15 minutes to 24 hours, depending on the derivatives used.
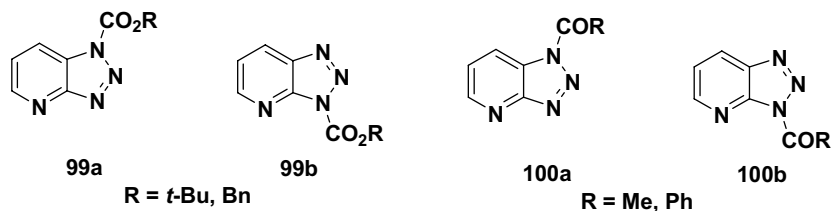
Figure 7.1 Alkoxycarbonyl (**99a-b**) and acyl (**100a-b**) triazolopyridine derivatives [113]
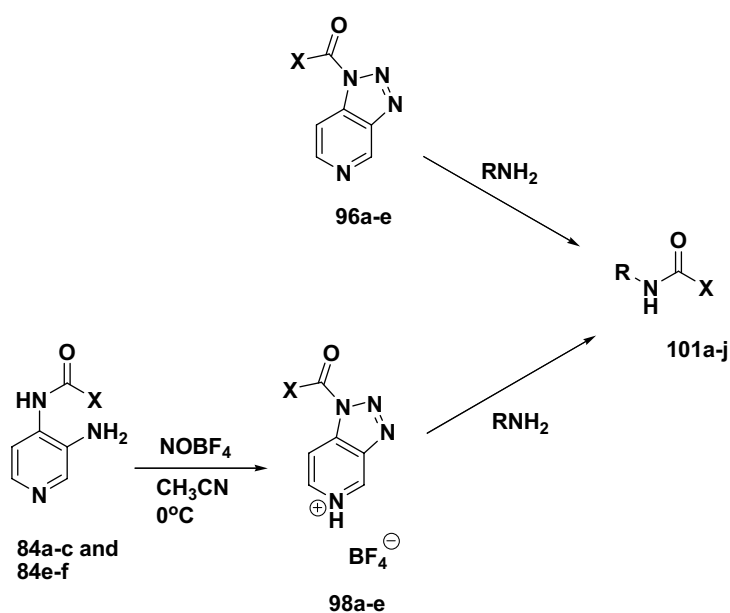
Scheme 7.7 Comparison of the reactivity of triazolopyridine derivatives (**96a-e**) and their tetrafluoroborate salts (**98a-e**) in the acylation of amines

Based on previous reports in the literature [113, 119], acyl- and alkoxycarbonyl triazolopyridine derivatives (**96a-e**) were investigated as acylating agents for amines. Correspondingly *iso*-propyl amine and benzyl amine were used. Compounds (**96a-e**) (Scheme 7.7), made in the same way as described earlier (Scheme 7.5) proved to react slowly with both amines. The conversion was monitored by ^{1}H NMR. The acylated products (**101a-j**) were observed after 24 hours.

The corresponding tetrafluoroborate salts (**98a-e**) were tested in a similar manner. The whole procedure was carried out *in situ*. The tetrafluoroborate salts (**98a-e**) were made from the respective carbamates (**84a-c**) and amides (**84e-f**) followed by the addition of the amines directly upon generation (Scheme 7.7 and 7.8). All steps were monitored by ^{1}H NMR.

The tetrafluoroborate salts (**98a-e**), however, proved to be much more reactive than the derivatives (**96a-e**). This may be due to the tetrafluoroborate salt, which would increase the electron-deficient nature of the pyridine ring, making the acyl or alkoxycarbonyl groups extremely reactive. The protection of both amines were completed within a few minutes, as shown by ^{1}H NMR independently of the triazolopyridine derivative used as acylating reagent. The one-pot procedure (Scheme 7.8) was carried out within minutes.
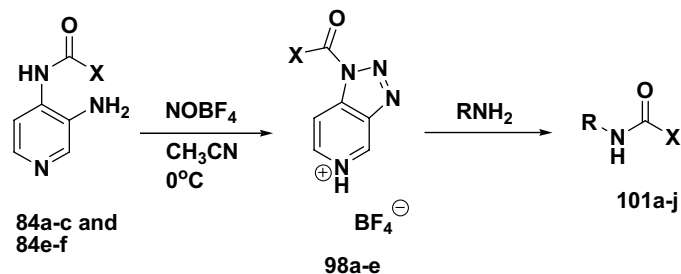
Scheme 7.8 One-pot procedure for the acylation of amines using the tetrafluoroborate salts (**98a-e**)

Table 3: *N*-Acylation and *N*-alkoxycarbonylation of amines

Product	X	R	Yield
(**101a**) [125]	OMe	*i*-Pr	76 %
(**101b**) [126]	OMe	Bn	84 %
(**101c**) [127]	OEt	*i*-Pr	73 %
(**101d**) [128]	OEt	Bn	73 %
(**101e**) [129]	O*t*-Bu	*i*-Pr	74 %
(**101f**) [130]	O*t*-Bu	Bn	73 %
(**101g**) [131]	Me	*i*-Pr	76 %
(**101h**) [132]	Me	Bn	72 %
(**101i**) [133]	Ph	*i*-Pr	72 %
(**101j**) [134]	Ph	Bn	73 %

The method was further developed, and it was experienced that the workup step for the isolation of the products (**101a-j**) could be left out. Direct purification by flash column chromatography afforded the respective amides and carbamates in high yields (Table 3) [125-138].
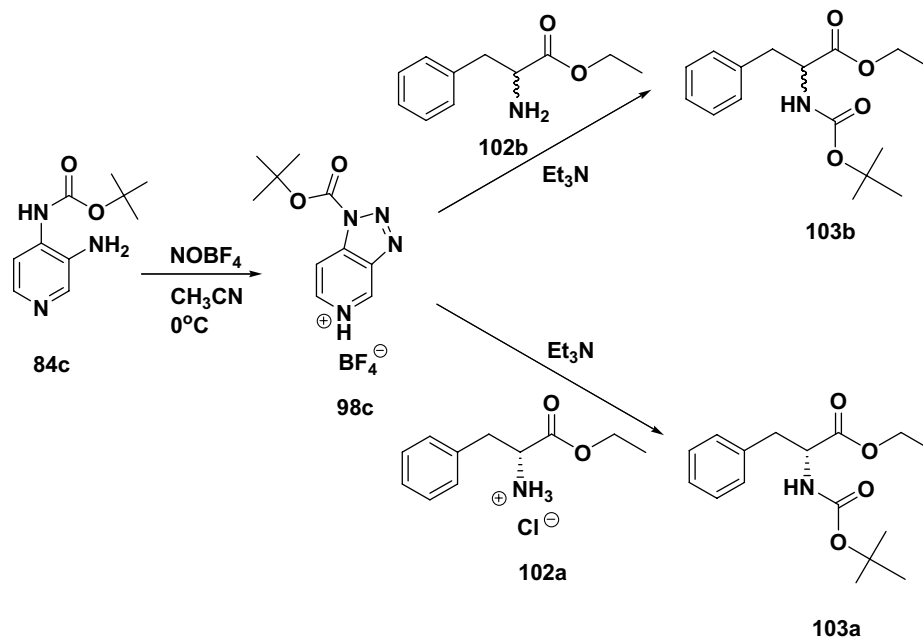
7.6 *N*-Alkoxycarbonylation of amino acids

Protective groups are important in the chemistry of amino acids. In particular, carbamates are used as protective groups for amino acids in order to minimize racemisation in peptide synthesis. The *tert*-butyl carbamate, the Boc group is one of the most applied carbamates in protection of amino acids.

Based on this fact, the application of the Boc-triazolopyridine derivative (**98c**) for the protection of the amino acid *L*-phenylalanine ethyl ester (**102a**) was investigated (Scheme 7.9 and Table 4). In a similar manner as described above for the primary amines, amino acid (**102a**) was reacted with tetrafluoroborate salt (**98c**) prepared *in situ* to afford the Boc-protected amino acid (**103a**) [135, 136]. Complete conversion to the Boc-protected amino acid (**103a**), as shown by ^{1}H NMR, was obtained after four days. Product (**103a**) was isolated in 76 % yield.

The reaction with the amino acid however, proved to be slower than the previous reactions with amines. This is most likely due to that the amino acid is larger and more sterically hindered than the primary amines. Another reason might be the presence of triethylamine which is used to avoid racemisation. Deprotonation of the tetrafluoroborate salt (**98c**) into derivative (**96c**) after the addition of triethylamine was observed, as shown by ^{1}H NMR. As previously discussed, derivative (**96c**) is by far not so reactive as the corresponding tetrafluoroborate salt (**98c**). This may explain the long reaction time needed for the acylation of amino acids.

The chirality of the Boc-protected amino acid (**103a**) was not lost during the reaction, as shown by optical rotation [135, 136]. Compound (**102a**) was racemized by treatment with 10 % NaOH. The racemic amino acid (**102b**) was subjected to the same conditions. The racemic Boc-protected amino acid (**103b**) was obtained in 61 % yield after four days. Optical rotation showed no rotation of the product.

Scheme 7.9 One-pot procedure for the acylation of phenylalanine ethyl ester (**102**) using the tetrafluoroborate salt (**98c**) [135, 136]

Table 4: *N*-Alkoxycarbonylation of amino acids

Boc-protected amino acid	Yield
Boc-*rac*-Phenylalanine ethyl ester (**103b**)	61 %
Boc-*L*-Phenylalanine ethyl ester hydrochloride salt (**103a**)	76 %

7.7 Summary

The *N*-acylating and *N*-alkoxycarbonylating abilities of the derivatives of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine (**96a-e**) have been studied. The alkoxycarbonyl triazolopyridine derivatives (**96a-c**) were readily prepared in 81-96 % yield. The corresponding tetrafluoroborate salts (**98a-c**) were formed in > 95 % yield.

1*H*-1,2,3-Triazolo[4,5-*c*]pyridine (**86**) has been shown to function as a good leaving group in the acylation and alkoxycarbonylation of amines and protection of amino acids. Protection of both *iso*-propyl amine and benzyl amine were completed within a few minutes, affording the amides and carbamates (**101a-j**) in high yields (72-84 %). Longer reaction time was needed for the protection of the amino acid phenylalanine ethyl ester (**102a**). Phenylalanine ethyl ester (**102a**) was converted to the Boc-derivative (**103a**) in four days, and isolated in 76 % yield without loss of optical rotation.

The development of the *in situ* preparation of the tetrafluoroborate salts (**98a-e**) offered the advantage of performing the synthetic transformations by a one-pot procedure. The *N*-acyl and *N*-alkoxycarbonyl tetrafluoroborate salts (**98a-e**) were formed in four steps from 4-aminopyridine (**36**) through amine protection, nitration, reduction and diazotization/cyclization.

This strategy offers an efficient and convenient protocol for the protection of amines through a one-pot procedure by preparation of the triazolopyridine derivatives *in situ*. All reactions were performed quickly in high yields under mild conditions. This protocol may represent a supplement to the benzotriazole methodology and show potential for a series of other synthetic transformations.

Chapter 8: Experimental

8.1 General

Chemicals

All chemicals used were from VWR International, Sigma-Aldrich, Fluka or Acros Chemicals. All solvents used were of *pro analysi* quality. Silica gel used for flash column chromatography was from sds (60 Å, 40-63 μm).

Instrumentation

^{1}H-, ^{13}C- and ^{19}F-spectra were recorded on Bruker Avance DPX 300 and 400 MHz spectrometers. Chemical shifts are reported in ppm downfield from TMS. Hexafluorobenzene was correspondingly used as an internal standard for ^{19}F NMR. *J* values are given in Hz.

MS spectra were recorded on a Finnigan MAT 95 XL mass spectrometer using electron ionization (EI) at 70 eV.

IR spectra were recorded on a Nicolet 20SXC FT-IR spectrometer. The compounds were either analysed as KBr tablets or films (between NaCl plates).

All melting points are uncorrected, measured by a Griffin or Stuart apparatus.

Elemental analyses were performed by the Laboratory of Organic Elemental Analysis at the Institute of Chemical Technology in Prague, Czech Republic.

Optical rotation was performed on a Perkin-Elmer 243 B polarimeter at 598 nm and 25°C.

8.2 Aromatic nucleophilic substitution with carbon and halogen nucleophiles

Substitution products (16e-i), carbon nucleophiles

Methyl 3-nitro-4-pyridyl carboxylate (**9**, 200 mg, 1.09 mmole) was dissolved in dry DMSO (5 mL). The appropriate carbon nucleophile (6.59 mmole) and base (6.59 mmole) was added and the mixture heated at 80°C or refluxed for a period of 20 minutes up to 24 hours. The reaction was monitored by ^{1}H NMR. Only nitropyridine (**9**) could be observed.

Substitution products (16j), halogen nucleophiles

Methyl 3-nitro-4-pyridyl carboxylate (**9**, 200 mg, 1.09 mmole) was dissolved in dry DMSO (5 mL). The appropriate halogen nucleophile (6.59 mmole) was added and the mixture heated at 80°C for 20 minutes. The reaction was monitored by ^{1}H NMR. Only nitropyridine (**9**) could be observed.

8.3 *N*-Oxidation and *N*-alkylation of pyridine derivatives

4-(Methoxycarbonyl)-3-nitropyridine 1-oxide (72)

Methyl 3-nitro-4-pyridyl carboxylate (**9**, 1.00 g, 5.50 mmole) was dissolved in CH$_2$Cl$_2$ (100 mL). MCPBA (9.48 g, 55.0 mmole, 10 equivalents) was added and the mixture refluxed for 20 hours. The mixture was not subjected to any workup and directly purified by flash column chromatography using *n*-pentane:acetone 1:1 as eluant, affording 4-(methoxycarbonyl)-3-nitropyridine 1-oxide (**72**) as offwhite crystals in 78 % yield (850 mg).

^{1}H NMR (d_6-DMSO): 9.09 (d, 1H, J = 1.7 Hz), 8.55 (dd, 1H, J = 6.8 and 1.7 Hz), 7.92 (d, 1H, J = 6.8 Hz), 3.85 (s, 3H)

^{13}C NMR (d_6-DMSO): 161.7, 147.3, 142.3, 135.2, 127.2, 118.7, 53.5

IR (film): 3034 (w), 1731 (s), 1556 (s), 1368 (s), 1261 (s), 947 (s) cm^{-1}

MS: 198 (M$^+$, 100), 167 (58), 152 (8), 151 (9), 136 (6), 121 (5), 93 (18)

HRMS: Calculated for $C_7H_6N_2O_5$: 198.027671; observed for $C_7H_6N_2O_5$: 198.027690

Melting point: 143-144°C

Calculated: C: 42.42, H: 3.05, N: 14.14; found: C: 42.29, H: 3.02, N: 14.45

4-(Methoxycarbonyl)-1-methyl-3-nitropyridinium iodide (76)

Methyl 3-nitro-4-pyridyl carboxylate (**9**, 200 mg, 1.09 mmole) was dissolved in acetonitrile (30 mL). Iodomethane (468 mg, 0.21 mL, 3.27 mmole) was added and the mixture refluxed for 24 hours. Diethyl ether (300 mL) was then added. No precipitate was formed and the solvent was removed *in vacuo*. The crude product showed a complex mixture of unidentifiable compounds, as shown by ^{1}H NMR. No attempts of purification were made.

8.4 Attempts to prepare 1*H*-pyrazolo[3,4-*c*]pyridin-3(2*H*)-one (71)

Substitution product (16k)

Methyl ester (**9**, 200 mg, 1.09 mmole) was dissolved in dry DMSO (5 mL). Hydrazine (330 mg, 0.33 mL, 6.59 mmole) was added and the mixture heated at 80°C for 20 minutes. The reaction was monitored by ^{1}H NMR and showed a complex mixture of compounds. No attempts at purification were made.

1*H*-Pyrazolo[3,4-*c*]pyridin-3(2*H*)-one (71)

Methyl ester (**9**, 200 mg, 1.09 mmole) was dissolved in ethanol (5 mL). Hydrazine (330 mg, 0.33 mL, 6.59 mmole) and either HCl or NaOH (1 M, 0.2 mL) were added and the mixture refluxed for 24 hours. The reaction was monitored by ^{1}H NMR. Only hydrazide (**10**) could be observed along with other byproducts.

Hydrazide (**10**, 200 mg, 1.09 mmole) was dissolved in dry DMSO (5 mL). HCl (1 M, 0.2 mL) was added and the mixture heated at 80°C for 20 minutes. The reaction was monitored by ^{1}H NMR. Only hydrazide (**10**) could be observed.

Hydrazide (**10**, 200 mg, 1.09 mmole) was dissolved in dry DMSO (5 mL). Na$_2$CO$_3$ (698 mg, 6.59 mmole) was added and the mixture heated at 80°C for 20 minutes. The reaction was monitored by ^{1}H NMR. A new compound could be observed. Na$_2$CO$_3$ was filtered off and the solvent removed *in vacuo*. The compound decomposed when it was purified by flash column chromatography.

3-Oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*c*]pyridine 6-oxide (75)

4-(Methoxycarbonyl)-3-nitropyridine 1-oxide (**72**, 200 mg, 1.01 mmole) was dissolved in ethanol (5 mL). Hydrazine (55.62 mg, 0.055 mL, 1.11 mmole) and either HCl or NaOH (1 M, 0.2 mL) were added and the mixture refluxed for 24 hours. The reaction was monitored by ^{1}H NMR and showed a complex mixture of compounds. No attempts at purification were made.

4-(Hydrazinecarbonyl)-3-nitropyridine 1-oxide (73) or 3-hydrazinyl-4-(methoxycarbonyl)pyridine 1-oxide (74)

4-(Methoxycarbonyl)-3-nitropyridine 1-oxide (**72**, 200 mg, 1.01 mmole) was dissolved in ethanol (5 mL). Hydrazine (55.62 mg, 0.055 mL, 1.11 mmole) was added and the mixture refluxed for 24 hours. The reaction was monitored by ^{1}H NMR and showed a complex mixture of compounds. No attempts at purification were made.

8.5 [2+4]-Cycloaddition reaction with diphenylketene

Diphenylketene

Diphenylacetylchloride (3.45 g, 15.0 mmole) was dissolved in dry THF (30 mL) and left stirring at 0°C under a N_2 atmosphere. Triethylamine (2.1 mL, 15.1 mmole) was added dropwise over a period of 30 minutes. Triethylammoniumchloride which precipitated in the reaction mixture was filtered off and washed with dry THF under a N_2 atmosphere. The solvent was removed *in vacuo* to afford a red viscous oil as crude product in more than quantitative yield (3.285 g). The oil was distilled at approximately 80°C and 0.018 mbar to afford diphenylketene as an orange oil in 63 % yield (1.84 g). It was stable in the freezer for several weeks.

3,3-Diphenyl-7-nitro-2*H*-pyrido[1,2-*a*]pyrimidin-2,4(3*H*)-dione (59)

5-Nitro-2-pyridine carbonyl azide (**22**, 28.9 mg, 0.150 mmole) was dissolved in dry benzene (10 mL). Diphenylketene (33.7 mg, 0.174 mmole) was dissolved in dry benzene (5 mL) and added to the carbonyl azide solution. The reaction mixture was refluxed for 1 hour and 15 minutes. All attempts to isolate product (**59**) were unsuccessful.

^{1}H NMR (CDCl$_3$): 9.22 (d, 1H, H-6, J = 2.5 Hz), 8.03 (dd, 1H, H-8, J = 10.0 and 2.6 Hz), 7.36 - 7.42 (m, 6H, m/p-phenyl), 7.05 - 7.09 (m, 4H, o-phenyl), 6.97 (d, 1H, H-9, J = 9.9 Hz)

^{13}C NMR (CDCl$_3$): 176.7, 170.7, 154.7, 133.9 (C-8), 129.3 (o-phenyl), 129.2 (p-phenyl), 129.1 (m-phenyl), 129.1 (C-6), 125.9 (C-9), 71.7 (C-3)

MS: 195 (5), 194 (34), 167 (5), 166 (38), 165 (100), 164 (12), 163 (12), 139 (12), 115 (6), 83 (13), 82 (22), 70 (8), 63 (8)

N-(5-Nitro-2-pyridyl)-α-phenyl benzeneacetamide (60)

Diphenylketene (112.3 mg, 0.5782 mmole) was dissolved in dry benzene (5 mL) and 5-nitro-2-aminopyridine (**25**, 81.0 mg, 0.582 mmole) was added. The reaction mixture was refluxed for 1 hour. The solvent was removed *in vacuo* to yield a yellow solid which was recrystallized from acetone and pentane to afford product (**60**) as white crystals in 85 % yield (based on ^{1}H NMR of the reaction mixture).

^{1}H NMR (d_6-DMSO): 11.70 (s, 1H, NH), 9.18 (d, 1H, H-6, J = 2.7 Hz), 8.61 (dd, 1H, H-4, J = 9.3 and 2.8 Hz), 8.34 (d, 1H, H-3, J = 9.4 Hz), 7.20 - 7.36 (m, 10H, phenyl), 5.47 (s, 1H, methine)

^{13}C NMR (d_6-DMSO): 171.7 (C=O), 156.0 (C-2), 144.8 (C-6), 140.1 (phenyl-1), 139.1 (C-4), 134.4 (C-5), 128.6 (phenyl), 128.5 (phenyl), 127.1 (p-phenyl), 112.7 (C-3), 56.8 (methine)

IR (KBr): 3280 (br), 3061 (w), 3030 (w), 2924 (m), 2853 (w), 1813 (m), 1760 (m), 1687 (s), 1605 (m), 1580 (m), 1536 (w), 1508 (w), 1455 (w), 1389 (m), 1347 (s), 1310 (w), 1299 (w), 1278 (m), 1184 (w), 1163 (w), 1114 (m), 1081 (w), 1032 (w), 1010 (w), 980 (m), 945 (m), 909 (w), 889 (m), 846 (m), 767 (m), 743 (m), 699 (s), 611 (m) cm^{-1}

MS: 335 (1), 334 (M$^+$+1, 9), 333 (M$^+$, 4), 195 (6), 194 (42), 168 (32), 167 (100), 166 (22), 165 (40), 152 (18), 139 (4)

HRMS: Calculated for C$_{19}$H$_{15}$N$_3$O$_3$: 333.1113; observed for C$_{19}$H$_{15}$N$_3$O$_3$: 333.1110

5-Nitro-2-pyridinecarboxamide (61)

5-Nitro-2-pyridyl carbonyl azide (**22**, 83.6 mg, 0.432 mmole) was dissolved in benzene (10 mL) and triethylamine (0.12 mL, 0.86 mmole) was added. Phenylacetylchloride (0.09 mL, 0.7 mmole) dissolved in benzene (10 mL) was added dropwise to the mixture over 1 hour under reflux. After addition was completed the mixture was refluxed for 1 hour. The reaction mixture was purified by flash column chromatography using diethyl ether:dichloromethane 1:1, diethyl ether and acetone, respectively. The most pure fractions were recrystallized from acetone and *n*-pentane to afford a offwhite product in 76 % yield (55 mg).

^{1}H NMR (d_6-DMSO): 9.36 (d, 1H, H-6, J = 2.5 Hz), 8.74 (dd, 1H, H-4, J = 8.6 and 2.6 Hz), 8.37 (s, 1H, NH), 8.25 (d, 1H, H-3, J = 8.6 Hz), 7.78 (s, 1H, NH)

^{13}C NMR (d_6-DMSO): 164.3 (C=O), 154.5 (C-2), 145.6 (C-5), 143.9 (C-6), 133.2 (C-4), 122.9 (C-3)

IR (KBr): 3413 (s), 3278 (w), 3149 (br), 3104 (w), 2861 (w), 2756 (w), 1681 (s), 1602 (s), 1580 (w), 1529 (s), 1424 (s), 1355 (s), 1285 (m), 1260 (m), 1216 (w), 1169 (w), 1116 (m), 1022 (s), 956 (m), 879 (m), 862 (m), 815 (m), 792 (w), 779 (m), 728 (m), 675 (w), 631 (w), 584 (s) cm^{-1}

MS: 168 (M$^+$+1, 4), 167 (M$^+$, 36), 125 (6), 124 (100), 123 (10), 78 (38), 77 (9), 76 (7), 52 (5), 51 (23), 50 (13), 44 (24), 30 (5), 28 (8)

HRMS: Calculated for $C_6H_5N_3O_3$: 167.0331; observed for $C_6H_5N_3O_3$: 167.0337

Melting point: 247°C (lit. 246-247°C)

Chapter 8 Experimental

References

1. Scriven, E. F. V. and Jones, G., In Boulton, A. J. and McKillop, A., Eds., *Comprehensive Heterocyclic Chemistry*, Pergamon, Oxford 1984, Vol. 2; Commins, D. L., Joseph, S. P. and Jones, G., In McKillop, A., Ed., *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford 1996, Vol. 5

2. Katritzky, A. R. and Ridgewell, B. J., *J. Chem. Soc.* 3753-3764, 3882 (1963)

3. den Hertog Jr., H. J. and Overhoff, J., *Recl. Trav. Chim. Pays-Bas*, **49**, 552 (1930)

4. Bakke, J. M., *J. Heterocyclic Chem.*, **42**, 463-474 (2005)

5. Bakke, J. M.; Hegbom, I.; Øvreeide, E. and Aaby, K., *Acta Chem. Scand. 48* (1994), 1001-1006

6. Bakke, J. M. and Ranes, E., *Synthesis* (1997), 281-283

7. Katritzky, A. R. *et al.*, *Org. and Biomol. Chem.*, **3**(3), 538-541 (2005)

8. L´abbe, G., *Synthesis* (1987), 525-531

9. Hyden, S. and Wilbert, G., *Chem. Ind.* (1967) 1406-1407

10. Chambers, J. and Reese, C. B., *Tetrahedron Lett.*, **32**, 2783-2786, 1975

11. von Gizycki, V. U., *Angew. Chem.*, 83, 11, 1971, 406-408

12. March, J., *Advanced Organic Chemistry*, *Reaction Mechanisms, and Structure*, Fourth Edition, John Wiley & Sons, 1992, 1083-1085 and 1090-1092

13. Clark-Lewis, J. W. and Singh, R. P., *J. Chem. Soc. Abstract*, 2379 (1962)

14. Cooper, G. H. and Rickard, R. L., *Synthesis*, 31 (1971)

15. Saikachi, H. and Kitagawa, T., *Chem. Pharm. Bull.*, 25, 7, 1651-1657 (1977)

16. Bakke, J. M., Svendsen, H. and Trevisan, R., *J. Chem. Soc. Perkin Trans. 1*, 376 (2001)

17. Broda, W., Dehmlow E. V. and Schulz, H.-J., *Israel Journal of Chemistry*, 26, 1985, 222-224

18. Gilchrist, T. L., *Heterocyclic Chemistry*, Addison Weasley Longman Limited, Third Edition, 1997, 91-106

19. March, J., *Advanced Organic Chemistry*, *Reaction Mechanisms, and Structure*, Fourth Edition, John Wiley & Sons, 1992, 836-839

20. Vandensavel, J-M., Smets, G. and L'abbe, G., *J. Org. Chem.* **1973**, *38*, 675-678

21. Scheiner, P., *Tetrahedron*, **24**, 2757-2766, 1968

22. Stout, D. M., Takaya, T. and Meyers, A. I., *J. Org. Chem.* **1975**, *40*, 563-569

23. Horwitz, J. P., Fisher, B. E. and Tomazevski, A. J., *J. Am. Chem. Soc.*, **1959**, *81*(12), 3076-3079

24. Quast, H. and Nahr, U., *Chem. Ber.* **116**, 3427-3437 (1983)

25. Tsuge, O., Urano, S. and Oe, K., *J. Org. Chem.* **1980**, *45*, 5130-5136

26. Toselli, M. and Zanirato, P., *J. Chem. Soc. Perkin Trans. 1 (9)*, 1992, 1101-1104

27. Birkofer, L. and Wegner, P., *Chem. Ber.*, **99**, 2512-2517 (1966)

28. Ettenhuber, E. and Rühlmann, K., *Chem. Ber.*, **101**, 743-750 (1968)

29. Washburne, S. S. and Peterson, W. R., *J. Organomet. Chem.*, **21**, 427-430 (1970)

30. Kricheldorf, H. R., *Synthesis*, 551-553 (1972)

31. MacMillan, J. H. and Washburne, S. S., *J. Org. Chem.* **1973**, *38*, 2982-2984

32. Kricheldorf, H. R., *Chem. Ber.*, **105**, 3958-3965 (1972)

33. Washburne, S. S., Peterson, Jr., W. R. and Berman, D. A., *J. Org. Chem.* **1972**, *37*(11), 1738-1742

34. MacMillan, J. H. and Washburne, S. S., *J. Heterocyclic Chem.*, **12**, 1215-1220 (1975)

35. Kricheldorf, H. R., *Chem. Ber.*, **106**, 3765-3768 (1973)

36. Goto, T. *et al.*, *EP* 672663 (1995)

37. Theodoridis, G., *US* 4909829 (1990)

38. Covey, R. A. and Moore, R. C., *US* 4839349 (1989)

39. Janssens, F., Torremans, J. and Janssen, P. A. J., *J. Med. Chem.* **1986**, *29*, 2290-2297

40. Harano, K., Kondo, R., Murase, M., Matsuoka, T. and Hisano, T., *Chem. Pharm. Bull.*, **34**(3), 966-974 (1986)

41. Abramovitch, R. A., Shinkai, I. and Van Dahm, R., *J. Heterocyclic Chem.*, **13**(1), 171-172 (1976)

42. Matsuoka, T., Harano, K., Kubo, H. and Hisano, T., *Chem. Pharm. Bull.*, **34**(2), 572-581 (1986)

43. Hisano, T., Matsuoka, T., Fukunaga, K. and Ichikawa, M., *Chem. Pharm. Bull.*, **30**(10), 3776-3781 (1982)

44. Harano, K., Suematsu, F., Matsuoka, T. and Hisano, T., *Chem. Pharm. Bull.*, **34**(2), 543-552 (1984)

45. Hisano, T., Matsuoka, T., Tsutsumi, K., Muraoka, K. and Ichikawa, M., *Chem. Pharm. Bull.*, **29**(12), 3706-3712 (1981)

46. Matsuoka, T., Shinada, M., Suematsu, F., Harano, K. and Hisano, T., *Chem. Pharm. Bull.*, **32**(6), 2077-2090 (1984)

47. Matsuoka, T. and Harano, K., *Tetrahedron*, **51**, 23, 6451-6458, 1995

48. Hisano, T., Harano, K., Fukuoka, R., Matsuoka, T., Muraoka, K. and Shinohara, I., *Chem. Pharm. Bull.*, **34**(4), 1485-1492 (1986)

49. Sustmann, R., *Tetrahedron Lett.*, **12**(29), 2717-2720 and 2721-2724 (1971)

50. Fiksdahl, A., Plüg, C. and Wentrup, C., *J. Chem. Soc. Perkin Trans. 2*, 2000, 1841-1845

51. Fiksdahl, A. and Wentrup, C., *ARKIVOC 1(3)* (2000), 438-444

52. Bodeker, J. and Courault, K., *Tetrahedron*, **34**, 101-104, 1978

53. Gullu, M., Liaquat, A. R., Utley, J. H. P., King, R. J. and White, G. R., *Tetrahedron*, **47**, 4/5, 675-684, 1991

54. Dvortsák, P., Resofszki, G., Huhn, M., Zalántai, L. and Kiss, Á. I., *Tetrahedron*, **32**, 2117-2120, 1976

55. Shur, M. and Israelstam, S. S., *J. Org. Chem.* **1968**, *33*(8), 3015-3020

56. Plüg, C., Wallfisch, B., Andersen, H. G., Bernhardt, P. V., Baker, L.-J., Clark, G. R., Wong, M. W. and Wentrup, C., J. Chem. Soc. Perkin Trans. 2, 2000, 2096-2108

57. Taylor, E. C., McKillor, A. and Hawks, G. H., *Org. Synth.* **Coll. Vol VII**, 549-551

58. March, J., *Advanced Organic Chemistry*, *Reaction Mechanisms, and Structure*, Fourth Edition, John Wiley & Sons, 1992, Chapter 13: Aromatic Nucleophilic Substitution, 641-676

59. Effenberger, F., Koch, M. and Streicher, W., *Chem. Ber.*, **124**, 163 (1991)

60. Beck, J. R., *Tetrahedron*, **34**, 2057 (1978)

61. Ranes, E. and Bakke, J. M., *Ph. D* Thesis, NTNU, 1999

62. Connon, S. J. and Hegarty, A. F., *Tetrahedron Lett.*, **42**, 735-737, 2001

63. Dejardin, J. V. and Lapiere, C. L., *Bull. Soc. Chem. France*, **3**, 530 (1976)

64. Sugiyama, T., Kusano, Y., Yagi, K., Ito, Y. and Sugimori, A., *Bull. Chem. Soc. Japan*, **57**, 1882 (1984)

65. Sugiyama, T., Yagi, K., Ito, Y. and Sugimori, A., *Chem. Lett.*, **6**, 917 (1982)

66. Hawkins, A. F., Lewis, T. and Jones, I., *BR* 7702236 (1978); *Chem. Abstr.* **90**, 98558 (1978)

67. Sinnott, D. M., Chow, H. F., Ehr, R. J., Lubetkin, S. D., Bales, S. E. and Inbasekaran, M. N., *US* 5447960 (1995); *Chem. Abstr.* **123**, 249190 (1995)

68. Tjosås, F. and Fiksdahl, A., *J. Heterocyclic Chem.*, in preparation

69. Tjosås, F. and Fiksdahl, A., *Molecules,* submitted

70. Sekikawa, I., Nishie, J., Tono-oka, S. Tanaka, Y. and Kakimoto, S., *J. Heterocyclic Chem.*, **10**(6), 931 (1973)

71. Badger, G. M. and Rao, R. P., *Aust. J. Chem.*, 1965, **18**, 379-387

72. Tserng, K.-Y. and Bauer, L., *J. Heterocyclic Chem.*, **11**(2), 163 (1974)

73. Taylor, E. C. and Barton, J. W., *J. Am. Chem. Soc.*, **1959**, *81*(10), 2448-2452

74. Riha, J. and Bakke, J. M., *Ph. D* Thesis, NTNU, 2000

75. Curtin, M. L. *et al.*, *J. Med. Chem.*, **1998**, 41, 74

76. Barraclough, P. *et al.*, *J. Chem. Res (S)*, 196 (1997)

77. Barraclough, P. *et al.*, *J. Med. Chem.*, **1990**, 33, 2231-2239

78. Jiang, B., *Organic Process Research & Development* **1998**, *2*, 425-427

79. Bakke, J. M. and Riha, J., *J. Heterocyclic Chem.*, **36**, 1143 (1999)

80. Kim, C. S. *et al.*, *WO* 9429321 (1994); *Chem. Abstr.*, **122**, 239449 (1995)

81. Barlin, G. B., *J. Chem. Soc. B*, 285 (1966)

82. Delluca, G. V., *US* 5763469 (1998); *Chem. Abstr.*, **129**, 67775 (1998)

83. Yoshida, T., Kambe, N., Murai, S. and Sonoda, N., *Bull. Chem. Soc. Jpn.*, **60**, 1793 (1987)

84. Debeljak-Sustar, M., Stanovnik, B., Tisler, M. and Zrimsek, Z., *J. Org. Chem.* **1978**, *43*, 393

85. Tomzic, A., Tisler, M. and Stanovnik, B., *J. Heterocyclic Chem.*, **16**, 861 (1979)

86. Israel, M. and Jones, L. C., *J. Heterocyclic Chem.*, **8**, 797 (1971)

87. El-Enany, M., Ghoneim, K. M. and Khalifa, *Pharmazie*, **32**, 79 (1977)

88. Robinson, M. M., *US* 3759933 (1973); *Chem. Abstr.*, **79**, 146522 (1973)

89. Wright, G. C., *J. Heterocyclic Chem.*, **13**, 601 (1976)

90. Frankowski, A., *Tetrahedron*, **42**, 1511 (1986)

91. Consention, U. *et al.*, *Molecular Structure (Theochem)*, **286**, 275 (1993)

92. Czarnocka-Janoicz, A., Janowiec, M. and Stambrowska, A., *Acta Polon. Pharm.*, **40**, 21 (1983)

93. Meanwell, N. A. *et al.*, *J. Org. Chem.* **1995**, *60*, 1565

94. Meanwell *et al.*, *Bioorg. Med. Chem. Lett.*, **6**, 1641 (1996)

95. Yoshikazu, I. *et al.*, *EP* 0990653 (1998); *Chem. Abstr.*, **130**, 52418 (1999)

96. Berényi, E., Benkó, P., Zólyomi, G. and Tamás, J., *J. Heterocyclic Chem.*, **18**, 1537 (1981)

97. Papamicaël, C., Dupas, G., Quéguiner, G. and Bourguignon, J., *Heterocycles*, **47**, 991 (1998)

98. Dornow, A. and Plessen, H. v., *Chem. Ber.* **99**, 244 (1966)

99. Salemink, C. A. and van der Want, G. M., *Rec. Trav. Chem.*, **68**, 1013 (1949)

100. Coburn, C., *WO* 9927930 (1999); *Chem. Abstr.*, **131**, 31937 (1999)

101. Ho, W. *et al.*, *J. Med. Chem.*, **38**, 794 (1995)

102. Chen, Y. L., *EP* 0778277 (1997); *Chem. Abstr.*, **127**, 95290 (1997)

103. Bantick, J. R. *et al.*, *Bioorg. Med. Chem. Lett.*, **4**, 127 (1994)

104. Bakke, J. M., Gautun, H. S. H. and Svensen, H., *J. Heterocyclic Chem.*, **40**, 585 (2003)

105. Bakke, J. M., Ranes, E. Riha, J. and Svensen, H., *Acta Chem. Scand.*, **53**, 141 (1999)

106. Clark, R. L., Pessolano, A. A. and Shen, T.-Y., *DE 2623414* (1976); *Chem. Abstr.* **86**, 106600 (1976)

107. Briekiesz-Lewandowska, B. and Talik, Z., *Rocz. Chem.*, *44*, 69 (1970); *Chem. Abstr.* **73**, 45415 (1970)

108. Heckendorn, R., *EP 74929* (1983); *Chem. Abstr.* **99**, 53786 (1983)

109. Nagano, E. and Yoshida, R., *EP 116928* (1984); *Chem. Abstr.* **102**, 45951 (1984)

110. Jones, G., *Advances in Heterocyclic Chemistry*, 83, 2002, 1-70

111. May, Jr., J. A. and Townsend, L. B., *J. Org. Chem.* **1976**, *41*(8), 1449-1456

112. Bremer, O., *J. Liebigs Ann. Chem.*, **518**, 274 (1935)

References

113. Torrini, I., Zecchini, G. P., Agrosi, F. and Paradisi, M. P., *J. Heterocyclic Chem.*, **23**, 1459 (1986)

114. Deng, Y., Shen, Y. and Zhong, Y., *Huaxi Yaoxue Zachi*, **16**, 273 (2001); *Chem. Abstr.* **136**, 369660 (2001)

115. Du, B. and Han, H., *Henan Yike Daxue Xuebao*, **36**, 350 (2001); *Chem. Abstr.* **136**, 294771 (2001)

116. Buechner, R., Brendel, H., Rauhut, H., Eitner, B. and Hartmann, K., *DD 273630* (1989); *Chem. Abstr.* **112**, 235324 (1989)

117. Damschroder, R. E. and Peterson, W. D., *Org. Synth.*, **20**, 6 (1940)

118. Katritzky, A. R. and Rogovoy, B. V., *Chem. Eur. J.* **2003**, *9*, 4586-4593

119. Katritzky, A. R., He, H.-Y. and Suzuki, K., *J. Org. Chem.* **2000**, *65*, 8210-8213

120. Katritzky, A. R. and Pastor, A., *J. Org. Chem.* **2000**, *65*, 3679-3682

121. Katritzky, A. R., Abdel-Fattah, A. A. A. and Wang, M., *J. Org. Chem.* **2003**, *68*, 1443-1446

122. Katritzky, A. R., Abdel-Fattah, A. A. A. and Wang, M., *J. Org. Chem.* **2003**, *68*, 4932-4934

123. Katritzky, A. R., Suzuki, K., Singh, S. K. and He, H.-Y., *J. Org. Chem.* **2003**, *68*, 5720-5723

124. Campbell, J. B., Greene, J. M., Lavagnino, E. R., Gardner, D. N., Pike, A. J., Snoddy, J. and Taylor, E. C., *J. Heterocyclic Chem.*, **23**, 669 (1986)

125. Bovet, D., Jacob, R., Ducrot, R. and Courvoisier, S., *Compt. rend.*, **224**, 496 (1947)

126. Hendrickson, J. B. and Bergeron, R., *Tetrahedron Lett.*, **46**, 4607, 1973

127. Haridasan, V. K., Ajayaghosh, A. and Rajasekharan Pillai, V. N., *J. Org. Chem.* **1987**, *52*, 2662

128. Ho, T.-L., *Synth. Comm.*, **7**, 393 (1977)

129. Mullier, M. and Smets, G., *J. Polym. Sci.*, **23**, 915 (1957)

130. de la Saulniere, P. C., *Ann. di Chim. Appl.*, **17**, 353 (1942)

131. Van der Werf, S. and Engberts, J. B. F. N., *Rec. Trav. Chim. Pays-Bas*, **89**, 423 (1970)

132. Chen, L. C. and Yang, S. C., *J. Chinese Chem. Soc.*, **33**, 347 (1986)

133. Szirtes, T., Palosi, E., Ezer, E., Szporny, L. and Kisfaludy, L., *Acta Pharm. Hung.*, **43**, 224 (1973)

134. Carpino, L. A., *J. Am. Chem. Soc.*, **1957**, *79*, 4427

135. Leplawy, M. and Stec, W., *Bull. de l'Academie Polonaise des Sciences, Series des Sciences Chim.*, **12**, 21 (1964)

136. Aoki, S., Cao, L., Matsui, K., Rachmat, R., Akiyama, S. and Kobayashi, M., *Tetrahedron*, **60**, 7053 (2004)

137. Murphy, J. A. and Roome, S. J., *J. Chem. Soc. Perkin Trans. 1*, 1349 (1995)

138. Srinivas, K. V. N. S. and Das, B., *J. Org. Chem.* **2003**, *68*, 1165

References

Appendices

Paper I is not included due to copyright.

Paper II

Holt, Jarle and Fiksdahl, Anne
Nitropyridyl isocyanates in 1,3-dipolar cycloaddition reactions

Paper II is not included due to copyright.

Paper III

Holt, Jarle, Tjosås, Freddy, Bakke, Jan M. and Fiksdahl, Anne

Nucleophilic aromatic substitution of methyl 3-nitropyridine-4-carboxylate

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Paper IV

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Paper V

Holt, Jarle and Fiksdahl, Anne

N-Acyl and *N*-alkoxycarbonyl derivatives of 1*H*-1,2,3-triazolo[4,5-*c*]pyridine; preparation and application

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