

# Synthesis and Functionalization of 3-Nitropyridines

Dr. ing. thesis by  
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Harald Svensen  
Trondheim, December 2001



# TABLE OF CONTENTS

## Acknowledgements

## Table of contents

## List of Articles

## Abbreviations & Symbols

## Summary

1. Introduction .....	1
2. Properties of pyridines .....	3
2.1. Reactions of pyridines with electrophiles .....	4
2.1.1. <i>Electrophilic attack at ring nitrogen</i> .....	4
2.1.2. <i>Electrophilic attack at ring carbon</i> .....	4
2.2. Reaction of pyridines with nucleophiles.....	5
2.3. References.....	8
3. Nitration of pyridines .....	9
3.1. Introduction.....	9
3.2. The nitration of pyridines with dinitrogen pentoxide and $\text{SO}_2/\text{HSO}_3^-$ .....	10
3.2.1. <i>Background for the present project</i> .....	10
3.2.2. <i>Results and discussion</i> .....	11
3.3. Conclusion .....	17
3.4. References.....	18
4. The reaction mechanism of the nitration of pyridine .....	19
4.1. Previous investigations .....	19
4.1.1. <i>Reaction outline</i> .....	19
4.1.2. <i>The migration of the nitro group</i> .....	20
4.2. Result and discussion.....	22
4.2.1. <i>NMR studies of nitration of 3-substituted pyridines</i> .....	22
4.2.2. <i>Intermediates in nitration of 3-acetylpyridine</i> .....	23
4.2.3. <i>Intermediates in nitration of 3-methylpyridine</i> .....	26
4.2.4. <i>Yields in nitrations of 3-substituted pyridines</i> .....	27
4.2.5. <i>Viscosity of the solvent</i> .....	27
4.3. Conclusion .....	28
4.4. References.....	29

5. Selective vicarious nucleophilic amination of 3-nitropyridines	31
5.1. Introduction	31
5.1.1. Vicarious nucleophilic amination of nitroaromatics	31
5.1.2. Amination of 3-nitropyridines	35
5.2. Results and discussion	36
5.2.1. Amination of 3-nitropyridine with hydroxylamine	36
5.2.2. Amination of 3-nitropyridine (24) with 4-amino-1,2,4-triazole	39
5.2.3. Amination of 4-methyl-3-nitropyridine	40
5.2.4. Amination of 5-methyl-3-nitropyridine	41
5.2.5. Amination of methyl 3-nitroisonicotinate	42
5.2.6. Amination of 4-cyano-3-nitropyridine	43
5.2.7. Amination of 4-(1,3-dioxolan-2-yl)-3-nitropyridine	44
5.2.8. Amination of 4-acetyl-3-nitropyridine	45
5.2.9. Amination of 4-phenyl-3-nitropyridine	46
5.2.10. Amination of 5-phenyl-3-nitropyridine	46
5.2.11. Amination of 4-nitroisoquinoline	47
5.2.12. General trends and side reactions	49
5.3. Conclusion	51
5.4. References	53
6. The selective oxidative amination of 3-nitropyridines	55
6.1. Introduction	55
6.1.1. Oxidative nucleophilic substitution of hydrogen	55
6.1.2. Mechanism of oxidative amination	55
6.2. Oxidative amination of azaaromatic	57
6.2.1. Introduction	57
6.2.2. Oxidative amination of 3-nitropyridines	58
6.3. Results and discussion	59
6.3.1. Amination of 3-nitropyridines with ammonia	59
6.3.2. Oxidative amination of 3-nitropyridines with primary amines	63
6.3.3. Oxidative amination of 3-nitropyridines with secondary amines	66
6.3.4. Limitations and side reactions	68
6.4. Conclusion	69
6.5. References	70
7. Nucleophilic alkylations of 3-nitropyridines	71
7.1. Introduction	71
7.1.1. Reactions of aromatic and heteroaromatic compounds with C-nucleophiles	71
7.1.2. Reactions of 3-nitropyridines with C-nucleophiles	73
7.2. Results and discussion	76
7.2.1. Chloroform as nucleophile	76

7.2.2. <i>Methyl chloroacetate and ethyl 2-chloropropionate as nucleophiles</i>	80
7.2.3. <i>General trends</i>	82
7.3. Conclusion	83
7.4. References	84
<b>8. Transformations of 3-nitropyridines</b>	<b>85</b>
8.1. Introduction	85
8.2. Results and discussion	86
8.3. Conclusion	89
8.4. References	90
<b>9. Experimental</b>	<b>91</b>
9.1. General	91
9.2. Nitration	92
9.2.1. <i>General nitration procedures</i>	92
9.2.2. <i>Nitration of substituted pyridines</i>	93
9.3. The reaction mechanism of nitration of pyridine	100
9.3.1. <i>From the reaction of 3-acetylpyridine</i>	100
9.3.2. <i>From the reaction of 3-methylpyridine</i>	101
9.4. Selective vicarious nucleophilic amination of 3-nitropyridines	103
9.4.1. <i>General</i>	103
9.4.2. <i>Amination procedures</i>	103
9.4.3. <i>Amination of 3-nitropyridines</i>	103
9.5. The oxidative amination of 3-nitropyridines	110
9.5.1. <i>Oxidative aminations with ammonia</i>	110
9.5.2. <i>Oxidative amination with n-butylamine</i>	112
9.5.3. <i>Oxidative amination with diethylamine</i>	114
9.6. Nucleophilic alkylation of 3-nitropyridines	117
9.6.1. <i>Reaction with chloroform</i>	117
9.6.2. <i>Reaction of 3-nitropyridines with methyl chloroacetate</i>	120
9.6.3. <i>Reaction of 3-nitropyridine (24) with ethyl 2-chloropropionate</i>	121
9.7. Transformation of 3-nitropyridines	122
9.8. References	124

## List of Compounds

## Appendixes

<b>Appendix 1</b>	<b>Article 1</b>
<b>Appendix 2</b>	<b>Article 2</b>
<b>Appendix 3</b>	<b>Article 3</b>
<b>Appendix 4</b>	<b>Article 4</b>





## List of Articles

1. J. M. Bakke, E. Ranes, J. Riha and H. Svensen  
The Synthesis of  $\beta$ -nitropyridine compounds  
*Acta Chemica Scandinavia*, **53**, 141 (1999)
2. J. M. Bakke, H. Svensen and E. Ranes  
The reaction mechanism of the nitration of  
pyridine compounds by  $\text{N}_2\text{O}_5$ - $\text{NaHSO}_3$   
*J. Chem. Soc., Perkin trans. 2*, 2477 (1998)
3. J. M. Bakke, H. Svensen and R. Trevisan  
Selective vicarious nucleophilic amination of 3-nitropyridines  
*J. Chem. Soc., Perkin trans. 1*, 376 (2001)
4. J. M. Bakke and H. Svensen  
The oxidative amination of 3-nitropyridines  
*Tetrahedron Letters*, **42**, 4393 (2001)



## Abbreviations & Symbols

calcd	calculated
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
e.g.	<i>exempli gratia</i> , for example
Et	ethyl
g	gram
GC	gass chromatography
HRMS	High resolution mass spectroscopy
Hz	hertz
IR	Infrared spectroscopy
lit.	literature
Me	methyl
MHz	megahertz
mp.	melting point
MS	Mass spectroscopy
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhouser Effect
Ph	Phenyl
ppm	parts per million
rel. int.	relative intensity
THF	Tetrahydrofuran

### NMR assignments:

d	doublet
J	coupling constant
m	multiplet
s	singlet

### IR assignments:

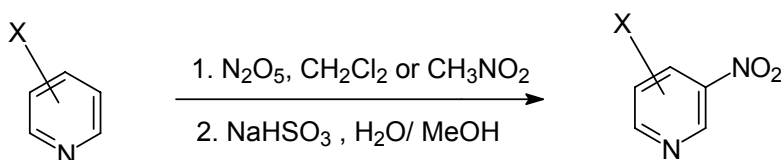
m	medium
s	strong
w	weak



## Summary

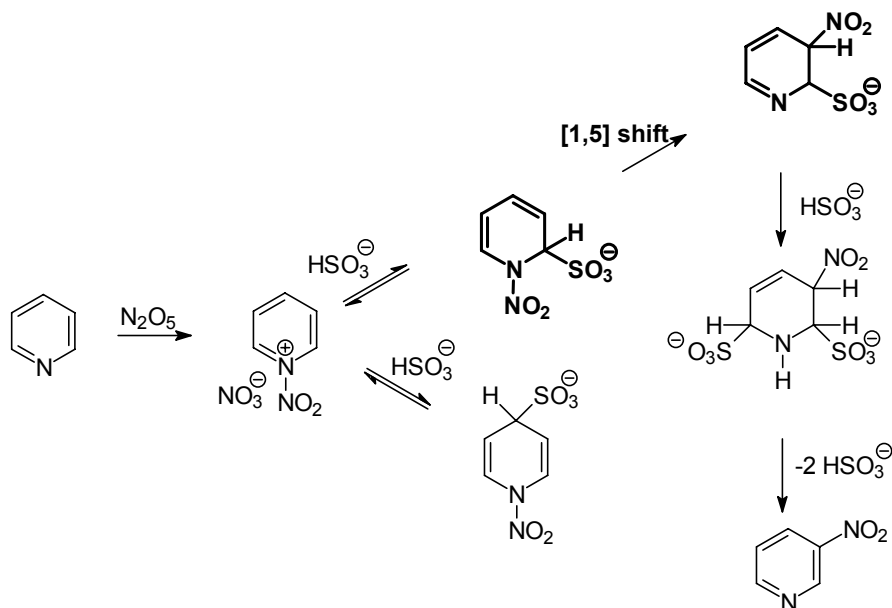
The goals for the project “Synthesis and Functionalization of 3-Nitropyridines” were first to further optimize the procedures for nitration of 3-nitropyridines, and then investigate some aspects of the mechanism. Further was the reactivity of 3-nitropyridines investigated, especially the reactivity toward nitrogen nucleophiles.

Pyridines can be nitrated by reacting the pyridine with dinitrogen pentoxide in an organic solvent and then pour the slurry formed into an aqueous solution of sodium bisulfite. After some hours of stirring, the 3-nitropyridine can be isolated.

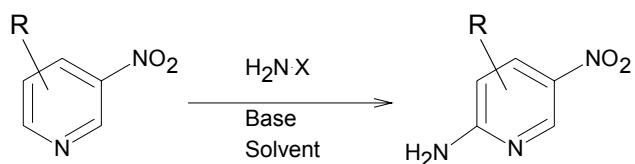


After investigation of the effect of changes in sodium bisulfite concentration, reaction medium and temperature a modified procedure for the nitration was developed. In this procedure the pyridine compound was reacted with dinitrogen pentoxide in dichloromethane or nitro methane and the resulting slurry poured into a solution of bisulfite dissolved in methanol/water (3:1). After some hours of stirring at room temperature the 3-nitropyridine was isolated.

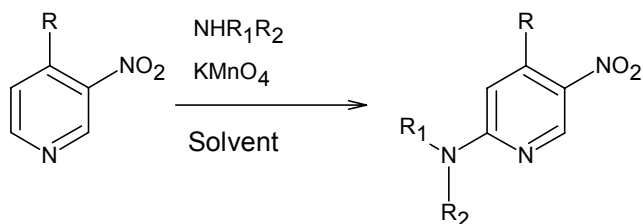
The mechanism of the nitration of pyridines with dinitrogen pentoxide was studied, and is shown in the next scheme. The author studied the migration of the nitro group from the nitrogen to the  $\beta$ -carbon. It has been by others shown that pyridine and dinitrogen pentoxide forms *N*-nitro pyridinium nitrate. Which is attacked by the bisulfite nucleophile in either 2- or 4- position to give *N*-nitro-2-dihydropyridine-2-sulfonate and *N*-nitro-1,4-dihydropyridine-4-sulfonate. The nitro group in *N*-nitro-2-dihydropyridine-2-sulfonate migrates to the  $\beta$ -carbon, to give via addition of one more bisulfite ion a tetrahydro intermediate. From this the 3-nitropyridine is formed by loss of two bisulfite ions. The mechanism for the nitro group migration was previously not known. The results presented in this thesis together with previous results conclude with that the migration takes place as a [1,5] sigmatropic shift.



Nine 3-nitropyridines and 4-nitroisquinoline was aminated by hydroxylamine and 4-amino-1,2,4-triazole in a vicarious nucleophilic substitution reaction in moderate to good yields. Both reagents selectively gave amination in the *para* position to the nitro group.



Oxidative amination of 3-nitropyridines in liquid ammonia at  $-33\text{ }^\circ\text{C}$  is reported in literature to give mixture of isomers. A new method for selective amination of 3-nitropyridine have been developed by performing the reaction at room temperature. When 3-nitropyridine was reacted in DMSO/water (3:1) saturated with ammonia in the presents of potassium permanganate, 2-amino-5-nitropyridine was formed with high selectivity. A 66 % yield of 2-amino-5-nitropyridine was isolated.



3-Nitropyridine and some 4-substituted 3-nitropyridines were oxidative aminated by n-butylamine and diethylamine to give 2-alkylamino-5-nitropyridines. High regioselectivity was achieved when the right reaction conditions were used.

Vicarious nucleophilic substitution with carbon nucleophiles like the anions of chloroform, methyl chloroacetate and ethyl 2-chloropropionate were tried for some 3-nitropyridines. For 3-nitropyridine all nucleophiles attacked preferably in the 4-position. When the 4-position was blocked chloroform attacked mainly in the *para* position to the nitro group. Methyl chloroacetate did not react with 4-substituted substrates, and ethyl 2-chloro were not tried for 4-substituted substrates

3-nitropyridine-4-yl carbamates are key intermediates in the synthesis of 3,4-diaminopyridines and dihydro-2H-imidazo[4,5-c]pyridin-2-ones. Attempts to produce methyl 3-nitropyridine-4-yl carbamate by a hoffman rearrangement of isonicotinamide were abandoned due to poor yields.





## 1. Introduction

This project started in January 1998, and was a continuation of the project “Nitration by the use of dinitrogen pentoxide” started in Prof. Bakke’s group by Dr. Ingrid Hegbom in 1991 and continued by Dr. Eli Ranes (1994 - 1998) and Dr. Jaroslav Riha (1997 - 2000). During this project it was found that pyridines could be nitrated by dinitrogen pentoxide and sulfur dioxide/sodium bisulfite in good yields.

When this project started several methods for the nitration of pyridine with dinitrogen pentoxide were developed and most of the details for the mechanism were established. But still some work on optimization of the nitration reaction had to be done and some aspects of the mechanism was not known.

The project therefore had two main goals: to finish the work on the nitration of pyridines, and then explore the chemistry of the 3-nitropyridines.

The work on optimization of the nitration reaction and studies of the reaction mechanism were done in close cooperation with Dr. Eli Ranes and Dr. Jaroslav Riha. The work of the author can not be presented without referring to their work.

In order to optimize the yield of the nitration reaction several parameters were studied. This work is presented in Chapter 3. The author’s results together with the results of Dr. Eli Ranes and Dr. Jaroslav Riha are published in Article 1.

The results from the studies of the reaction mechanism for the nitration are given in Chapter 4. The reaction intermediates were identified by low temperature NMR spectroscopy, and their concentrations as a function of time were monitored. These results together with Dr. Eli Ranes’s results lead to a proposed mechanism for the nitration. The results are published in Article 2.

The nitration method for pyridines developed in Prof. Bakke’s group have made a whole range of 3-nitropyridines readily available for the first time. Especially 4-substituted 3-nitropyridines have previously been difficult to obtain. It was therefore natural to study the reactivity of these compounds, to find new methods for further functionalization.

Since 3-nitropyridines are electron deficient compounds they should be susceptible for nucleophilic attack. The two major methods for nucleophilic substitution of hydrogen in arenes are vicarious nucleophilic substitution (VNS) and oxidative nucleophilic substitution of hydrogen (ONSH).

In Chapter 5 the results from vicarious nucleophilic substitutions with nitrogen nucleophiles are presented. Several substituted 3-nitropyridines were reacted with two different amination reagents. The results are published in Article 3.

The results from oxidative amination of 3-nitropyridines with nitrogen nucleophiles are presented in Chapter 6. Some 3-nitropyridines were oxidative aminated by amines in the presence of an oxidizing agent. The results are published in Article 4.

In Chapter 7 some introductory experiments from reaction of carbon nucleophiles with 3-nitropyridines are presented.

Some transformations of substituted 3-nitropyridines are described in Chapter 8.

All experimental details are given in Chapter 9, also data given in the articles. Most compounds mentioned in this thesis are given a number, and a list of compounds with number and structure are given at the end of the thesis.

## 2. Properties of pyridines

Pyridine (**1**) and its derivatives are among the most important heterocycles.

Pyridine (**1**) is a water-miscible liquid, with a boiling point of 115 °C, with an unpleasant odor. It is an excellent polar solvent, a base ( $pK_a = 5.23$ ) and a donor ligand in metal complexes. Most pyridines are thermally and photochemically stable.

Pyridine (**1**) is the prototype of electron-poor six-membered heterocycles. The replacement of a CH in benzene by N leads to far-reaching changes in typical reactivity: pyridines are much more susceptible to nucleophilic attack and much less susceptible to electrophilic substitution than benzene. When the ring nitrogen is protonated electrophilic attack at ring carbons is even less favorable.

The pyridine skeleton is incorporated in a whole range of natural products, pharmaceuticals, dyes and other commercial products<sup>1,2,3,4</sup>.

The pyridine ring plays a key role in many biological processes, most important is the oxidation/reduction coenzyme nicotinamide (NADP). Pyridoxine (vitamin B<sub>6</sub>) is another important coenzyme. Nicotine, a highly toxic alkaloid, is the major active component in tobacco. Isoniazide is a major antituberculosis agent. Epibatidine, isolated from a South American frog, is promising as an analgetic agent. Davicil is a fungicide, and Nemertelline is a neurotoxin from a marine worm.

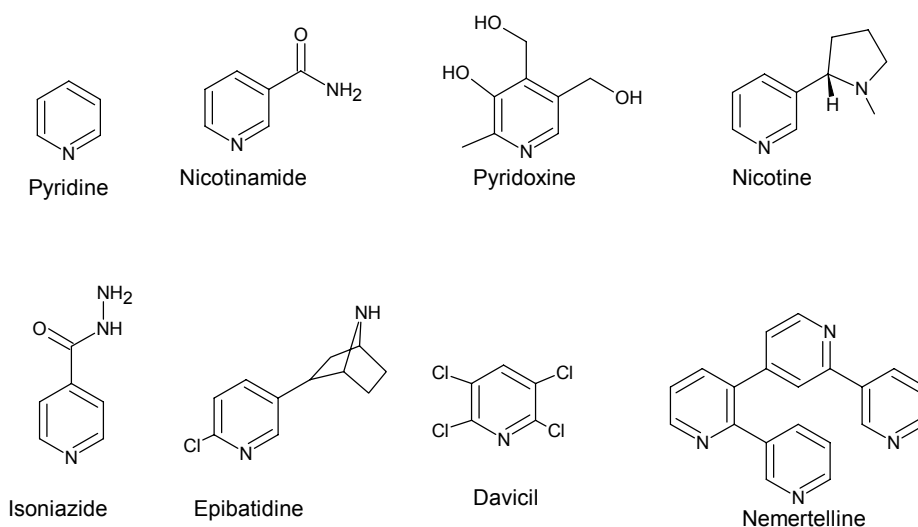


Figure 2.1. Examples of important pyridine derivatives.

## 2.1. Reactions of pyridines with electrophiles

### 2.1.1. Electrophilic attack at ring nitrogen

The nitrogen in the pyridine ring is a good nucleophile and reacts with a whole range of electrophiles. It can be protonated, nitrated, sulfonated, alkylated, acylated, oxidized and halogenated (examples in Figure 2.2.). Some of these compounds are used in organic synthesis as electrophile donors, e.g. in brominations, sulfonations, nitrations and acylations.

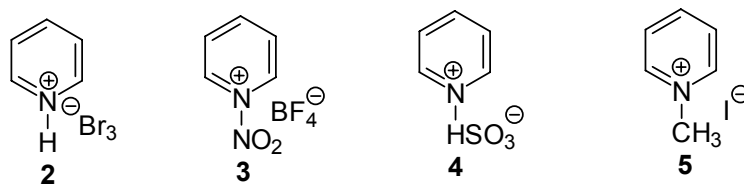


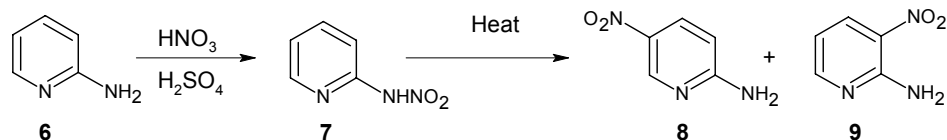
Figure 2.2. Examples of reaction products from reactions of pyridine (1) and electrophiles.

### 2.1.2. Electrophilic attack at ring carbon

Electrophilic aromatic substitution at carbon is a difficult process. Pyridine (1) is itself about a million times less reactive than benzene, and the pyridinium cation (the major species under traditional electrophilic substitution conditions) is about  $10^{-20}$  times less reactive than benzene.<sup>4</sup>

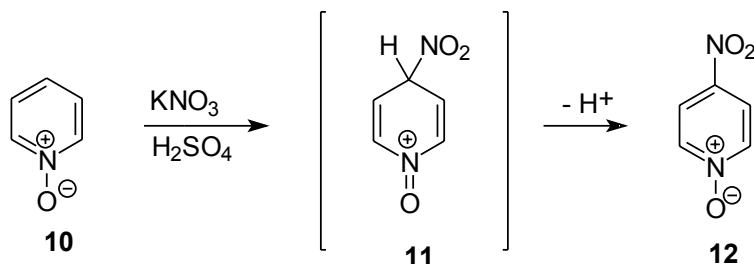
When reaction occur, the 3- and 5-positions, which are less deactivated by the N-atom, are preferentially attacked. The reaction is activated by electron donating groups. Some typical electrophilic substitution reactions do not occur at all, such as Friedel-Crafts alkylations and acylations.

Electrofilic aroamtic substitution of pyridine (1) gives poor yields (6 %) even under vigorous conditions, such as potassium nitrate in oleum at 300 °C.<sup>5</sup> Pyridines with one methyl substituent are not activated enough to be nitrated, but dimethylpyridines can be nitrated. Side chain oxidation is a problem in nitration of methylpyridines.<sup>6</sup> Pyridines with strong electron donating substituents such as hydroxy and amino groups can be nitrated in good yield. Nitration of 2-aminopyridine (6) goes via a nitramine 7, which upon heating rearranges to either 2-amino-5-nitropyridine (9) or 2-amino-3nitropyridine (8)(Scheme 2.1.).<sup>7</sup>



Scheme 2.1. The nitramine rearrangement.

Pyridine *N*-oxide (**10**) can be nitrated in 4-position as shown in Scheme 2.2.



Scheme 2.2. Nitration of pyridine *N*-oxide.

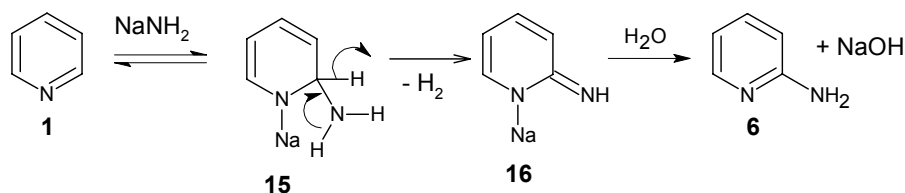
Pyridine (**1**) is sulfonated in low yield by concentrated sulfuric acid or oleum, but addition of mercuric sulfate in catalytic quantities gives sulfonation in good yield.<sup>8</sup>

3-Bromopyridine (**13**) can be produced in good yield by reacting pyridine (**1**) with bromine in oleum.<sup>9</sup> Direct chlorination is more difficult and 3-chloropyridine (**14**) is produced in 33 % yield by reaction of pyridine (**1**) with chlorine in the presence of aluminium chloride at 100 °C.<sup>10</sup>

## 2.2. Reaction of pyridines with nucleophiles

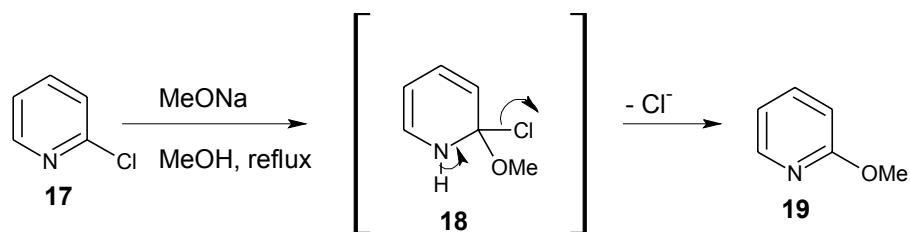
Since the pyridine ring is electron deficient compared to benzene it is also more susceptible to nucleophilic attack. Nitropyridines are even more activated than pyridines. Nucleophilic substitution usually proceeds via a two step sequence. The first step is an addition of the nucleophile, followed by an elimination of the leaving species, e.g. a halide or a hydride.

Only strong nucleophiles react with pyridine (**1**), e.g. amides and hydroxide ions, and they preferentially react at the 2-position. The best known reaction is the Chichibabin reaction (Scheme 2.3.), by which 2-aminopyridine (**6**) is formed from pyridine (**1**) and sodium amide.<sup>11</sup>



Scheme 2.3. The Chichibabin reaction.

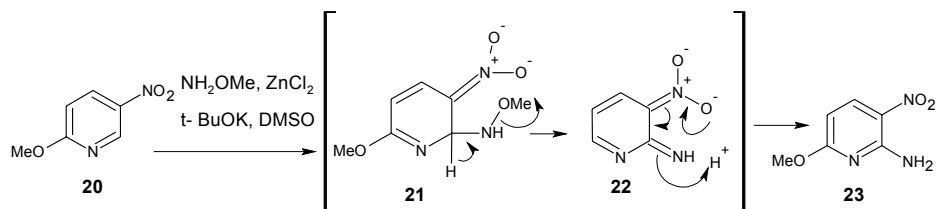
Good leaving groups such as halides can be displaced by a number of nucleophiles. One example is given in Scheme 2.4, where 2-chloropyridine (**17**) is converted to 2-methoxypyridine (**19**) in 95% yield.<sup>14</sup>



Scheme 2.4. Nucleophilic substitution of chlorine.

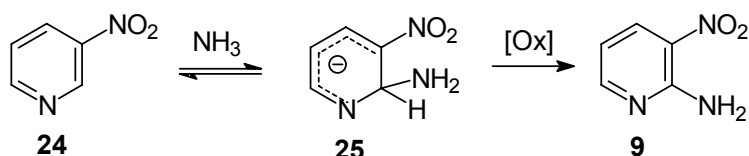
Hydride is a poor leaving group. Therefore, methods have been developed in order to perform nucleophilic substitutions on activated pyridines (e.g. nitropyridines), not functionalized with good leaving groups.

Vicarious nucleophilic substitution (VNS) permits the introduction of amino groups *ortho* or *para* to the nitro group by reaction with methoxyamine as illustrated in Scheme 2.5., where 2-methoxy-5-nitropyridine (**20**) is reacted with methoxyamine and base to give **23**.<sup>12</sup>



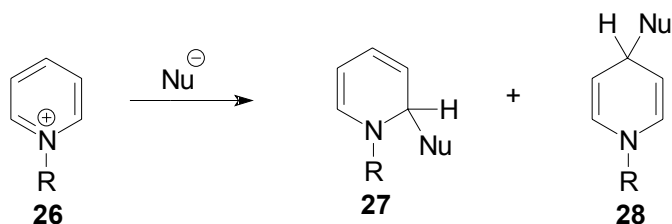
Scheme 2.5. Vicarious nucleophilic substitution of hydrogen.

Oxidative nucleophilic substitution of hydrogen (ONSH) is another method. The intermediate from the reaction of 3-nitropyridine (**24**) and the nucleophile is oxidized by an oxidizing agent, e.g. potassium permanganate, and the pyridine ring is then rearomatized by loss of a proton to give the aminated 3-nitropyridine (**9**). Low selectivity is often a problem in ONSH reactions.<sup>13</sup> Scheme 2.6. shows the reaction for the main isomer, but the other isomers are also formed.



*Scheme 2.6. Mechanism for the formation of the main isomer (9) in the oxidative nucleophilic substitution of hydrogen of 3-nitropyridine (24).*

Pyridine *N*-oxide (**10**) and pyridinium salts (**26**) are more susceptible to nucleophilic attack than pyridine (**1**) itself, as the positively charged ring nitrogen can act as an electron sink. Pyridinium salts (**26**) can react with nucleophiles such as hydroxide, chloride, amines, carbanions and sulfite. Pyridinium cations react with hard nucleophiles mainly at the 2-position, and with soft nucleophiles at the 4-position,<sup>15</sup> but in many cases mixtures are obtained (Scheme 2.7.).



*Scheme 2.7. Nucleophilic addition on pyridinium salts (26).*

### 2.3. References

1. A. R. Katritzky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry* 2nd ed., Pergamon, Oxford, 2000.
2. J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell Science, Oxford, 2000.
3. T. L. Gilchrist, *Heterocyclic Chemistry*, Longman, Essex, 1997.
4. G. R. Newkome and W. W. Paudler, *Contemporary Heterocyclic Chemistry*, Wiley, New York, 1995.
5. H. J. Den Hertog and J. Overhoff, *Recl. Trav. Chim. Pays-Bas*, **49**, 552 (1930).
6. E. V. Brown and R. H. Neil, *J. Org. Chem.*, **26**, 3546 (1961).
7. L. N. Pino and W. S. Zehring, *J. Am. Chem. Soc.*, **77**, 3154 (1955).
8. S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.*, **65**, 2233 (1943).
9. H. J. Den Hertog, L. V. den Does, C. A. Laandheer, *Recl. Trav. Chim. Pays-Bas*, **91**, 864 (1962).
10. D. E. Pearson, W. W. Hargreave, J. K. T. Chow and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).
11. M. T. Leffler, *Org. Reactions*, **1**, 91 (1942); C. K. McGill and A. Rappa, *Adv. Heterocycl. Chem.*, **44**, 2 (1988); H. Vorbrüggen, *Adv. Heterocycl. Chem.*, **49**, 117 (1990).
12. S. Seko, K. Miyake, *Chem. Commun.* 1519 (1998).
13. A. Baranski, B. Szpakiewics, *Liebigs. Ann.*, 875 (1991).
14. H. Yamanaka and S. Ohba, *Heterocycles*, **31**, 895 (1990).
15. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester, 1976.



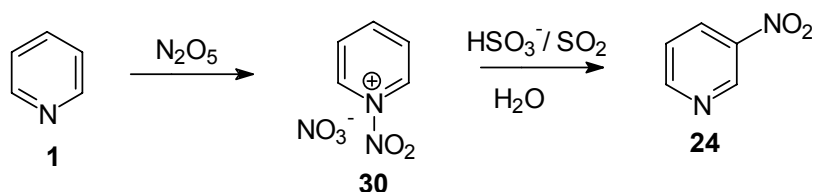
### 3. Nitration of pyridines

#### 3.1. Introduction

Nitration of pyridines by electrophilic aromatic substitution takes place with great difficulty, and low yields are obtained even under very harsh conditions. Typically nitration of pyridine (**1**) with potassium nitrate in fuming sulfuric acid at 350 °C gave a 6 % yield of 3-nitropyridine (**24**).<sup>1</sup> Gaseous nitration with a mixture of dinitrogen tetroxide and carbon dioxide at 115-120 °C gave a 7-10 % yield of 3-nitropyridine (**24**).<sup>2</sup> Pyridine (**1**) was nitrated with nitryl fluoride, in a violent reaction, to give **24** in 10 % yield.<sup>3</sup>

In 1993 Suzuki and co-workers reported the nitration of pyridine (**1**) with nitrogen dioxide and ozone in dichloromethane at room temperature. They obtained a 3.5 % yield of 3-nitropyridine (**24**) and 1.2 % of 3,5-dinitropyridine (**29**).<sup>4</sup>

Bakke and co-workers reported in 1994 that pyridine (**1**) could be nitrated by dinitrogenpentoxide in liquid sulfur dioxide to give a 63 % yield of 3-nitropyridine (**24**) (Scheme 3.1).<sup>5</sup> Later this method was modified and the yield was increased to 77 %.<sup>6</sup> Suzuki showed in 1997 that the dinitrogen pentoxide could be generated *in situ*.<sup>7</sup>



Scheme 3.1. Nitration of pyridine (**1**) by  $N_2O_5$  and  $SO_2$  or  $NaHSO_3$  in water.

3-Nitropyridines can also be synthesized by oxidation of 3-aminopyridine (**31**) with hydrogen peroxide in fuming sulphuric acid in 45 % yield.<sup>8</sup> Nitration of 2,6-dichloropyridine (**32**) with nitronium tetrafluoroborate gave a 11 % yield of 3-nitropyridine (**24**) after dehalogenation.<sup>9</sup> **24** has also been prepared from 2-chloro-3-nitropyridine (**33**).<sup>10</sup>

Electron donating substituents like amino and hydroxy groups facilitate nitration reaction. Electron withdrawing groups deactivate the pyridine ring and makes

nitration even more difficult than for pyridine (**1**). For pyridines with substituents such as acetyl, carbaldehyde, phenyl, carboxylic acid/esters and cyano, Bakke and co-workers were the first to report nitration.<sup>5,6</sup>

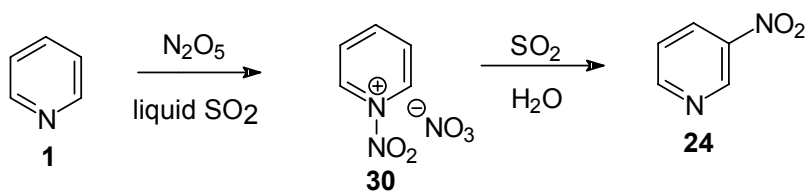
### 3.2. The nitration of pyridines with dinitrogen pentoxide and $\text{SO}_2/\text{HSO}_3^-$

#### 3.2.1. Background for the present project

The metode for nitration of pyridine (**1**) with dinitrogenpentoxide was discovered in Prof. Bakkes group in 1994, by Dr. Ingrid Hegbom. The work was continued by Dr. Eli Raner and Dr. Jaroslav Riha. Both the reaction mechanism and new alternative procedures for the nitration reaction were studied in detail.<sup>5,6</sup>

The author started his work at the end of the projects of Dr Eli Raner and Dr. Jaroslav Riha. The work on the optimalization of the nitration reaction was therefore done in close cooperation with them. The results can not be presented in a complete way without referring to their work, as their results directly influenced the direction of the present project. An overview of the nitration project is therefore needed.

In 1994 Bakke and co-workers reported that pyridine (**1**) and some substituted pyridines could be nitrated by reaction of the pyridine compound with dinitrogen pentoxide (DNP) in liquid sulfur dioxide.<sup>5</sup> The sulfur dioxide mixture was poured over ice water and stirred at room temperature for some hours. Mechanical studies showed that this was not an electrophilic aromatic substitution.<sup>6</sup> It was discovered that the pyridine (**1**) reacted with DNP to form *N*-nitropyridinium nitrate (**30**), and that sulfur dioxide was essential in the next step where the nitro groupe migrated to give 3-nitropyridine (**24**) (Scheme 3.2.).

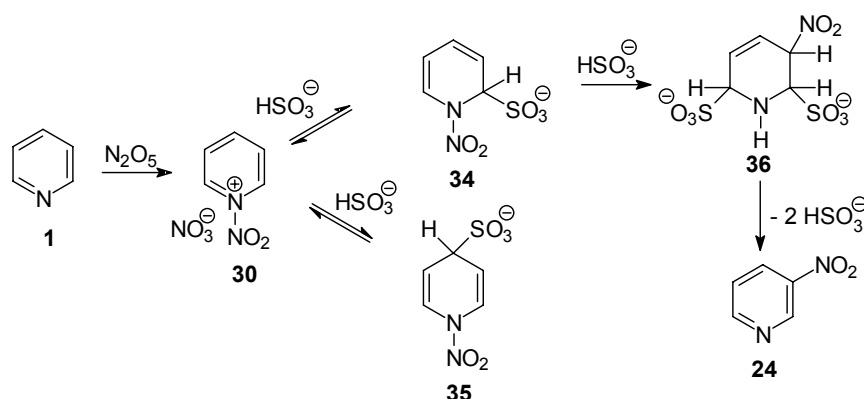


Scheme 3.2. Nitration of pyridine (**1**) with dinitrogen pentoxide in liquid sulfur dioxide/water.

Sulfur dioxide was found to act as nucleophile, which attacked in either 2- or 4-position of the *N*-nitropyridinium nitrate (**30**), followed by a migration of the nitro group.

Other nucleophiles were tried and a new procedure without use of liquid sulfur dioxide was developed. In this procedure pyridine and DNP was reacted in an organic solvent, such as nitromethane or dichloromethane, to form **30**. This reaction mixture was poured into a aqueous solution of sodium bisulfite, which after some hours of stirring yielded 3-nitropyridine (**24**).

The nitration was found to go by the mechanistical path described in Scheme 3.3. For a more detailed discussion of the mechanism see chapter 4.



Scheme 3.3. Reaction mechanism for nitration of pyridine (1).

### 3.2.2. Results and discussion

When this work started three different procedures for the nitration had been reported.<sup>5,6</sup> Pyridine (**1**) was either reacted with dinitrogen pentoxide (DNP) in liquid sulfur dioxide and the reaction mixture poured into water before work-up (Procedure A), reacted with DNP in a mixture of liquid sulfur dioxide and an organic solvent and then poured into water (Procedure B) or reacted with DNP in an organic solvent and poured into water containing a nucleophile (HSO<sub>3</sub><sup>-</sup>) (Procedure C).

Dr. Eli Ranes showed in her dr. thesis<sup>11</sup> that the yields from procedure C could be improved by adjusting the pH in the aqueous bisulfite solution (Procedure D). The yield of 3-nitropyridine (**24**) was risen from 68 to 77 %, the yield of 4-acetyl-3-

nitropyridine (**37**) was raised from 50 to 67 %. The author of this thesis simultaneously worked with other methods for improving the yields.

Procedure C and D gave good yields for some substrates, but 4-substituted pyridines in many cases gave lower yields by procedure C and D compared to procedure A. Further investigations were made in order to improve the yields when the *N*-nitro pyridinium nitrates were reacted in aqueous bisulfite solutions.

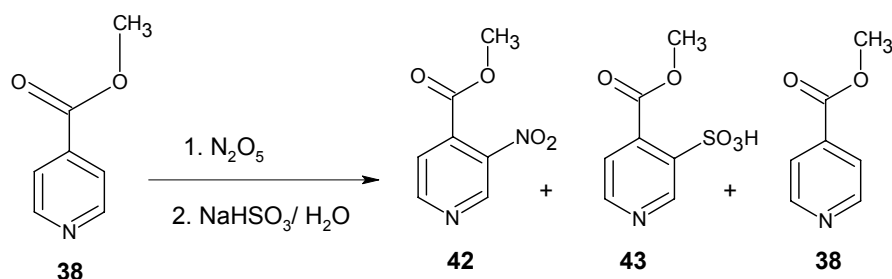
Methyl isonicotinate (**38**) was used as a test substrate. The ester group is an electron withdrawing substituent, and this substrate had not been investigated before. Pyridines with other electron withdrawing functional groups such as carboxylic acid and nitrile had earlier been nitrated in only 15-35% yield by methods C and D. Methyl 3-nitroisonicotinate (**42**) was also an interesting starting material for further transformation reactions, like Hoffmann and Curtius rearrangements.

To further improve the yield the following parameters were studied:

1. The effect of concentration of the nucleophile
2. The effect of the reaction medium
3. The effect of the temperature

### The effect of concentration of nucleophile

In procedure C the products from the nitration of methyl isonicotinate reaction were the methyl 3-nitroisonicotinate (**42**), unreacted methyl isonicotinate (**38**) and the by-product 3-pyridinesulfonic acid (**43**) (Scheme 3.4.). The mechanism of the formation of this by-product is not known but the bisulfite ion is probably involved.



Scheme 3.4. Products from nitration of substituted pyridines

The effect of changes in the bisulfite ion concentration in the aqueous solution was studied. The nitration of methyl isonicotinate (**38**) was used as a test reaction. The nitration was done by 6 and 3 equivalents of sodium bisulfite. The isolated

yield of methyl 3-nitroisonicotinate (**52**) was respectively 38 and 55 % (Table 3.1.). The amount of recovered starting material was about the same, so the increase in yield of nitrated product was caused by an decrease of the 3-pyridinesulfonic acid (**43**). A further reduction of the bisulfite concentration to 1.5 equivalents resulted in a yield of nitrated product **42** of about 25 % (yield from <sup>1</sup>H-NMR of reaction mixture). The main component in the product mixture from this reaction was unreacted starting material. These experiments showed that the concentration of bisulfite in the aqueous phase is very important. A too high concentration leads to formation of the biproduct **43**, and to low a concentration increase the amount of unreacted starting material. Three equivalents of sodium bisulfite seemed to be a good compromise.

*Table 3.1 Yield of 4-methoxycarbonyl-3-nitropyridine (**42**) from nitration of methyl isonicotinate (**38**) with different amounts of sodium bisulfite in the aqueous phase.*

Eqv. NaHSO <sub>3</sub>	Yield (%)
6	38
3	55
1.5	~25

### The effect of the reaction medium

Before the present investigation all reactions of *N*-nitropyridinium nitrates (**44**) with a nucleophile had been performed in an aqueous solution. It was therefore interesting to investigate the effect upon changing the polarity of the reaction mixture. The range of possible solvents was limited by solubility of sodium bisulfite. A methanol/ water system was therefore chosen.

The reaction rate of the intermediates in the nitration reaction has been found by Dr. Eli Raner to be independent of the polarity of the reaction media.<sup>11</sup> The rate of the reaction giving the nitropyridine was therefore not expected to be significantly affected by the change in polarity, but the rate of formation of the main by-product, the pyridinesulfonic acid, could be affected.

Methyl 3-nitroisonicotinate (**38**) was nitrated with an increasing proportion of methanol in the bisulfite solution. The results are shown in Table 3.2.

Table 3.2 Yield of methyl 3-nitroisonicotinate (**42**) from nitration with different proportions of methanol in a H<sub>2</sub>O/MeOH solution

% MeOH	Yield (%)
0	61
25	68
50	74
75	75

The results showed an increase of the yield of nitrated product when increasing proportions of methanol were used. From <sup>1</sup>H-NMR spectroscopy of the reaction mixture, only traces of the 3-pyridinesulfonic acid (**43**) was found in the reaction mixtures with 75% methanol (Figure 3.2.), in the reaction in 100% water some 3-pyridinesulfonic acid was (**43**) observed (Figure 3.1.) This indicated that the higher yield in methanol/water solutions than in a water solution could be explained by that less of the intermediates react to the **43**.

Another effect of using methanol/water as solvent is that the reaction mixture becomes more homogenous, giving one phase instead of a two phase system of water and nitromethane (or dichloromethane).

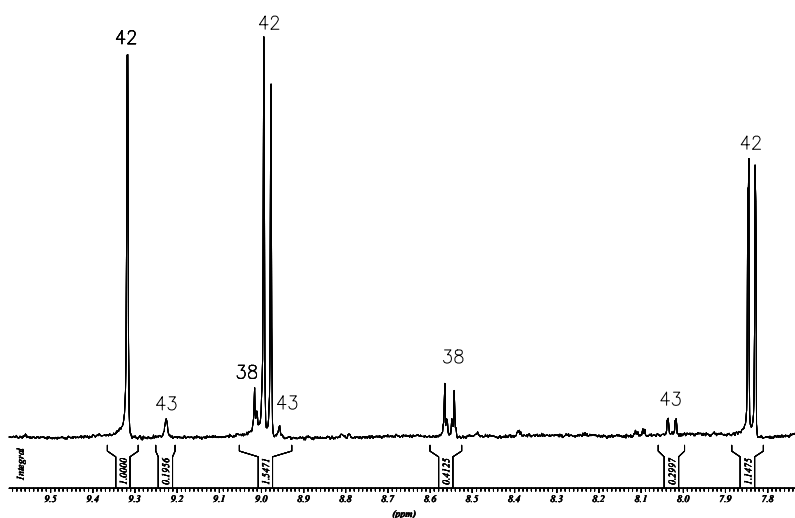


Figure 3.1. <sup>1</sup>H-NMR specter of a reaction mixture from nitration of methyl isonicotinate with N<sub>2</sub>O<sub>5</sub> and NaHSO<sub>3</sub> in water. Methyl 3-nitroisonicotinate (**42**): Methyl 3-sulfonicacid isonicotinate (**43**), unreacted methyl isonicotinate (**38**).

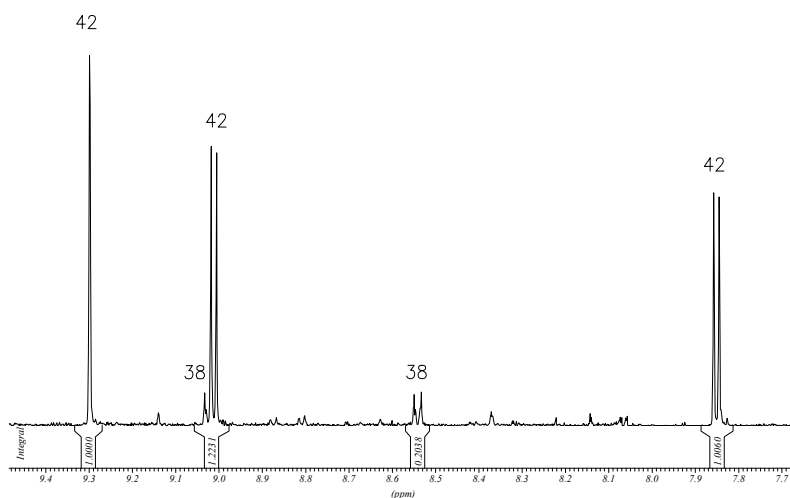


Figure 3.2.  $^1\text{H}$ -NMR spectrum of a reaction mixture from nitration of methyl isonicotinate with  $\text{N}_2\text{O}_5$  and  $\text{NaHSO}_3$  in 75% methanol in water. Methyl 3-nitroisonicotinate (**42**), unreacted methyl isonicotinate (**38**)

The method with use of 3 equivalents of bisulfite in a solution of 75% methanol in water was named procedure E. This procedure was tried on several substituted pyridines.

Table 3.3. shows the results from nitration of pyridine (**1**) and substituted pyridines by the different procedures developed in Prof. Bakke's group. The results in the table is the collective work of the group. Procedure E was developed by the author, but this method has later been used on several substrates by other members of the group. Some of the pyridine substrates have been nitrated by several persons using the same method, in these cases the author have reported his own results. The numbers in bold are nitrations performed by the author of this thesis.

Table 3.3. Results from nitration of pyridine (**1**) and substituted pyridines, by different methods. Yields in bold are nitration done by the author.

Product	A (%)	C (%)	D (%)	E (%)
3-Nitropyridine ( <b>24</b> )	63	68	77	77
2-Methyl-5-nitropyridine ( <b>45</b> )	42	19	36	36
3-Methyl-5-nitropyridine ( <b>46</b> )	<b>26</b>	5	24	20
3-Acetyl-5-nitropyridine ( <b>47</b> )	33		18	
3-Chloro-5-nitropyridine ( <b>48</b> )	15		11	
4-Methyl-3-nitropyridine ( <b>49</b> )	<b>54</b>	24	33	39
4-Acetyl-3-nitropyridine ( <b>37</b> )	<b>75</b>	<b>56</b>	67	<b>58</b>
4-Benzoyl-3-nitropyridine ( <b>50</b> )	74			
3-Nitropyridine-4-carboxylic acid ( <b>51</b> )	<b>60</b>	36	15	<b>48</b>
Methyl 3-nitroisonicotinate ( <b>42</b> )		<b>55</b>		<b>75</b>
3-Nitropyridine-4-carboxamide ( <b>52</b> )	50			
3-Nitro-4-pyridinecarbaldehyde <sup>A</sup> ( <b>53</b> )		35		
4-Cyano-3-nitropyridine ( <b>54</b> )	<b>33</b>		26	45
4-Phenyl-3-nitropyridine ( <b>55</b> )	37		<b>69</b>	
5-Phenyl-3-nitropyridine ( <b>56</b> )			<b>23</b>	
2,3-Dimethyl-5-nitropyridine ( <b>57</b> )	46	14		37
2,4-Dimethyl-5-nitropyridine ( <b>58</b> )	66	45		64
3,4-Dimethyl-5-nitropyridine ( <b>59</b> )	58	14		20
3-Nitroquinoline ( <b>60</b> )	16	7	10	
4-Nitroisoquinoline ( <b>61</b> )	<b>32</b>	<b>35</b>	32	<b>42</b>

A) Protected as the dioxolane

Table 3.3 shows that procedure E gave higher yields than procedure C and D for some substrates. Procedure E was better for pyridine-4-carboxylic acid (**62**), isoquinoline (**63**), methyl isonicotinate (**38**), 4-cyanopyridine (**64**), 4-methylpyridine (**65**), 2,3-dimethylpyridine (**66**), 2,4-dimethylpyridine (**67**) and 3,4-dimethylpyridine (**68**). Procedure A gave in general better yields than procedure E exceptions are pyridine (**1**), 4-cyanopyridine (**64**) and isoquinoline (**63**). Procedure E is simple and do not require use of liquid sulfur (procedure A) dioxide or adjustment of pH (procedure D). Procedure E may therefore be the methode of choice in many cases.



### The effect of the temperature

The use of methanol-water solutions made it possible to run the reaction at low temperature. The possibility that the rate of formation of 3-pyridinesulfonic acid (**41**) was influenced by the temperature could then be checked.

methyl isonicotinate (**38**) was reacted with sodium bisulfite in a methanol/water (3:1) solution at three different temperatures: 25, 5 and -20 °C. The reactions were stopped after 68 hours, and the yields of **42** (from GC with internal standard) were respectively 75, 58 and 40 %. NMR analysis of samples taken from the reaction mixture before work-up showed that the reactions performed at 5 and -20 °C were not finished after 68 hours, the reaction intermediates could still be seen in the <sup>1</sup>H-NMR spectrum. This explained the lower yield in these experiments compared with the reaction at 25 °C. A new experiment at -20 °C was therefore performed. This experiment showed that even after 6 days the reaction was not completed. It was therefore concluded that low temperature did not seem to give any improvement in the yield, and even if the yield could be improved the very long reaction time would make the reaction unpractical.

### 3.3. Conclusion

The effects of different parameters in the nitration of pyridines with N<sub>2</sub>O<sub>5</sub> and then sodium bisulfite were investigated to optimize the yields.

The number of equivalents of sodium bisulfite was found to be important in the nitration reaction. Too many equivalents gave more of the sulfonic acid by-product (**41**), to few equivalents gave low conversion.

The effect upon changes in polarity of the reaction media were investigated. When the reaction was performed in a 3:1 methanol/water solution instead of only water the yield of methyl 3-nitroisonicotinate (**42**) was increased.

When the reaction was performed at low temperatures no significant improvement was observed, and the reaction time became unpractical long, more than 6 days.

From the results obtained, a new procedure for nitration of pyridine (**1**) and substituted pyridines was developed. In this new procedure named E, the *N*-nitropyridinium nitrate (**44**) was poured into a solution of methanol/water (3:1) containing three equivalents sodium bisulfite. This reaction was performed at room temperature.

Procedure E can for many of the substrates compete well with previous presented procedures for nitration in aqueous sodium bisulfite solutions. This procedure do not require pH adjustments of the water phase and is therefore simple to perform.

### 3.4. References.

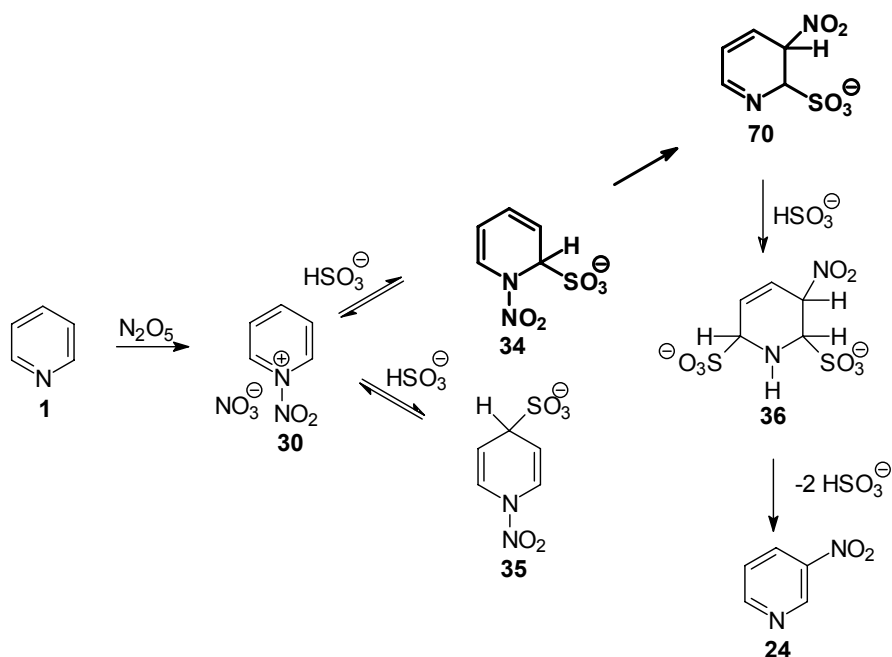
1. H. J. den Hertog and J. Overhoff, *Recl. Trav. Chim. Pays-Bas*, **49**, 552 (1930).
2. P. Schorigin and A. Toptschiew, *Ber.*, **69**, 1874 (1936).
3. G. Hetherington and P. L. Robinson, *J. Chem. Soc.*, 3512 (1954).
4. H. Suzuki, I. Kozai and T. Murashima, *J. Chem. Res. (S)*, 156 (1993).
5. J. M. Bakke and I. Hegbom, *Acta Chem. Scand.*, **48**, 181 (1994); J. M. Bakke, I. Hegbom, E. Øvreeide and K. Aaby, *Acta Chem. Scand.*, **48**, 1001, (1994).
6. J. M. Bakke and I. Hegbom, *J. Chem. Soc., Perkin Trans. 2*, 1211, (1995); B. Arnestad, J. M. Bakke, I. Hegbom and E. Ranes, *Acta Chem Scand.*, **50**, 556 (1996); J. M. Bakke and E. Ranes, *J. Chem. Soc., Perkin Trans 2*, 1919 (1997); J. M. Bakke and E. Ranes, *Synthesis*, 281 (1997).
7. H. Suzuki, M. Iwaya and T. Mori, *Tetrahedron lett.*, **38**, 5647 (1997).
8. K. E. Taylor and J. B. Jones, *J. Am. Chem. Soc.*, **98**, 5689 (1976).
9. J. L. Duffy and K. K. Laali, *J. Org. Chem.*, **56**, 3006 (1991).
10. G. B. Barlin, *Org. Prep. Proc. int.*, **4**, 63 (1973).
11. E. Ranes, *Nitration of pyridine compounds*, Dr. ing. thesis, NTNU, Trondheim 1998.

## 4. The reaction mechanism of the nitration of pyridine

### 4.1. Previous investigations

#### 4.1.1. Reaction outline

The reaction mechanism for the nitration of pyridines with dinitrogen pentoxide, has been studied in great detail by several members of Prof. Bakke's group, and several papers have been published.<sup>1,2,3,4,5</sup> Most of the mechanistic studies were done by Dr. Eli Raner and Dr. Jaroslav Riha and are described in their Dr. theses.<sup>6,7</sup> The mechanism is complicated, and it is not a normal electrophilic aromatic substitution reaction.<sup>4</sup> The reaction was found to proceed as described in Scheme 4.1.



*Scheme 4.1. Proposed mechanism for the nitration of pyridine with dinitrogen pentoxide. The step in bold shows the step investigated by the author.*

Pyridine (**1**) reacts with dinitrogen pentoxide (DNP) in an organic solvent to give N-nitropyridinium nitrate (**30**). On reaction of **30** with an aqueous solution of SO<sub>2</sub>/xH<sub>2</sub>O-HSO<sub>3</sub><sup>-</sup>, 1,2-dihydropyridine (**34**) and 1,4-dihydropyridine (**35**) compounds were formed. **34** reacted rapidly, via **70** (not observed by NMR), to give the tetrahydropyridine derivative (**36**), which gives 3-nitropyridine (**24**) on

further reaction. The decrease in the concentration of **35** was followed by an increase in the concentration of 3-nitropyridine (**24**). Originally it was not known whether **35** reacted directly to **24**, or was in an equilibrium with **30** and reacted through intermediate **34** to give **24**. Dr. Jaroslav Riha later showed that **35** was in an equilibrium with **30**, which again was in equilibrium with **34**.<sup>5</sup>

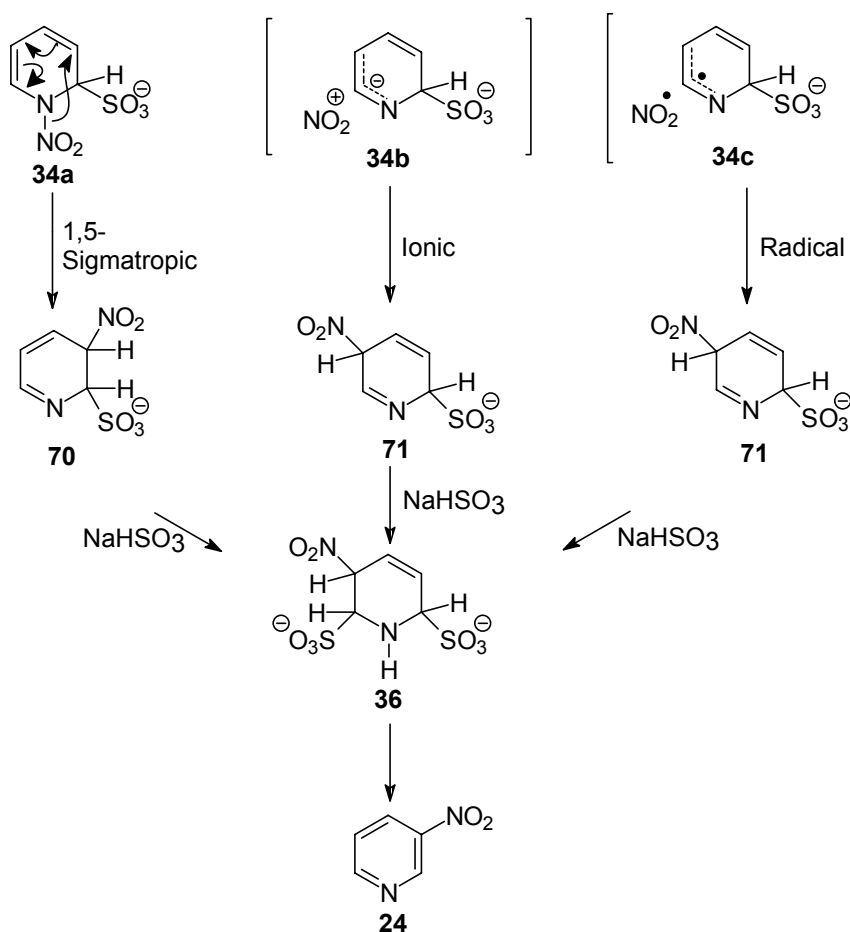
The reaction step in bold shows the step where the nitro group migrates from the ring nitrogen to the  $\beta$ -position. The mechanism for this step was not known. In this project the goal was to find the correct mechanism for the migration.

#### 4.1.2. The migration of the nitro group

The migration of the nitro group could take place either as a concerted reaction by a [1,5]-sigmatropic shift, by migration in a solvent cage of a nitronium ion (**34b**) or by migration of a nitrogen dioxide radical (**34c**) formed by a heterolytic cleavage of the N-N bond. The three different routes are shown in Scheme 4.2.

Dr. Eli Ranes found that the ionic mechanism could be excluded because a change in the ionic strength of the reaction medium did not change the reaction rate of the 1,2-dihydropyridine intermediate (**34**).<sup>6</sup>

Kinetic results from the reaction of the 1,2-dihydropyridine intermediate (**34**), obtained by dr. Eli Ranes, also pointed toward a concerted mechanism. But the reaction by a radical pair with a homolytic cleavage of the N-NO<sub>2</sub> bond could not be ruled out.<sup>6</sup>



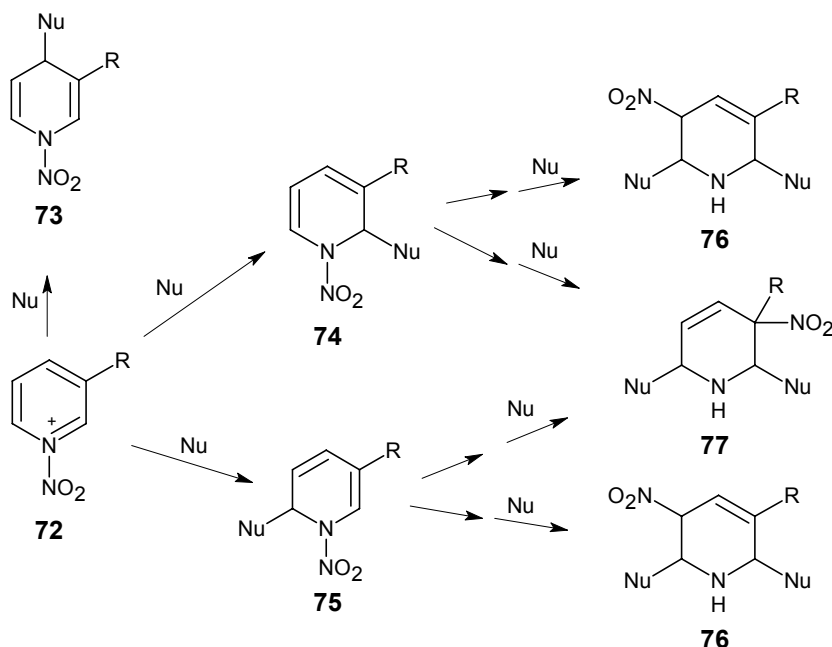
*Scheme 4.2. Possible pathways for the nitro group migration from 1 to 3 position in the reaction intermediates.*

A fourth possible mechanism where the nitro group migrated via the nucleophile in 2-position could be ruled out due to the fact that two stereoisomers (cis and trans) of the 1,4-tetrahydrointermediate (**36**) were observed at low temperature by Dr. Eli Ranes.<sup>6</sup> A mechanism with migration via the nucleophile in 2-position would give only one stereoisomer.

## 4.2. Result and discussion

### 4.2.1. NMR studies of nitration of 3-substituted pyridines

With 3-substituted pyridines, an attack of the nucleophile in either 2- or 6-position gives two different isomers (**74** and **75**). This is in contrast to pyridine itself and 4-substituted pyridines, which give only one isomer, either the nucleophile attacks at the 2- or the 6-position. This gives rise to two different possible intermediates (**76** and **77**) as shown in Scheme 4.3. These different intermediates made it possible to study the regioselectivity of the nitro group migration. A regioselective migration would point toward a 1,5-sigmatropic shift, and low or no regioselectivity would indicate a radical pair mechanism.



*Scheme 4.3. Possible intermediates in nitration of 3-substituted pyridines with dinitropentoxide.*

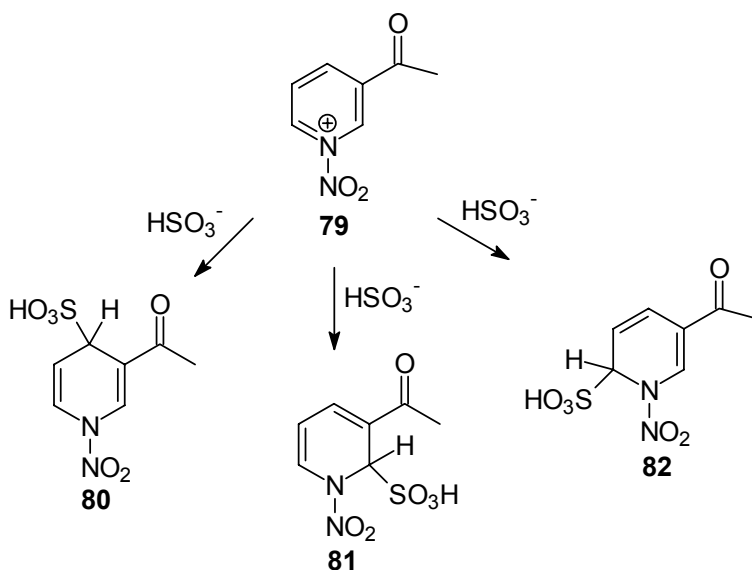
The intermediates formed when 3-substituted pyridines were nitrated with dinitrogen pentoxide and further reacted by sodium bisulfite were therefore studied by low temperature NMR spectroscopy. Low temperature was needed in order to slow down the reaction rate, so that the lifetime of the intermediates would be long enough to obtain good NMR spectra.

3-Acetylpyridine (**78**) and 3-methylpyridine (**87**) were chosen as substrates for this study. They were the 3-substituted pyridines which had been nitrated with best yields. Since the acetyl group is an electron-withdrawing group, and the methyl group a electron-donating group, this would give an indication of whether the electron-donating or withdrawing effect influenced the selectivity and the reaction rate.

#### 4.2.2. Intermediates in nitration of 3-acetylpyridine (**78**)

The nitration reaction for 3-acetylpyridine (**78**) was performed in an NMR tube, using a 1:1 mixture of deuterated water and deuterated methanol as solvent. The tube was inserted into the NMR probe cooled to  $-30\text{ }^{\circ}\text{C}$ . At this temperature the reaction rate was so low that the intermediates could be identified by  $^1\text{H}$  NMR, as well as,  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$ -correlation NMR spectroscopy.

Reaction of the 3-acetyl-*N*-nitropyridinium nitrate (**79**) with the nucleophile gave the three intermediates **80**, **81** and **82** as shown in Scheme 4.4. in a 0.4 : 1.0 : 0.15 ratio. Intermediate **81** and **82** reacted rapidly with similar first order rate constant ( $\sim 4 \times 10^{-4} \text{ s}^{-1}$  at  $0\text{ }^{\circ}\text{C}$ ). The concentration of **80** was relatively constant, but with a slow decrease during the reaction.



Scheme 4.4. Intermediates from the reaction of 3-acetyl-*N*-nitropyridinium nitrate (**79**) with sodium bisulfite.

In Figure 4.1. the variation of concentration of the different intermediates with time are shown. The temperature was  $-30^{\circ}\text{C}$  during the first 55 minutes,  $0^{\circ}\text{C}$  for the next 180 minutes and then  $+7^{\circ}\text{C}$ .

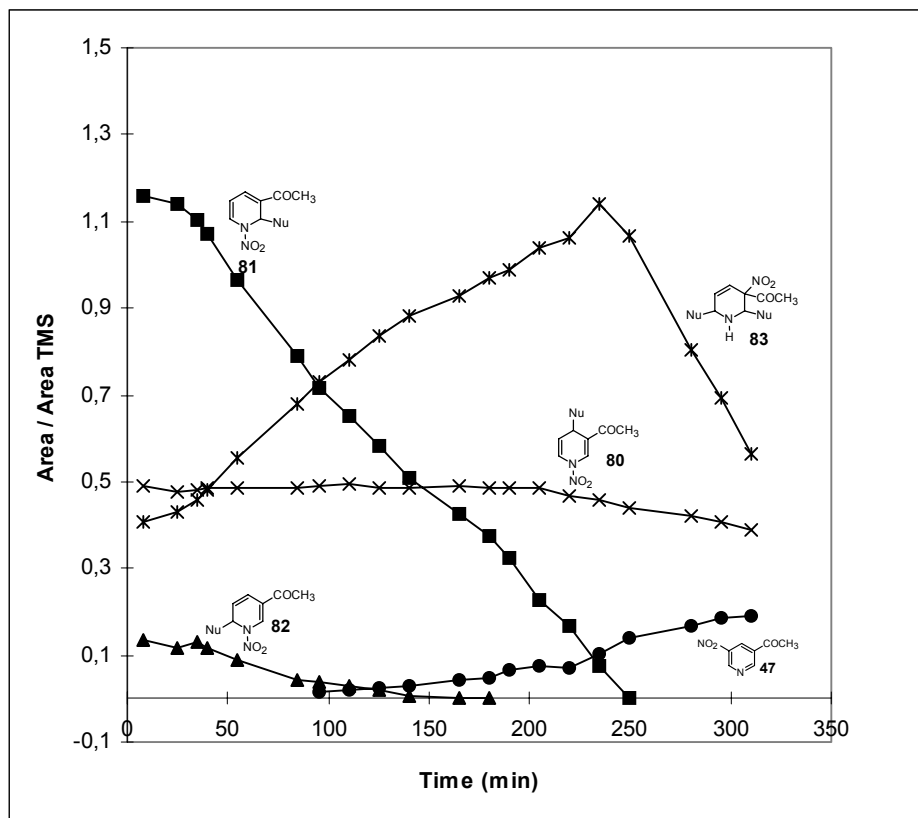


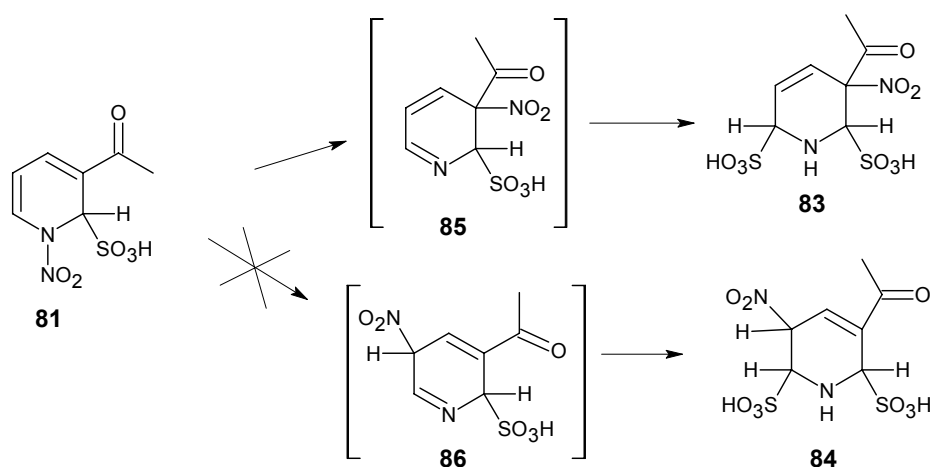
Figure 4.1. Variation of concentration of the different intermediates with time. The temperature was  $-30^{\circ}\text{C}$  the first 55 minutes,  $0^{\circ}\text{C}$  the next 180 minutes and then  $+7^{\circ}\text{C}$ .

Intermediate **82** was only observed at a low concentration, and it was therefore not possible to have a certain identification of the product of its reaction. However as the concentration of **82** decreased, an approximate equivalent increase in concentration of 5-acetyl-3-nitropyridine (**47**) was observed. This could suggest that **82** via its tetrahydropyridine intermediate (**86**) (not observed) reacted to **47**.

The decrease in concentration of **81** was accompanied by an increase in the concentration of intermediate **83**. The migration of the nitro group from the *N*- to



the  $\beta$ -position is therefore regioselective. Intermediate **81** reacts via **85** to **83** and not to **84** via **86** (Scheme 4.5.)



Scheme 4.5. Reaction pathway for the migration of the nitro group in intermediate **81** to intermediate **83**.

In order to distinguish between intermediate **83** and **84** (Figure 4.2.),  $^1\text{H}$ - $^{13}\text{C}$  correlation NMR spectroscopy was used. In intermediate **83** proton 4 and 5 are both bonded to  $sp^2$  hybridized carbons, compared to **84** where proton 5 is bonded to an  $sp^3$  hybridized carbon. From  $^1\text{H}$ - $^{13}\text{C}$ -correlation NMR spectroscopy one found that proton 4 and 5 were bonded to carbons at respectively 131 and 123 ppm, typical shifts for  $sp^2$  hybridized carbons. Together with the other NMR results one could therefore conclude that **83** was the intermediate observed.

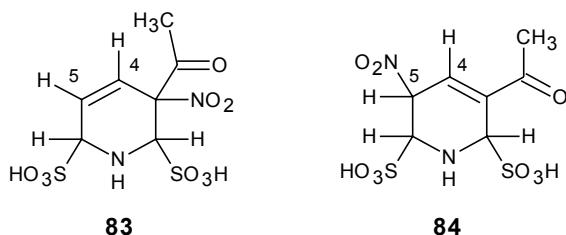
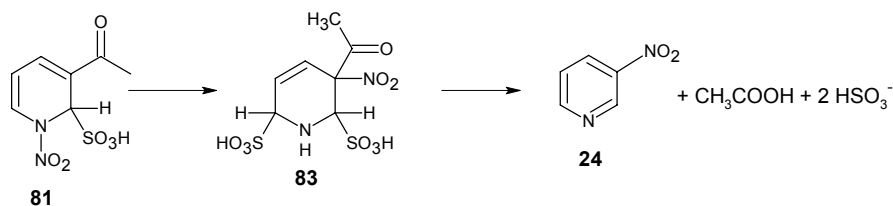


Figure 4.2. Possible tetrahydro intermediates in nitration of 3-acetylpyridine (**78**)

In the nitration of 3-acetylpyridine (**78**), 3-nitropyridine (**24**) was observed as a by-product, when the NMR tube was left at room temperature overnight. 3-nitropyridine (**24**) was probably formed from intermediate **83**, which by loss of acetic acid and bisulfite gave **24** (Scheme 4.6.).



Scheme 4.6. Possible reaction path for the formation of 3-nitropyridine (**24**) in the nitration of 3-acetylpyridine (**78**).

#### 4.2.3. Intermediates in nitration of 3-methylpyridine.

The results from 3-methylpyridine (**87**) were analogous to the those from 3-acetylpyridine (**78**), but the reaction was considerably faster than with **78**. This made it necessary to run the NMR experiments at  $-50$  to  $-55$  °C in order to slow down the reaction so it was possible to study the intermediates.

The 1,2-dihydropyridine intermediate (**88a**) from attack of the nucleophile on the same side as the methyl group, and the 1,4-dihydrointermediate (**88b**) (Figure 4.3.) were the only dihydropyridine intermediates observed and even these reacted fast at  $-55$  °C. Good  $^1\text{H}$  and  $^1\text{H}$ - $^1\text{H}$  correlation spectra were obtained so that the structures could be assigned. The  $^{13}\text{C}$  -  $^{13}\text{H}$  correlation spectra were in accordance with the suggested structures for the intermediates.

The 3-methyl-1,4-tetrahydropyridine intermediate **89** was also identified by  $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  correlation NMR at  $-55$ °C.  $^1\text{H}$ - $^{13}\text{C}$  correlation spectra were in accordance with the suggested structure (Figure 4.3.).

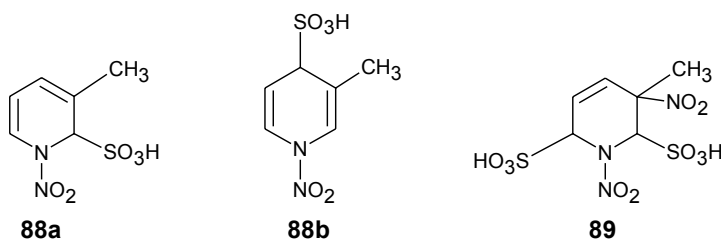
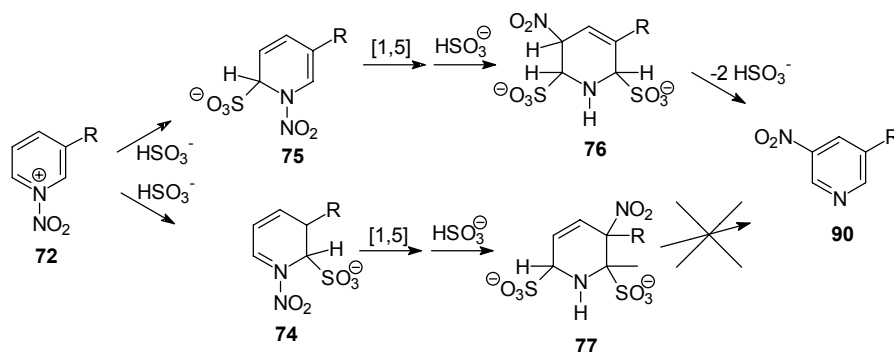


Figure 4.3. Intermediates in the nitration of 3-methylpyridine.

#### 4.2.4. Yields in nitrations of 3-substituted pyridines

Generally nitration of 3-substituted pyridines gives low yields, around 15-35 %. This can be explained from the results obtained from the low temperature NMR spectroscopy studies. The nucleophile attacks at both the 2- and 6-position of the 3-substituted *N*-nitropyridinium nitrate (**72**). This gives two different 1,2-dihydrointermediates (**74** and **75**), which again react selectively to give two different tetrahydro intermediates (**76** and **77**). Only one of them can give the 5-substituted 3-nitropyridine (**90**) (Scheme 4.7.).



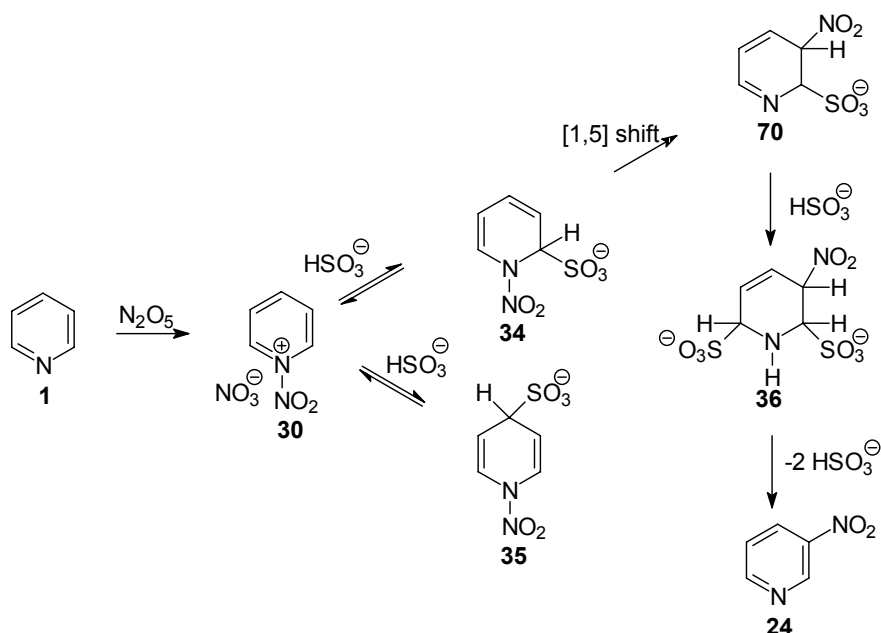
Scheme 4.7. Reaction scheme for the reaction of 3-substituted *N*-nitropyridinium nitrate with sodium bisulfite.

#### 4.2.5. Viscosity of the solvent

White<sup>8</sup> has reported that in the nitramine rearrangement, in which the nitro group is believed to migrate as a radical in a solvent cage, the yield of the reaction was dependent of the viscosity of the solvent. Use of glycerol with high viscosity increased the yield of nitrated product. This was explained by less tendency of the intermediate solvent cage radical to dissociate in the high viscosity solution. If the nitro group in the nitration reaction investigated in this chapter migrated as a radical in a solvent cage, a similar result would be expected. Pyridine (**1**) was therefore nitrated in a water solution and in a 60% glycerol solution in water. The yields (from <sup>1</sup>H-NMR with internal standard) was respectively 66 and 62%. Similarly methyl isonicotinate (**38**) was nitrated in a 75% methanol in water and a 60% glycerol in water solution and the yields was respectively 63 and 57%. These experiments show that increased viscosity did not increase the yield of 3-nitropyridines. These results, therefore did not support the theory that the nitro group migrates as a radical in a solvent cage.

### 4.3. Conclusion

The mechanism for the nitration of pyridine compounds has been investigated, especially the migration of the nitro group was studied. Based on previous investigations by other members of Prof. Bakke's group<sup>1,2,3,4,5,6</sup> and the results presented in this thesis, the mechanism is believed to be as described in Scheme 4.8.



Scheme 4.8. Reaction mechanism for the nitration of pyridine (1) with dinitropyridine and sodium bisulfite.

Pyridine (1) reacts with  $N_2O_5$  to form *N*-nitro pyridinium nitrate (30), which in the aqueous solution is attacked by bisulfite to form either the 1,2-dihydrointermediate (34) or 1,4-dihydrointermediate (35). The 1,4-dihydrointermediate (35) is in an equilibrium with the *N*-nitropyridinium nitrate (30).<sup>5</sup> The 1,2-dihydrointermediate (34) undergoes a [1,5] sigmatropic shift to give 70, which after addition of another bisulfite group forms 36, which by loss of two bisulfite groups yields the nitropyridine (24).

The low yields for 3-substituted pyridines were explained by the proposed mechanism.

#### 4.4. References

1. J. M. Bakke and E. Ranes, *Synthesis*, 281 (1997).
2. J. M. Bakke, I. Hegbom, E. Øvereeide and K. Aaby, *Acta Chem. Scand.*, **48**, 1001 (1994).
3. B. Arnestad, J. M. Bakke, I. Hegbom and E. Ranes, *Acta Chem. Scand.*, **50**, 556 (1996).
4. J. M. Bakke and E. Ranes, *J. Chem. Soc., Perkin Trans. 2*, 1919 (1997).
5. J. M. Bakke and J. Riha, *Acta Chem. Scand.*, **53**, 356 (1999).
6. E. Ranes, *Nitration of pyridine compounds*, Dr. ing. thesis, NTNU, Trondheim, 1998.
7. J. Riha, *Synthesis and Transformation of 3-nitropyridines*, Dr. ing. thesis, NTNU, Trondheim, 2000.
8. W. N. White, H. S. White and A. Fentiman, *J. Org. Chem.*, **41**, 3116 (1976).

The reaction mechanism of the nitration of pyridine

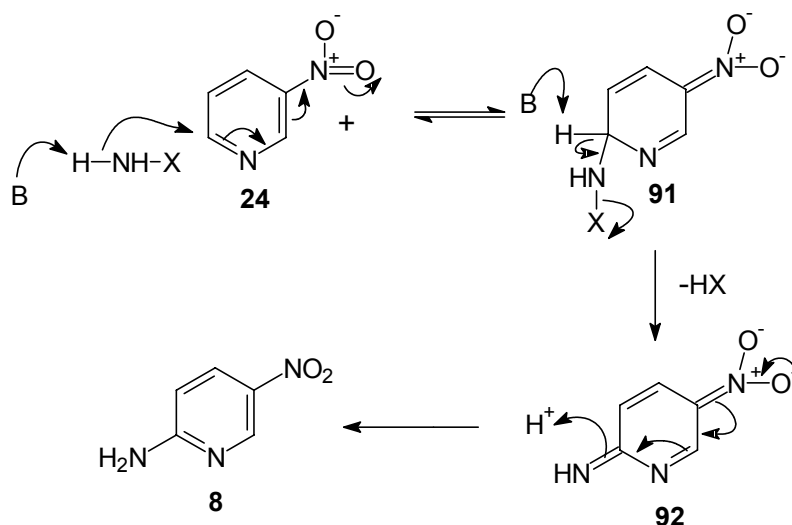
## 5. Selective vicarious nucleophilic amination of 3-nitropyridines

### 5.1. Introduction

#### 5.1.1. Vicarious nucleophilic amination of nitroaromatics

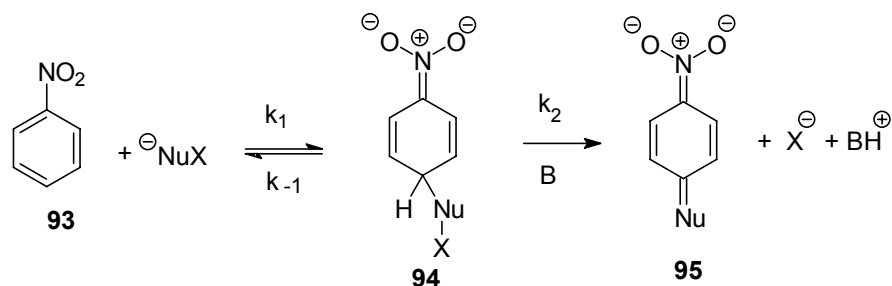
The concept of vicarious nucleophilic substitution of hydrogen in electron deficient arenes was introduced by Makosza in the late 1970s.<sup>1</sup> The concept is that the nucleophile carries a good leaving group (X) at its nucleophilic center. This creates the possibility that the  $\sigma^H$ -adduct can eliminate both the leaving group and the  $sp^3$ -hydrogen to give back the aromatic system.<sup>2</sup>

The example in Scheme 5.1. shows a nitrogen nucleophile, with a leaving group X, reacting with 3-nitropyridine (**24**). 2-amino-5-nitropyridine (**8**) is obtained after a base induced elimination of the  $sp^3$ -hydrogen and X.



Scheme 5.1. Mechanism for the vicarious nucleophilic substitution of hydrogen, where X is a good leaving group.

The kinetics of the vicarious nucleophilic substitution reaction is described in Scheme 5.2. The deprotonation of the nucleophile and protonation of the anionic products are both fast and therefore not kinetically important under the applied conditions.<sup>2</sup>



Scheme 5.2. Reaction scheme for vicarious nucleophilic substitution.

The overall rate for formation of **95** is assumed to be

$$\frac{d[\mathbf{95}]}{dt} = k_{VNS} \cdot [\text{Nu}] \cdot [\mathbf{93}] \quad (5.1)$$

where  $k_{VNS}$  is the observed rate constant.

As described in Scheme 5.2, the reaction can be divided into two steps. The rate of formation of **95** from intermediate **94** can be expressed as:

$$\frac{d[\mathbf{95}]}{dt} = k_2 \cdot [B] \cdot [\mathbf{94}] \quad (5.2)$$

Since it can be assumed that the  $\sigma^H$ -adduct **94** is short lived, the steady-state approximation can be applied, as described in equation 5.3:

$$\frac{d[\mathbf{94}]}{dt} = k_1 \cdot [\text{Nu}] \cdot [\mathbf{93}] - k_{-1} \cdot [\mathbf{94}] - k_2 \cdot [B] \cdot [\mathbf{94}] = 0 \quad (5.3)$$

Rearrangement of equation 5.3 gives the following expression for **[94]**:

$$[\mathbf{94}] = \frac{k_1 \cdot [\text{Nu}] \cdot [\mathbf{93}]}{k_{-1} + k_2 \cdot [B]} \quad (5.4)$$

Equation 5.4 is then inserted into equation 5.2:

$$\frac{d[\mathbf{95}]}{dt} = \frac{k_2 \cdot k_1 \cdot [\text{Nu}] \cdot [\mathbf{93}] \cdot [B]}{k_{-1} + k_2 \cdot [B]} \quad (5.5)$$



This gives the following expression for  $k_{VNS}$ :

$$k_{VNS} = \frac{k_1 \cdot k_2 \cdot [B]}{k_{-1} + k_2 \cdot [B]} \quad (5.6)$$

Equation 5.6 can be simplified under certain conditions to Equation 5.7 and 5.8:<sup>2</sup>

$$k_{VNS} = \frac{k_1}{k_{-1}} \cdot k_2 \cdot [B] \quad \text{when} \quad \frac{k_2 \cdot [B]}{k_{-1}} \ll 1 \quad (5.7)$$

$$k_{VNS} = k_1 \quad \text{when} \quad \frac{k_2 \cdot [B]}{k_{-1}} \gg 1 \quad (5.8)$$

In equation 5.7 the reaction rate is first order in base concentration, and it depends also on the base strength via the value of  $k_2$ . In equation 5.7 the rate is proportional to the equilibrium constant of the addition,  $K^H = k_1/k_{-1}$ . This can be considered as a thermodynamic controlled process.<sup>2</sup> In equation 5.8, the base does not effect the overall rate, and the VNS rate is identical with the rate of formation of  $\sigma^H$ -adduct. This represents kinetic control in the reaction.

Nitrogen nucleophiles are relatively weak nucleophiles compared to carbanion nucleophiles, and normally have high  $k_{-1}$  values. One would therefore normally have the situation described in equation 5.2. for nitrogen nucleophiles, a thermodynamic controlled system, favouring the product having the most thermodynamic stable  $\sigma^H$ -adduct. For nitroarenes this normally is *para* to the nitro group.

Vicarious nucleophilic substitutions with nitrogen nucleophiles have proved to be a useful tool for direct amination of nitroarenes.<sup>3B</sup> Reagents used are hydroxylamine (**96**), 4-amino-1,2,4-triazole (**97**), 4-alkylamino-1,2,4-triazoles (**98**) and sulfenamides (**99**) (Figure 5.1.).

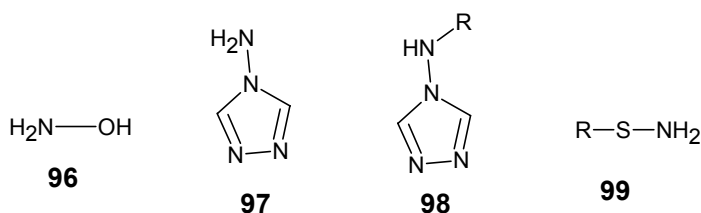
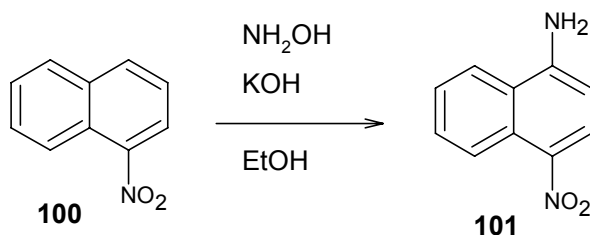


Figure 5.1. Reagents used in vicarious nucleophilic amination of nitroarenes: hydroxylamine (**96**), 4-amino-1,2,4-triazole (**97**) and 4-alkylamino-1,2,4-triazoles (**98**) and sulfenamides (**99**).

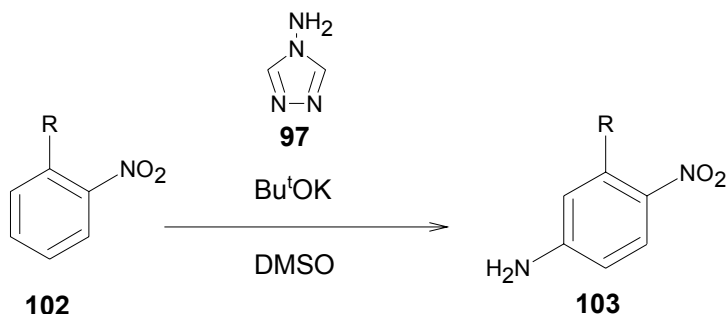
With use of hydroxylamine (**96**) the hydroxy anion is the leaving group together with the  $sp^3$ -proton. Price and Voong aminated 1-nitronaphthalene (**100**) with **96** to give 4-nitro-1-naphthylamine (**101**) in 55-60% yield (Scheme 5.3.).<sup>11</sup>



Scheme 5.3. Amination of nitronaphthalene (**100**) with hydroxylamine (**96**)

For 4-amino- or alkylamino-1,2,4-triazole (**97**, **98**) the aromatization is facilitated by the elimination of the 1,2,4-triazole ring. It has been reported that amination of nitrobenzenes is regioselective when 4-amino-1,2,4-triazole is used, giving exclusively the *para*-isomer.<sup>4,5</sup>

Katritzky and Lorenzo aminated substituted nitrobenzenes (**102**) in good yield with 4-amino-1,2,4-triazole (**97**) as aminating agent (Scheme 5.4.).<sup>4,5</sup>



Scheme 5.4. Amination of substituted nitrobenzenes (**102**) with 4-amino-1,2,4-triazole (**97**).

Sulfenamides ( $\text{RSNH}_2$ ) (**99**) have also been proved to be effective in amination of nitroarenes.<sup>6</sup> These reagents are stable if they have electron-withdrawing substituents at the nitrogen atom. The reaction is not as selective as with 4-amino-1,2,4-triazole (**97**).<sup>6</sup>

### 5.1.2. Amination of 3-nitropyridines

2-Amino-5-nitropyridines have previously been synthesized by oxidative amination of nitropyridines in liquid ammonia,<sup>7</sup> and by nitration of aminopyridines. The nitramines formed were rearranged to amino-nitropyridines.<sup>8</sup> The disadvantage with both of these methods is the mixtures of isomers obtained, which have to be separated.

Hydroxy, methoxy and halogens can be exchanged by an amine. Therefore, if the *para* hydroxy, methoxy or halogen substituted 3-nitropyridine are available, one can produce the corresponding 2-amino-5-nitropyridine.

Seko and Miyake have reported the amination of a few 2- and 6-substituted 3-nitropyridines by use of *O*-methylhydroxylamine (**104**) as the aminating agent.<sup>9</sup> However, 3-nitropyridine (**24**) and 4- or 5-substituted 3-nitropyridines were not aminated by this method. The 6-substituted 3-nitropyridines were aminated mainly in the 2-position, and the 2-substituted 3-nitropyridines mainly in the 6-position.

Makosza and Bialecki aminated some nitropyridines by sulfenamides (**99**). Amination of 4-ethoxy-3-nitropyridine (**105**) gave 2-amino-4-ethoxy-5-nitropyridine (**106**) in 75% yield and amination of 6-methoxy-3-nitropyridine (**107**) gave 2-amino-3-nitro-6-methoxypyridine (**108**) in 42% yield.<sup>10</sup>

## 5.2. Results and discussion

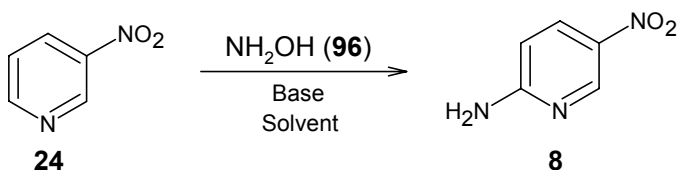
As shown in Chapter 5.1.2., there are three main reagents for amination of nitroarenes: hydroxylamine (**96**), 4-amino-1,2,4-triazoles (**97** and **98**) and sulfenamides (**99**). **96** and **97** have not previously been used on 4- or 5-substituted 3-nitropyridines. Some sulfenamides (**99**) have earlier been used on 4-ethoxy-3-nitropyridine (**105**) in good yield.

**96** and **97** are both commercial available, but **99** have to be prepared from the respective thiolates with ammonia and sodium hypochlorite.<sup>6</sup> Therefore it was practical to do the vicarious nucleophilic amination using first hydroxylamine (**96**) and then 4-amino-1,2,4-triazole (**97**) as aminating agents.

The procedures for amination by **96** and **97** were first optimized for 3-nitropyridine (**24**). This compound was available in a multigram scale in our laboratories, from large scale nitration experiments. The procedures found to give the best yields for amination of 3-nitropyridine (**24**) were then used on eight substituted 3-nitropyridines and 4-nitroisoquinoline (**61**). The amination of the different substituted 3-nitropyridines were not optimized for each substrate.

For experimental details see Chapter 9, where the procedures, melting points and spectroscopical data for all products are given.

### 5.2.1. Amination of 3-nitropyridine with hydroxylamine



*Scheme 5.5. Amination of 3-nitropyridine (**24**) with hydroxylamine (**96**).*

3-Nitropyridine (**24**) was reacted with hydroxylamine (**96**) as described by Price and Voong.<sup>11</sup> Ethanol was used as solvent and potassium hydroxide as base. The reaction mixture was heated at 50 °C for 2 hours. 2-Amino-5-nitropyridine (**8**) was isolated in a 28 % yield (Entry 1, Table 5.1) as the only product in the organic phase after extraction. This selectivity is in contrast to the poor selectivity in the oxidative amination of **24** in liquid ammonia/KMnO<sub>4</sub>.<sup>19</sup>

Table 5.1 Results from amination of 3-nitropyridine (**24**) with hydroxylamine (**96**)

	Solvent	Base	Ekv. Base	Ekv. NH <sub>2</sub> OH	Catalyst	Temp. (°C)	Rx. time (h)	Isolated yield (%)
1	EtOH	KOH	5	3	-	50	2	28 <sup>a</sup>
2	EtOH	KOH	5	3	-	50	2	42 <sup>b</sup>
3	EtOH	KOH	5	3	-	50	2	45 <sup>c</sup>
4	EtOH	KOH	1	3	-	50	2	mixture
5	EtOH	KOH	3	3	ZnCl <sub>2</sub>	50	2	51
6	EtOH	KOH	5	3	ZnCl <sub>2</sub>	50	2	52
7	EtOH	KOH	5	3	ZnCl <sub>2</sub>	22	16	54
8	MeOH	Bu <sup>t</sup> OK	4	3	ZnCl <sub>2</sub>	22	16	42
9	H <sub>2</sub> O	KOH	7	3	ZnCl <sub>2</sub>	22	16	26
10	DMSO	Bu <sup>t</sup> OK	2	1,5	ZnCl <sub>2</sub>	0	2	mixture
11	EtOH	KOH	5	3	CuCl <sub>2</sub>	22	16	21

a) KOH added to a solution of hydroxylamine (**96**) and 3-nitropyridine (**24**)

b) Hydroxylamine (**96**) added to a solution of KOH and 3-nitropyridine (**24**)

c) 3-Nitropyridine (**24**) added to a solution of KOH and hydroxylamine (**96**)

Since the yield in the amination was low, further optimization was necessary. In the original procedure the base was added to a stirring solution of the nitroarene and the hydrochloric salt of hydroxylamine. This gives a high concentration of 3-nitropyridine (**24**) compared to the concentration of base, and this could lead to side reactions as inter- and intramolecular oxidations of the  $\sigma^H$ -adduct by **24** (see chapter 5.2.12. for a further discussion of side reactions).

In order to prevent these side reactions, the procedure was changed so that the hydroxylamine (**96**) was added to the solution of base and 3-nitropyridine (**24**). This would ensure that the base concentration was high compared to the concentration of **24**. This new procedure increased the yield to 42% (entry 2, Table 5.1.), again with the same regioselectivity.

To make sure that the concentration of unreacted 3-nitropyridine (**24**) was low compared to concentration of  $\sigma$ -adduct, the procedure was changed so that **24** was added to the solution of base and hydroxylamine (**96**) (entry 3, Table 5.1.).

Now the yield was 45% of 2-amino-5-nitropyridine (**8**). An attempt to reduce the amount of base to 1 equivalent resulted in a mixture of starting compound and product (entry 4, Table 5.1.).

Seko and Miyake used the Lewis acid zinc dichloride as a catalyst in their reactions with *O*-methylhydroxylamine (**104**) and claimed it to be essential for the reaction.<sup>9</sup> A slight increase in the yield was obtained when zinc dichloride was used as a catalyst (entry 3 vs. entries 5, 6 and 7, Table 5.1.)

When the reaction was performed at room temperature instead of 50 °C, the reaction time was increased from 2 to 16 hours, but the yield was essentially the same (entry 6 vs. 7, Table 5.1.)

Since the yield still was only moderate by use of potassium hydroxide in ethanol, some attempts to increase the yield by changing the base or/ and the solvent was done.

Use of a stronger base such as potassium *tert*-butoxide in dry methanol, to give potassium methoxide, resulted in a slightly lowering of the yield to 42 % (entry 8, Table 5.1.).

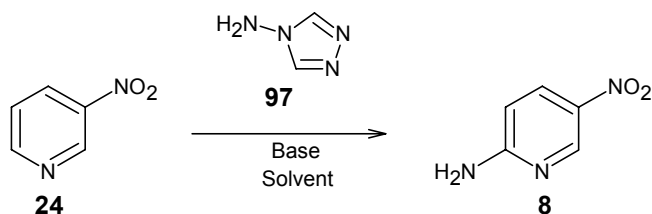
Water was tried as solvent and potassium hydroxide as base, but then only a 26% yield of 2-amino-5-nitropyridine (**8**) was obtained (entry 9, Table 5.1).

Finally when the reaction was done in DMSO and with potassium *tert*-butanol as base a complex mixture of products was obtained.(entry 10, Table 5.1)

Attempts to change the Lewis acid from ZnCl<sub>2</sub> to CuCl<sub>2</sub> gave a yield of only 21 % (entry 11, Table 5.1).

In conclusion, the best yield (54 %) was obtained when 3-nitropyridine (**24**) was added to a stirring solution of hydroxylamine (**96**) and base. Use of ethanol as solvent and potassium hydroxide as base gave the best yield. Stirring at room temperature overnight gave a slightly better yield than heating at 50 °C for 2 hours. These were therefore the conditions used in reactions with other substrates, as described in the following chapters.

The advantage of this procedure was the use of inexpensive and ready available reagents. No inert atmosphere was required, and the pure product was obtained directly by evaporation of the organic phase after extraction, without further purification.

5.2.2. Amination of 3-nitropyridine (**24**) with 4-amino-1,2,4-triazole (**97**)Scheme 5.6. Amination of 3-nitropyridine (**24**) with 4-amino-1,2,4-triazole (**97**).

Katritzky and Laurenco have shown that 4-amino-1,2,4-triazole (**97**) can be used in vicarious nucleophilic amination of substituted nitrobenzenes (**102**).<sup>4,5</sup> We therefore wished to investigate whether this method could be used on 3-nitropyridine (**24**) and other substituted 3-nitropyridines.

3-Nitropyridine (**24**) was aminated with 4-amino-1,2,4-triazole (**97**) (Scheme 5.6.). First the original procedure by Katritzky was used and then different bases and solvents were tried. The results are given in Table 5.2. In all reactions 2-amino-5-nitropyridine (**8**) was the only isomer observed. The regioselectivity was as good as for the amination with hydroxylamine (**96**).

Table 5.2. Results from amination of 3-nitropyridine (**24**) by 4-amino-1,2,4-triazole (**97**).

Entry	Solvent	Base	Rx time (h)	Yield (%)
1	DMSO	<i>t</i> -BuOK	5	76
2	DMSO	<i>t</i> -BuOK	5	74 <sup>a</sup>
3	DMSO	KOH	5	56
4	MeOH	<i>t</i> -BuOK	5	----
5	MeCN	<i>t</i> -BuOK	5	26
6	DMF	<i>t</i> -BuOK	5	44

a) Base added to a stirring solution of **24** and **97**.

When 3-nitropyridine (**24**) was aminated by the Katritzky procedure,<sup>4,5</sup> 2-amino-5-nitropyridine (**8**) was obtained as the only product in 76% yield (entry 1, Table 5.2). The only change from the original procedure was that the reaction was run in a more dilute solution. In some introductory experiments this seemed

to be favorable. This can be explained by that 3-nitropyridine (**24**) has a higher reactivity than nitrobenzene (**93**) toward nucleophiles, as **24** is more electron deficient.

In entry 1, **24** was added to a stirred solution of potassium *tert*-butanol and 4-amino-1,2,4-triazole (**97**) in DMSO. When the procedure was changed so that the base was added to a DMSO solution of **24** and **97**, the yield was 74% (entry 2, Table 5.2.).

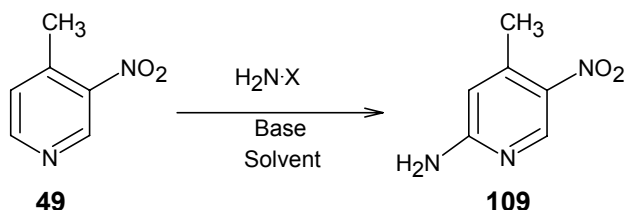
Use of potassium hydroxide as base instead of potassium *tert*-butanol reduced the yield to 56 % (entry 3, Table 5.2). When the reaction was performed in methanol instead of DMSO, no product was observed (entry 4, Table 5.2).

Acetonitrile and DMF as solvents gave yields of 26 and 44%, respectively (entries 5 and 6, Table 5.2.).

In conclusion, the original procedure used on nitrobenzene (**93**) proved to be the best also for 3-nitropyridine (**24**). This procedure was therefore used for the 5- and 4-substituted 3-nitropyridines aminated in the following chapters.

### 5.2.3. Amination of 4-methyl-3-nitropyridine (**49**)

4-Methyl-3-nitropyridine (**49**) was first aminated with hydroxylamine (**96**) and potassium hydroxide in methanol with  $\text{ZnCl}_2$  as catalyst.



*Scheme 5.7. Amination of 4-methyl-3-nitropyridine (**49**).*

After heating to 50 °C for 2 hours, 2-amino-4-methyl-5-nitropyridine (**109**) could be isolated in a 25 % yield. When the reaction conditions were changed to stirring at room temperature overnight the yield increased to 42 %.

By following the reaction on GC, this reaction was found to be slower than the reaction with 3-nitropyridine (**24**), and extra base and hydroxylamine had to be added to get complete conversion. The difference in reactivity can be explained



by the fact that the methyl substituent is electron-donating and therefore makes 4-methyl-3-nitropyridine (**49**) less electrophilic than 3-nitropyridine (**24**).

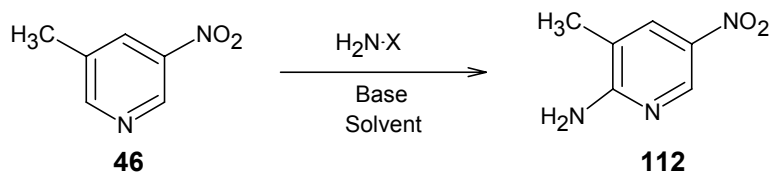
Amination of 4-methyl-3-nitropyridine (**49**) with 4-amino-1,2,4-triazole (**97**) in DMSO and potassium *t*-butoxide as base gave a 61% yield.

In both systems the isomer with the amine *para* to the nitro group was the only isomer obtained. No diamination was observed. The melting point and spectroscopic data for the product from both methods were in accordance with data reported in literature.

2-Amino-4-methyl-5-nitropyridine (**109**) has previously been made by nitration of 2-amino-4-methylpyridine (**110**) followed by rearrangement of the resulting nitramine. This gave a 2:1 mixture of 2-amino-4-methyl-5-nitropyridine (**109**) and 2-amino-4-methyl-3-nitropyridine (**111**). After sublimation a yield of 47 % **109** was isolated.<sup>8</sup>

#### 5.2.4. Amination of 5-methyl-3-nitropyridine (**46**)

5-Methyl-3-nitropyridine (**46**) was aminated by hydroxylamine (**96**) in ethanol with potassium hydroxide as base and ZnCl<sub>2</sub> as catalyst.



Scheme 5.8. Amination of 5-methyl-3-nitropyridine (**46**).

A 56% yield of 2-amino-3-methyl-5-nitropyridine (**112**) was obtained as the only product. The reaction was monitored by GC, and more base and hydroxylamine (**96**) had to be added to get a complete conversion.

**46** was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with potassium *tert*-butoxide as base. After five hours the reaction was not complete and more base and **97** was added, and the reaction stirred for one more hour. **112** was isolated in a 59 % yield.

The low reactivity in both reactions can be explained by the electron donating methyl group, and also by possible steric hindrance from the methyl group in the

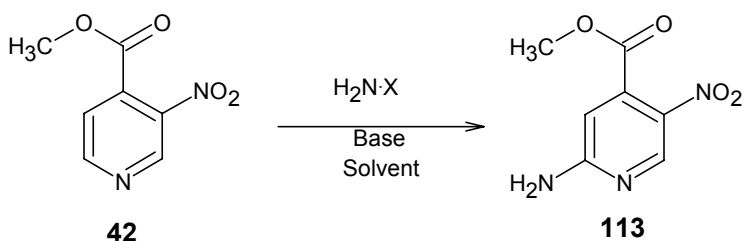
5-position on the 3-nitropyridine. But in spite of this possible steric hindrance the regioselectivity was the same. The *para* isomer was the only observed isomer.

The melting point and spectroscopic data for the products obtained from both methods were in accordance with literature data.

2-Amino-3-methyl-5-nitropyridine (**112**) has previously been synthesized by nitration of 2-amino-3-methylpyridine (**9**), followed by a rearrangement of the resulting nitramine. This gave 90 % yield of **112**.<sup>8</sup>

### 5.2.5. Amination of methyl 3-nitroisonicotinate (**42**)

Methyl 3-nitroisonicotinate (**42**) was aminated by hydroxylamine (**96**) in dry methanol with sodium methoxide as base and ZnCl<sub>2</sub> as catalyst.

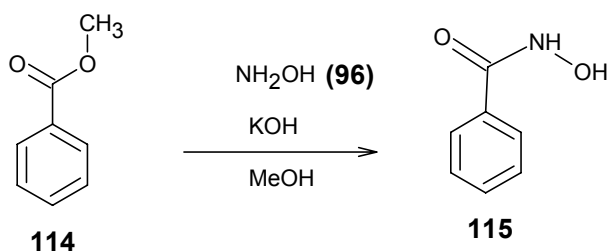


Scheme 5.9. Amination of methyl 5-nitroisonicotinate (**42**).

Methanol as solvent and methoxide as base were chosen because an attack on the ester group from the base would give the methyl ester back and not the acid as would be the case if hydroxide was the base. This reaction gave methyl 2-amino-5-nitroisonicotinate (**113**) in a 30 % yield.

Amination of **42** in DMSO with 4-amino-1,2,4-triazole (**97**) and potassium-*tert*-butoxide, gave only a 11 % yield of **113**.

Esters can react with nitrogen nucleophiles as hydroxylamine, giving the *N*-hydroxyamides. An example is shown in Scheme 5.10.<sup>17</sup> This would give water soluble by-products which are eliminated by extraction.

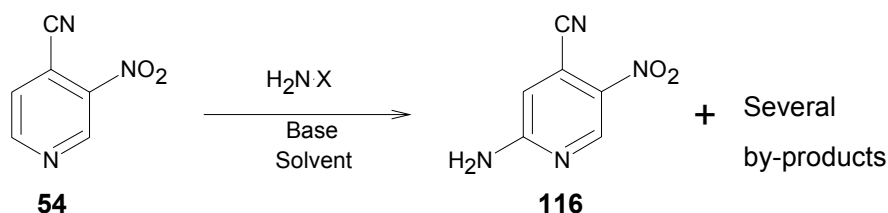


Scheme 5.10. Reaction of methyl benzoate (**114**) with hydroxylamine (**96**) to give N-hydroxy benzamide (**115**).

No literature references were found for methyl 2-amino-5-nitroisonicotinate (**113**). Elemental analysis was in good accordance with calculated values. The spectroscopical data was also in accordance with the suggested structure.

### 5.2.6. Amination of 4-cyano-3-nitropyridine (**54**)

Amination of 4-cyano-3-nitropyridine (**54**) both with hydroxylamine (**96**) and 4-amino-1,2,4-triazole (**97**) gave a mixture of several products.

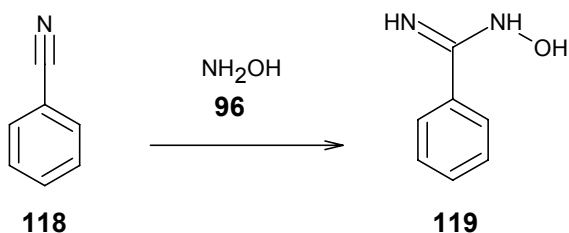


Scheme 5.11. Amination of 4-cyano-3-nitropyridine (**54**)

For the reaction with **97** a GC-MS of the product mixture was performed. One of the peaks in the GC chromatogram had a MS spectrum with a peak at 164 *m/z*. 2-Amino-4-cyano-5-nitropyridine (**116**) has a M<sup>+</sup> peak at 164 *m/z*, so probably some of the desired product was formed. The products in the reaction mixture were not separated.

One possible side reaction for **54** is substitution of the nitro group. Dr. Eli Ranesh showed in her Dr. thesis that when **54** was reacted with sodium azide in DMSO, 3-azido-4-cyanopyridine (**117**) was formed in 82% yield.<sup>12</sup>

Cyano groups can also react with nitrogen nucleophiles as shown in Scheme 5.12.<sup>16</sup> This reaction would produce by-products in the amination reaction.

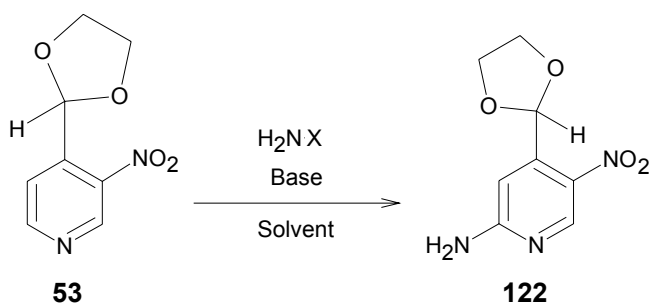


Scheme 5.12. Reaction of 4-cyanobenzene (**118**) with hydroxylamine (**96**).

### 5.2.7. Amination of 4-(1,3-dioxolan-2-yl)-3-nitropyridine (**53**)

As the aldehyde group of 4-pyridinecarboxaldehyde (**120**) is very reactive, it has to be protected in order to be nitrated and aminated. The aldehyde was protected with ethyleneglycol to give 4-(1,3-dioxolan-2-yl)-pyridine (**121**), which was nitrated to give 4-(1,3-dioxolan-2-yl)-3-nitropyridine (**53**) (for details see Chapter 2.).

**53** was aminated with hydroxylamine (**96**) in ethanol with KOH as base and  $ZnCl_2$  as catalyst. 2-Amino-4-(1,3-dioxolan-2-yl)-5-nitropyridine (**122**) was obtained in 47 % yield as the only isomer.



Scheme 5.13. Amination of protected 4-carbaldehyde-3-nitropyridine (**53**).

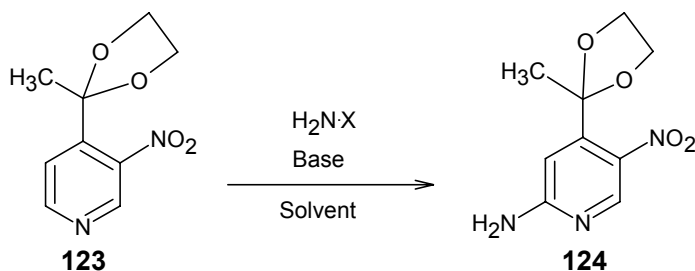
**53** was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with potassium *t*-butoxide as base. **122** was obtained in a 47 % yield.

Elemental analysis was in good accordance with calculated values. The spectroscopical data were also in accordance with the suggested structure. No literature references were found for **122**.

### 5.2.8. Amination of 4-acetyl-3-nitropyridine (**37**)

An attempt to aminate 4-acetyl-3-nitropyridine (**37**) with hydroxylamine (**96**) in ethanol with KOH as base resulted in a mixture of several products on GC. The carbonyl group is electrophilic and is easily attacked by nucleophiles. The 4-acetyl-3-nitropyridine (**37**) was therefore protected with ethyleneglycol to give 4-(2-methyl-1,3-dioxolan-2-yl)-3-nitropyridine (**123**) in 86 % yield.

**123** was aminated with hydroxylamine (**96**) in ethanol with KOH as base and  $\text{ZnCl}_2$  as catalyst. Additional **96** and base had to be added to get complete conversion. 2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (**124**) was isolated in a 63 % yield as the only isomer.



*Scheme 5.14. Amination of protected 4-acetyl-3-nitropyridine (**123**) to yield 2-amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (**124**).*

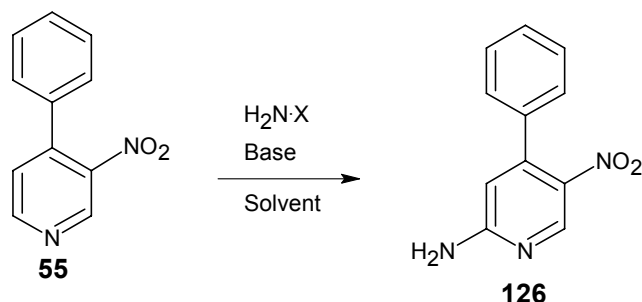
**123** was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with *t*-butoxide as base. **124** was obtained in a 65%.

Elemental analysis was in good accordance with calculated value. The spectroscopical data were also in accordance with the suggested structure. No literature references were found for **124**.

**124** was deprotected in a 66% hydrochloric acid solution in a 98 % yield of 2-amino-4-acetyl-5-nitropyridine (**125**). No literature references were found for **125**. Spectroscopical data for the product were in accordance with the suggested structure.

### 5.2.9. Amination of 4-phenyl-3-nitropyridine (**55**)

4-Phenyl-3-nitropyridine (**55**) was aminated with hydroxylamine (**96**) in ethanol with KOH as base and ZnCl<sub>2</sub> as catalyst. Additional **96** had to be added in order to obtain complete conversion. 2-Amino-4-phenyl-5-nitropyridine (**126**) was obtained in a 64 % yield.



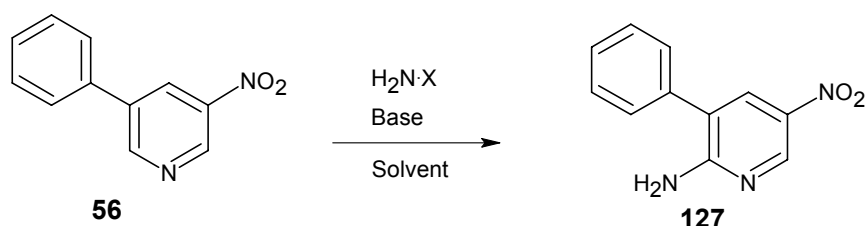
*Scheme 5.15. Amination of 4-phenyl-3-nitropyridine (**55**) to yield 2-amino-4-phenyl-5-nitropyridine (**126**).*

**55** was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with potassium *tert*-butoxide as base. **126** was obtained in 79 % yield.

Elemental analysis was in good accordance with calculated values. Melting point and spectroscopic data were in accordance with the proposed structure. No references for **126** were found in literature.

### 5.2.10. Amination of 5-phenyl-3-nitropyridine (**56**)

5-Phenyl-3-nitropyridine (**56**) was aminated with hydroxylamine (**96**) in ethanol with KOH as base and ZnCl<sub>2</sub> as catalyst. 2-Amino-3-phenyl-5-nitropyridine (**127**) was isolated in 35 % yield.



Scheme 5.16. Amination of 4-phenyl-3-nitropyridine (**56**) to yield 2-amino-3-phenyl-5-nitropyridine (**127**).

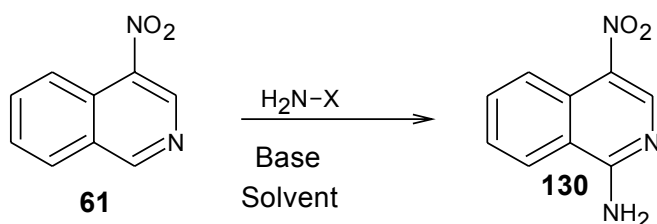
5-Phenyl-3-nitropyridine (**56**) was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with potassium *tert*-butoxide as base. 2-Amino-3-phenyl-5-nitropyridine (**127**) was isolated in 66% yield.

Melting point and spectroscopical data were in accordance with literature.

**127** has previously been synthesized from reaction of 5-nitropyrimidine (**128**) with  $\alpha$ -phenylacetamide (**129**) in 86% yield.<sup>15</sup> Neither of the starting compounds in this synthesis are commercially available.

### 5.2.11. Amination of 4-nitroisoquinoline (**61**)

4-Nitroisoquinoline (**61**) was aminated with hydroxylamine (**96**) in ethanol with KOH as base and ZnCl<sub>2</sub> as catalyst. 1-Amino-4-nitroisoquinoline (**130**) was isolated as the only isomer in 23% yield.



Scheme 5.17. Amination of 4-nitroisoquinoline (**61**) to yield 1-amino-4-nitroisoquinoline (**130**).

4-Nitroisoquinoline (**61**) was also aminated with 4-amino-1,2,4-triazole (**97**) in DMSO with potassium *tert*-butoxide as base. 1-Amino-4-nitroisoquinoline (**130**) was isolated as the only isomer in 65 % yield.

Elemental analysis was in accordance with the suggested structure. The melting point was found to be 277.0-280.0 °C. A Japanese patent reports a melting point at 283-287 °C,<sup>13</sup> but another reference reports the melting point to be approximately 250 °C.<sup>14</sup> The spectroscopical data were in accordance with the literature data.

Since there were no reports in the literature of the other possible isomer, 3-amino-4-nitroisoquinoline (**131**), NMR analyses were necessary to prove that the isolated product was **130** and not **131** (Figure 5.2.). The <sup>1</sup>H-NMR-spectrum of the product showed a singlet at 8.97, apparently belonging to the proton in the pyridine ring. From a <sup>1</sup>H-<sup>13</sup>C correlation spectra the corresponding carbon signal was assigned to be the signal at 147 ppm in the <sup>13</sup>C-spectrum. A gated decoupled <sup>13</sup>C-NMR spectrum was recorded to study the coupling constants of this carbon in order to find out whether it was carbon 1 in **131** or carbon 3 in **130**.

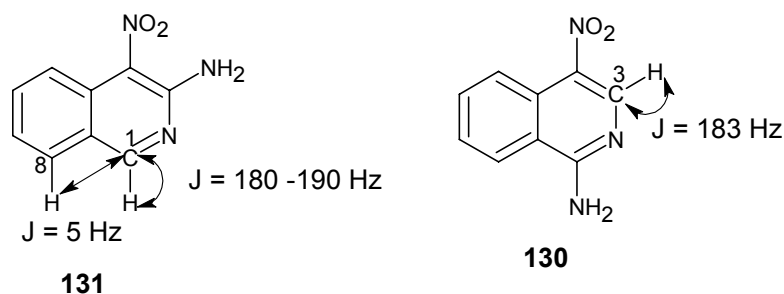


Figure 5.2. Two possible isomers for the product from amination of 4-nitroisoquinoline (**61**) with expected coupling constants respectively for carbon 1 in **131** and carbon 3 in **130**.

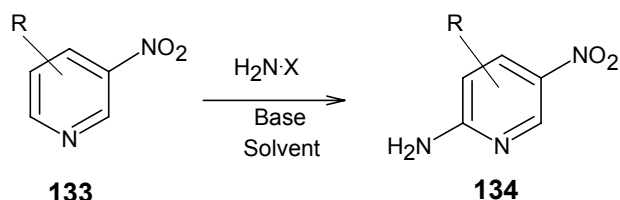
Carbon 3 in **130** do not have any geminal or vicinal protons, so the only expected coupling would be to the proton which it is directly bounded to. Carbon 1 in **131** would in addition to coupling to the carbon it is bounded to, also have a small coupling to the proton at carbon 8. Dr. Jaroslav Riha showed in his dr. thesis<sup>18</sup> that in 4-amino-3-chloroisoquinoline (**132**) carbon 1 had a coupling constant of 5.1 Hz to the vicinal proton at carbon 8. Gated decoupled <sup>13</sup>C-NMR spectroscopy of the observed carbon showed a doublet with a coupling constant of 183 Hz. No small coupling constant at around 5 Hz was observed.



The conclusion is therefore that the obtained product was the *para* isomer **130**.

### 5.2.12. General trends and side reactions

The yields of substituted 2-amino-5-nitropyridines (**134**) from amination of ten different nitropyridines (**133**) with both hydroxylamine (**96**) and 4-aminotriazole (**97**) are given in Table 5.3. Details are presented in the chapters describing each substrate.



Scheme 5.18. Amination of substituted 3-nitropyridine (**133**).

Table 5.3 Yields (isolated) for the amination of *R*-3-nitropyridine (**133**) to give *R*-2-amino-5-nitropyridine (**134**).

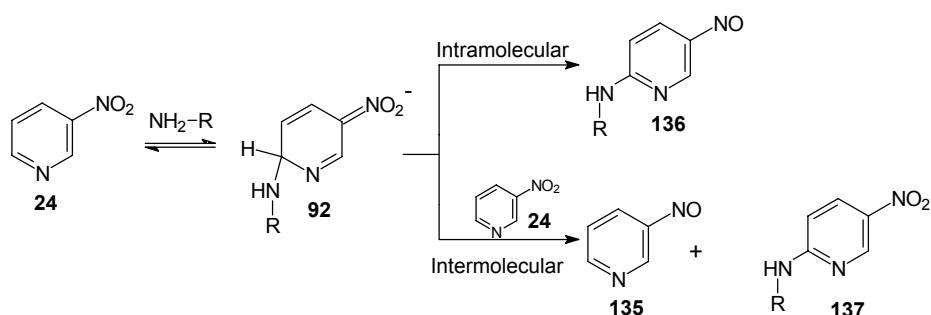
R ( <b>133</b> )	X = NH <sub>2</sub> OH	X = 4-amino- 1,2,4-triazole	R ( <b>134</b> )	Details in chapter:
H ( <b>24</b> )	54	76	H ( <b>8</b> )	5.2.1., 5.2.2.
4-CH <sub>3</sub> ( <b>49</b> )	42	61	4-CH <sub>3</sub> ( <b>109</b> )	5.2.3.
5-CH <sub>3</sub> ( <b>46</b> )	56	59	3-CH <sub>3</sub> ( <b>112</b> )	5.2.4.
4-CO <sub>2</sub> CH <sub>3</sub> ( <b>42</b> )	30	11	4-CO <sub>2</sub> CH <sub>3</sub> ( <b>113</b> )	5.2.5.
4-CN ( <b>54</b> )	mix	mix	4-CN ( <b>116</b> )	5.2.6.
4-CHO <sup>A</sup> ( <b>53</b> )	47	47	4-CHO <sup>A</sup> ( <b>122</b> )	5.2.7.
4-COCH <sub>3</sub> <sup>A</sup> ( <b>123</b> )	63	65	4-COCH <sub>3</sub> <sup>A</sup> ( <b>124</b> )	5.2.8.
4-Ph ( <b>55</b> )	64	79	4-Ph ( <b>126</b> )	5.2.9.
5-Ph ( <b>56</b> )	35	66	3-Ph ( <b>127</b> )	5.2.10.
4-nitroisoquinoline ( <b>61</b> )	23	65	1-Amino-4-nitro isoquinoline ( <b>130</b> )	5.2.11.

A) Protected as dioxolan

It is difficult to find some general trends for the effect of the different substituents, because there are several side reactions that can influence the yields. Three possible side reactions are substitution of the nitro group, inter or intramolecular oxidation of the  $\sigma$ -<sup>H</sup>adduct (Scheme 5.19.) or reactions on the substituents.

Electron withdrawing substituents make the nitropyridine more electrophilic. Such substrates would react faster with the nucleophiles than 3-nitropyridine itself. However if the ring becomes to electron deficient the nitro group might be substituted. It have been reported that the nitro group in 4-cyano-3-nitropyridine (**54**), can be substituted with an azide in good yield.<sup>12</sup> This is one possible explanation of the poor yields of **54** and methyl 3-nitroisonicotinate (**42**)

When the system is activated by an electron withdrawing substituent the rate of the inter- or intramolecular oxidation of the  $\sigma$ -adduct may also be higher, leading to by-products like **135**, **136** and **137** (Scheme 5.19.).



Scheme 5.19. Pathway for inter- and intramolecular oxidation of the  $\sigma$ -adduct (**92**) in the oxidative aminations of 3-nitropyridine (**24**)

For the 4-cyano-3-nitropyridine (**54**) and methyl 3-nitroisonicotinate (**42**) the nucleophile could react with respectively the carbonyl or cyano group to give by-products.<sup>16,17</sup>

The amination procedure with hydroxylamine (**96**) is probably more suitable than the 4-amino-1,2,4-triazole (**97**) for large scale synthesis. It uses inexpensive reagents, no inert atmosphere is needed and extraction gives the products without further purification. The 4-amino-1,2,4-triazole (**97**) procedure require use of DMSO as a solvent and use of an inert atmosphere.

In general **97** gave better yields than hydroxylamine (**96**). Methyl 5-nitroisonicotinate (**42**) was the only substrate for which **96** gave the best yield. The 4-amino-

1,2,4-triazole (**97**) system is particularly better for 5-phenyl-3-nitropyridine (**56**) and 4-nitroisoquinoline (**61**).

In general the amination reaction was much faster with the 4-amino-1,2,4-triazole (**97**) system. This indicates that this system is a more powerful aminating system. A stronger base is used and the 1,2,4-triazole ring is probably a better leaving group than the hydroxyl group. This could explain the better yields for **56**, which has a large phenyl group that could cause steric hindrance for the nucleophilic attack.

4-amino-1,2,4-triazole (**97**) is also a bulkier nucleophile than hydroxylamine (**96**) and this may lead to less substitution of the nitro group.

Many of the aminated products have not been reported before. The vicarious nucleophilic amination is competitive for all the products reported earlier except for the 2-amino-3-methyl-5-nitropyridine (**112**). For **112** the nitramine rearrangement gives only the *para* isomer, as the two *ortho* positions are blocked.

### 5.3. Conclusion

Nine different substituted 3-nitropyridines together with 4-nitroisoquinoline (**61**) have been aminated by two different methods. Both methods gave selectively substituted 2-amino-5-nitropyridines. With a few exceptions the substrates were aminated in good yield. Several of the products reported have not been previously reported. Especially the 4-substituted 2-amino-5-nitropyridines have been difficult to synthesize by other methods.

By this a general method for the selective preparation of 3- and 4-substituted 2-amino-5-nitropyridines was obtained. This selectivity is difficult to achieve by other methods as the nitramine-rearrangement or oxidative aminations.

The use of hydroxylamine (**96**) is the simpler and cheaper method. All the reagents are inexpensive, the procedure is simple and does not require an inert atmosphere, and the work-up procedure is very easy. This procedure should therefore be suitable for large scale preparations.

The use of 4-amino-1,2,4-triazole (**97**) gave better yields for most of the substrates, but require the use of inert atmosphere and DMSO as solvent. This procedure could be the preferred procedure for small-scale preparations.



## 5.4. References

1. J. Golinski and M. Makosza, *Tetrahedron Lett*, 3495 (1978).
2. M. Makosza, A. Kvast, *J. Phys. Org. Chem.*, **11**, 341 (1998).
3. O. N. Chupakhin, V. N. Charushin, H. C. van der Plas, *Nucleophilic aromatic substitution of hydrogen*, Academic press, 1994, A) pp 41-49 and B) pp 59-66.
4. A.R. Katrizky and K.S. Lorenzo, *J. Org. Chem.*, **51**, 5039 (1986).
5. A.R. Katrizky and K.S. Lorenzo, *J. Org. Chem.*, **53**, 3978 (1988).
6. M. Makosza and M. Bialecki, *J. Org. Chem.*, **57**, 4784 (1992).
7. M. Wozniak, A. Baranski and B. Szpakiewicz, *Liebigs Ann. Chem.*, 875 (1991).
8. N. P. Lewis and S. Z. Winfield, *J. Am. Chem. Soc.*, **77**, 3154 (1955).
9. S. Seko and K. Miyake, *Chem. Commun.*, 1519 (1998).
10. M. Makosza and M. Bialecki, *J. Org. Chem.*, **63**, 4878 (1998).
11. C. C. Price and S. T. Voong, *Org. Synth.*, Coll. vol. **3**, 664 (1955).
12. E. Ranes, *Nitration of pyridine compounds*, Dr. ing. thesis, NTNU, Trondheim 1998.
13. JP 59172472, 1984 (Chem. Abstr., 1984, **102**, 113322z).
14. E. Ochiai and Y. Kawazoe, *Chem. Pharm. Bull (Tokyo)*, **8**, 26 (1960).
15. V. N. Charushin and H. C. van der Plas, *J. Org. Chem*, **48**, 2667 (1983).
16. S. A Bakunov, A. V. Rukavishnikov, A. V. Tkachev, *Synthesis*, **8**, 1148 (2000).
17. A. Liguori, G. Sindona, G. Romeo, N. Uccella, *Synthesis*, **2**, 168 (1987).
18. J. Riha, *Synthesis and Transformations of 3-Nitropyridines*, Dr. ing. thesis, NTNU, Trondheim (2000).
19. M. Makosza and K. Stalinski, *Synthesis*, 1631 (1998).

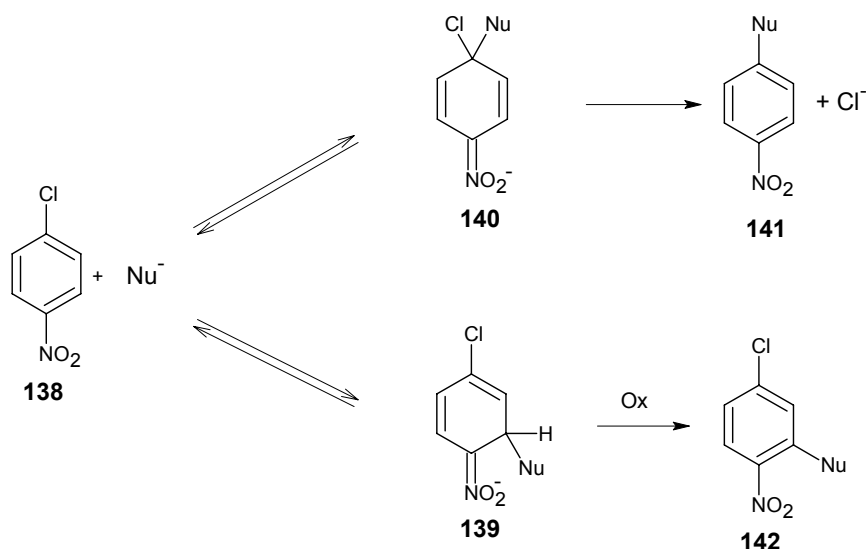


## 6. The selective oxidative amination of 3-nitropyridines

### 6.1. Introduction

#### 6.1.1. Oxidative nucleophilic substitution of hydrogen

Nucleophilic substitution of halogens in halonitroarenes is a well known process of great practical value, and has been known for more than 100 years.<sup>1,2,3</sup> Later one found that in presence of an oxidizing agent one could selectively substitute a hydrogen instead of the halogen. The two different reaction paths are outlined for *p*-chloronitrobenzene (**138**) in Scheme 6.1. The oxidative nucleophilic substitution of hydrogen (ONSH) takes place by that the nucleophile attacks at a carbon attached to a hydrogen and forms a  $\sigma^H$  adduct (**139**). Since a hydride anion can not act as a leaving group, **139** must be oxidized and deprotonated to give back the aromatic system.

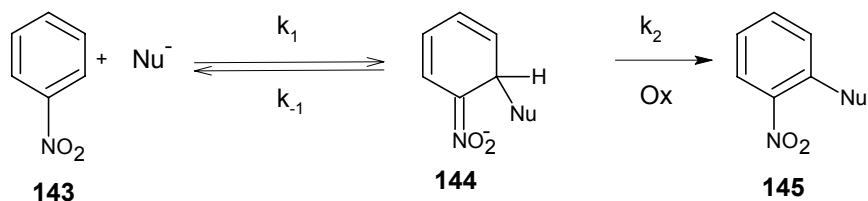


Scheme 6.1. Two different routes for reaction of *p*-chloronitrobenzene (**138**) with a nucleophile.

#### 6.1.2. Mechanism of oxidative amination

An outline of the mechanism is given in Scheme 6.2. with nitrobenzene (**143**) as example. The nucleophile adds reversible to the ring carbon to form a  $\sigma^H$  adduct

(144). This adduct can either react further to the products of the nucleophilic substitution of hydrogen or it can dissociate back to the starting compounds. A hydride anion is removed from the  $\sigma^H$  adduct by oxidation to give the substituted product.



Scheme 6.2. Reaction scheme for the oxidative nucleophilic substitution of hydrogen.

The overall rate for formation of product **145** is assumed to be

$$\frac{d[\mathbf{145}]}{dt} = k_{OXAM} \cdot [\text{Nu}] \cdot [\mathbf{143}] \quad (6.1)$$

where  $k_{OXAM}$  is the observed rate constant

The reaction is assumed to follow the pathway in Scheme 6.2. If the concentration of oxidant is assumed to be constant during the reaction, and the steady state approximation can be used on intermediate **144**, then:

$$k_{OXAM} = \frac{k_1 \cdot k_2 \cdot [\text{Ox}]}{k_{-1} + k_2 \cdot [\text{Ox}]} \quad (6.2)$$

For details on how the expression for  $k_{OXAM}$  was found see Chapter 5.1.1. Equation 6.2 can be simplified under certain conditions to Equation 6.3 and 6.4:

$$k_{OXAM} = \frac{k_1}{k_{-1}} \cdot k_2 \cdot [\text{Ox}] \quad \text{when} \quad \frac{k_2 \cdot [\text{Ox}]}{k_{-1}} \ll 1 \quad (6.3)$$

$$k_{OXAM} = k_1 \quad \text{when} \quad \frac{k_2 \cdot [\text{Ox}]}{k_{-1}} \gg 1 \quad (6.4)$$

In equation 6.3 the reaction rate is first order in oxidating agent concentration, and it depends also on the oxidating agent strength via the value of  $k_2$ . The rate is proportional to the equilibrium constant of the addition ( $K^H = k_1/k_{-1}$ ), this can be

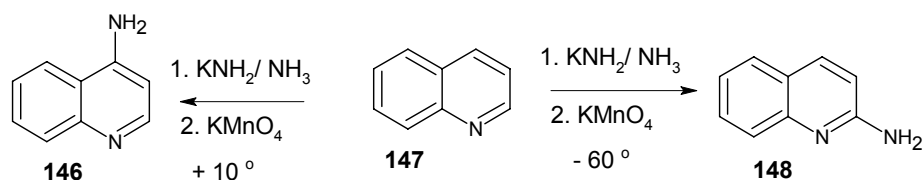


considered as a thermodynamic controlled process. In equation 6.4 the oxidating agent does not effect the overall rate and the oxidation rate is identical with the rate of formation of  $\sigma^{\text{H}}$ -adduct (**144**). This represents kinetic control in the reaction.

## 6.2. Oxidative amination of azaaromatics<sup>5,6</sup>

### 6.2.1. Introduction

Van der Plas and Wozniak have reported oxidative amination of a number of azaaromatics.<sup>5,6</sup> Reaction with  $\text{KNH}_2$  or  $\text{NH}_3$  as nucleophiles in liquid ammonia and  $\text{KMnO}_4$  as oxidizing agent makes a whole range of aminated azaaromatics available. The regioselectivity can, in some cases, be controlled by using the right reaction conditions, especially the temperature is important. Generally at low temperature the regioselectivity is under kinetic control and the position of addition is determined by the electron density at the ring carbons. However, at higher temperatures the position of addition is more determined by the thermodynamic stability of the  $\sigma^{\text{H}}$  adduct formed.<sup>5</sup> This is illustrated in Scheme 6.3. where low temperature amination of quinoline (**147**) gives 1-aminoquinoline (**148**) via attack at the less electron dense carbon 2. At higher temperature attack at carbon 4, giving the most thermodynamic stable  $\sigma^{\text{H}}$ -adduct, is favoured and 4-aminoquinoline (**146**) is formed.



Scheme 6.3. Amination of quinoline by  $\text{KNH}_2$  in  $\text{NH}_3$ / $\text{KMnO}_4$  at different temperatures.<sup>5</sup>

In some cases the  $\sigma^{\text{H}}$ -adducts are stable enough to be identified by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectroscopy. This shows that the reactions go via these  $\sigma^{\text{H}}$  adducts, and by studying the stability of these adducts it is possible to predict what will be the preferred product when the reaction are under thermodynamic control. In Scheme 6.3. the  $\sigma^{\text{H}}$  adduct **149** from attack at C4 carbon has the most stable resonance structures, leaving one aromatic ring intact in two of the resonance structures (**149a** and **149b**, Figure 6.1.).

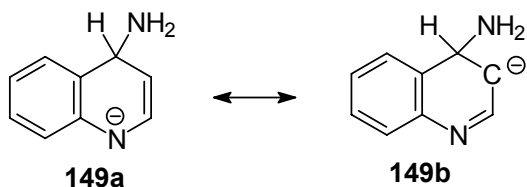
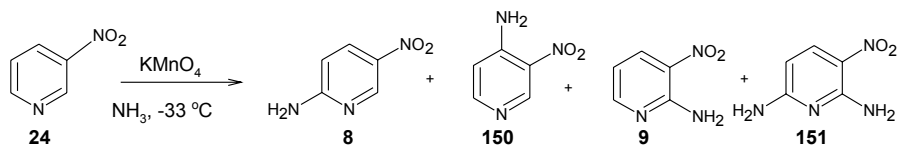


Figure 6.1. Resonance structures of the most thermodynamic stable  $\sigma^H$  adduct (**149**) from amination of quinoline (**147**)

### 6.2.2. Oxidative amination of 3-nitropyridines

Wozniak and coworkers have aminated some 3-nitropyridines by the liquid ammonia/  $\text{KMnO}_4$  method at  $-33\text{ }^\circ\text{C}$ .<sup>7</sup> Amination of 3-nitropyridine gave a mixture of 2-amino-3-nitro-pyridine (**9**) (33 %, yield), 4-amino-3-nitro-pyridine (**150**) (24 %, yield), 2-amino-5-nitro-pyridine (**8**) (19%,yield) and 2,6-diamino-3-nitropyridine (**151**) (2 %, yield) (Scheme 6.4.).



Scheme 6.4. Oxidative amination of 3-nitropyridine (**24**) by liquid ammonia /  $\text{KMnO}_4$  at  $-33\text{ }^\circ\text{C}$

In this reaction no intermediate  $\sigma$ -adduct was observed by  $^1\text{H-NMR}$  spectroscopy. The equilibrium between 3-nitropyridine (**24**) and the amino  $\sigma^H$  adduct were assumed to be so far to the left that its concentration was too low to be detected by  $^1\text{H-NMR}$  spectroscopy. The authors concluded that the observed regioselectivity could be explained by coulombic interactions. This means that the system is under kinetic control and that the nucleophilic attack is controlled by the electron density at the different ring carbons.

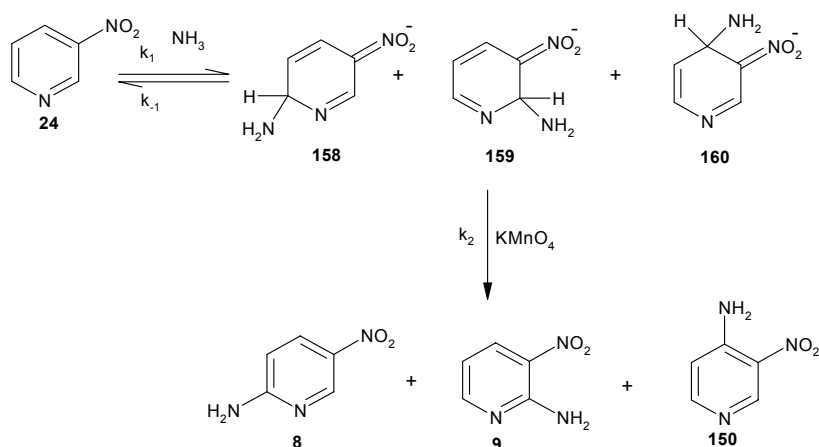
Some substituted 3-nitropyridines were aminated by the same method.<sup>7</sup> 4-Chloro- 3-nitropyridine (**152**) gave 8 % yield of 2-amino-4-chloro-3-nitropyridine (**153**), 54 % yield of 2-amino-4-chloro-5-nitropyridine (**154**), 10 % yield of diaminated product (**155**) and some substitution of the chloro substituent. When the 6-position was blocked by a substituent, attack in 2-position was highly favoured over the 4-position.

Wozniak and Szpakiewicz also reported that when 3-nitropyridine (**24**) was reacted with methylamine and potassium permanganate at  $-7\text{ }^{\circ}\text{C}$ , a 65% yield of 2-methylamino-5-nitropyridine (**156**) and 3% of the di-methylaminated product (**157**) were obtained.<sup>8</sup> Some chloro, methoxy and amino substituted 3-nitropyridines could also be methylaminated.

## 6.3. Results and discussion

### 6.3.1. Amination of 3-nitropyridines with ammonia

Reported amination of 3-nitropyridine (**24**) with  $\text{KMnO}_4$  in liquid ammonia at  $-33\text{ }^{\circ}\text{C}$  gave a mixture of isomers.<sup>7</sup> The possible intermediates leading to the three different isomers (**8**, **9** and **150**) are shown in Scheme 6.5.



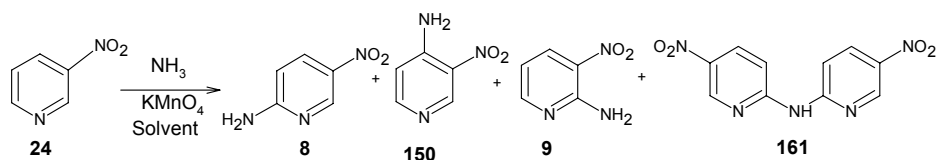
*Scheme 6.5. Outline of the reaction steps in the oxidative amination of 3-nitropyridine with ammonia/ $\text{KMnO}_4$ .*

At low temperature these oxidative nucleophilic substitutions of hydrogens (ONSH) are often under kinetic control, and the nucleophilic attack is controlled by the electron density of the ring carbons. Calculations have shown that when the system is under charge control attack at carbon 2 (**159**) is favored over carbon 6 (**158**) which again is favored over carbon 4 (**160**).<sup>7</sup> Some examples in the literature have indicated that at higher temperatures the selectivity is under

thermodynamic control.<sup>5</sup> We therefore wished to investigate the amination with ammonia/KMnO<sub>4</sub> at higher temperatures.

The low boiling point of ammonia made use of other solvents necessary. There are also some limitations due to the reaction conditions. The use of the strong oxidizing agent KMnO<sub>4</sub> made the use of alcohols and other easily oxidizable solvents impossible, since they would be readily oxidized and deactivate the KMnO<sub>4</sub>. Another limitation was the solubility of ammonia in the solvents to be used. A third problem was oxidation of the nucleophile (ammonia). In liquid ammonia, the solvent also being the nucleophile, some oxidation of ammonia was no problem. But when other solvents were used the concentration of ammonia was important. Oxidation of ammonia might then lower the concentration of the nucleophile considerably.

3-Nitropyridine (**24**) was aminated by ammonia and KMnO<sub>4</sub> in different solvents and under different conditions (Scheme 6.6.). The results from these oxidative aminations are given in Table 6.1.



Scheme 6.6. Product from amination of 3-nitropyridine (**24**) with ammonia/  
*KMnO*<sub>4</sub>

Table 6.1. Reaction of 3-nitropyridine (**24**) with ammonia in the presence of *KMnO*<sub>4</sub> to give 2-amino-5-nitropyridine (**8**), 2-amino-3-nitropyridine (**9**), 4-amino-3-nitropyridine (**150**) and di-2-(5-nitropyridyl)amine (**161**)..

Solvent	Conditions	Reaction time (h)	Conversion (%) GC	Composition (%) GC			
				<b>8</b>	<b>9</b>	<b>150</b>	<b>161</b>
Water, NH <sub>3</sub> 28%	Stirring	20	20	7	3	10	-
Water, NH <sub>3</sub> 28%	Supersonic mixing	3	80	68	1	11	-
DMSO, NH <sub>3</sub> atmosphere		3	80	43	0.2	37	-
DMSO/ <i>t</i> -BuOK 50/ 50, NH <sub>3</sub> atmosphere		6	78	59	-	19	-
DMSO/Water 75/25, NH <sub>3</sub> 7%		15	85	37	-	1	47
DMSO/Water 75/25, NH <sub>3</sub> 7%	Stream of NH <sub>3</sub> passed through	15	90	88	-	2	-
				66 <sup>a</sup>			

a) Isolated yield

Use of ammonia (28 %) in water at room temperature was tried. This resulted in a low conversion even with a large excess of both *KMnO*<sub>4</sub> and ammonia. A mixture of the three isomers were observed by GC. The ratio was similar to the ratio observed in liquid ammonia at -33 °C,<sup>7</sup> but slightly less of the 4-amino-3-nitropyridine (**150**) was observed. A major problem in this reaction system was the low solubility of 3-nitropyridine (**24**) in the water solution, making this reaction partly heterogeneous. This system seemed to be under kinetic control (equation 6.4, chapter 6.1.2.).

In order to increase the homogeneity of the system, supersonic mixing was used. This greatly increased the rate of reaction and, the conversion increased from 20 to 80 %. A much higher selectivity was also observed. The *para* isomer (**8**) was the favoured isomer, in contrast to the liquid ammonia system<sup>7</sup> where it was the minor isomer.

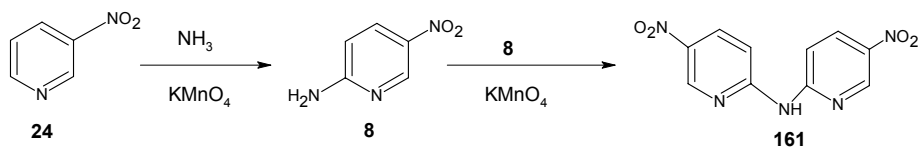
By using DMSO as a solvent the problem with solubility of **24** was solved, but the solubility of ammonia in DMSO was not very good. The reaction in DMSO was therefore performed under a NH<sub>3</sub> atmosphere. Now the reaction was fast and the conversion good, but the selectivity between **8** and **150** was poor. Only traces of the 2-amino-3-nitropyridine (**9**) was observed. This low selectivity was probably caused by the high activity of the permanganate anion in DMSO, due to the high degree of solvation of the permanganate anion in the polar aprotic DMSO solution. The  $\sigma$ -adducts were oxidated before an equilibrium was obtained (kinetic control), as described in equation 6.4 in chapter 6.1.2.

An experiment with a 50/50 mixture of DMSO/ *t*-butanol under a NH<sub>3</sub> atmosphere was tried in an attempt to increase the solubility of NH<sub>3</sub> in the solvent and reduce the activity of KMnO<sub>4</sub>. The reaction was slower (6 vs. 3 hours) and the selectivity between **8** and **150** was better (59/19 vs. 43/37), but still not good.

To obtain thermodynamic control in the system  $k_2[\text{Ox}]$  must be considerably smaller than  $k_{-1}$  (Equation 6.3, chapter 6.1.2.). This means that the equilibrium reaction must compete effectively with the oxidation of the  $\sigma$ -adduct. In a thermodynamic controlled system the product originating from the most stable  $\sigma$ -adduct will be the main product obtained. One could assume that the adduct with the nucleophile in *para* position to the nitro group would be the most stable isomer for steric reasons. In the benzene series it has been shown that a nitro group in *para* position to the carbon attacked by the nucleophile is more capable of resonance stabilization, than a nitro group in the *ortho* position<sup>12</sup>.

By changing the solvent to a DMSO/water (saturated with ammonia) system, the activity of KMnO<sub>4</sub> should be further reduced, making sure that the rate of oxidation of the adducts is not too fast compared to the rate of equilibrium. The experimental results showed that the reaction was slower, and in this case a high selectivity for the *para*-isomer (**8**) was obtained.

In this system the initial concentration of ammonia was 7 %, and during the reaction this was reduced both by reaction with 3-nitropyridine (**24**) and by oxidation with KMnO<sub>4</sub>. This allowed the amine **8** formed in the reaction to effectively compete with ammonia as a nucleophile. Therefore the di-2-(5-nitropyridyl)amine (**161**) was formed as the main product (Scheme 6.7.).



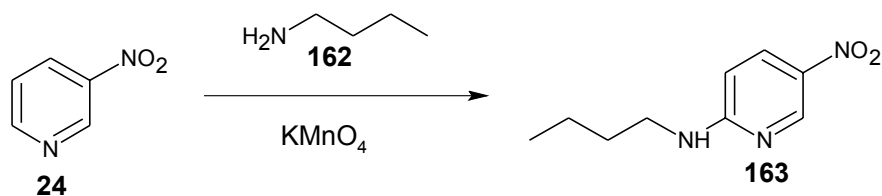
Scheme 6.7. Route to formation of di-2-(5-nitropyridyl)amine (**161**).

This side reaction was suppressed by bubbling NH<sub>3</sub> into the solution and thereby maintaining a constant concentration of ammonia, and now the 2-amino-5-nitropyridine (**8**) was obtained with good selectivity in a good yield. The isolated yield of **8** was 66 %.

These results show that the oxidative amination of 3-nitropyridine can be selective if the right reaction conditions are used. In order to get high selectivity one must have a system under thermodynamic control.

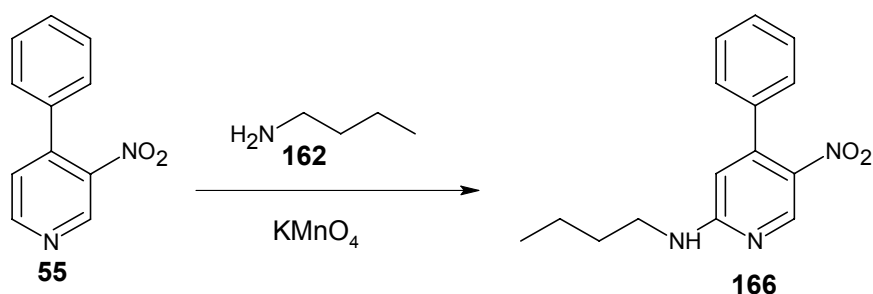
### 6.3.2. Oxidative amination of 3-nitropyridines with primary amines

Wozniak and Szpakiewicz reported that several nitropyridines reacted with KMnO<sub>4</sub> in liquid methylamine at -7 °C. Reaction of 3-nitropyridine gave a 65% yield of 2-methylamino-5-nitropyridine (**156**) together with a 3% yield of 2,6-dimethylaminopyridine (**157**).<sup>8</sup> Based on these results and the results presented in chapter 6.3.1. from the oxidative amination with ammonia, 3-nitropyridine (**24**) was reacted with KMnO<sub>4</sub> in liquid *n*-butylamine (**162**) at room temperature (Scheme 6.8.).



Scheme 6.8. Oxidative amination of 3-nitropyridine (**24**) by *n*-butylamine (**162**) and KMnO<sub>4</sub>

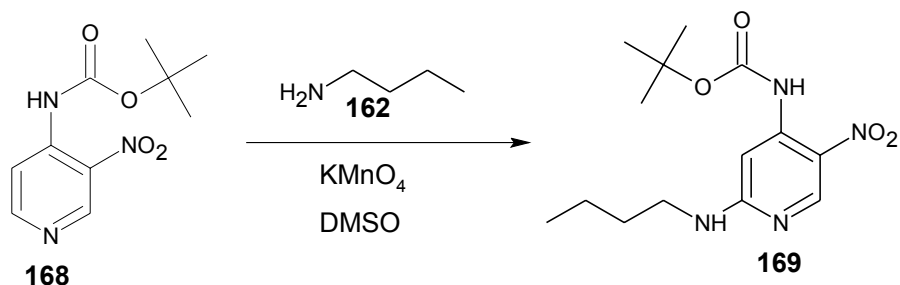
From this reaction a 92 % isolated yield of 2-butylamino-5-nitropyridine (**163**) was obtained. GC analysis of the reaction mixture showed only around 2% each of the two *ortho* isomers. This procedure was very simple, 3-nitropyridine (**24**) was dissolved in the *n*-butylamine (**162**) and some more KMnO<sub>4</sub> was added every hour until the conversion was complete. No inert atmosphere was used.



Scheme 6.9. Oxidative amination of 4-phenyl-3-nitropyridine (**55**) by *n*-butylamine (**162**) and KMnO<sub>4</sub>.

4-Phenyl-3-nitropyridine (**55**) was reacted with *n*-butylamine (**162**) and KMnO<sub>4</sub> as described for 3-nitropyridine (**24**). 2-*n*-Butylamino-4-phenyl-5-nitropyridine (**166**) was isolated in a 75% yield. Only trace of the *ortho*-isomer (**167**) was observed by GC. The reaction was also performed with a mixture of DMSO/ *n*-butylamine (1:1). This reaction was faster and **166** was isolated in 81% yield.

*t*-Butyl N-(3-nitropyridin-4-yl) carbamate (**168**) was reacted with *n*-butylamine (**162**) as solvent and nucleophile and with KMnO<sub>4</sub> as oxidant (Scheme 6.10.).



Scheme 6.10. Oxidative amination of 4-(*tert*-Butoxycarbonylamino)-3-nitropyridine (**168**) with *n*-butylamine (**162**) and KMnO<sub>4</sub>

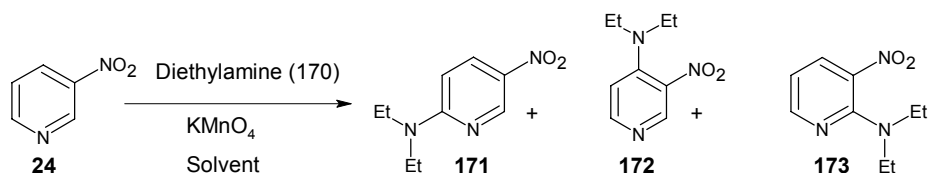
After four hours of stirring, no conversion was observed so DMSO was added to give a 1:1 solution of *n*-butylamine/ DMSO. After two more hours the reaction



was stopped. A 56% yield of t-Butyl N-(2-*n*-butylamino-5-nitropyridin-4-yl) carbamate (**169**) was isolated. Some unreacted starting material (**168**) was recovered. No other products were observed. This experiment shows that oxidative amination can be used on substrates with sensitive substituents, like carbamates, in reasonable yields.

### 6.3.3. Oxidative amination of 3-nitropyridines with secondary amines

The result from reaction of different 3-nitropyridines by *n*-butylamine made it natural to try the oxidative amination of 3-nitropyridines with a secondary amine.  $\text{KMnO}_4$  was therefore added to a stirred solution of 3-nitropyridine in diethylamine (**170**). In this reaction no conversion of the 3-nitropyridine (**24**) was observed. The solubility of  $\text{KMnO}_4$  in diethylamine (**170**) was low. Mixtures of **170** and other solvents were therefore used in the amination reaction (Scheme 6.11.). The results are given in Table 6.2.



Scheme 6.11. Oxidative amination of 3-nitropyridine (**24**) by diethylamine (**170**) and  $\text{KMnO}_4$ .

Table 6.2 Results from oxidative amination of 3-nitropyridine (**24**) with diethylamine (**170**) at 20 °C.

Solvent (% in diethylamine)	Conversion 24 h GC (%)	<i>para</i> -isomer (%, GC) <b>171</b>	<i>ortho</i> -isomers (%, GC) <b>172 + 173</b>
100% Diethylamine	0	----	-----
50% DMF	90	75	25
5% DMF	70	87	13
75% Ethyl acetate	6	90	10
75% Diglyme	65	45	55
50% Diglyme	52	66	34
75% Water	<1	-----	-----
75% DMSO	98 (60 <sup>A</sup> )	98	2

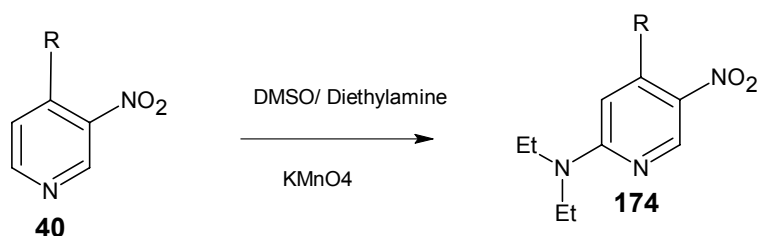
#### A) Isolated yield

Use of polar solvents like DMF and diglyme increased the conversion, probably due to increased solubility of and thereby also increased activity of  $\text{KMnO}_4$ . Reaction in DMF and diglyme gave acceptable conversion after 24 hours, but the selectivity was very low. Ethylacetate gave a low conversion, probably because of low solubility of  $\text{KMnO}_4$ . When water was used as solvent a very low

conversion was observed. In this reaction heat was evolved probably from oxidation of diethylamine by  $\text{KMnO}_4$ .

When the reaction was performed in 75 % DMSO the conversion was almost complete and the selectivity for the *para* isomer was very good (98:2). Work-up of this reaction gave a 60 % isolated yield of 2-diethylamino-5-nitropyridine (**171**).

The reaction system with DMSO/diethylamine (**170**) (75/25) was used on some 4-substituted 3-nitropyridines (**40**) (Scheme 6.12.). The results are given in Table 6.3.



Scheme 6.12. Amination of 4-substituted 3-nitropyridines (**40**) with diethylamine (**170**)/  $\text{KMnO}_4$ .

Table 6.3 Reaction of 4-R-3-nitropyridines (**40**) with diethylamine (**170**)/DMSO 25/75 and  $\text{KMnO}_4$  at 22 °C.

R	Product	Yield (%)
CN	2-Diethylamino-4-cyano-5-nitropyridine ( <b>175</b> )	41
$\text{COOCH}_3$	2-Diethylamino-4-methoxycarbonyl-5-nitropyridine ( <b>176</b> )	48
$\text{COCH}_3^A$	4-Acetyl-2-diethylamino-5-nitropyridine <sup>A</sup> ( <b>177</b> )	72

A) Protected with ethylene glycol

As seen in Table 6.3., the DMSO/diethylamine (**170**) system gave moderate to good yields for the different 4-substituted-3-nitropyridines (**174**). The 4-cyano-3-nitropyridine (**54**) gave a 41 % yield of 2-diethylamino-4-cyano-5-nitropyridine (**175**). This is not a high yield, but compared to the vicarious nucleophilic substitutions in Chapter 5. were no aminated product was observed for the 4-cyano-3-nitropyridine (**54**) it is an important improvement. The yield for 4-methoxycarbonyl-3-nitropyridine (**42**) was 48 %. This is also higher than the yield in the vicarious nucleophilic substitution. For the protected 4-acetyl-3-nitropyridine (**123**) the yield is similar to the yields in the vicarious

nucleophilic substitution. No literature data for the products in Table 6.3. were found.

#### 6.3.4. Limitations and side reactions

The use of  $\text{KMnO}_4$  makes some limitations for these reactions. As mentioned earlier solvents that is easily oxidized can not be used, because the solvent would be oxidized instead of the  $\sigma^{\text{H}}$ -adducts. This exclude all alcohols, except *t*-butanol. Also DMSO can be oxidized to dimethyl sulfone (**178**). This was observed., and dimethyl sulfone (**178**) was identified by its signal at 3,15 ppm in  $^1\text{H-NMR}$  spectra.<sup>10</sup> This made the use of excess  $\text{KMnO}_4$  necessary and made the work-up procedure more complicated, since **178**, which is a solid, had to be separated from the amine product. Oxidations with  $\text{KMnO}_4$  produced solid  $\text{MnO}_2$ , which had to be removed during the work-up.

The amines used as nucleophiles can be oxidized by  $\text{KMnO}_4$ . In acidic solution the majority of amines are resistant to oxidation, but in alkaline solution the primary, secondary and tertiary amines are usually attacked with ease.  $\text{KMnO}_4$  removes hydrogen from the amino group to give a radical which subsequently undergoes various transformations.<sup>9</sup> With primary amines, the radical formed by loss of hydrogen usually rearranges to an imine. The imine can hydrolyze to ammonia and carbonyl compounds.<sup>9</sup> With secondary amines the radical first dimerizes to a tetra-substituted hydrazine which may then undergo further reactions.<sup>9</sup> Ammonia itself is slowly oxidized by permanganate to a mixture of products, mainly nitrogen, nitrites, and nitrates.<sup>11</sup>

The product from the oxidative amination can also react either as a nucleophile to give a dimer, or be oxidized. Both these reactions would decrease the yield of the desired amination product. Reaction to dimer was normally no problem since a large excess of the nucleophile was used. An exception was ammonia in DMSO/water where the initial concentration of the nucleophile was low. Here oxidation of ammonia was a problem. The problem with oxidation of the amine product, must be controlled by a correct balance between amount of  $\text{KMnO}_4$  and the amine nucleophile. The concentration of product must be low compared to the concentration of the nucleophile.

These several possible side reactions in the oxidative amination of 3-nitropyridines, makes it important to optimize each reaction. Small changes in properties of the amine or the nitropyridine substrate might change the delicate

balance between desired oxidative amination and undesired side reactions, lowering the yields.

## 6.4. Conclusion

New methods have been developed to selectively aminate 3-nitropyridine (**24**) in the *para* position, providing 2-amino-5-nitropyridine (**8**) in good yield, with high regioselectivity. This is in contrast to oxidative aminations with liquid ammonia and  $\text{KMnO}_4$  at  $-33\text{ }^\circ\text{C}$ , which give a 33:24:19 mixture of the three possible regioisomers.<sup>7</sup> The selectivity was achieved by performing the reaction at room temperature and using DMSO as the solvent.

*n*-Butylamine (**162**) and diethylamine (**170**) were also used as nucleophiles in oxidative amination, yielding 2-alkylamino-5-nitropyridines (**179**) with high regioselectivity. Sometimes the amine was used as both solvent and nucleophile, but in many cases a mixture of DMSO/amine was the best solvent. For diethylamine (**170**) other solvents than DMSO was tried without success.

The high regioselectivity is explained by that under the reaction conditions used, the reaction is under thermodynamic control and not kinetic control as in liquid ammonia at  $-33\text{ }^\circ\text{C}$ .

The method developed makes it possible to aminate 3-nitropyridines with substituents that is not stable under the basic conditions used in the vicarious nucleophilic substitution reactions. E.g. 4-cyano-3-nitropyridine (**54**) and methyl 3-nitroisonicotinate (**42**) were aminated in respectively 41 and 48 % yield.

## 6.5. References

1. J. F. Bunnet and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
2. J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.
3. F. Terrier, *Nucleophilic Aromatic Displacement*, VCH, Weinheim, 1991.
4. M. Makosza and K. Stalinski, *Polish J. Chem.*, **73**, 151-161 (1999).
5. H. C. van der Plas and M. Wozniak, *Croat. Chemica Acta*, **59**, 33 (1986).
6. M. Wozniak and H. C. van der Plas, *Acta Chem. Scand.*, **47**, 95 (1993).
7. M. Wozniak, A. Baranski and B. Szpakiewicz, *Liebigs Ann. Chem.*, 875 (1991).
8. B. Szpakiewicz and M. Wozniak, *J. Pract. Chem.*, 341 (1999).
9. I. Millar and H. D. Springall, *The Organic Chemistry of Nitrogen*, 3rd. ed, Clarendon Press, Oxford, 1966.
10. C. J. Pouchert., *The Aldrich library of NMR spectra*, 2nd ed., 1(1), 1418c, Milwaukee : Aldrich Chemical Company, 1983.
11. K. B. Wiberg (ed), *Oxidation in organic chemistry, part A*, Academic press, New York and London, 1965.
12. F. Terrier, *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group.* , VCH, Cambridge, 1991.

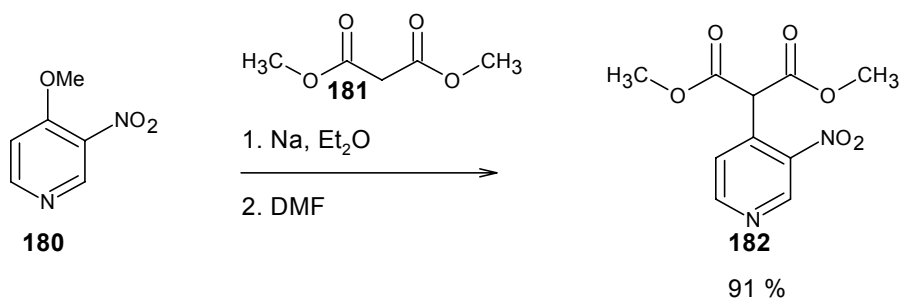
## 7. Nucleophilic alkylations of 3-nitropyridines

### 7.1. Introduction

#### 7.1.1. Reactions of aromatic and heteroaromatic compounds with C-nucleophiles

Carbon-carbon bond formation is of great importance in organic synthesis. Much work has been done on reaction of carbon nucleophiles with nitroarenes, especially nitrobenzenes. Some work has also been done on 3-nitropyridines.

If the nitropyridine contains a good leaving group such as methoxy or a halogen, this group can be substituted with a carbon nucleophile, forming a new carbon-carbon bond as shown in Scheme 7.1.<sup>2</sup>



*Scheme 7.1. Substitution of the methoxy group in 4-methoxy-3-nitropyridine (**180**) by the dimethyl malonate anion.<sup>2</sup>*

If the substrate does not contain a leaving group, nucleophilic substitution can be done by e.g. vicarious nucleophilic substitution of hydrogen (VNS) and oxidative nucleophilic substitution of hydrogen (ONSH).

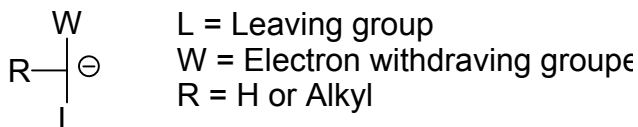
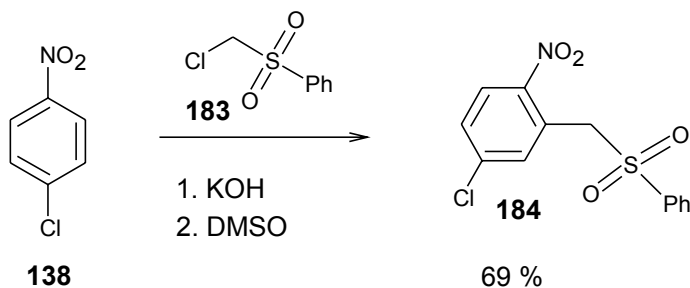
Vicarious nucleophilic substitution

Figure 7.1. Carbon nucleophile for vicarious nucleophilic substitutions

Many carbanions with the structure  $[\text{R}(\text{W})\text{-C-L}]^{\ominus}$  (Figure 7.1.), where L represents a leaving group (Cl, PhO, PhS, etc.) and W is an electron withdrawing group (CN, COR, COOR,  $\text{SO}_2\text{Ar}$ , etc.) stabilizing the formation of the carbanion, have been used in vicarious substitution of hydrogen.<sup>1</sup> One example is shown in Scheme 7.2. where Cl is the leaving group (L), and  $\text{SO}_2\text{Ph}$  is the electron-withdrawing group (W).<sup>3</sup>

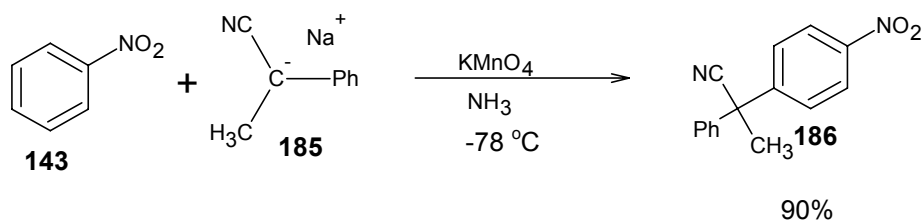
Scheme 7.2. Vicarious nucleophilic substitution on 4-chloronitrobenzene (138) with chloromethyl phenyl sulfone (183).<sup>3</sup>

With the proper nucleophile the vicarious substitution is faster than conventional substitution of halogen or other good leaving groups.<sup>3</sup>

Oxidative nucleophilic substitution

Makosza and co-workers reacted nitroarenes with the 2-phenylpropanenitrile carbanion (**185**) in an oxidative nucleophilic substitution of hydrogen.<sup>9</sup> Scheme 7.3. shows the reaction between nitrobenzene (**143**) and the **185**, which gave a 90% yield of 2-(4-nitrophenyl)-2-phenylpropanenitrile (**186**).

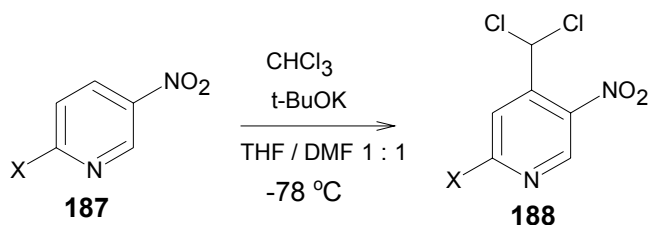




*Scheme 7.3. Oxidative nucleophilic substitution of nitrobenzene (83) with 2-phenylpropanenitrile carbanion (185).<sup>9</sup>*

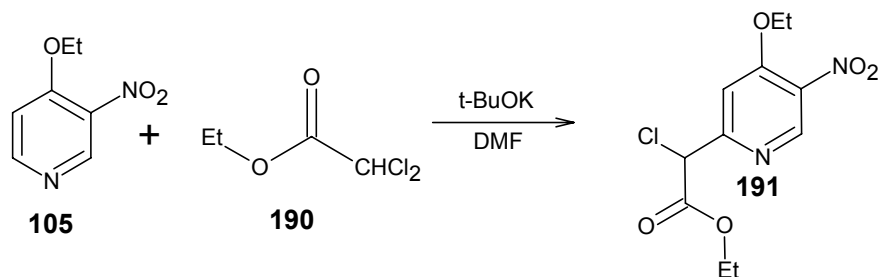
### 7.1.2. Reactions of 3-nitropyridines with C-nucleophiles

Makosza and Owczarczyk reacted 3-nitropyridine (**24**) and 2-substituted 5-nitropyridines (**187**) with chloroform and potassium *t*-butoxid.<sup>4</sup> This yielded the corresponding dihalides (**188**) (Scheme 7.4.) in a vicarious nucleophilic substitution reaction. For **24** the hydrogen in 4-position was replaced. In 2-methoxy-5-nitropyridine (**107**) the hydrogen in position 6 was replaced and with 2-chloro-5-nitropyridine (**189**), the substitution occurred both at 4 and 6 position. The total yields were from 72 to 90 %.



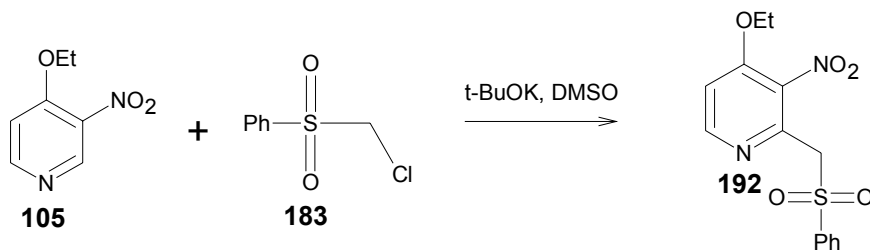
*Scheme 7.4. Reaction of 3-nitropyridines(24) with chloroform and potassium *t*-butoxide.<sup>4</sup>*

Makosza and co-workers also reacted 4-ethoxy-3-nitropyridine (**105**) with ethyl dichloroacetate (**190**) and potassium *t*-butoxide in DMF. The product was ethyl chloro-(4-ethoxy-5-nitropyridine-2-yl)acetate (**191**) in 71% yield (Scheme 7.5.).<sup>5</sup>



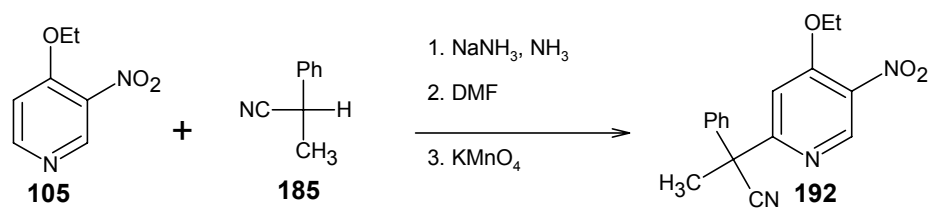
Scheme 7.5. Reaction of 4-ethoxy-3-nitropyridine (**105**) with ethyl dichloroacetate (**190**).

Makosza and Ludwiczak reacted 4-methoxy-3-nitropyridine (**105**) and chloromethyl phenyl sulfone (**183**) in DMSO with potassium *t*-butoxide as base<sup>6</sup>. 4-ethoxy-3-nitro-2-[(phenylsulfonyl)methyl]pyridine (**192**) was isolated in 77 % yield. Notice that the nucleophile attacked in the *ortho* position to the nitro group, in contrast to ethyl dichloroacetate (**190**) which attacked in the *para* position when the 4-position was blocked (Scheme 7.5. vs. Scheme 7.6.).



Scheme 7.6. Reaction of 4-methoxy-3-nitropyridine (**105**) with chloromethyl phenyl sulfone (**183**).<sup>6</sup>

Some examples of oxidative nucleophilic substitution of 3-nitropyridines is also known. Makosza and Stalinski reacted 4-ethoxy-3-nitropyridine (**105**) with the carbanion of 2-phenylpropanenitrile (**185**) in the presence of  $\text{KMnO}_4$  as oxidant<sup>7</sup>. 2-(Ethoxy-5-nitropyridine-2-yl)-2-phenylpropanenitrile (**192**) was isolated in a 43% yield.



*Scheme 7.7. Reaction of 4-ethoxy-3-nitropyridine (**105**) with 2-phenylpropanenitrile carbanion (**185**) and KMnO<sub>4</sub>.<sup>7</sup>*

## 7.2. Results and discussion

As 3-nitropyridines now are readily available from the nitration method developed in Prof. Bakkes group, it was natural to study their reactivity toward carbon nucleophiles. Especially 4-substituted 3-nitropyridines (**40**) have been particularly difficult to obtain, and therefore very little chemistry have been done on these compounds. A good starting point was to use known procedures and try them on new substrates. Since Makosza and Owczarczyk<sup>4</sup> have used chloroform as a vicarious nucleophilic substitution on some 3-nitropyridines, this was tried first.

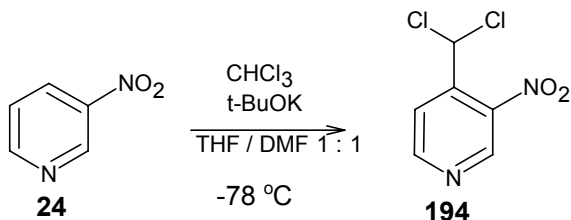
### 7.2.1. Chloroform as nucleophile

No 4-substituted 3-nitropyridines (**40**) were reacted with chloroform by Makosza and Owczarczyk. They studied the regioselectivity for the reaction with 3-nitropyridine (**24**) and 2-substituted 5-nitropyridines (**187**).<sup>4</sup> For these compounds the hydrogen in 4- and/or 6-position were substituted depending on the substituent.

Two problems are described for these reactions. The first is the stability of the chloroform carbanion, which can dissociate to dichlorocarbene (**193**). The second problem is the instability of nitroarene dihalide carbanions, produced in the VNS reaction. These are known to undergo a variety of reactions, mainly via single-electron transfer, which can result in dimerization and polymerization.

As a start Makosza and Owczarczyk's results<sup>4</sup> were repeated (Scheme 7.8.).

3-Nitropyridine (**24**) was reacted with chloroform, with potassium *t*-butoxide as base, at -78 °C in a 1:1 mixture of THF and DMF. 4-Dichloromethyl-3-nitropyridine (**194**) was isolated in a 57% yield (Scheme 7.8.).



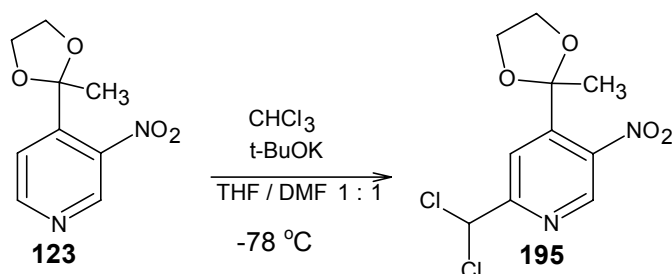
*Scheme 7.8. Vicarious nucleophilic substitution of 3-nitropyridine (**24**) with chloroform.*

This was in accordance with Makosza and Owczarczyk's results. The <sup>1</sup>H-NMR spectrum of the product was in good accordance with the <sup>1</sup>H-NMR data reported

in literature.<sup>4</sup> The 4-position was clearly the favored position for substitution in 3-nitropyridine (**24**).

Since 4-substituted 3-nitropyridines (**40**) have not been reacted under these conditions before, their reactivity and regioselectivity were studied.

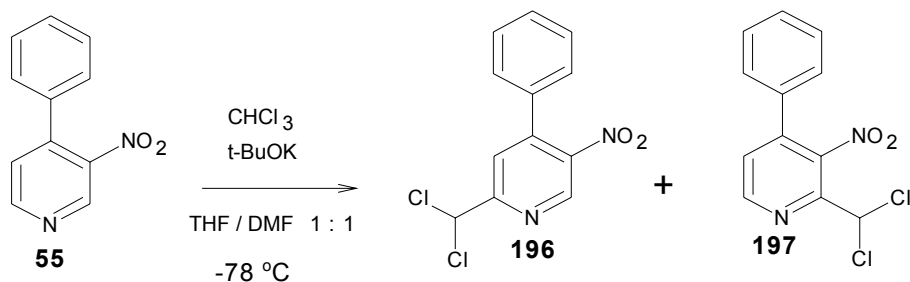
4-(2-Methyl-1,3-dioxolan-2-yl)-3-nitropyridine (**123**) was reacted with chloroform in THF/DMF (1:1) at -78 °C with potassium *t*-butoxide as base (Scheme 7.9.).



Scheme 7.9. Vicarious nucleophilic substitution of 4-(2-methyl-1,3-dioxolan-2-yl)-3-nitropyridine (**123**) with chloroform.

2-(Dichloromethyl)-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (**195**) was isolated in a 83% yield. GC analysis of the crude product showed only traces (1-2%) of other products, which were not isolated and characterized. The position of the substituents were assigned by <sup>1</sup>H-NMR spectroscopy. No references to this compound were found in literature.

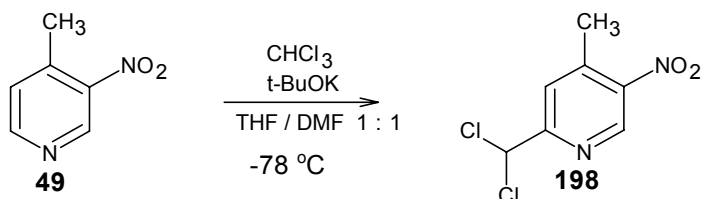
4-Phenyl-3-nitropyridine (**55**) was reacted with chloroform in THF/DMF (1:1) at -78 °C with potassium *t*-butoxide as base (Scheme 7.10.).



Scheme 7.10. Vicarious nucleophilic substitution of 4-phenyl-3-nitropyridine (**55**) with chloroform.

An approximately 5:1 mixture of 2-(dichloromethyl)-4-phenyl-5-nitropyridine (**196**) and 2-(dichloromethyl)-4-phenyl-3-nitropyridine (**197**) was isolated in 72 % total yield. 11 % of the starting compound was recovered. The two isomers were not separated, and were identified by  $^1\text{H-NMR}$  spectroscopy. GC-MS of the product mixture showed two compounds which both had the right molecular ion.

4-Methyl-3-nitropyridine (**49**) was reacted with chloroform in THF/DMF (1:1) at  $-78\text{ }^\circ\text{C}$  with potassium *t*-butoxide as base (Scheme 7.10.).

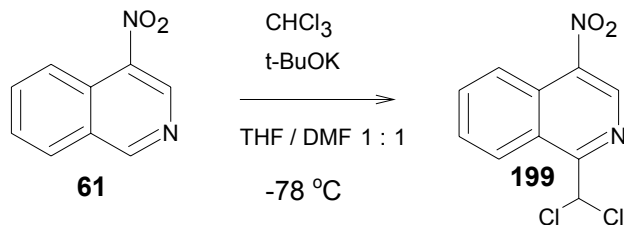


Scheme 7.11. Vicarious nucleophilic substitution of 4-methyl-3-nitropyridine (**49**) with chloroform.

GC analyses of the crude product showed that it contained approximately 60 % starting material (**49**) and 40 % product (**198**). Purification of the crude product yielded 38 % of 2-(dichloromethyl)-4-methyl-5-nitropyridine (**198**). The structure of **198** was assigned by  $^1\text{H-NMR}$  spectroscopy.

The low reactivity of this substrate can be explained by the electron donating methyl group, which makes the nitropyridine less electrophilic.

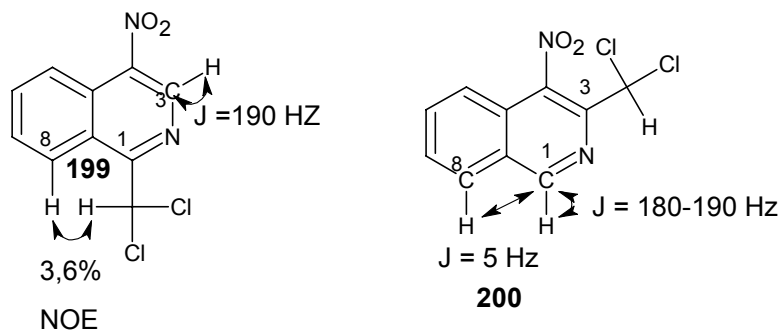
4-Nitroisoquinoline (**61**) was reacted with chloroform in THF/DMF (1:1) at  $-78\text{ }^\circ\text{C}$  with potassium *t*-butoxide as base (Scheme 7.12.).



Scheme 7.12. Vicarious nucleophilic substitution of 4-nitroisoquinoline (**61**) with chloroform and potassium *t*-butoxide.

1-(Dichloromethyl)-4-nitroisoquinoline (**199**) was isolated in 69% yield. Starting compound was recovered (10 %), and only traces of other products were observed by GC analysis.

The position of the substituent in the product was identified by NOE and gated decoupled  $^{13}\text{C}$ -NMR spectroscopy. The two possible isomers (**199** and **200**) are shown in Scheme 7.13.



Scheme 7.13. Two possible products from reaction of 4-nitroisoquinoline (**61**) with chloroform.

Irradiation of the proton in the  $\text{CHCl}_2$  group, gave a positive NOE effect of 3.6 % on what must be the proton at carbon 8 (**199**, Scheme 7.13.). The other possible isomer (3-(dichloromethyl)-4-nitroisoquinoline) (**200**) would not be expected to have any NOE effect by irradiation of the  $\text{CHCl}_2$  proton. The proton in the pyridine ring was identified, and the corresponding carbon was identified by C-H correlation spectroscopy. A gated decoupled  $^{13}\text{C}$ -NMR spectrum showed that this carbon was a doublet with a coupling constant at 190 Hz. This is also in accordance with the **199** isomer. For **200** one would for the C-1 carbon expect an additional vicinal coupling to the C-8 proton at about 5 Hz. Dr. Jaroslav Riha in his Dr. thesis observed a coupling constants at 183.8 and 5.1 Hz for the C-1 carbon in 3-chloro-4-amino-isoquinoline (**132**).<sup>8</sup>

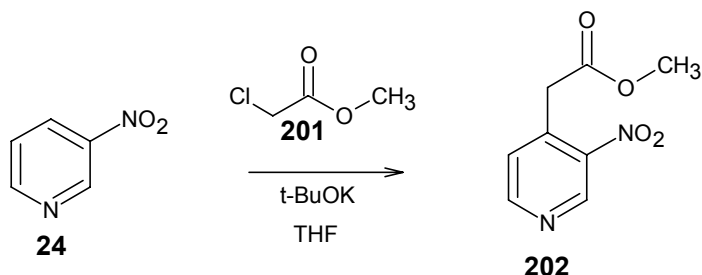
In conclusion, the reaction of 4-substituted 3-nitropyridines (**40**) gave mainly substitution *para* to the nitro group, but for 4-phenyl-3-nitropyridine (**55**) some *ortho* substitution was also observed.

### 7.2.2. Methyl chloroacetate and ethyl 2-chloropropionate as nucleophiles

Some introductory experiments with methyl chloroacetate (**201**) and ethyl 2-chloropropionate (**203**) as nucleophiles were performed. These reagents both have an activated carbon containing a chloro substituent that can act as a leaving group. They should therefore be suitable candidates for vicarious nucleophilic substitution reactions, and they are both commercially available. These reagents have not previously been used as vicarious nucleophilic substitution reagents in reaction with 3-nitropyridines.

None of these experiments were optimized, and more work has to be done on these reaction before any general conclusions can be made. But these experiments could give some useful information about the reactivity of 3-nitropyridines toward carbon nucleophiles.

First 3-nitropyridine (**24**) was reacted with methyl chloroacetate (**201**) in THF with potassium *t*-butoxide as base (Scheme 7.14.).

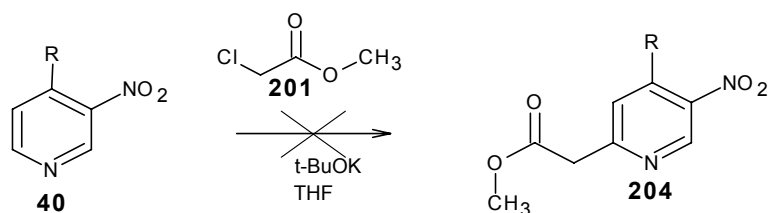


*Scheme 7.14. Reaction of 3-nitropyridine (24) with methyl chloroacetate (201) and potassium *t*-butoxide.*

The reaction was performed at room temperature. Methyl (3-nitropyridin-4-yl)acetate (**201**) was isolated as the only isomer in a 63% yield, only traces of other products (2-3%) were observed by GC analysis of the crude product. The position of the substituent in the isolate product was assigned from <sup>1</sup>H-NMR spectroscopy. No references to this compound were found in the literature.

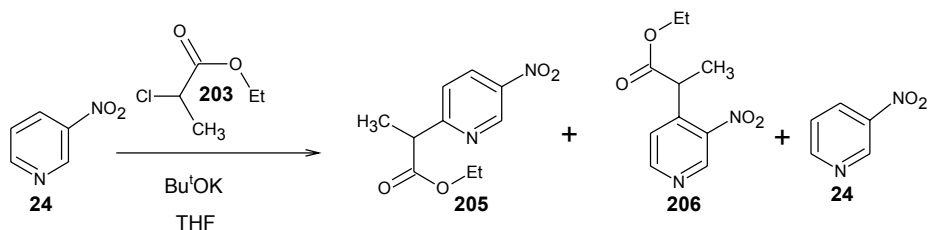
Different 4-substituted 3-nitropyridines (**40**) were then reacted with **201** in THF with potassium *t*-butoxide as base (Scheme 7.15.). The substituents tried were (2-methyl-1,3-dioxolan-2-yl), phenyl and methyl. All of these reactions gave mainly starting compound and a mixture of several other products.





Scheme 7.15. Attempts to react 4-substituted 3-nitropyridines (**40**) with methyl chloroacetate (**201**) and potassium *t*-butoxide.

Ethyl 2-chloropropionate (**203**) was tested as vicarious nucleophilic substitution reagent by reacting it with 3-nitropyridine (**24**) in THF with potassium *t*-butoxide as base (Scheme 7.16.).



Scheme 7.16. Reaction of 3-nitropyridine (**24**) with ethyl 2-chloropropionate (**203**) and potassium *t*-butoxide.

The reaction was performed at room temperature. An approximately 1:1:1 mixture (GC) of 3-nitropyridine (**24**), ethyl 2-(3-nitropyridin-4-yl)propionate (**205**) and ethyl 2-(5-nitropyridin-2-yl)propionate (**206**) was identified in the crude product. The two product isomers (**205** and **206**) were identified by  $^1\text{H-NMR}$  spectroscopy. The two isomers were not separated and not further characterized.

### 7.2.3. General trends

For 3-nitropyridine (**24**) the 4-position was the preferred carbon for substitution both for the chloroform and methyl chloroacetate (**201**) anion nucleophile. The ethyl 2-chloropropionate anion (**203**) nucleophile gave an approximately 1:1 mixture of 4- and 6-substitution.

This distinct difference in regioselectivity between **201** and **203** under the same reaction conditions might be explained by more steric hindrance for the latter nucleophile. This may have changed the equilibrium constant for the reaction between 3-nitropyridine (**24**) and the nucleophile, and by this give more of the most thermodynamic stable product. The difference in thermodynamic stability for the *ortho* and *para* intermediates would be larger with a more bulky nucleophile, favoring the *para* product. It has been reported that the vicarious nucleophilic substitution reaction is very sensitive to the steric hindrance created by the nitro group. Carbanions with substantial steric hindrance tend to react in positions *para* to the nitro group.<sup>10,11</sup>

When the 4-position was blocked by a substituent, reaction with chloroform gave preferably 2-dichloromethyl-4-substituted 5-nitropyridines in good yields. A exception was the 4-phenyl-3-nitropyridine (**55**) where also some of the *ortho* isomer **197**, was observed. The electron donating methyl group gave a low conversion, but high selectively for the *para* isomer, while the electron withdrawing phenyl group gave high conversion but lower regioselectivity.

Methyl chloroacetate (**201**) did not react under the conditions used when the 4-position in 3-nitropyridine was blocked by a substituent. Apparently the 2- and 6-position was not activated enough.

### 7.3. Conclusion

Some 4-substituted 3-nitropyridines (**40**) were reacted with chloroform in vicarious nucleophilic substitution reactions. For all substrates substitution of the hydrogen in the *para* position to the nitro group were favored. Substituents like (2-methyl-1,3-dioxolan-2-yl) and methyl gave the *para* isomer with high selectivity, only traces of the *ortho* isomer were observed. When the substituent was a phenyl group an approximately 5:1 mixture of the *para* and *ortho* isomer was observed.

When methyl chloroacetate (**201**) was tried as vicarious nucleophilic substitution reagent, 3-nitropyridine (**24**) was substituted in the 4-position. With the 4-position blocked by substituents no vicarious nucleophilic substitution were observed.

The more bulkier nucleophile ethyl 2-chloropropionate (**203**) gave a 1:1 mixture of substitution at the 4- and 6- position in 3-nitropyridine (**24**).

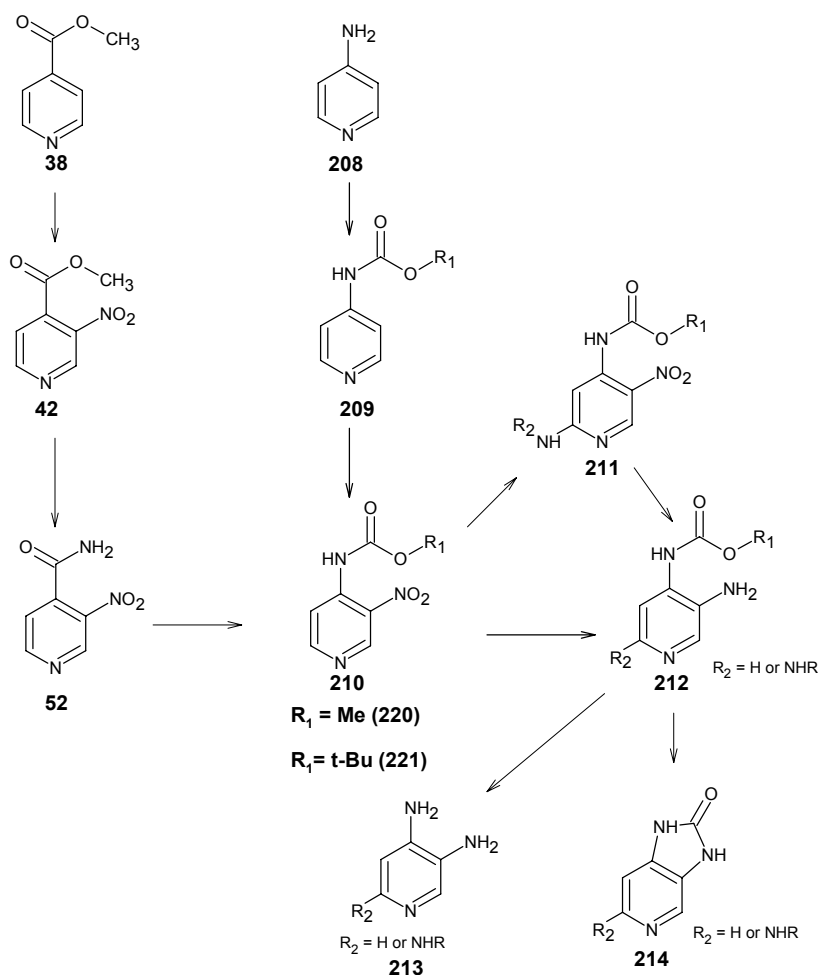
## 7.4. References

1. O. N. Chupakhin, V. N. Charushin, H. C. van der Plas, *Nucleophilic aromatic substitution of hydrogen*, Academic press, 1994, pp 41-49
2. S. P. Gromov, M. M. Bkhaumik, Y. G. Bundel, *Khim. Geterotsykl. Soedin.*, **4**, 488-96 (1987).
3. M. Makosza and J. Golinski, *J. Org. Chem.*, **49**, 1488 (1984).
4. M. Makosza and Z. Owczarczyk, *J. Org. Chem.*, **54**, 5094 (1989).
5. M. Makosza, K. Sienkiewicz and K. Wojciechowski, *Synthesis*, 850 (1990).
6. M. Makosza and S. Ludwiczak, *Pol. J. Chem.*, **72**, 1168 (1998).
7. M. Makosza and K. Stalinski, *Synthesis*, 1631 (1998).
8. J. Riha, *Synthesis and transformations of 3-nitropyridines*, Dr. ing. thesis, NTNU, 2000.
9. M. Makosza, K. Stalinski and C. Klepka, *Chem. Commun.*, 837 (1996).
10. M. Makosza and A. Kwast, *J. of Physical Organic Chemistry*, **11**, 341 (1998).
11. Makosza, B. Chylinska and B. Mydryk, *Liebigs Ann. Chem.* **8** (1984).

## 8. Transformations of 3-nitropyridines

### 8.1. Introduction

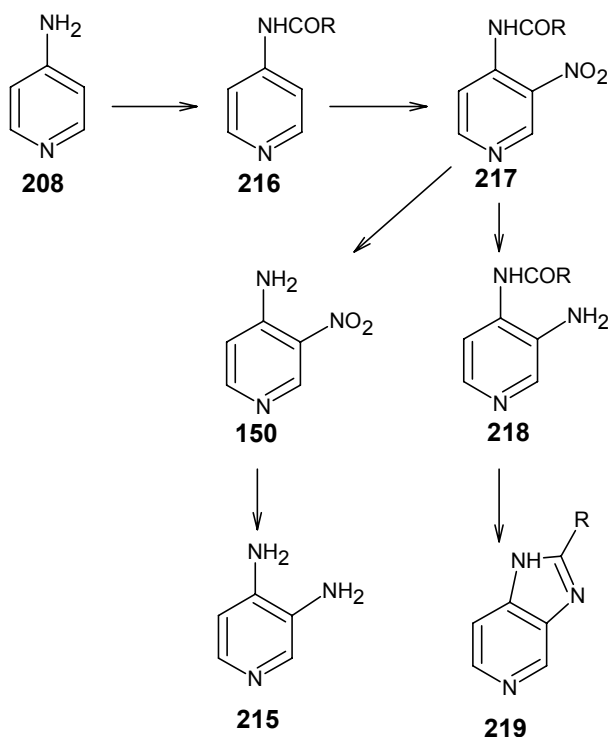
In Prof. Bakke's group several members have been working with parallel strategies toward the synthesis of some substituted pyridines. Two interesting target molecules have been substituted 3,4-diaminopyridine (**213**) and substituted 1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (**214**). The key molecules for both of these molecules were the nitrated carbamates (**210**) (Scheme 8.1.). Two synthetic routes starting from methyl isonicotinate (**38**) and 4-aminopyridine (**208**) were chosen for synthesis of **210**.



Scheme 8.1. Synthetic route to substituted 3,4-diaminopyridines (**213**) and substituted 1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (**214**).

3,4-Diaminopyridine (**215**) and imidazo[4,5-c]pyridines (**219**) have previously been synthesized by Dr. Jaroslav Riha by a similar strategy (Scheme 8.2).<sup>1</sup> The overall yield of **215** was 66% from **208**.

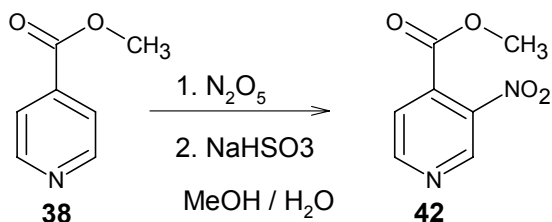
The imidazo[4,5-c]pyridines (**219**) were synthesized in 52 - 65 % overall yield from **208**.



Scheme 8.2. Synthetic route to 3,4-diaminopyridine (**215**) and imidazo[4,5-c]pyridines (**219**).<sup>1</sup>

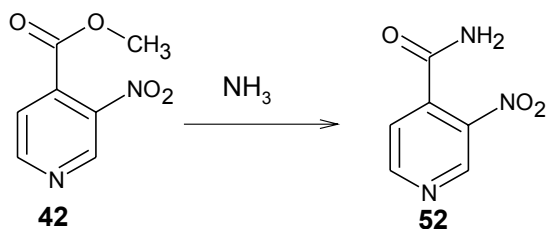
## 8.2. Results and discussion

The key compound in the synthetic route in Scheme 8.1. is the nitrated carbamate **210**, which was assumed to be available from a three step synthesis starting from available methyl isonicotinate (**38**). The nitration of **38** have been reported in Chapter 3, in 75 % yield. In order to find out if this route was a good alternative the two last steps in this synthesis were investigated.



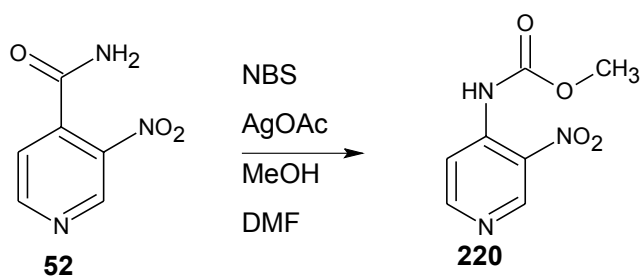
Scheme 8.3. Nitration of methyl isonicotinate (**38**).

Methyl isonicotinate (**38**) was nitrated by  $\text{N}_2\text{O}_5$  and sodium bisulfite in methanol/water as described in procedure E, Chapter 3. Methyl 3-nitroisonicotinate (**42**) was isolated in 75 % yield.



Scheme 8.4. Synthesis of 3-nitroisonicotinamide (**52**) from reaction of methyl 3-nitroisonicotinate (**42**) and ammonia.

The procedure for conversion of the methyl ester group to an amide was based on a literature procedure for the benzene analogue.<sup>2</sup> Methyl 3-nitroisonicotinate (**42**) was dissolved in 28 % aqueous ammonia solution and refluxed. The solvent was evaporated and the crude product was purified by flash chromatography to give a 74 % yield of 3-nitroisonicotinamide (**52**).



Scheme 8.5. Hofmann rearrangement of 3-nitroisonicotinamide (**52**).

The amide substituent in 3-nitroisonicotinamide (**52**) was transformed by a Hofmann rearrangement to the methyl carbamate (**220**). A procedure developed by Jew and coworkers was used.<sup>3</sup> This literature procedure was chosen because it reported that the amide group in nicotinamide was transformed into its corresponding carbamate in high yield.

AgOAc, **52** and methanol was dissolved in dry DMF and NBS in dry DMF was added slowly. The reaction was stirred overnight under an argon atmosphere at room temperature. The solvent was evaporated to give a crude product that was washed and purified by flash chromatography to give a 24 % yield of methyl *N*-(3-nitropyridin-4-yl) carbamate (**220**).

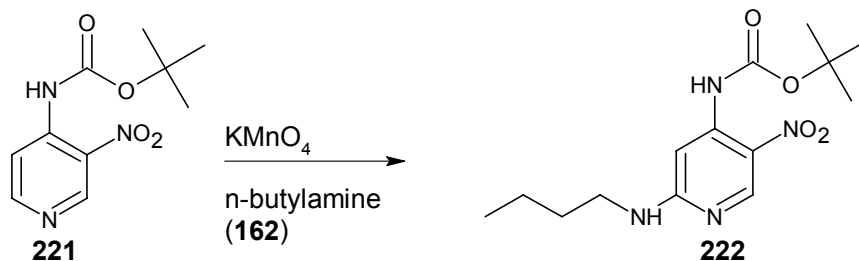
The conversion seemed to be good from <sup>1</sup>H-NMR spectroscopy of the reaction mixture, but probably some of the carbamate decomposed during work up on the silica column. Attempts to avoid column chromatography by crystallization failed.

Since the yield in the Hofmann rearrangement was low, alternative routes to **220** are under investigation by other members of Prof. Bakkes group (Scheme 8.1.). Introductory experiments by Dr. Hanna S. H. Gautun and ERASMUS student Miguel González-Garces Perez have shown that both the methyl and *t*-butyl carbamate (**209**) of 4-aminopyridine (**208**) can be made in excellent yields. These carbamates have also been nitrated by N<sub>2</sub>O<sub>5</sub> and sodium bisulfite to give respectively methyl *N*-(3-nitropyridin-4-yl) carbamate (**220**) and *t*-butyl *N*-(3-nitropyridin-4-yl) carbamate (**221**).

The synthetic route to 3,4-diaminopyridine (**215**) from methyl isonicotinate via a Hofmann rearrangement was not competitive with the route developed by dr. Jaroslav Riha (Scheme 8.2.), because the yield of the Hofmann rearrangement was too low.

Some preliminary experiments were done to see if it was possible to do oxidative aminations on the nitrated carbamates (Scheme 8.6.).





Scheme 8.6. Oxidative amination of *t*-butyl-3-nitropyridin-4-yl carbamate.

*t*-Butyl *N*-(3-nitropyridin-4-yl) carbamate (**221**) provided by Dr. Hanna S. H. Gautun was dissolved in *n*-butylamine (**162**) and then  $\text{KMnO}_4$  was added. After 3 hours of stirring, most of the starting material was unreacted. DMSO was added so that the solvent was a 1:1 mixture of DMSO/*n*-butylamine. After two more hours of stirring the reaction was stopped. Work up of the reaction mixture gave *t*-butyl *N*-(2-*n*-butylamino-5-nitropyridin-4-yl) carbamate (**222**) in 56 % yield. The only other compound observed in the reaction mixture was unreacted starting material. Further optimization must be done in order to increase the conversion and thereby also the yield. For details about the oxidative amination, see Chapter 6.

### 8.3. Conclusion

Methyl 3-nitropyridin-4-yl carbamate (**220**) was synthesized in three steps in a overall yield of 13 % from methyl isonicotinate (**38**). The nitration of the methyl isonicotinate (**38**) gave a 75 % yield of methyl 3-nitroisonicotinate (**42**), which was converted to 3-nitroisonicotinamide (**52**) in 74 % yield. The yield of the Hofmann rearrangement of the amid was only 24 %. Due to the low overall yield this route was abandoned. Another route starting from 4-aminopyridine (**208**) are currently under investigation by other members of Prof. Bakke's group.

*t*-Butyl *N*-(3-nitropyridin-4-yl) carbamate (**221**) was aminated with *n*-butylamine (**162**) and  $\text{KMnO}_4$  to give *t*-butyl *N*-(2-*n*-butylamino-5-nitropyridin-4-yl) carbamate (**222**) in 56 % yield. This reaction was not optimized. The result showed that oxidative amination can be used on pyridine carbamates, and that target molecules **213** and **214** (Scheme 8.1.) probably can be synthesized with several different alkylamino substituents.

#### 8.4. References

1. J. M. Bakke and J. Riha, *J. Heterocyclic Chemistry*, **36**, 1143 (1999).
2. M. Charton, R. Gawinecki, D. Rasala, W. Kraus, P. Tomasik, *Chem. Scrip.*, **25**, 340 (1985).
3. S. Jew, H. G. Park, H. Park, M. Park and Y. Cho, *Tetrahedron Lett.*, **31**, 1559 (1990).

## 9. Experimental

### 9.1. General

#### *Chemicals*

All chemicals and solvents were of synthetic grade and were used without further purification unless otherwise indicated. DMSO, DMF, THF was distilled and stored over molecular sieves. Nitromethane was purified by a reported procedure.<sup>1</sup> Dinitrogen pentoxide was prepared from dinitrogen tetroxide and ozone and stored at -30 °C.<sup>2</sup>

#### *Instrumentation*

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on Bruker Avance DPX300 or 400 instruments. Chemical shifts are reported in ppm relative to tetramethylsilane or sodium 3-(trimethylsilyl)propionate-2,2,3,3-*d*<sub>4</sub> that was used in deuterium oxide.

Infrared spectra were obtained on a Nicolet 20SXC Ft-IR Spectrometer.

MS spectra were recorded on a Finnigan MAT 95 XL instrument.

GC analyses were performed on a Chrompack 9000 with split injection and CP-Sil5CB column (25 m, 0.32 mm ID, D<sub>f</sub> 0.4 μm) with a flame ionisation detector and a Shimadzu C-R5A integrator.

GC-MS spectra were recorded on a Fision Instruments TRIO 1000 GC-MS System.

Melting points are uncorrected and were measured using a Büchi melting point apparatus.

Elemental Analyses were determined by the Laboratory of Organic Elemental Analysis, Prague Institute of Chemical Technology, Czech Republic.

## 9.2. Nitration

### 9.2.1. General nitration procedures

#### *Procedure A*

Sulphur dioxide (25ml) and dinitrogen pentoxide (2.7 g, 25 mmol) were mixed at -30 °C with stirring. The substrate (~12.5 mmol) was added with a syringe through a septum or as a solid in portions. After a reaction period of 5 minutes, the solution was poured onto ice (100 g).

#### *Procedure C*

A solution was made of either nitromethane or dichloromethane (12.5 ml) and dinitrogen pentoxide (1.35 g, 12.5 mmol) at 0 °C with stirring. The substrate (~6.25 mmol) was either added with a syringe through a septum or as a solid in portions. This resulted in a slurry which after 5 minutes was poured into a solution of water (50 ml) containing sodium bisulfite (2.0 g, 19 mmol).

#### *Procedure D*

A solution was made of either nitromethane or dichloromethane (12.5 ml) and dinitrogen pentoxide (1.35g, 12.5 mmol) at 0 °C with stirring. The substrate (~6.25 mmol) was either added with a syringe through a septum or as a solid in portions. This resulted in a slurry which after 5 minutes was poured into a solution of water (50 ml) containing sodium bisulfite (2.0 g, 19 mmol). The pH of the solution was adjusted with 3N HNO<sub>3</sub> before and after the addition of the organic phase.

#### *Procedure E*

A solution was made of either nitromethane or dichloromethane (12.5 ml) and dinitrogen pentoxide (1.35g, 12.5 mmol) at 0 °C with stirring. The substrate (~6.25 mmol) was either added with a syringe through a septum or as a solid in portions. This resulted in a slurry which after 5 minutes was poured into a solution of water (12.5 ml) and methanol (37.5 ml) containing sodium bisulfite (2.0 g, 19 mmol).

### *Work up procedure*

The acidic water solution was allowed to react at room temperature for 2-100 hours before extraction with dichloromethane (3x 80 ml). The combined organic extracts were washed with 10% HCl solution (150 ml), saturated bicarbonate solution (150 ml) and water (150 ml), dried over MgSO<sub>4</sub> and concentrated.

### **9.2.2. Nitration of substituted pyridines**

#### 3-Methyl-5-nitropyridine (46)

3-Methylpyridine (**87**) was nitrated by procedure A. The product, 3-methyl-5-nitropyridine (**46**), was collected as a yellow solid in 26% yield. The melting point was 94.5- 96.0 °C (lit.<sup>10</sup> 95.5- 96.5 °C).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.26 (1H, d, J = 2.3 Hz, H-2), 8.75 (1H, d, J = 1.0 Hz, H-6) 8.30 (1H, dd, J = 2.3, 1.0 Hz, H-4), 2.5 (3H, s, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 156, 144, 143, 134, 132, 19 ppm.

IR (KBr): 3042 (m), 2967 (w), 2931 (w), 2867 (w), 1610 (w), 1596 (w), 1570 (m), 1522 (s), 1450 (m), 1354 (s), 1317 (w), 1250 (w), 1149 (m), 1112 (w), 1045 (w), 1025 (m), 976 (w), 926 (w), 902 (m), 805 (s), 745 (m), 892 (m), 875 (m), 559 (w) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 139 (M+1, 3), 138 (M, 63), 92 (100), 86 (22), 84 (44), 69 (8), 65 (80), 57 (10), 51 (11), 49 (47).

#### 4-Methyl-3-nitropyridine (49)

4-Methylpyridine (**65**) was nitrated by procedure A. The product, 4-methyl-3-nitropyridine (**49**), was isolated in 54% yield as a yellow oil. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR data were in accordance with literature data.<sup>7</sup>

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.15 (1H, s, H-2), 8.64 (1H, d, J = 5.02 Hz, H-6), 7.30 (1H, d, J = 5.02 Hz, H-5), 2.15 (3H, s, CH<sub>3</sub>) ppm.

$^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ): 153, 146, 146, 143, 128, 20 ppm.

IR (neat): 3062 (w), 2990 (w), 2933 (w), 2865 (w), 1609 (s), 1554 (m), 1524 (s), 1486 (m), 1445 (m), 1403 (w), 1380 (w), 1351 (s), 1297 (w), 1240 (m), 1221 (m), 1060 (w), 1036 (w), 999 (w), 932 (w), 863 (s), 841 (m), 802 (m), 750 (m), 679 (m)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %): 139 (M+1, 1), 138 (M, 11), 121 (37), 92 (24), 88 (12), 86 (65), 84 (100), 65 (24), 51 (28), 49 (76), 47 (11).

#### 4-Acetyl-3-nitropyridine (37)

4-Acetylpyridine (**223**) was nitrated by procedure E, 4-acetyl-3-nitropyridine (**37**) was obtained in 58% yield, as a yellow solid with a melting point of 33.0-34.5 °C (lit.<sup>7</sup> 35-36.5 °C).  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR data were in accordance with literature data.<sup>7</sup>

$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ): 9.38 (1H, s, H-2), 8.97 (1H, d, J = 4.85 Hz, H-6), 7.36 (1H, d, J = 4.85 Hz, H-5), 2.60 (3H, s,  $\text{CH}_3\text{CO}$ ) ppm.

$^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ): 155, 146, 145, 141, 121, 198, 30 ppm.

IR (KBr): 3188 (w), 3078 (w), 3017 (w), 2922 (w), 2873 (v), 1772 (v), 1715 (s), 1607 (m), 1527 (s), 1480 (w), 1410 (w), 1355 (s), 1284 (w), 1239 (s), 1192 (w), 1147 (w), 1079 (m), 1053 (m), 880 (s), 772 (m), 602 (m)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %): 167 (M+1, 1), 166 (M, 14.2), 152 (4), 151 (48), 136 (6), 124 (11), 78 (14), 52 (6), 51 (10), 50 (21), 44 (7), 43 (100).

#### 3-Nitropyridine-4-carboxylic acid (51)

Pyridine-4-carboxylic acid (**62**) was nitrated by Procedure A. The reaction mixture was continuously extracted with diethylether for 5 hours. The organic phase was concentrated and the crude product was recrystallized from methanol/water to give light yellow needles of 3-nitropyridine-4-carboxylic acid (**51**) in 60% yield. The product decomposed at 225°C (lit.<sup>5</sup> 222 °C decomp.).

$^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and IR spectra were in accordance with literature data<sup>3,4</sup>.

$^1\text{H-NMR}$  (300 MHz, DMSO): 9.26 (1H, s, H-2), 9.01 (1H, d,  $J = 4.9$  Hz, H-6), 7.86 (1H, d,  $J = 4.9$  Hz, H-5) ppm.

$^{13}\text{C-NMR}$  (75 MHz, DMSO): 164, 155, 150, 145, 136, 123 ppm.

IR (KBr): 3060(v), 2427 (m), 1854 (m), 1728 (m), 1613 (w), 1556 (s), 1478 (v), 1412 (w), 1375 (s), 1302 (s), 1268 (s), 1233 (m), 1187 (m), 1152 (m), 1058 (s), 810 (m), 796 (m), 697 (m), 663 (s)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %): 169 (M+1, 6), 168 (M, 85), 124 (10), 123 (32), 122 (100), 106 (10), 94 (80), 78 (35), 77 (7), 76 (12), 67 (27), 66 (21).

#### Methyl 3-nitroisonicotinate (42)

Methyl isonicotinate (**38**) was nitrated by procedure E, in 75% yield. Methyl 3-nitroisonicotinate (**42**) was isolated as orange solid with a melting point of 88.0-92.0 °C (lit.<sup>4</sup> oil, bp. 140.5-142.0 °C (10 torr)).

$^{13}\text{C-NMR}$ <sup>3</sup>,  $^1\text{H-NMR}$ <sup>4</sup> and IR<sup>4</sup> were in accordance with literature.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.18 (1H, s, H-2), 8.85 (1H, d,  $J = 5.0$  Hz, H-6) 7.71 (1H, d,  $J = 5.0$  Hz, H-5) 3.86 (3H, s,  $\text{CH}_3$ ) ppm.

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 169, 157, 148, 145, 138, 123, 57 ppm.

IR (KBr): 3100 (v), 3070 (m), 2800 (w), 2700-2200 (w, br) 1750 (s), 1650 (m), 1590 (m), 1490 (s), 1350 (s), 1313 (s), 1251 (s), 1096 (s), 1018 (m), 1009 (s), 882 (m), 857 (m), 830 (s), 772 (s), 726 (s), 550 (s), 536 (s), 422 (s)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %): 183 (M+1, 8), 182 (M, 85), 152( 8), 151 (100), 137 (11), 136 (100), 122 (6), 121 (5), 106 (10), 94 (6), 93 (43), 78 (66), 51(13), 50 (40).

4-Cyano-3-nitropyridine (54)

4-Cyanopyridine (**64**) was nitrated by procedure A. The crude product was crystallized from diethylether/pentane (3:1) to give light brown needles of 4-cyano-3-nitropyridine (**54**) in 33% yield. The melting point was 42.0-43.5 °C (lit.<sup>4</sup> 39.5- 41.0).

IR spectrum was in accordance with literature data.<sup>4</sup>

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.61 (1H, s, H-2), 9.14 (1H, d, J = 4.9 Hz, H-6) 7.86 (1H, d, J = 4.9 Hz, H-5) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 156, 147, 143, 128, 116, 113 ppm.

IR (KBr): 3099 (w), 3056 (w), 2869 (w), 2242 (w), 1604 (s), 1548 (s), 1530 (s), 1405 (m), 1350 (s), 1222 (m), 1178 (w), 1045 (w), 861 (s), 850 (m), 781 (w), 761 (m), 693 (m), 571 (s) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 150 (M+1, 4), 149 (M, 63), 103 (100), 91 (9), 76 (48), 75 (12), 64 (5).

4-Phenyl-3-nitropyridine (55)

4-Phenylpyridine (**24**) was nitrated using procedure D. The pH in the water phase was adjusted to around 1 before addition of the organic phase. 4-Phenyl-3-nitropyridine (**55**) was isolated in 69% yield as a yellow solid with a melting point of 72.5-73.5 °C (lit.<sup>9</sup> 72.0-72.5 °C.).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.09 (1H, s, H-2), 8.82 (1H, d, J = 5.05 Hz, H-5), 7.43 (1H, d, J = 5.05 Hz, H-6), 7.45-7.55 (3H, m, phenyl protons), 7.35 -7.4 (2H, m, phenyl protons) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 153, 146, 145, 144, 134, 130, 129, 128, 126 ppm.

IR (KBr): 3051 (w), 2868 (w), 1594 (m), 1536 (s), 1518 (s), 1473 (w), 1443 (w), 1403 (w), 1357 (s), 1265 (w), 1221 (w), 1188 (m), 1040 (w), 849 (s), 777 (m), 750 (s), 694 (m), 614 (w), 588 (w), 553 (w), 516 (w).

MS (m/z, rel. int. %): 201 (M+1, 3), 200 (M, 26), 199 (9), 184 (5), 173 (13), 172 (100), 171 (23), 170 (36), 155 (17), 154 (12), 147 (6), 145 (21), 144 (17), 143 (18), 142 (9), 141 (8), 140 (6), 130 (9), 129 (7), 128 (18), 127 (99), 126 (39), 117



(15), 116 (17), 115 (45), 102 (6), 101 (19), 87 (7), 77 (41), 76 (10), 75 (16), 74 (11), 63 (20), 51 (18).

#### 5-Phenyl-3-nitropyridine (56)

3-Phenylpyridine (**225**) was nitrated by procedyre D. The pH of the bisulfite solution was adjusted to 1, before addition of the organic phase. 5-Phenyl-3-nitropyridine (**56**) was isolated as a yellow solid with a melting point of 91.0-92.0 °C (lit.<sup>8</sup> 92.5-93.5 °C)

<sup>1</sup>H-NMR, <sup>13</sup>C-NMR and IR spectra were in accordance with literature.<sup>8</sup>

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.43 (1H, d, J = 2.4 Hz, H-2), 9.16 (1H, d, J = 2.0 Hz, H-6) 8.68 (1H, dd, J = 2.4, 2.0 Hz, H-4) 7.4-7.65 (5H, m, Phenyl protons) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 153.6, 144.9, 143.8, 138.0, 135.6, 129.9, 129.8, 129.3, 127.7 ppm.

IR (KBr): 3033 (w), 2921 (w), 2852 (w), 1593 (w), 1562 (m), 1522 (s), 1499 (m), 1446 (w), 1352 (s), 1236 (w), 1163 (w), 1018 (w), 908 (w), 885 (m), 772 (m), 749 (m), 703 (m), 695 (m), 673 (w), 612 (w), 562 (w) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 201 (M+1, 13), 200 (M, 100), 155 (11), 154 (67), 153 (8), 128 (10), 127 (46), 126 (11), 77 (18).

#### 4-(1,3-Dioxolan-2-yl)-3-nitropyridine (53)

##### *4-(1,3-Dioxolan-2-yl)-pyridine (121)*

Pyridine-4-carbaldehyde (**120**) (6.72 g, 0.063mol) was dissolved in toluene (20 ml), and treated dropwise with concentrated hydrochloric acid (5 ml) . 1,2-Ethandiol (12 ml) and *p*-toluenesulfonic acid (0.8 g, 0.0042 mol ) were added, and the solution refluxed, with azeotropic removal of water, for 5.5 hours. The reaction mixture was then cooled, quenched with sodium carbonate (8 g), and stirred for 15 minutes. Water (30 ml) was added to the solution to dissolve excess sodium carbonate. The two phases where separated, the water phase was extracted with ethylacetate (3 x 100ml ). The organic layers were combined and concentrated to give 4-(1,3-dioxolan-2-yl)-pyridine (**121**) (6.60 g, 85% yield) as a

solid with a melting point around room temperature. The purity was 96% from GC.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.66 (2H, d,  $J = 6.0$  Hz, H-2 and H-6), 7.40 (2H, d,  $J = 6.0$  Hz, H-3 and H-5), 5.83 (1H, s, R'R''CH), 4.08 (4H, m,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ) ppm.

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 150, 147, 121, 102, 77 ppm.

IR (KBr): 3040 (w), 2979 (w), 2691 (w), 1728 (m), 1605 (m), 1566 (m), 1479 (m), 1411 (s), 1394 (m), 1329 (m), 1306 (m), 1289 (s), 1235 (m), 1105 (s), 1063 (m), 1027 (m), 984 (m), 942 (m), 821 (m), 758 (w), 707 (w), 686 (w), 639 (w)  $\text{cm}^{-1}$ .

MS ( $m/z$ , rel. int. %): 152 (M+1, 2), 151 (M, 10), 150 (M-1, 20), 149 (25), 121 (5), 119 (10), 106 (15), 103 (49), 93 (5), 92 (7), 91 (6), 79 (20), 76 (50), 73 (100).

#### *4-(1,3-Dioxolan-2-yl)-3-nitropyridine (53)*

4-(1,3-Dioxolan-2-yl)-pyridine (**121**) was nitrated by procedure C.

4-(1,3-Dioxolan-2-yl)-3-nitropyridine (**53**) was isolated as a yellow oil in a 35% yield after flash chromatography on silica gel (eluent: dichloromethane).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.15 (1H, s, H-2), 8.86 (1H, d,  $J = 5.1$  Hz, H-6), 7.74 (1H, d,  $J = 5.1$  Hz, H-5), 6.54 (1H, s, R'R''CH), 4.05 (4H, m,  $\text{OCH}_2\text{CH}_2\text{O}$ ) ppm.

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 154, 146, 142, 138, 121, 99, 66 ppm.

IR (KBr) 3040 (w), 2963 (w), 2892 (w), 1728 (s), 1605 (m), 1566 (m), 1478 (m), 1411 (s), 1394 (s), 1329 (m), 1306 (s), 1283 (s), 1235 (m), 1105 (s), 1063 (m), 1027 (m), 1010 (w), 984 (w), 942 (w), 821 (s)  $\text{cm}^{-1}$ .

MS ( $m/z$ , rel. int. %): 197 (M+1, 5), 195 (M-1, 5), 180 (5), 179 (40), 150 (6), 149 (83), 136 (12), 123 (7), 122 (95), 109 (10), 106 (20), 105 (48), 94 (35), 78 (42), 73 (100).

4-Nitroisoquinoline (61)

Isoquinoline (**226**) was nitrated by procedure E.

4-Nitro-isoquinoline (**61**) was isolated as a yellow solid in 42 % yield, with melting point of 60.0-61.5°C (lit.<sup>6</sup> 63 °C)

The <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were in accordance with literature.<sup>7</sup>

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.48 (1H, s, H-1), 9.30 (1H, s, H-3), 8.69 (1H, d, J = 8.7 Hz, H-5), 8.16 (1H, d, J = 7.1 Hz, H-8), 8.00 (1H, dd, J = 8.1, 7.1 Hz, H-6), 7.82 (1H, dd, J = 8.7, 8.1 Hz, H-7) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 158, 141, 141, 134, 129, 129, 128, 127, 123 ppm.

IR (KBr): 3064 (w), 2856 (w), 2336 (w), 1733 (w), 1700 (w), 1624 (s), 1584 (s), 1580 (m), 1517 (s), 1495 (m), 1410 (m), 1348 (s), 1321 (s), 1255 (s), 1219 (m), 1189 (s), 921 (m), 886 (m), 796 (m), 775 (s), 734 (m), 684 (m) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 175 (M+1, 8), 174 (M, 81), 144 (26), 133 (7), 129 (19), 128 (100), 127 (5), 116 (21), 105 (6), 102 (14), 101 (36), 100 (6), 89 (13), 77 (28), 76 (8), 75 (32), 74 (12), 72 (9), 62 (9), 59 (11), 57 (11), 55 (11), 51 (24).

### 9.3. The reaction mechanism of nitration of pyridine

The reaction intermediates formed when 3-acetylpyridine (**78**) and 3-methylpyridine (**87**) were studied using low temperature NMR. The NMR samples were prepared as described below.

#### 9.3.1. From the reaction of 3-acetylpyridine

3-Acetylpyridine (**78**) (375 mg, 3.10 mmol) was added to a solution of  $N_2O_5$  (6.4 mmol) in nitromethane (6 ml). After 5 min the suspension was poured into  $D_2O$  (6 ml) containing  $NaHSO_3$  (15.2 mmol) kept at  $-5\text{ }^\circ\text{C}$ . A sample of the aqueous phase ( $\sim 0.4$  ml) was as rapid as possible transferred to an NMR tube containing  $CD_3OD$  (0.4 ml) precooled to  $-78\text{ }^\circ\text{C}$ . The tube was inserted to the NMR instrument precooled to  $-30\text{ }^\circ\text{C}$

##### *Compound 80:*

$^1\text{H-NMR}$  (300 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 8.70 (1H, s, H-2), 7.76 (1H, dd,  $J_{6,5} = 7.39$  Hz,  $J_{6,4} = 1.42$  Hz, H-6), 5.64 (1H, dd,  $J_{5,6} = 7.39$  Hz,  $J_{5,4} = 5.88$  Hz, H-5), 4.90 (1H, dd,  $J_{4,5} = 5.88$  Hz,  $J_{4,6} = 1.42$  Hz, H-4), 2.5 (3H, s,  $CH_3$ ).

$^{13}\text{C-NMR}$  (75 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 125 (C-6), 108 (C-5), 55 (C-4), 25 ( $CH_3$ ). Shift values for (C-2), (C-3) and (CO) were not observed.

Compound **81**:  $^1\text{H-NMR}$  (300 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 7.85 (1H, dd,  $J_{4,5} = 6.54$  Hz,  $J_{4,6} = 1.32$  Hz, H-4), 7.48 (1H, dd,  $J_{6,5} = 7.48$  Hz,  $J_{6,4} = 1.32$  Hz, H-6), 7.10 (1H, s, H2), 5.93 (1H, dd,  $J_{5,4} = 7.85$  Hz,  $J_{5,6} = 7.48$  Hz, H-5), 2.5 (3H, s,  $CH_3$ ).

$^{13}\text{C-NMR}$  (75 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 134 (C-6), 130 (C-4), 109 (C-5), 69 (C-2), 25 ( $CH_3$ ). Shift value for (C3) was not observed.

Compound **82**:  $^1\text{H-NMR}$  (300 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 8.60 (1H, s, H-2), 6.81 (1H, dd,  $J_{4,5} = 9.67$  Hz,  $J_{4,6} = 1.61$  Hz, H-4), 6.50 (1H, dd,  $J_{6,5} = 10.19$  Hz,  $J_{6,4} = 1.61$  Hz, H-6), 6.17 (1H, dd,  $J_{5,4} = 9.67$  Hz,  $J_{5,6} = 10.19$  Hz, H-5), 2.5 (3H, s,  $CH_3$ ).  $^{13}\text{C}$  spectrum was not obtained.

Compound **83**:  $^1\text{H-NMR}$  (300 MHz,  $D_2O-CD_3OD$ ,  $-10\text{ }^\circ\text{C}$ ) 6.61 (1H, dd, H4,  $J_{4,5} = 11.13$  Hz,  $J_{4,6} = 1.03$  Hz, H-4), 6.43 (1H, dd,  $J_{5,4} = 11.13$  Hz,  $J_{5,6} = 2.59$  Hz, H-

5), 5.47 (1H, s, H-2), 4.83 (1H, dd,  $J_{6,5} = 2.59$  Hz,  $J_{6,4} = 1.03$  Hz, H-6), 2.00 (3H, s, COCH<sub>3</sub>).

<sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -10 °C) 131 (C-5), 123 (C-4), 72 (C-2), 69 (C-6). Shift values for (C-3) and (COCH<sub>3</sub>) were not observed.

### 9.3.2. From the reaction of 3-methylpyridine (**87**)

3-methylpyridine (**87**) (0.853 g, 9.16 mmol) in dichloromethane (12.5ml) was reacted with N<sub>2</sub>O<sub>5</sub> (1.35 g, 12.5 mmol) at 0 °C for 10min. The obtained slurry was filtered and the crystals (3-methyl-*N*-nitropyridiniumnitrate, **227**) washed with dichloromethane, dried with N<sub>2</sub> and placed at -20 °C overnight. **227** (0.12 g, 0.60 mmol) was dissolved in 0.5 ml solvent in an NMR tube, and sodium bisulfite (0.15 g, 1.44 mmol) in D<sub>2</sub>O-CD<sub>3</sub>OD (1:2) (0.5 ml) was added at -78 °C. The NMR tube was then placed in the NMR instrument at the appropriate temperature.

Compound **88b**: <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -50 °C) 7.69 (1H, dd,  $J_{6,5} = 7.98$  Hz,  $J_{6,4} = 1.52$  Hz, H-6), 7.54 (1H, s, H-2), 5.56 (1H, dd,  $J_{5,6} = 7.98$  Hz,  $J_{5,4} = 5.62$  Hz, H-5), 4.33 (1H, dd,  $J_{4,5} = 5.62$  Hz,  $J_{4,6} = 1.52$  Hz, H-4), 2.05 (3H, s, CH<sub>3</sub>).

<sup>13</sup>C-NMR (75 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -50 °C) 127 (C-6), 123 (C-2), 110 (C-5), 64 (C-4), 20.6 (CH<sub>3</sub>). Shift values for C3 not observed.

Compound **88a**: <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -55 °C) 7.4 (1H, d,  $J_{6,5} = 7.9$ , H-6), 6.3 (1H, s, H-2), 6.2 (1H, d,  $J_{4,5} = 7.4$  Hz, H-4), 5.7 (1H, dd,  $J_{5,4} = 7.4$  Hz,  $J_{5,6} = 7.9$  Hz, H-5).

<sup>13</sup>C (75 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -55 °C) 124 (C-4), 123 (C-6), 113 (C-5), 77 (C-2). Shift value for (C-3) was not observed.

Compound **89**: <sup>1</sup>H-NMR (300 MHz, D<sub>2</sub>O-CD<sub>3</sub>OD, -50 °C) 6.26 (1H, dd,  $J_{5,4} = 9.99$  Hz,  $J_{5,6} = 3.05$  Hz, H-5), 6.11 (1H, dd,  $J_{4,5} = 9.99$  Hz,  $J_{4,6} = 2.34$  Hz, H-4), 5.29 (1H, s, H-2), 4.68 (1H, dd,  $J_{6,5} = 3.05$  Hz,  $J_{6,4} = 2.34$  Hz, H-6), 1.86 (3H, s, CH<sub>3</sub>).

Experimental

$^{13}\text{C}$ -NMR (75 MHz,  $\text{D}_2\text{O}-\text{CD}_3\text{OD}$ ,  $-50\text{ }^\circ\text{C}$ ) 133 (C-4), 128 (C-5), 74 (C-2), 72 (C-6), 23 ( $\text{CH}_3$ ). Shift value for C-3 was not observed.

## 9.4. Selective vicarious nucleophilic amination of 3-nitropyridines

### 9.4.1. General

The starting compounds were prepared as described in chapter 9.2.

### 9.4.2. Amination procedures

#### Amination of 3-nitropyridines with hydroxylamine (96)

The 3-nitropyridine compound (10 mmol) in ethanol (50 ml) was added dropwise to a stirred solution of hydroxylamine hydrochloride (30 mmol), potassium hydroxide (80 mmol) and zinc dichloride (10 mmol) in ethanol (100 ml). In some cases more hydroxylamine (15 mmol) and potassium hydroxide (20 mmol) were added after 5 hours of stirring. The reaction mixture was stirred overnight at room temperature, and poured into water (200 ml). The water phase was extracted with dichloromethane (3 x 100 ml), the combined organic phases were washed with water, dried and evaporated to give the 2-amino-5-nitropyridine (**103**) compound.

#### Amination of 3-nitropyridines with 4-amino-1,2,4-triazole (97)

The 3-nitropyridine compound (10 mmol) in dimethylsulfoxide (30 ml) was added dropwise to a stirred solution of 4-amino-1,2,4-triazole (35 mmol), potassium *tert*-butoxide (20 mmol) in dimethyl sulfoxide (60 ml) under nitrogen atmosphere. The reaction mixture was stirred for 5 hours at room temperature, and then poured into water (200 ml) saturated with NH<sub>4</sub>Cl.

The water phase was extracted with dichloromethane (3 x 100 ml), the combined organic phases evaporated, and the residue was recrystallized from water-methanol to give the 2-amino-5-nitropyridine (**103**) compound.

### 9.4.3. Amination of 3-nitropyridines

Nine different 3-nitropyridines and 4-nitroisquinoline were aminated with both hydroxylamine (**96**) and 4-amino-1,2,4-triazole (**97**) as described above. The yields of the different products with the two procedures are given in Chapter 5.2.12., Table 5.3. The melting point and spectroscopical data of the isolated products are given below. For compounds with no references to literature, elemental analyses were performed.

2-Amino-5-nitropyridine (8)

Compound **8** was a light yellow solid with a melting point of 188.0-189.0 °C (lit.<sup>11</sup> 188 - 189 °C).

IR (KBr): 3501 (m), 3363 (s), 1648 (s), 1632 (s), 1583 (s), 1570 (m), 1494 (m), 1473 (s), 1333 (s), 1285 (s), 1129 (m), 842 (m) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): 8.84 (d, 1H, , J = 2.78 Hz, H-6), 8.12 (dd, 1H, H-4, J = 2.80, 9.31 Hz), 7.52 (br s, 2H, NH<sub>2</sub>), 6.50 (d, 1H, H-3, J = 9.39 Hz) ppm.

Elemental analysis calculated for C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.59; H, 3.66; N, 29.87.

2-Amino-4-methyl-5-nitropyridine (109)

Compound **109** was a light yellow solid with a melting point of 219-220°C (lit.<sup>12</sup> 220 °C).

IR (KBr):3406 (s), 3329 (w), 3121 (m), 1654 (m), 1608 (m), 1544 (m), 1492 (w), 1452 (w), 1372 (w), 1332 (m), 1290 (s), 1279 (s), 1109 (w), 954 (w), 841 (w) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.93 (s, 1H, H-6), 6.33 (s, 1H, H-3), 5.03 (br s, 2H, NH<sub>2</sub>), 2.61 (s, 3H, CH<sub>3</sub>) ppm.

2-Amino-3-methyl-5-nitropyridine (112)

Compound **112** was a light yellow solid with a melting point of 256.0-257.0 °C (lit.<sup>12</sup> 255°C)

;  
IR (KBr): 3450 (m), 3321 (w), 3119 (m), 1851 (s), 1595 (s), 1583 (s), 1477 (m), 1422 (m), 1343 (s), 1292 (s), 1109 (m), 1040 (w), 1018 (w), 941 (w), 770 (m) cm<sup>-1</sup>.



$^1\text{H-NMR}$  (300 MHz, DMSO- $d_6$ ): 8.74 (d, 1H,  $J = 1.94$  Hz, H-6), 8.02 (d, 1H,  $J = 1.94$  Hz, H-4), 5.03 (br s, 2H,  $\text{NH}_2$ ), 2.11 (s, 3H,  $\text{CH}_3$ ) ppm.

*Methyl 2-amino-5-nitroisonicotinate (113)*

Compound **113** was a light brown solid, with a melting point of 205-206°C.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.82 (s, 1H, H-6), 7.84 (br s, 2H,  $\text{NH}_2$ ), 6.52 (s, 1H, H-3), 3.85 (s, 3H,  $\text{CH}_3$ ) ppm.

IR (KBr): 3441 (s), 3309 (w), 1733 (s), 1649 (s), 1607 (m), 1559 (m), 1493 (w), 1457 (s), 1344 (m), 1303 (m), 1279 (s), 1180 (w), 1079 (m), 986 (m), 876 (w), 847 (w)  $\text{cm}^{-1}$ .

Elemental analysis calculated for  $\text{C}_7\text{H}_7\text{N}_3\text{O}_4$ : C, 42.65; H, 3.58; N, 21.31. Found: C, 42.50; H, 3.87; N, 21.25.

*2-Amino-4-(1,3-dioxolan-2-yl)-5-nitropyridine (122)*

Compound **122** was a yellow solid, with a melting point of 175-177 °C.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.89 (s, 1H, H-6), 6.80 (s, 2H,  $\text{NH}_2$ ), 6.57 (s, 1H, H-3), 5.18 (s, 1H, dioxolane proton), 3.9-4.3 (q, 4H, dioxolane protons) ppm.

IR, 3461 (s), 3220 (w), 3160 (m), 1634 (m), 1609 (s), 1548 (s), 1493 (w), 1442 (w), 1329 (s), 1295 (s), 1261 (m), 1184 (w), 1081 (w), 975 (w)  $\text{cm}^{-1}$ .

Elemental analysis calculated for  $\text{C}_8\text{H}_9\text{N}_3\text{O}_4$ : C, 45.50; H, 4.27; N, 19.91. Found: C, 45.27; H, 4.33; N, 19.56.

2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine(124)*4-(2-Methyl-1,3-dioxolan-2-yl)-3-nitropyridine (123)*

4-acetyl-3-nitropyridine (**223**) ( 5.20 g, 0.032mol ) was dissolved in 15 ml of toluene, and treated dropwise with concentrated hydrochloric acid (3 ml). 1,2-ethandiol (6 ml) and p-toluenesulfonic acid (0.4 g, 0.0021 mol ) was added, and the solution refluxed, with azeotropic removal of water, for 5.5 hours. The reaction mixture was then cooled and quenched with sodium carbonate (8 g), and stirred for 15 minutes. Water was added to the solution to dissolve excess sodium carbonate. The two phases were separated, the water phase was extracted with ethylacetate (3 x 50ml ). The organic layers were combined and concentrated to give 4-(2-methyl-1,3-dioxolan-2-yl)-3-nitropyridine (**123**)( 5.75 g, 86% yield) as a light yellow solid with a melting point of 69.5-70.5 °C.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.74 (1H, s, H-2), 8.72 (1H, d, J = 5.2 Hz, H-6) 7.60 (1H, d, J = 5.2 Hz, H-5), 4.09 (2H, m, dioxolane protons), 3.72 (2H, m, dioxolane protons), 2.07 (3H, s, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 152, 146, 144, 145, 122, 107, 65, 27 ppm.

IR (KBr) 2995 (w), 2980 (w), 2962 (w), 2907 (w), 2695 (m), 1594 (w), 1554 (m), 1533 (s), 1476 (w), 1407 (m), 1374 (s), 1367 (s), 1266 (w), 1238 (m), 1205 (s), 1136 (w), 1116 (w), 1062 (w), 1045 (m), 1027 (s), 950 (m), 880 (m), 856 (m), 849 (m), 763 (w), 705 (w), 684 (w), 609 (m), 514 (w) cm<sup>-1</sup>.

MS (m/z, rel. int. %) 205 (M-15 (CH<sub>3</sub>), 2), 195 (23), 151 (15), 150 (7), 149 (66), 121 (9), 97 (4), 87 (96), 78 (13), 51 (16)

*2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (124)*

4-(2-methyl-1,3-dioxolan-2-yl)-3-nitropyridine (**123**) was aminated by hydroxylamine (**96**) and 4-amino-1,2,4-triazole (**97**) to give 2-amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (**124**) as an orange solid with a melting point of 172.0-173.0 °C.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.42 (s, 1H, H-6), 6.69 (s, 1H, H-3), 5.01 (br s, 2H, NH<sub>2</sub>), 4.02 (m, 2H, dioxolane protons), 3.72 (m, 2H, dioxolane protons) ppm.

IR (KBr): 3459 (s), 3314 (m), 3191 (m), 1691 (s), 1559 (w), 1521 (s), 1425 (w), 1369 (s), 1203 (m), 1026 (m), 877 (m)  $\text{cm}^{-1}$ .

Elemental analysis calculated for  $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4$ : C, 48.00; H, 4.92; N, 18.66.  
Found: C, 48.08; H, 4.79; N, 18.67.

### *2-Amino-4-acetyl-5-nitropyridine (125)*

2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (**124**) (0.200 g, 0.88 mmol) was dissolved in 66 % Hydrochloric acid (20 ml), and stirred overnight. The solution was neutralized by  $\text{NaHCO}_3$ , and extracted with dichloromethane (3x 50 ml). The organic phases were combined, washed with water (50 ml), dried ( $\text{MgSO}_4$ ) and concentrated to give 2-amino-4-acetyl-5-nitropyridine (**125**) (0.158 g, 98 %) as a light yellow solid with a melting point of 177.5-179.0  $^\circ\text{C}$

$^1\text{H-NMR}$  (300 MHz,  $\text{CD}_3\text{OD}$ ): 8.84 (1H, s, H-2), 6.34 (1H, s, H-5), 2.48 (3H, s,  $\text{CH}_3$ )

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 200, 171, 163, 148, 147, 131, 103, 28 ppm.

IR (KBr): 3466 (m), 3299 (w), 3152 (w), 3073 (w), 1714 (m), 1630 (s), 1602 (m), 1540 (s), 1483 (m), 1442 (w), 1416 (w), 1355 (w), 1340 (m), 1323 (m), 1296 (s), 1275 (s), 1236 (m), 1152 (w), 1054 (w), 1017 (w), 956 (w), 865 (w), 844 (w), 523 (m)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %) 182 (M+1, 10), 181 (95), 151 (10), 139 (24), 122 (13), 109 (5), 93 (15), 92 (16), 81 (10), 80 (13), 71 (4), 69 (5), 68 (15), 66 (18), 65 (12), 64 (5), 57 (7), 50 (16), 43 (40)

2-Amino-4-phenyl-5-nitropyridine (126)

Compound **126** was a yellow solid, with a melting point of 165-166 °C.

IR (KBr): 3412 (s), 3319 (w), 3156 (m), 1652 (s), 1611 (m), 1598 (s), 1538 (m), 1481 (m), 1449 (w), 1327 (s), 1296 (s), 1134 (m), 848 (m)  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.85 (s, 1H, H-6), 7.43 (m, 3H, Ph protons), 7.29 (m, 2H, Ph protons), 6.37 (s, 1H, H-3), 5.20 (br s, 2H,  $\text{NH}_2$ ) ppm.

Elemental analysis calculated for  $\text{C}_8\text{H}_9\text{N}_3\text{O}_4$ : C, 61.39; H, 4.22; N, 19.53. Found: C, 61.24; H, 4.42; N, 19.27.

2-Amino-3-phenyl-5-nitropyridine (127)

Compound **127** was a yellow solid, with a melting point of 175.0 - 176.5 °C (lit.<sup>13</sup> 176.5 - 177.0 °C).

IR (KBr): 3473 (s), 3299 (m), 3116 (m), 1645 (s), 1585 (m), 1574 (s), 1485 (s), 1444 (m), 1353 (m), 1334 (s), 1307 (s), 1127 (m), 733 (m), 703 (w)  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.02 (d, 1H,  $J=J$  2.58 Hz, H-6), 8.18 (d, 1H,  $J=$  5.28 Hz, H-4), 7.50-7.60 (m, 5H, Ph protons), 5.36 (br s, 2H,  $\text{NH}_2$ ) ppm.

Elemental analysis calculated for  $\text{C}_8\text{H}_9\text{N}_3\text{O}_2$ : C, 61.39; H, 4.22; N, 19.53. Found: C, 61.19; H, 4.68; N, 19.06

*l*-Amino-4-nitroisoquinoline (130)

±

Compound **130** was a yellow solid with a melting point of 277 - 280 (lit.<sup>14</sup> 283 - 287 °C).

IR (KBr): 3417 (s), 3338 (w), 3087 (m), 1671 (m), 1617 (m), 1580 (s), 1510 (s), 1492 (s), 1449 (w), 1401 (w), 1363 (w), 1285 (s), 1256 (s), 1030 (m), 769 (s) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): 8.97 (s, 1H, H-3), 8.72 (d, 1H, J = 8.58 Hz, H-5), 8.45 (br s, 2H, NH<sub>2</sub>), 8.40 (d, 1H, J = 8.30 Hz, H-8), 7.87 (dd, 1H, J = 8.30, 8.58 Hz, H-6), 7.65 (dd, 1H, J = 8.30, 8.58 Hz, H-7) ppm.

<sup>13</sup>C- NMR (75 MHz, DMSO-d<sub>6</sub>): 163, 147 (1C, d, J = 183 Hz, C-3), 134, 131, 130, 127, 125, 123, 116 ppm.

Elemental analysis calculated for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: C, 57.14; H, 3.73; N, 22.21; Found: C, 57.89; H, 4.13; N, 22.09.

## 9.5. The oxidative amination of 3-nitropyridines

### 9.5.1. Oxidative aminations with ammonia

Several different procedures were tried for the oxidative amination of 3-nitropyridine (**24**) by ammonia and  $\text{KMnO}_4$ . The yields and isomer ratios for the different procedures are given in Chapter 6.3.1., Table 6.1. Details of the different procedures, identification of the isomers, isolation of 2-amino-5-nitropyridine (**8**) and spectroscopical data are given below.

#### Reaction procedures

##### *Reaction in aqueous solution of ammonia*

The 3-nitropyridine (**24**) (124 mg, 1.00 mmol) was added to a aqueous solution of ammonia (10 ml).  $\text{KMnO}_4$  (474 mg, 3.00 mmol) was added and the solution mechanically stirred or mixed by supersonic mixing. The reaction was monitored by taking out small samples that were extracted with dichloromethane. The organic phase was then analysed on GC. For the reaction with mechanical stirring more  $\text{KMnO}_4$  (316 mg, 2 mmol) was added twice after 5 and 10 hours, respectively. The sample with supersonic mixing, more  $\text{KMnO}_4$  (316 mg 2.00 mmol) was added after 1 hour.

##### *Reaction in DMSO and DMSO/*t*-butanol, with ammonia atmosphere*

The 3-nitropyridine (124 mg, 1.00 mmol) and  $\text{KMnO}_4$  (316 mg, 2.00 mmol) were dissolved in DMSO (20 ml) (or DMSO/ *t*-butanol). Gaseous ammonia was bubbled through the solution, and a reservoir of ammonia was connected. The reaction mixture was stirred for 3 (DMSO) or 6 (DMSO/*t*-butanol) hours.

##### *Reaction in DMSO/water, 7% $\text{NH}_3$*

The 3-nitropyridine (124 mg, 1.00 mmol) was dissolved in DMSO (37.5 ml) and 28% ammonia in water (12.5 ml).  $\text{KMnO}_4$  (474 mg, 3.00 mmol) was added and the mixture was stirred. The reaction was followed by GC analyses. After 4 hours more  $\text{KMnO}_4$  (474 mg, 3.00 mmol) was added.

In the experiments giving the best yield of 2-amino-5-nitropyridine, a stream of ammonia gas was bubbled through the solution to keep the reaction mixture saturated with ammonia.

### Determination of the isomer ratio in amination of 3-nitropyridine

The ratio of the three isomers 2-amino-5-nitropyridine (**8**), 2-amino-3-nitropyridine (**9**) and 4-amino-3-nitropyridine (**150**) was determined by GC chromatography. The retention times for the different peaks were found by co-chromatography. 2-amino-5-nitropyridine (**8**) was produced in the vicarious nucleophilic substitution of 3-nitropyridine ( see chapter 5), and 4-amino-3-nitropyridine (**150**) was provided by Dr. Jaroslav Riha, who synthesised this compound as a intermediate in his synthesis of 3,4-diaminopyridine<sup>18</sup>. The third product peak was then assumed to be the 2-amino-3-nitropyridine. The retention times were also in good accordance with the melting points reported for the three compounds.<sup>11</sup>

#### 2-amino-5-nitropyridine (**8**)

2-Amino-5-nitropyridine (**8**) was isolated from the reaction in DMSO/water (3:1) saturated with ammonia, by bubbling ammonia gas through the solution, in 66 % yield. The product was isolated as described below.

The reaction was quenched with methanol, and the reaction mixture was poured into water. The aqueous phase was then filtered and extracted by dichloromethane. The product was transferred to an aqueous phase by extraction of the dichloromethane by a 10% aq. HCl solution. The aqueous extract was neutralised, and extracted with ethyl acetate. Evaporation of the ethyl acetate extract gave a crude product, which was recrystallised from water/methanol to give 2-amino-5-nitropyridine.

the melting point and spectroscopical data was in accordance with data reported in Chapter 9.4.3.

#### Di-2-(5-nitropyridyl)amine (**161**)

The <sup>1</sup>H-NMR spektrum were in accordance with literature.<sup>20</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300MHz): 9.23 ( 2H, d, J = 2.7 Hz, H-6), 8.56 (1H, br. s, NH ), 8.48 (2H, dd, J = 9.22, 2.7 Hz, H-4), 7.9 ( 2H, d, J = 9.22 Hz, H-3) ppm.

### 9.5.2. Oxidative amination with *n*-butylamine

#### 2-*n*-Butylamino-5-nitropyridine (163)

3-Nitropyridine (**24**) (0.50 g, 4.00 mmol) was dissolved in *n*-butylamine (**162**) (5 ml) and  $\text{KMnO}_4$  (1.0 g, 6.3 mmol) was added. The reaction mixture was stirred for 3 hours. More  $\text{KMnO}_4$  (1g, 6.3 mmol) was added after one and two hours, respectively. The reaction mixture was poured into water (50 ml). The water solution was filtered and extracted with dichloromethane (3x 50ml). The organic phase was washed with water (3 x50 ml) and concentrated to give a crude product, which was crystallized from water/methanol to give 2-*n*-butylamino-5-nitropyridine (**163**) (0.731 g, 92 % yield) as a light brown solid with a melting point of 100.5 - 101.5 °C ( lit.<sup>17</sup> 102 °C)

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.00 (1H, d,  $J = 2.60$  Hz, H-6), 8.17 (1H, dd,  $J = 9.31, 2.60$  Hz, H-4), 6.38 (1H, d,  $J = 9.31$  Hz, H-3), 3.40 (2H, br. m,  $\text{NCH}_2$ ), 1.62 (2H, tt,  $J = 7.4, 7.3$  Hz,  $\text{HNCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.43 (2H, tq,  $J = 7.4, 7.3$  Hz,  $\text{HNCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.97 (3H, t,  $J = 7.3$  Hz,  $\text{HNCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ) ppm.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 161, 147, 136, 132, 105, 42, 31, 20, 14 ppm.

IR (KBr) 3234 (m), 2995 (w), 2952 (w), 2927 (m), 2866 (w), 1605 (s), 1588 (m), 1550 (w), 1496 (m), 1462 (w), 1424 (m), 1355 (m), 1326 (s), 1288 (s), 1166 (w), 1134 (m), 1117 (m), 1011 (8w), 834 (8m), 766 (m), 669 (m)  $\text{cm}^{-1}$ .

MS ( $m/z$ , rel. int. %) 196 (M+1, 2), 195 (M, 17), 179 (7), 166(20), 153 (19), 152 (100), 139 (24), 106 (60), 78 (9).

#### 2-*n*-Butylamino-4-phenyl-5-nitropyridine (166)

##### *n*-Butylamine (**162**) as solvent

4-Phenyl-3-nitropyridine (**55**) (1.00 g, 5.00 mmol) was dissolved in *n*-butylamine (**162**) (10 ml) and  $\text{KMnO}_4$  (1.5 g, 9.45 mmol) was added. The reaction mixture was stirred for 10 hours. More  $\text{KMnO}_4$  (1.0g, 6.3 mmol) was added every hour. The reaction mixture was poured into water (75 ml). The water solution was filtered and extracted with dichloromethane (3 x 75ml). The organic phase was washed with water (3 x 75 ml) and concentrated to give a crude product, which



was crystallized from water/methanol to give 2-*n*-butylamino-4-phenyl-5-nitropyridine (**166**) (1.016g, 75% yield).

*n*-Butylamine (**162**)/ DMSO (1:1) as solvent

4-Phenyl-3-nitropyridine (**55**) (1.00 g, 5.00 mmol) was dissolved in *n*-butylamine (**162**) (5 ml) and DMSO (5 ml). KMnO<sub>4</sub> (1.5 g, 9.45 mmol) was added. The reaction mixture was stirred for 4 hours. More KMnO<sub>4</sub> (1g, 6.3 mmol) was added every hour. The reaction mixture was poured into water (75 ml). The water solution was filtered and extracted with dichloromethane (3 x 75ml). The organic phase was washed with water (3 x 75 ml) and concentrated to give a crude product, which was crystallized from water/methanol to give 2-*n*-butylamino-4-phenyl-5-nitropyridine (**166**) (1.098g, 81% yield).

The product was a yellow solid with a melting point of 105.0 -106.0 °C

IR (KBr): 3339 (w), 3225 (m), 3093 (w), 3001 (w), 2956 (m), 2927 (w), 2864 (m), 1609 (s), 1582 (m), 1526 (w), 1493 (m), 1438 (w), 1385 (w), 1337 (s), 1306 (s), 1280 (s), 1245 (s), 1141 (m), 1132 (m), 1037 (w), 1015 (w), 952 (w), 860 (m), 840 (m), 760 (m), 739 (m), 698 (m) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.89 (1H, s, H-6), 7.43 (3H, m, Ph), 7.29 (2H, m, Ph), 7.26 (1H, s, NH), 6.19 (1H, s, H-3), 3.36 (2H, t, J = 6.7 Hz, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.61 (2H, m, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.41 (2H, m, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.96 (3H, t, J = 7.1 Hz, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (300 MHz, CDCl<sub>3</sub>): 160, 148, 147, 136, 135, 129, 128, 127, 107, 45, 31, 20, 14 ppm.

MS (m/z, rel. int. %) 272 (M+1, 6), 271 (M, 29), 255 (8), 243 (6), 242 (37), 241 (14), 229 (33), 228 (100), 225 (13), 215 (28), 212 (7), 199 (7), 198 (30), 197 (7), 196 (7), 195 (17), 185 (10), 169 (8), 156 (12), 155 (65), 154 (17), 128 (11), 127 (11), 115 (12).

**2-*n*-Butylamino-4-(*tert*-Butoxycarbonylamino)-5-nitropyridine (169)**

4-(*t*-butoxycarbonylamino)-3-nitropyridine (**168**) (0.200 g, 0.84 mmol) was dissolved in *n*-butylamine (**162**) (5 ml) and KMnO<sub>4</sub> (0.5 g, 3.15 mmol) was added. The reaction mixture was stirred for 4 hours. DMSO (5 ml) was added to the reaction mixture and stirring was continued for 2 more hours. More KMnO<sub>4</sub>

(0.30 g, 1.8 mmol) was added every hour. The reaction mixture was poured into water (50 ml). The water solution was filtered and extracted with dichloromethane (3 x 50 ml). The organic phase was washed with water (3 x 50 ml) and concentrated to give a crude product, which was crystallized from water/methanol to give 2-*n*-butylamino-4-(*t*-butoxycarbonylamino)-5-nitropyridine (**169**) (0.145 g, 56%) as a yellow solid with a melting point of 154.0-155.5 °C.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 10.1 (1H, s, NH), 9.00 (1H, s, H-6), 7.45 (1H, s, H-3), 5.33 (1H, br.s, NH), 3.50 (2H, br. m, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) 1.6 (2H, m, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.57 (9H, s, CH<sub>3</sub>), 1.45 (2H, m, NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.98 (3H, t, J = 7.29 Hz) ppm.

<sup>13</sup>C-NMR (300 MHz, CDCl<sub>3</sub>): 162, 154, 151, 150, 125, 113, 82, 42, 31, 28, 20, 13 ppm.

IR (KBr): 3341 (m), 3229 (s), 2291 (w), 2957 (m), 2932 (m), 2663 (w), 1736 (s), 1616 (s), 1577 (s), 1554 (m), 1514 (w), 1495 (w), 1454 (w), 1422 (m), 1368 (w), 1343 (m), 1302 (m), 1280 (s), 1248 (m), 1200 (w), 1154 (s), 1134 (m), 876 (w), 846 (w) cm<sup>-1</sup>.

MS (m/z, rel. int. %) 311 (M+1, 3), 310 (M, 18), 294 (6), 293 (27), 267 (5), 254 (12), 238 (10), 237 (32), 225 (41), 212 (32), 211 (78), 210 (14), 209 (5), 198 (38), 194 (9), 193 (26), 192 (19), 191 (4), 182 (7), 181 (39), 177 (5), 176 (5), 168 (23), 167 (93), 163 (10), 154 (26), 150 (14), 149 (53), 147 (13), 139 (8), 135 (15), 133 (10), 122 (10), 121 (54), 120 (20), 119 (13), 111 (12), 109 (10), 106 (11), 105 (8), 97 (17), 93 (15), 92 (13), 85 (16), 83 (18), 81 (17), 79 (15), 57 (100).

### 9.5.3. Oxidative amination with diethylamine

#### *General procedure:*

The 4-R-3-nitropyridine (**102**) (2 mmol) was dissolved in diethylamine (**170**)(3 ml) and DMSO (9 ml). KMnO<sub>4</sub> (0.80 g, 3.15 mmol) was added. The reaction mixture was stirred 1- 8 hours. More KMnO<sub>4</sub> (0.80 g, 3.15 mmol) was added after 0.5- 4 hours. The reaction mixture was poured into water (50 ml). The water solution was filtered and extracted with dichloromethane (3 x 50 ml). The organic phase was washed with water (3 x 50 ml) and concentrated to give a crude product, which was recrystallized from water/methanol to give 2-diethylamino-4-R-5-nitropyridine (**174**).

**2-Diethylamino-5-nitropyridine (171)**

$^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  data were in accordance with literature.<sup>16</sup>

The product was a yellow solid with a melting point of 75.0-76.0 °C ( lit.<sup>15</sup> 75.2-76.2 °C, lit.<sup>16</sup> 72-74 °C).

IR (KBr): 2987 (w), 2925 (w), 1596 (s), 1588 (m), 1527 (m), 1475 (w), 1430 (m), 1327 (s), 1292 (s), 1279 (s), 1268 (m), 1187 (w), 1157 (w), 1113 (s), 1075 (w), 1015 (w), 992 (w), 829 (m), 764 (w), 740 (w)  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.07 (1H, d,  $J = 2.7$  Hz, H-6), 8.18 (1H, dd,  $J = 9.5, 2.7$  Hz, H-4), 6.43 (1H, d,  $J = 2.7$  Hz, H-3) 3.63 (4H, q,  $J = 7.1$  Hz,  $\text{NCH}_2$ ), 1.25 (6H, t,  $J = 7.1$  Hz,  $\text{CH}_3$ ).

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 159, 147, 134, 133, 103, 43, 13 ppm.

MS ( $m/z$ , rel. int. %): 196 (M+1, 5), 195 (M, 55), 181 (8), 180 (100), 167 (6), 166 (75), 152 (60), 134 (27), 120 (42), 106 (41), 78 (17).

**2-Diethylamino-4-cyano-5-nitropyridine (175)**

The product was light brown needles, with a melting point of 116.5-118.0 °C

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.92 (1H, s, H-6), 6.75 (1H, s, H-3), 3.65 (4H, br s,  $\text{CH}_3\text{CH}_2\text{NH}$ ), 1.28 (6H, t,  $J = 7.1$  Hz,  $\text{CH}_3\text{CH}_2\text{NH}$ ) ppm.

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 159, 149, 132, 117, 115, 110, 43, 13 ppm.

IR (KBr): 3104 (w), 2979 (w), 2937 (w), 1597 (s), 1551 (s), 1482 (m), 1448 (m), 1366 (w), 1330 (s), 1297 (m), 1278 (s), 1096 (w), 1079 (w)  $\text{cm}^{-1}$ .

MS ( $m/z$ , rel. int. %): 221 (M+1, 3), 220 (M, 23), 205 (81), 191 (55), 181 (18), 177 (29), 175 (14), 169 (17), 159 (19), 149 (6), 147 (11), 145 (18), 104 (7), 103 (6), 84 (11), 44 (100).

HRMS: calculated for  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_2$ : 220.09603, observed: 220.09617

### **2-diethylamino-4-methoxycarbonyl-5-nitropyridine (176)**

The product was a light brown solid with a melting point of 84.5-86.5 °C.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.97 (1H, s, H-6), 6.46 (1H, s, H-3), 3.97 (3H, s, OCH<sub>3</sub>), 3.63 (4H, br s, CH<sub>3</sub>CH<sub>2</sub>NH), 1.25 (6H, t, J = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>NH) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 167, 159, 148, 139, 131, 103, 53, 44, 13 ppm.

IR (KBr): 3444 (w), 2983 (w), 2936 (w), 1736 (s), 1604 (s), 1553 (s), 1525 (m), 1492 (m), 1451 (m), 1335 (s), 1287 (s), 1267 (s), 1079 (m) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 254 (M+1, 4), 253 (M, 36), 238 (100), 225 (7), 224 (66), 210 (31), 148 (5), 134 (33), 120 (25), 106 (15).

HRMS: calculated for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>: 253.10626, observed: 253.10587

### **2-diethylamino-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (177)**

The product was a light brown solid with a melting point of 108.0-109.5 °C.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 8.56 (1H, s, H-6), 6.64 (1H, s, H-3), 4.03 (2H, t, J = 4.9 Hz, dioxolan protons) 3.72 (2H, t, J = 4.9 Hz, dioxolan protons), 3.67 (4H, br s, CH<sub>3</sub>CH<sub>2</sub>NH), 1.26 (6H, t, J = 7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>NH) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 159, 148, 147, 136, 108, 102, 65, 44, 27, 13 ppm.

IR (KBr): 2973 (w), 2931 (w), 1596 (s), 1546 (m), 1506 (m), 1436 (w), 1370 (w), 1340 (s), 1273 (m), 1190 (w), 1040 (m) cm<sup>-1</sup>.

MS (m/z, rel. int. %): 282 (M+1, 3), 253 (M, 20), 267 (5), 266 (40), 252 (12), 238 (10), 180 (25), 166 (28), 87 (100).

HRMS: calculated for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: 281.13756, Observed: 281.13801

## 9.6. Nucleophilic alkylation of 3-nitropyridines

### 9.6.1. Reaction with chloroform

#### General procedure:

A solution of the 3-nitropyridine (3.0 mmol) and chloroform (4.5 mmol) in dry DMF (3 ml) was added dropwise to a solution of potassium *tert*-butoxide (1.44 g, 12 mmol) in a mixture of dry DMF (2 ml) and dry THF (5 ml) precooled to -78 °C under nitrogen atmosphere. The reaction was stirred for 1 min after addition is finished, and then quenched with HCl (2ml) dissolved in methanol (4 ml). The mixture was allowed to reach room temperature and poured into water (100 ml). The water phase was extracted with dichloromethane (3 x 50 ml). The organic phase was washed with water (3 x 30 ml), dried with MgSO<sub>4</sub> and evaporated to yield the crude product.

#### 4-Dichloromethyl-3-nitropyridine (194)

The crude product was purified by column chromatography ( silica gel, hexane/EtOAc 5:1). The product was a light yellow liquid. The <sup>1</sup>H-NMR data were in accordance with literature.<sup>19</sup>

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.27 (1H, s), 9.00 (1H, d, J = 5.2 Hz), 8.11 ( 1H, d, J = 5.2 Hz), 7.60 (1H, s), 8.11 ( 1H, d, J = 5.2 Hz) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 158, 149, 145, 141, 126, 67 ppm.

MS (m/z, rel. int. %) 208 (M+2, 0.6), 207 (M+1, 0.6), 206 (M, 1), 176 (0.6), 173 (4), 162 (11), 161 (4), 160 (17), 144 (1), 143 (13), 140 (16), 136 (17), 135 (100), 134 (2), 133 (16), 125 (14), 124 (10), 114 (13), 113 (5), 112 (34), 97 (10).

#### 2-(dichloromethyl)-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (195)

The crude product was recrystallized from methanol/water to give a light brown solid with a melting point of 111.0-112.0 °C.

## Experimental

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ) 8.64 (1H, s, H-6), 8.05 (1H, s, H-3), 6.75 (1H, s,  $\text{CHCl}_2$ ), 4.08 (2H, m, dioxolan protons), 3.72 (2H, m, dioxolan protons), 1.87 (3H, s,  $\text{CH}_3$ ) ppm.

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 161, 148, 146, 144, 120, 108, 70, 65, 27 ppm.

IR (KBr) 3101, 2995, 2905, 1600, 1562, 1540, 1375, 1366, 1277, 1231, 1200, 1173, 1134, 1118, 1031, 954, 887, 838, 788, 765, 744, 712, 668, 645  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %) 281 (6), 279 (45), 277 (M-15, 68), 235 (7), 233 (15), 124 (7), 87 (100), 43 (52).

### Reaction of 4-phenyl-3-nitropyridine (55) with chloroform

The crude product was purified by dissolving it in a 10:1 pentane/dichloromethane solution. This solution was cooled to  $-25\text{ }^\circ\text{C}$  and left overnight. The solution was filtered and the filtrate was evaporated to give a mixture of the two isomers as a solid.

### *2-(dichloromethyl)-4-phenyl-5-nitropyridine (196)*

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.99 (1H, s, H-6), 7.88 (1H, s, H-3), 7.55 (3H, m, Ph protons), 7.38 (2H, m, Ph protons), 6.80 (1H, s,  $\text{CHCl}_2$ ) ppm.

GC-MS : (m/z, rel. int. %) 284 (M+2, 3), 282 (M, 5), 256 (15), 254 (25), 247 (15), 221 (25), 220 (12), 219 (75), 216 (9), 193 (10), 192 (13), 191 (28), 173 (10), 166 (13), 164 (20), 162 (12), 155 (15), 153 (10), 140 (25), 139 (100), 128 (22), 127 (45), 126 (35).

### *2-(Dichloromethyl)-4-phenyl-3-nitropyridine (197)*

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 8.88 (1H, d,  $J = 4.92\text{ Hz}$ , H-6), 7.55 (3H, m, Ph protons), 7.50 (1H, d,  $J = 4.92\text{ Hz}$ , H-5), 7.38 (2H, m, Ph protons), 6.92 (1H, s,  $\text{CHCl}_2$ ) ppm.

GC-MS : (m/z, rel. int. %) 284 (M+2, 5), 282 (M, 7), 267 (10), 265 (17), 258 (5), 256 (27), 254 (51), 247 (5), 239 (15), 237 (23), 230(7), 221 (15), 220 (10), 219 (52), 216 (19), 203 (9), 202 (13), 201 (14), 200 (14), 193 (7), 192 (5), 191 (20), 183 (28), 175 (10), 173 (22), 167 (27), 166 (45), 164 (30), 157 (5), 155 (65), 153 (45), 152 (17), 145 (50), 140 (99), 139 (100), 138 (22), 129 (15), 128 (35), 127 (80), 126 (90), 117 (45), 115 (62), 77 (99).

2-(dichloromethyl)-4-methyl-5-nitropyridine (198)

The crude product was dissolved in a pentane/dichloromethane solution (15:1), and this solution was cooled to and stored overnight at -25 °C for the starting material and by-products to precipitate. The solution was filtered and the filtrate was evaporated to give 2-(dichloromethyl)-4-methyl-5-nitropyridine (**198**) in 38% yield of a oil, with a purity of 93% (GC).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 9.11 (1H, s, H-6), 7.80 (1H, s, H-3), 6.75 (1H, s, CHCl<sub>2</sub>), 2.74(3H, s, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 161, 146, 145, 125, 125, 70, 31 ppm.

IR (neat): 3000 (w), 2961 (w), 2932 (w), 2667 (w), 1609 (s), 1556 (m), 1526 (s), 1470 (w), 1445 (w), 1376 (w), 1352 (s), 1302 (w), 1173 (w), 1096 (w), 1036 (w), 1014 (w), 957 (w), 840 (s), 806 (w), 785 (m), 747 (m).

MS (m/z, rel. int. %): 222 (M+2, 5), 220 (M, 9) 207 (3), 205 (21), 203 (29), 187 (33), 186 (10), 185 (100), 176 (8), 174 (12), 139 (18), 138 (17), 128 (14), 114 (13), 113 (15), 112 (33), 111 (33), 102 (11), 100 (14), 99 (6), 93 (15), 87 (7), 77 (42), 76 (14), 75 (24), 74 (7), 73 (12), 71 (34).

1-(dichloromethyl)-4-nitroisoquinoline (199)

The crude product was dissolved in pentane/dichloromethane solution (15:1). This solution was cooled overnight at -25°C. The solution was filtered and the filtrate evaporated to give 1-(dichloromethyl)-4-nitroisoquinoline (**199**) in a 69% yield, as a light yellow solid with a melting point of 144.0-145.5 °C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz) 9.13 (1H, s, H-3), 8.83 (1H, d,  $J = 8.6$  Hz, H-8), 8.63 (1H, d,  $J = 8.0$  Hz, H-5), 8.04 (1H, dd,  $J = 6.9, 8.6$  Hz, H-7), 7.91 (1H, dd,  $J = 6.9, 8.0$  Hz, H-6), 7.30 (1H, s,  $\text{CHCl}_2$ ) ppm.

Irradiation of the signal at 7.3 ppm ( $\text{CHCl}_2$ ) gave a 3.6 % positive NOE effect on signal at 8.83 ppm (H-8).

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ): 160, 138 (c-3, d,  $J = 190$  Hz), 133, 129.3, 129.1, 125, 124.9, 123, 70 ppm.

IR (KBr) 3022 (w), 1616 (w), 1588 (w), 1552 (w), 1519 (s), 1502 (m), 1379 (w), 1356 (w), 1323 (s), 1290 (w), 1241 (m), 830 (s), 803 (m), 774 (s), 652 (m)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %): 260 (M+4, 5), 259 (M+3, 4), 258 (M+2, 32), 257 (M+1, 6), 256 (M, 49), 242 (4), 228 (16), 226 (23), 224 (10), 223 (32), 222 (30), 221 (100), 212 (7), 210 (11), 192 (17), 191 (13), 177 (5), 176 (16), 175 (11), 174 (27), 173 (5), 164 (10), 163 (9), 162 (11), 156 (14), 149 (11), 141 (17), 140 (92), 139 (7), 129 (41), 128 (19), 127 (13), 115 (9), 114 (12), 113 (25), 101 (14), 97 (10), 95 (10).

### 9.6.2. Reaction of 3-nitropyridines with methyl chloroacetate (201)

*t*-BuOK (10 mmol) in 10 ml THF was added dropwise to a solution of the 3-nitropyridine (**24**) (3.0 mmol) and methyl chloroacetate (**201**) (5 mmol) dissolved in 10 ml THF. The reaction was stirred for 20 minutes and then quenched with water (20 ml) saturated with  $\text{NH}_4\text{Cl}$ . The reaction mixture was then extracted with dichloromethane (3x50 ml). The organic phase was washed with water (50 ml) and dried ( $\text{MgSO}_4$ ) and evaporated to give the crude product.

#### Methyl (3-nitropyridin-4-yl) acetate (202)

The crude product was dissolved in a 10:1 mixture of pentane/dichloromethane and stored at  $-25$  °C overnight, The solution was filtered and the filtrate was evaporated to give a light brown liquid in a 63 % yield.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 9.30 (1H, s, H-2), 8.79 (1H, d,  $J = 5.0$  Hz, H-6), 7.36 (1H, d,  $J = 5.0$  Hz, H-5), 3.93 (2H, s, Ar- $\text{CH}_2\text{-CO}_2\text{CH}_3$ ), 3.73 (3H, s,  $\text{CH}_3$ ) ppm.



$^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ): 170, 154, 146, 145, 138, 127, 52, 39 ppm.

MS (m/z, rel. int. %) 196 (M, 2) 166 (2), 165 (24), 151 (10), 150 (100), 138 (9), 135 (9), 92 (18), 79 (11).

IR (neat): 2955 (m), 1739 (s), 1608 (m), 1555 (w), 1529 (s), 1437 (w), 1405 (w), 1353 (s), 1298 (w), 1229 (m), 1173 (m), 1053 (w), 1000 (w), 901 (w), 871 (w), 849 (w), 824 (w), 726 (m), 688 (w)  $\text{cm}^{-1}$ .

### 9.6.3. Reaction of 3-nitropyridine (24) with ethyl 2-chloropropionate (203)

*t*-BuOK (10 mmol) in THF (10 ml) was added dropwise to a solution of 3-nitropyridine (24) (372 mg, 3.00 mmol) and ethyl 2-chloropropionate (203) (680 mg, 5 mmol) dissolved in THF (10 ml). The reaction was stirred for 20 minutes and then quenched with water (20 ml) saturated with  $\text{NH}_4\text{Cl}$ . The reaction mixture was then extracted with dichloromethane (3 x 50 ml). The organic phase was washed with water (50 ml), dried ( $\text{MgSO}_4$ ) and evaporated to give the crude product.

The crude product was dissolved in a 10:1 mixture of pentane/ dichloromethane and stored at  $-25\text{ }^\circ\text{C}$  overnight. The solution was then filtered. The filtrate was evaporated to give a light brown liquid. Which was an approximately 1:1 mixture of the ethyl 2-(3-nitropyridin-4-yl) propionate (204) and Ethyl 2-(3-nitropyridin-2-yl) propionate (205)

#### Ethyl 2-(3-nitropyridin-4-yl) propionate (204)

$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ): 9.05 (1H, s, H-2), 8.79 (1H, d,  $J = 5.16$  Hz, H-6), 8.45 (1H, d,  $J = 5.16$  Hz, H-5), 4.31 (1H, s,  $\text{CH}_3\text{CHRCO}_2\text{C}_2\text{H}_5$ ), 1.56 (2H, q,  $J = 7$ ,  $\text{CH}_2$ ), 1.20 (3H, t,  $J = 7$  Hz,  $\text{CH}_3$ ), 1.15 (3H, t,  $J = 7$  Hz,  $\text{CH}_3$ ) ppm.

#### Ethyl 2-(5-nitropyridin-2-yl) propionate (205)

$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ): 9.24 (1H, d,  $J = 2.55$  Hz, H-6), 8.37 (1H, d,  $J = 8.63$  Hz, H-3), 7.47 (1H, dd,  $J = 8.63, 2.55$  Hz, H-4), 4.31 (1H, s,  $\text{CH}_3\text{CHRCO}_2\text{C}_2\text{H}_5$ ), 1.56 (2H, q,  $J = 7$ ,  $\text{CH}_2$ ), 1.20 (3H, t,  $J = 7$  Hz,  $\text{CH}_3$ ), 1.15 (3H, t,  $J = 7$  Hz,  $\text{CH}_3$ ) ppm.

## 9.7. Transformation of 3-nitropyridines

### Methyl 3-nitroisonicotinate (42)

Experimental procedure and spectroscopical data is given in chapter 9.2.

### 3-Nitro isonicotinamide (52)

Methyl 3-nitroisonicotinate (**42**) (1.655 g, 9.03 mmol) was dissolved in a 28 % solution of ammonia in water (60 ml). The solution was refluxed for 45 min. More 28% ammonia solution (10 ml) was added and the solution refluxed for another 30 min. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc/hexane 9:1) to give 1.115 g (74 % yield) 3-nitroisonicotinamide (**52**) as a pale yellow solid with a melting point of 165.0-167.0 °C (lit.<sup>22</sup> 168-170 °C)

<sup>1</sup>H-NMR (D<sub>2</sub>O, 300 MHz): 9.37 (1H, s, H-2), 8.96 (1H, d, J = 5.0 Hz, H-6), 7.75 (1H, d, J = 5.0 Hz, H-5) ppm.

<sup>13</sup>C-NMR (75 MHz, CD<sub>3</sub>OD): 168, 154, 145, 142, 140, 123 ppm.

IR (KBr) 3354 (m), 3162 (m), 1680 (s), 1607 (m), 1548 (m), 1522 (s), 1485 (w), 1408 (m), 1391 (m), 1357 (s), 1237 (w), 1190 (w), 867 (m) cm<sup>-1</sup>.

MS (m/z, rel. int. %) 168 (M+1, 7), 167 (M, 66), 152 (8), 151 (100), 150 (8), 124 (16), 121 (15), 93 (33), 78 (29)

### Methyl N-(3-nitropyridin-4-yl) carbamate (220)

To a solution of 3-nitroisonicotinamide (**52**) (0.272 g, 1.62 mmol), AgOAc (0.334 g, 2 mmol) and methanol (1 ml) in dry DMF (10 ml), A solution of NBS (0.380, 2.1 mmol) in dry DMF (5 ml) was added. The reaction mixture was stirred overnight at room temperature under an argon atmosphere. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (300 ml) and washed with a 10% solution of NaHCO<sub>3</sub> (20 ml), saturated NaCl solution (20 ml) and water (20 ml). The organic phase was concentrated. The crude product was purified by flash chromatography (CHCl<sub>2</sub>/Et<sub>2</sub>O 9:1) giving methyl N-(3-nitropyridin-4-yl) carbamate (78 mg, 24%) as a white solid with a melting point of 141.5-143.0 °C (lit.<sup>21</sup> 140-142 °C).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): 10.04 (1H, s, NH), 9.37 (1H, s, H-2), 8.66 (1H, d, J = 6.0 Hz, H-6). 8.56 (1H, d, J = 6.0 Hz, H-5), 3.89 (3H, s,  $\text{OCH}_3$ ) ppm.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz) 155, 152, 147, 141, 131, 113, 53 ppm.

IR (KBr): 3432 (m), 3283 (m), 3138 (w), 2923 (w), 1740 (s), 1698 (m), 1605 (s), 1525 (m), 1494 (s), 1447 (m), 1411 (m), 1350 (s), 1244 (s), 1209 (m), 1176 (s), 1119 (w), 1054 (m), 948 (w), 875 (w), 843 (w), 767 (w)  $\text{cm}^{-1}$ .

MS (m/z, rel. int. %) 198 (M+1, 3), 197 (M, 35), 165 (6), 152 (9), 151 (100), 136 (19), 135 (6), 122 (8), 121 (9), 119 (10), 99 (9), 94 (16), 93 (10), 92 (10), 91 (9), 80 (7), 79 (31), 78 (11).


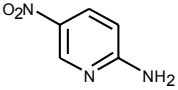
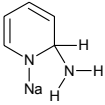
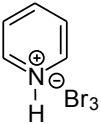
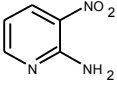
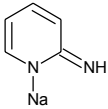
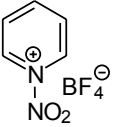


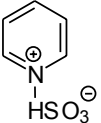
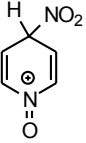
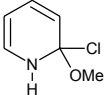
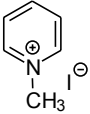
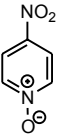
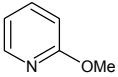
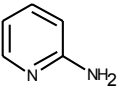
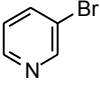
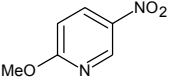
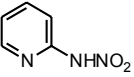
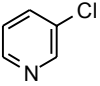
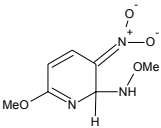
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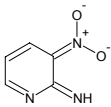
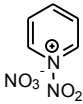
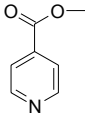
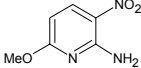
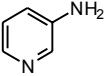
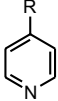
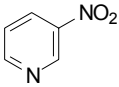
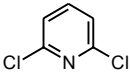
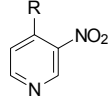
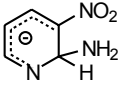
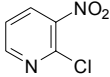
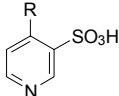

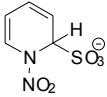
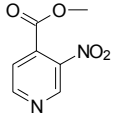

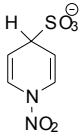
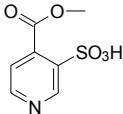
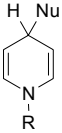
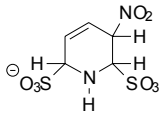
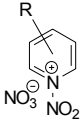
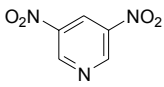
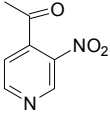
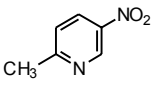
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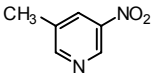
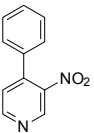

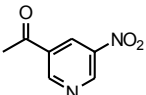
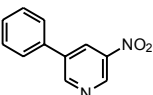

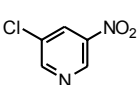
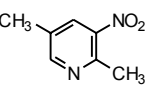

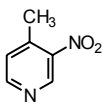
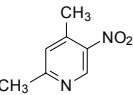

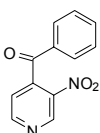
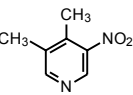

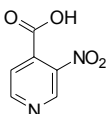
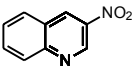
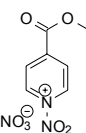
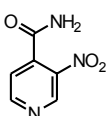


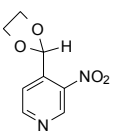
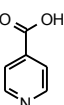
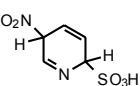
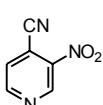


## 9.8. References

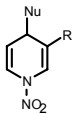
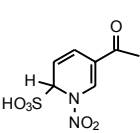
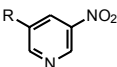

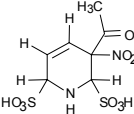
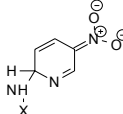
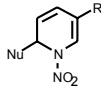
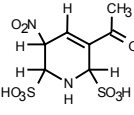
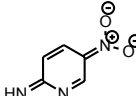
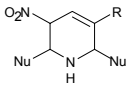
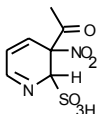

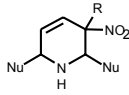
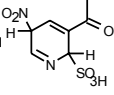
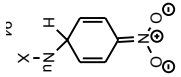


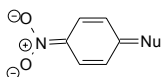
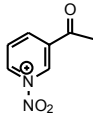

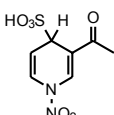
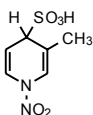

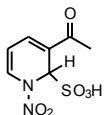
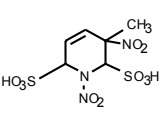

1. D. D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, Pergamon, Oxford (1988)
2. A. D. Harris, J. C. Trebellas and H. B. Jonassen, *Inorg. Synth.*, **9**, 83 (1967)
3. D. Rasala and R. Gawinecki, *Magn. Reson. Chem.*, **31**, 38 (1993)
4. M. Charlton, R. Ryszard, D. Rasala, W. Kraus, P. Tomasik, *Chem. Scr.* **25(4)**, 340 (1985)
5. E. V. Brown, *J. Am. Chem. Soc.*, **76**, 3167 (1954)
6. J. W. Bunting, W. G. Meathrel, *Org. Prep. Proc. Int.*, **4**, 9 (1972)
7. J. M. Bakke, E. Ranes, *Synthesis*, 281 (1997)
8. A. M. T. Marcelis, H. C. Van der Plas, *Tetrahedron*, **45(9)**, 2693 (1989)
9. I. Hegbom, *Nitrering av aromatiske og heteroaromatiske forbindelser, særlig med dinitrogenpentoksid som nitreringsreagens*, Dr. ing. thesis, Norges Tekniske Høyskole, Trondheim, 1994.
10. L. Achremowiz, *Rocz. Chem.*, **47**, 2367 (1973)
11. M. Wozniak, A. Baranski, B. Szpakiewicz, *Liebigs Ann. Chem.*, 875 (1991)
12. N. P. Lewis, S. Z. Winfield, *J. Am. Chem. Soc.*, **77**, 3154. (1955)
13. V. N. Charushin, H. C. Van der Plas, *J. Org. Chem.*, **48**, 2667 (1983)
14. Jap P 59172472/1984 (Chem. Abstr., 1984, **102**, 113322z)
15. H. Grube, H. Suhr, *Chem. Ber.*, 102(5), 1570 (1969)
16. A. J. Adamson, W. J. Jondi and A. E. Tipping, *J. Fluorine Chem.*, **76**, 67 (1996)
17. T. Talik and Z. Talik, *Pr. Nauk. Akad. Ekon. im Osakara Langedo Wroclawiu*, **398**, 99-109 (1987)
18. J. M. Bakke and J. Riha, *J. Heterocyclic Chem*, 1143 (1999)
19. M. Makosza and Z. Owczarczyk, *J. Org. Chem.*, **54**, 5094 (1989)
20. G. Verardo, A. G. Giumanini, M. Tolazzi and G. Cerioni, *Russian Journal of Organic Chemistry*, **36**, 731 (2000)
21. T. Takahaski and K. Ueda, *Chem. Pharm. Bull. (japan)*, **4**, 135 (1956)
22. J. M. Bakke and J. Riha, *J. Heterocyclic Chem*, 99 (2001)

## List of Compounds

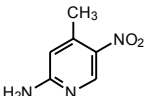
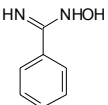
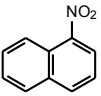
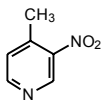
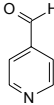
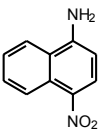
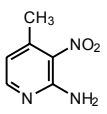
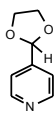
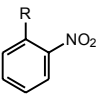
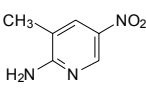
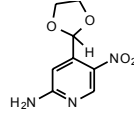
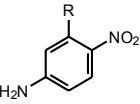
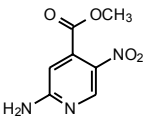
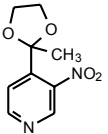
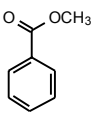
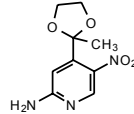
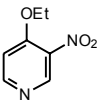
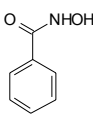
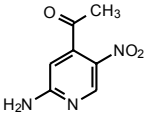
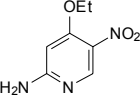
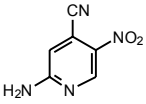
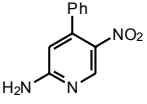
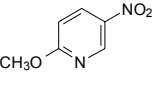

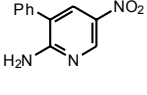
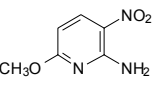

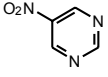
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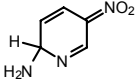
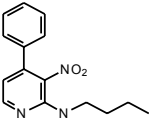

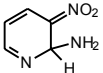
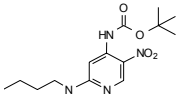
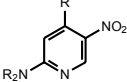



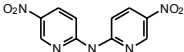
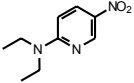
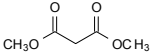
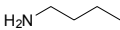

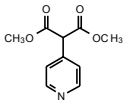
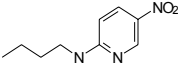
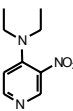

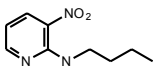
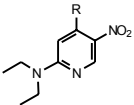
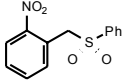
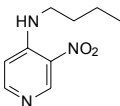
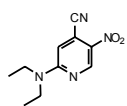

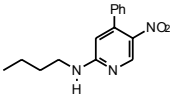
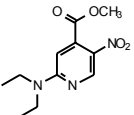
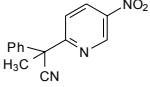
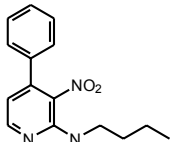
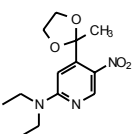
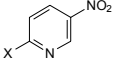
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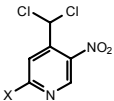
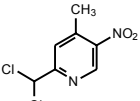

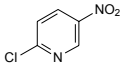
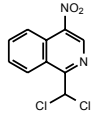
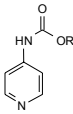

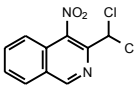
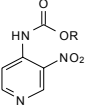
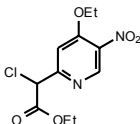
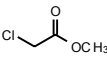
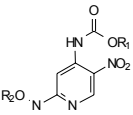
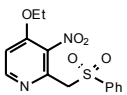
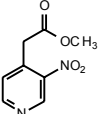
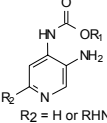

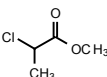

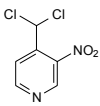
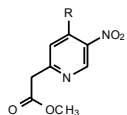
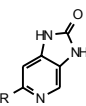
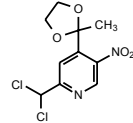
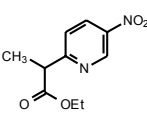

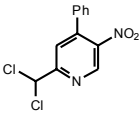
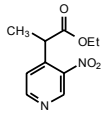
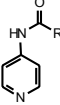
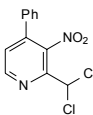
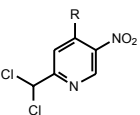
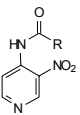
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<p><b>78</b></p> 	<p><b>87</b></p> 	<p><b>95</b></p> 
<p><b>79</b></p> 	<p><b>88a</b></p> 	<p><b>96</b></p> <p>NH<sub>2</sub>OH</p>
<p><b>80</b></p> 	<p><b>88b</b></p> 	<p><b>97</b></p> 
<p><b>81</b></p> 	<p><b>89</b></p> 	<p><b>98</b></p> 

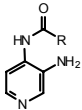
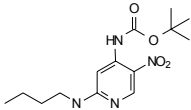

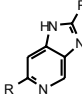


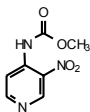
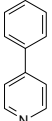
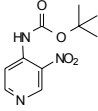


<b>99</b> $R-S-NH_2$	<b>109</b> 	<b>119</b> 
<b>100</b> 	<b>110</b> 	<b>120</b> 
<b>101</b> 	<b>111</b> 	<b>121</b> 
<b>102</b> 	<b>112</b> 	<b>122</b> 
<b>103</b> 	<b>113</b> 	<b>123</b> 
<b>104</b> $CH_3O-NH_2$	<b>114</b> 	<b>124</b> 
<b>105</b> 	<b>115</b> 	<b>125</b> 
<b>106</b> 	<b>116</b> 	<b>126</b> 
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<b>108</b> 	<b>118</b> 	<b>128</b> 

129		139		149 A	
130		140		149 B	
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<b>194</b> 	<b>204</b> 	<b>214</b> 
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<b>196</b> 	<b>206</b> 	<b>216</b> 
<b>197</b> 	<b>207</b> 	<b>217</b> 

<p><b>218</b></p> 	<p><b>222</b></p> 	<p><b>226</b></p> 
<p><b>219</b></p> 	<p><b>223</b></p> 	<p><b>227</b></p> 
<p><b>220</b></p> 	<p><b>224</b></p> 	
<p><b>221</b></p> 	<p><b>225</b></p> 