Pure Appl. Chem., Vol. 75, No. 10, pp. 1403–1415, 2003.

Nitropyridines: Synthesis and reactions*

Jan M. Bakke

Department of Chemistry, Norwegian University of Science and Technology, N-7491 Trondheim, Norway

Abstract: Reaction of pyridine and substituted pyridines with N_2O_5 in an organic solvent gives the *N*-nitropyridinium ion. When this is reacted with SO_2/HSO_3^- in water, 3-nitropyridine is obtained (77 % yield). With substituted pyridines, the method gives good yields for 4-substituted and moderate yields for 3-substituted pyridines. The reaction mechanism is not an electrophilic aromatic substitution, but one in which the nitro group migrates from the 1-position to the 3-position by a [1,5] sigmatropic shift. From 4-aminopyridine, imidazo[4,5-*c*]pyridines have been synthesized. From 3-nitropyridine, 5-nitropyridine-2-sulfonic acid is formed in a two-step reaction. From this, a series of 2-substituted-5-nitropyridines has been synthesized. 3-Nitropyridine and 4-substituted-3-nitropyridines have been substituted with ammonia and amines by the vicarious substitution method and by the oxidative substitution method in the position para to the nitro group. High regioselectivities and yields have been obtained in both cases to afford a series of 4-substituted-2-alkylamino-5-nitropyridines.

INTRODUCTION

The pyridine ring system occurs in the structures of many natural products, pharmaceutical and agrochemical compounds, and other commercial substances. A wide range of synthetic methods has, therefore, been developed, both for construction of the pyridine ring and for its substitution [1]. Unfortunately, one of the most important classes of aromatic substitution reactions, electrophilic aromatic substitution, takes place with great difficulty and only under forcing conditions [1], owing to the electron-deficient character of the pyridine ring. The partial rate factor for an electrophilic aromatic substitution of pyridine has been estimated to be 10^{-6} and for the pyridinium ion, in most cases formed under standard conditions for this type of reaction, to be 10^{-22} [2]. Typically, nitration of pyridine at 350 °C gave a 12 % yield of 3-nitropyridine, and even this low yield could not subsequently be reproduced by den Hertog et al., who obtained a 6 % yield under the same conditions [3]. Some time ago, we were investigating the nitration of aromatic compounds by dinitrogen pentoxide (N_2O_5) and found that with liquid SO_2 as solvent, this was an especially powerful nitrating system. In view of the reported difficulties with the nitration of pyridine, we decided to try this protocol on pyridine itself and on several substituted derivatives.

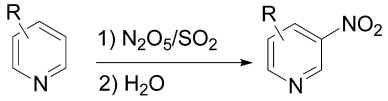
The first results were encouraging; in an exploratory investigation, a yield of 56 % of 3-nitropyridine was obtained. We have now tried this nitration under different conditions and on a number of pyridine compounds. We have further investigated the mechanism of the reaction and are now studying the reactions of β-nitropyridines, which have been difficult to obtain before.

*Lecture presented at the 4th Florida Heterocyclic Conference, Gainesville, FL, USA, 10–12 March 2003. Other presentations are published in this issue, pp. 1403–1475.

PREPARATION OF NITROPYRIDINES

We first treated the pyridines with N_2O_5 dissolved in liquid SO_2 at –11 °C and then poured the reaction mixture into water [4]. Table 1 gives a selection of the results from these experiments. The yields are all better than those reported from nitration with HNO_3/H_2SO_4, for instance, nitration of 2-methylpyridine with HNO_3/H_2SO_4 gave 4 % of 2-methyl-3-nitropyridine with HNO_3/H_2SO_4 [5]. Also important, the nitration of 4-phenylpyridine with HNO_3/H_2SO_4 gave exclusively nitration of the phenyl ring [6], suggesting that the nitration with N_2O_5/SO_2 did not go by the mechanism of an electrophilic aromatic substitution.

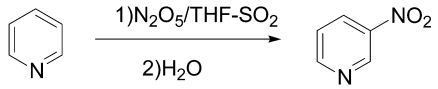
Table 1 Nitration of methyl- and phenylpyridines with N_2O_5/SO_2.



R	Product	Yield/%
2-Me	2-Me-3-NO_2	42
3-Me	3-Me-5-NO_2	29
4-Me	4-Me-3-NO_2	51
4-Ph	4-Ph-3-NO_2	31

To make this new nitration method more convenient, we considered the possibility of carrying out the reaction in an organic solvent with added SO_2. To investigate this, we conducted a series of experiments with varying concentrations of SO_2 (Table 2). The results showed that it was not necessary to run the reactions in liquid SO_2, the yields of 3-nitropyridine were almost constant down to a $[SO_2]$/[pyridine] of ca. 2. However, the last entry in Table 2 with $[SO_2]$/[pyridine] = 0 gave a 0 % yield of 3-nitropyridine, a very important result from a mechanistic standpoint and also because this might open up a new protocol for the nitration reaction.

Table 2 Nitration of pyridine with N_2O_5 in THF with SO_2 added.



$[SO_2]$/[Pyridine]	T/°C	Yield/%
24	–20	65
16	–20	57
4	0	68
2	0	69
0.8	0	23
0	0	0

In an attempt to understand the role of SO_2 in the reaction, we treated pyridine with N_2O_5 dissolved in nitromethane at 0 °C. The reaction mixture was then poured into water saturated with SO_2. In this first attempt, a 56 % yield of 3-nitropyridine was obtained. It was thus clear that a simple route to nitropyridines had been discovered, involving first the reaction of the pyridine compound with N_2O_5 in an organic solvent and then quenching with an aqueous solution of SO_2/HSO_3^-. We have nitrated a se-

ries of pyridine derivatives by this method, and the results are given in Table 3 together with the results from nitrations conducted in liquid SO_2 [7].

From Table 3, it is evident that the method is general for the direct nitration in the β(3)-position of pyridine compounds. The yields vary from excellent to acceptable. There are some patterns to the yields. In general, the yields are better for 4- than for 3-substituted pyridines. The reason for this will become evident from a consideration of the mechanism. Furthermore, most 2-substituted pyridines did not react under these conditions; only 2-methylpyridine gave an acceptable yield of 2-methyl-5-nitropyridine. In most cases, the yields obtained by method C were as good as or better than by the other two. This is important, not only because this is a convenient laboratory method, but also because N_2O_5 can be obtained on an industrial scale with CH_2Cl_2 as solvent.

Table 3 Nitration of pyridine and substituted pyridines with N_2O_5/HSO_3^-.

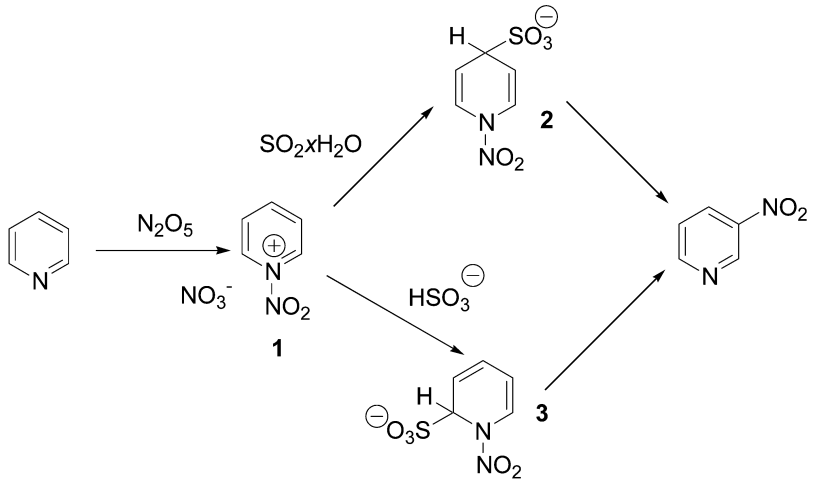
	Yields/% Method		
X	A	B	C
H	63	58	77
2-Me	42	41	36
3-Me	29	37	24
4-Me	70	54	33
4-Ph	31		68
3-Ac	19	19	
4-Ac	75	67	67
3-Cl	15		
4-CN	35		
4-CHO (protected)	62		
Quinoline	16	12	10
Isoquinoline	28	38	32

Method A: (1) N_2O_5/SO_2; (2) H_2O.
Method B: (1) $N_2O_5/CH_3NO_2/SO_2$; (2) H_2O.
Method C: (1) N_2O_5/CH_3NO_2; (2) HSO_3^-/H_2O.

REACTION MECHANISM

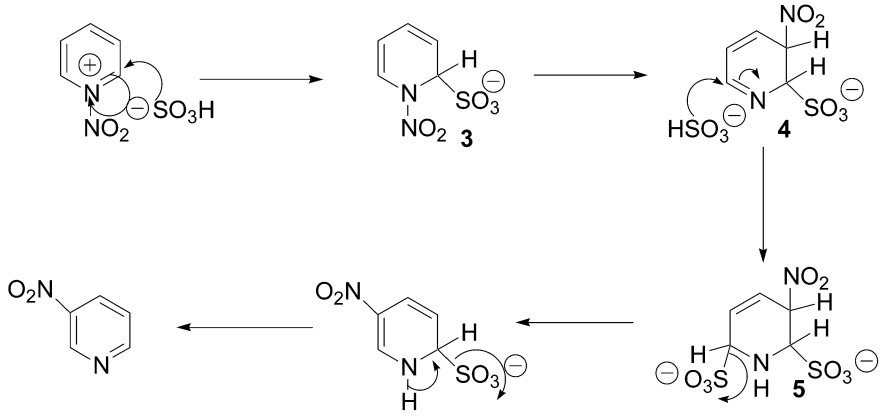
The results of preliminary cross-over experiments suggested that the reaction was intramolecular with respect to the pyridine compound [4]. The reaction was then investigated by NMR spectroscopy.

This showed that *N*-nitropyridinium nitrate (**1**) formed in the reaction of pyridine with N_2O_5 reacted with the pH dependent mixture of SO_2xH_2O and HSO_3^- to give the two dihydropyridine sulfonic acids **2** and **3** (Scheme 1). Of these, **2** was formed at lower pH with SO_2xH_2O being the dominant part of the equilibrium, compound **3** at higher pH. Of these two, **3** was the more reactive, only being observed at lower temperatures. The concentrations of both of these compounds decreased with time, and the concentration of 3-nitropyridine correspondingly increased.



Scheme 1

We will first discuss the reaction of the 1,2-dihydropyridine sulfonic acid **3**. We observed compounds **3** and **5** (Scheme 2) by NMR spectroscopy. As the concentration of compound **3** decreased, that of **5** increased and in turn decreased to give 3-nitropyridine. The kinetics of the reaction showed it to be first order in **3** with $\Delta H^{\#}$ = 18(1) kcal mol^{-1} and $\Delta S^{\#}$ = –5(4) cal mol^{-1}K^{-1} [8]. A reaction path in accordance with these data is summarized in Scheme 2.

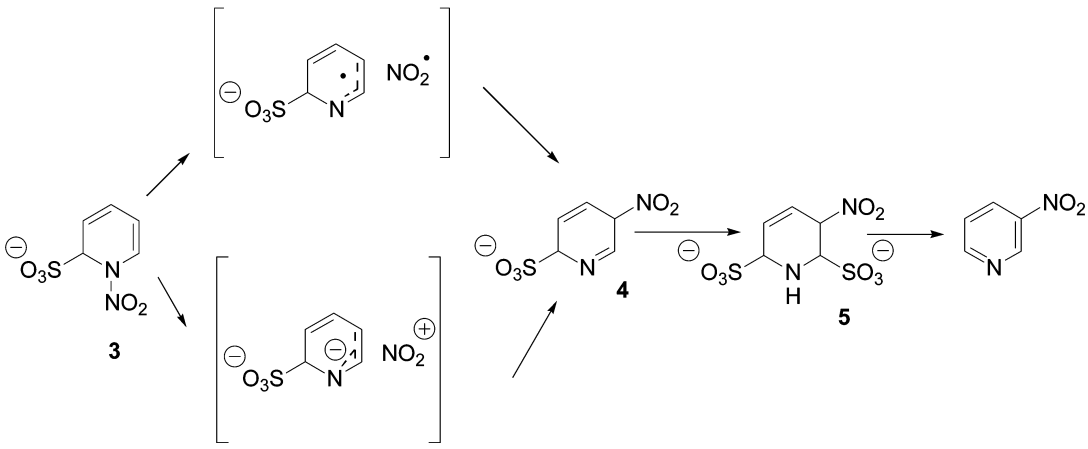


Scheme 2

The hydrogen sulfite ion nucleophile attacks the 2-position of the nitropyridinium ion. The nitro group of the resulting 1,2-dihydropyridine sulfonic acid migrates to the β-position to give **4** (not observed), which reacts with a new hydrogen sulfite ion at the electrophilic α-position to give the tetrahydropyridine compound **5**, which then rearomatizes to 3-nitropyridine.

Several modes appeared possible for the migration of the nitro group. Both from the cross-over experiments and the kinetic investigations, the migration appeared to be intramolecular. Possible reaction paths could be by an ion or radical path in a solvent cage (Scheme 3).

To distinguish between these two routes, the rates of reaction of **3** were determined with different solvents and under different ion strengths [8]. If the reaction went by the ion pair path (Scheme 3), we would expect large variations in the rate of reaction depending on the ionizing power of the solvent and on the salt concentration [9].



Scheme 3

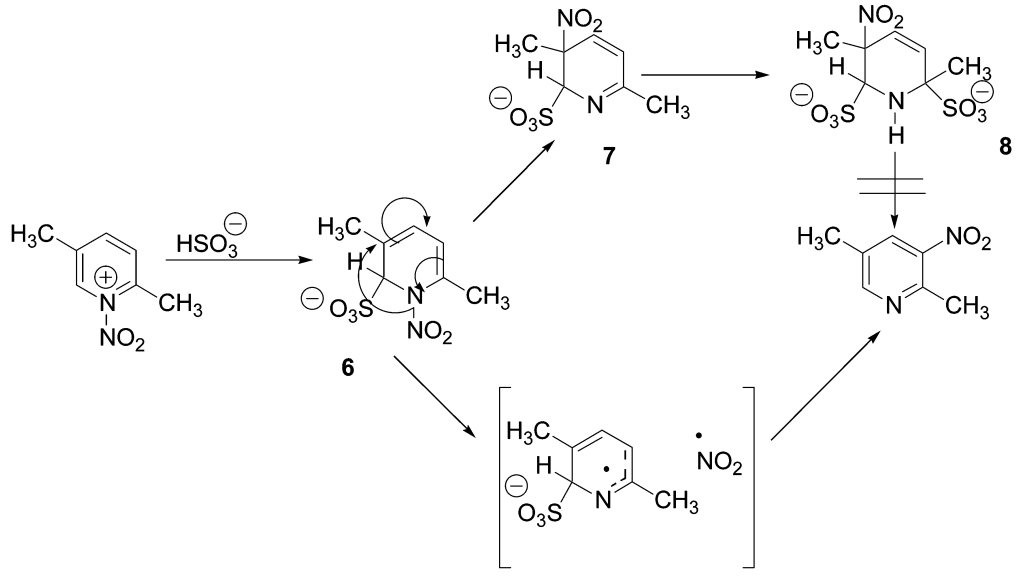
The results showed that there were not any significant variations in the rate of the reaction; certainly, no large increase when the ionizing power of the solvent or the concentration of salts was increased. From these results, the route by a solvent cage ion pair migration was excluded. The route by the radical pair was also supported by several reported analogies [10].

The data so far might, therefore, be explained by a nitro group migration via the radical pair route in Scheme 3. However, a set of results from the nitration of dimethylpyridines (Table 4) was difficult to explain by this mechanism [11].

Table 4 Nitration of dimethylpyridines by N_2O_5/SO_2.

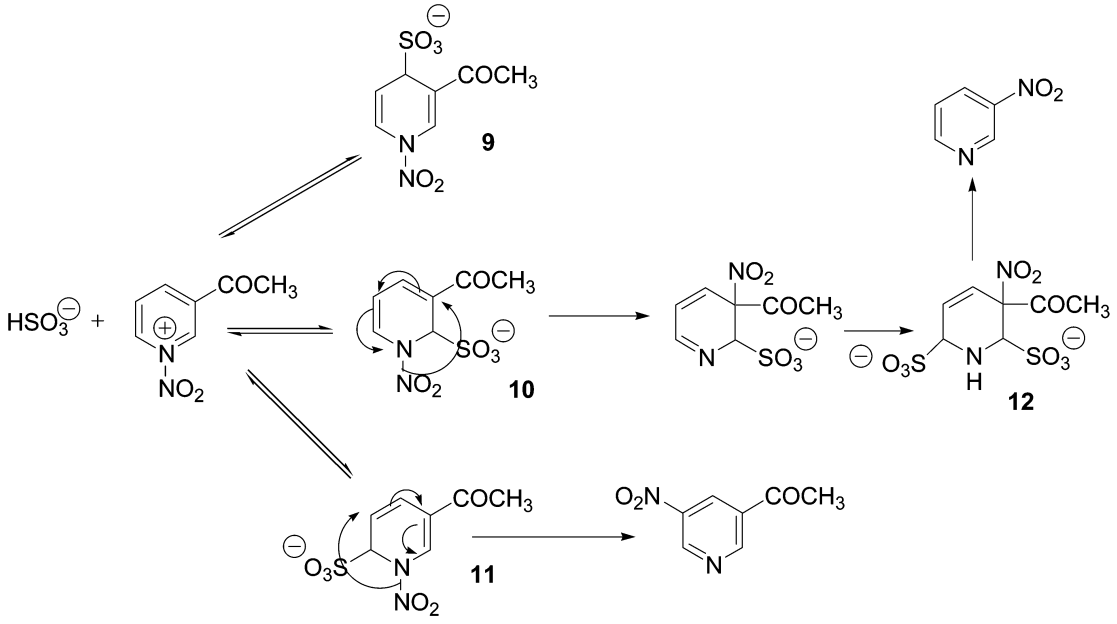
Positions of methyl groups	Positions of nitro group	Yield/%
2,3	5	46
2,4	5	66
2,5	3,4 (1:4)	<3
2,6	3	1
3,4	5	58
3,5		0

The yields from the reaction of 2,3-, 2,4-, and 3,4-dimethylpyridine were at the expected level. 2,5-, 2,6-, and 3,5-dimethylpyridine all gave zero or very low yields. For the 2,6- and 3,5-isomers, this may be explained by steric hindrance (2,6-) or occupied positions for the expected position of nitration (3,5-), but these explanations would not apply for the 2,5-isomer. One might argue that the methyl group in the 2-position would sterically hinder the migration of the NO_2 radical, although the migration would probably take place closer to the π-electrons of the ring. However, another possibility would be a migration by a [1,5] sigmatropic shift. Such a shift has been reported before for the reaction of *N*-nitropyrazole [12]. In Scheme 4, this is shown for the reaction of 2,5-dimethylpyridine. In this reaction, we observed compound **8**. By analogy with the reactions of 3-substituted pyridines (see below), this was presumably formed via the intermediates **6** and **7**. It would not be possible to get the expected nitration from **8**.



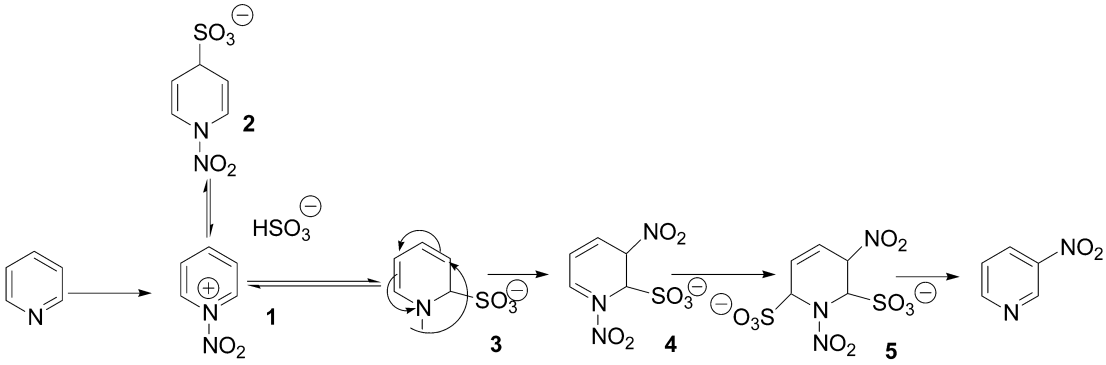
Scheme 4

Further evidence was obtained from the reaction of 3-acetylpyridine (Scheme 5) [8]. Here, we observed (NMR) the three intermediates **9**–**11** and their reactions. Compound **11** gave 17 % yield of 3-acetyl-5-nitropyridine, but **10** gave the tetrahydropyridine compound **12**. A low yield of 3-nitropyridine was obtained, presumably by loss of the acetyl group from **12** followed by aromatization. The mechanism by a [1,5] shift also explains the low yield of nitration of quinoline as compared with that of isoquinoline (Table 3). In quinoline, the 4a position would have been that for nitration by the [1,5] sigmatropic shift, making reaction by this path impossible.



Scheme 5

The reaction path from the 1,2-dihydropyridine sulfonic acid (**3**) to 3-nitropyridine, therefore, appears to have been explained in some detail. The reaction of the 1,4-dihydro derivative **2** (Scheme 1) was less clear, and several reaction paths appeared possible [11]. However, a cross-over experiment in which *N*-nitropyridinium and *N*-nitro-2,6-dideuteriopyridinium nitrates were reacted together showed that the 1,4-dihydropyridinesulfonic acid **2** was in equilibrium with the *N*-nitropyridinium ion (**1**), which was also in equilibrium with the 1,2-dihydro derivative **3**. But **2** was not on the direct reaction path to 3-nitropyridine [13]. The proposed reaction mechanism for the formation of 3-nitropyridine from the *N*-nitropyridinium ion is summarized in Scheme 6.



Scheme 6

REACTIONS OF β-NITROPYRIDINES

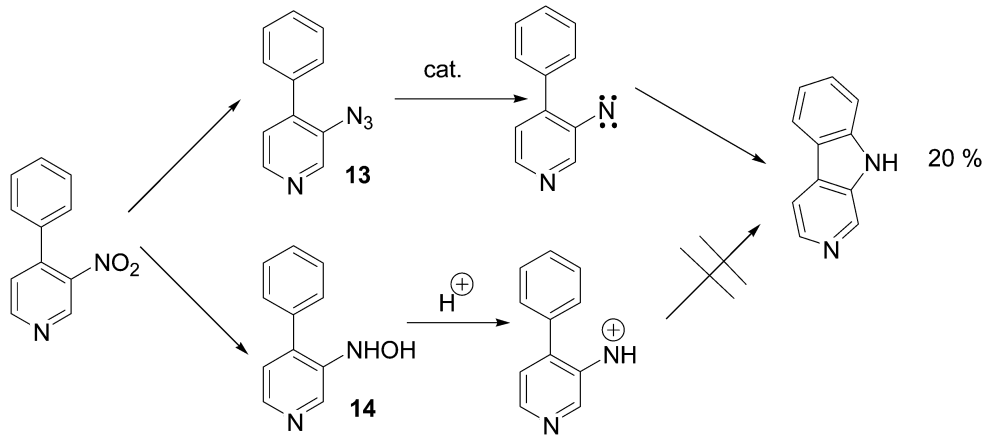
In general, β-nitropyridines have not been easily available. Most have been made by nitration of substrates activated for electrophilic substitutions, for example, by amino or by multiple alkyl groups [1]. In other instances, multistep syntheses with ring-forming reactions have been used. The nitration reaction discussed here has made a series of nitropyridines available, particularly 3-nitro-4-substituted ones. Because of this, we have investigated some of their reactions, particularly those that might be synthetically useful.

Ring-forming reactions

Carbazole was made in 83 % yield from 2-nitrobiphenyl by reaction with triethyl phosphite [14]. As 3-nitro-4-phenylpyridine was available in good yield from nitration of 4-phenylpyridine, this might open up a new route to β-carboline and its derivatives, compounds with important biological properties. However, with 3-nitro-4-phenylpyridine, the reaction with triethyl phosphite gave only tars [15]. Therefore, we tried the reaction of 3-azido-4-phenylpyridine (**13**, Scheme 7) with a number of Lewis and Brønstedt acids, transition-metal catalysts, and photochemical decomposition. However, the best yield of β-carboline was only 20 % in a reaction with $Ti(O\text{-}^{i}Pr)_4$ as catalyst [16].

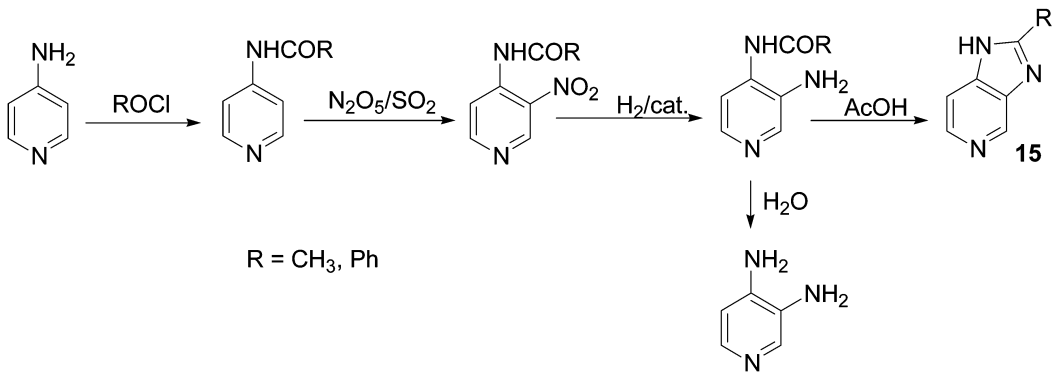
We also reduced 3-nitro- to 3-hydroxylamino-4-phenylpyridine (**14**, Scheme 7) and tried this in reactions with Lewis and Brøndstedt acids in attempts to form the nitrenium ion that might react to give β-carboline, but only traces were obtained [16].

In another series of experiments, inspired by Denmark's work on nitroalkenes [17], we tried to react 3-nitropyridine as a diene in an inverted Diels–Alder reaction with electron-rich dienophiles. However, even with 1,1-di-(*N*-piperidinyl)ethene, no reaction took place in diglyme at 160 °C for 24 h. In an attempt to increase the electrophilicity of the nitropyridine system, both the *N*-oxide and the *N*-methyl-derivatives were reacted under similar conditions without success [18].



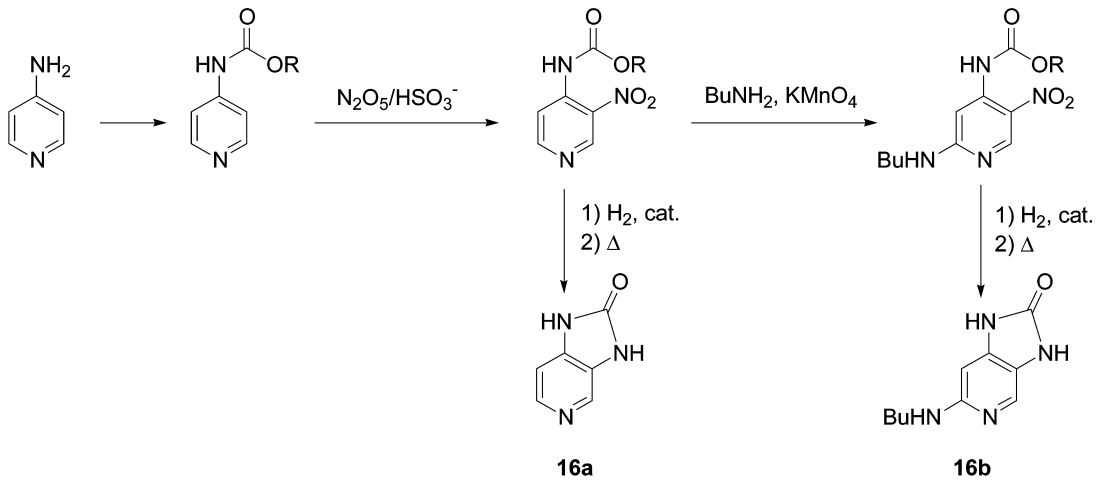
Scheme 7

The availability of 4-substituted-3-nitropyridines opens up the synthesis of the [*c*]pyridine bicyclic ring systems. We have investigated the synthesis of the imidazo[4,5-*c*]pyridine system, starting from readily available 4-aminopyridine. In one approach, by the acyl protected amino group, 2-substituted imidazo[4,5-*c*]pyridines (**15**, Scheme 8) were formed [19].



Scheme 8

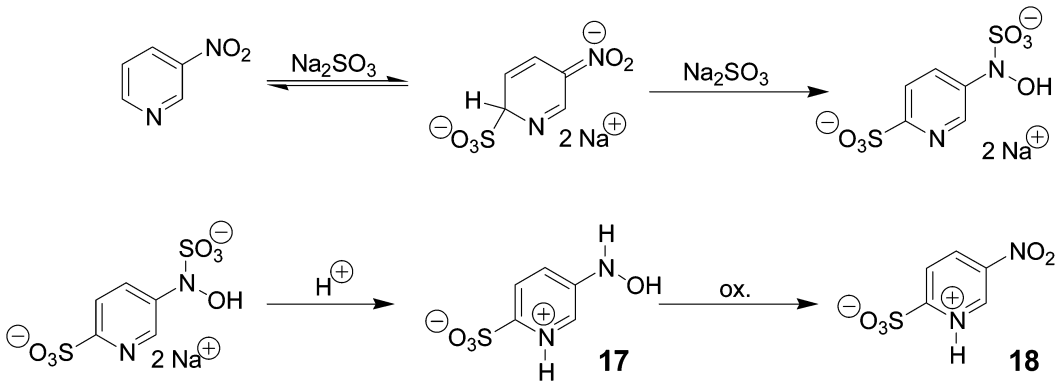
In another, starting with the amino group protected as alkyl carbamates, 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-ones were formed (**16**, Scheme 9) [20]. In the last sequence, the nitration of the pyridine carbamates with N_2O_5 did not result in hydrolysis of the carbamate group, indicating the usefulness of this reagent for the nitration of acid-sensitive compounds.



Scheme 9

Substitution reactions

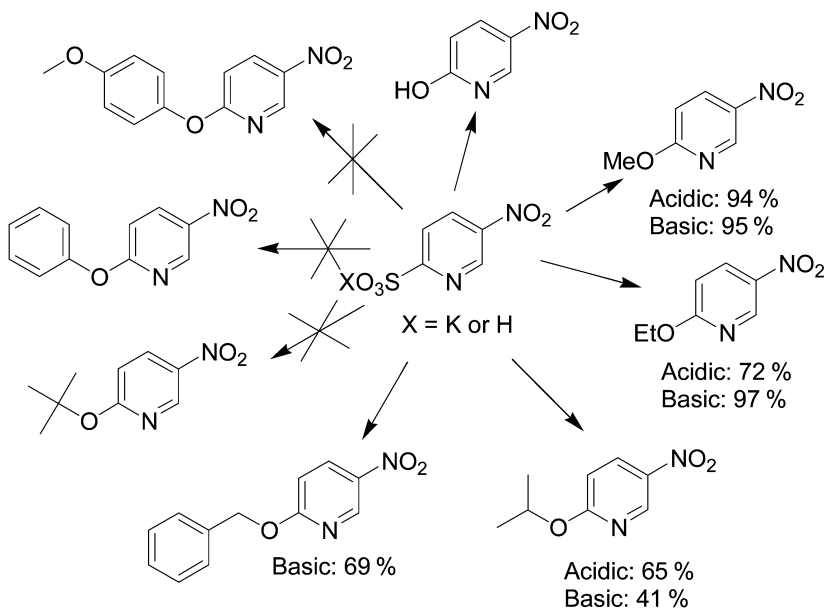
The pyridine ring is electrophilic, and this is increased by the presence of the nitro group, particularly in its ortho and para positions. This opens up the possibility of the formation of 2,5-substituted pyridines. This is a substitution pattern present in many biologically active compounds, and new synthetic methods might, therefore, be welcome [21]. We have reported the formation of 5-hydroxylaminopyridine-2-sulfonic acid (**17**, Scheme 10) and its oxidation to the corresponding nitro compound **18**. It was reasoned that the nitro group in the position para to the sulfonic acid would make this a better leaving group [22].



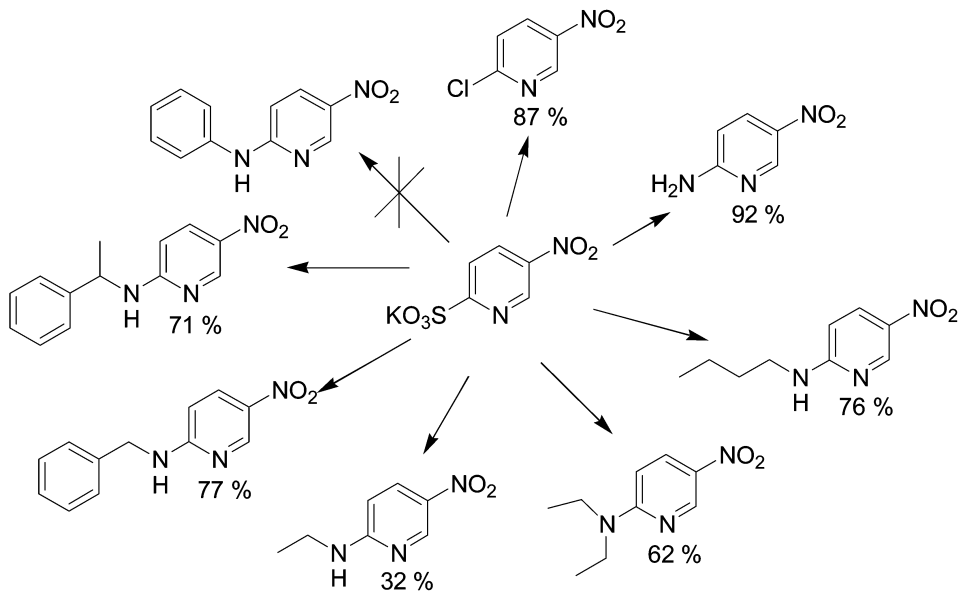
Scheme 10

We have, therefore, reacted **18** with a series of alcohols, phenols, amines, anilines, and phosphorous pentachloride. The results are given in Schemes 11 and 12. It is clear that the reactions with alcohols and amines gave the corresponding substitution products in high yields, but also that the phenols and anilines did not react. However, with PCl_5 a high yield of 2-chloro-5-nitropyridine was obtained [23]. This may be of special interest as 2-chloro-5-nitropyridine has served as starting material for a series of 2,5-substituted pyridines, although its synthesis appears to be more complicated than the one presented here [24].

We have also obtained the 2,5-substitution pattern by the use of vicarious nucleophilic substitution (VNS) [25] and the oxidative amination reaction (ONSH) [26].



Scheme 11

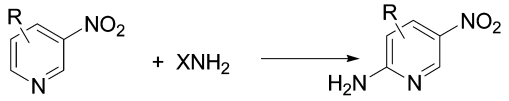


Scheme 12

We used the VNC procedure for amination of 3-nitropyridine and some substituted derivatives with hydroxylamine and 4-amino-1,2,4-triazole as aminating agents [27]. The results are given in Table 5.

The amination reaction gave acceptable-to-good yields for all the reacted nitropyridines. In general, the 4-amino-1,2,4-triazole gave the best results, but in many cases hydroxylamine gave comparable results and for methyl 3-nitroisonicotinate even the best yield. As hydroxylamine is more available then the aminotriazole, it may be the reagent of choice especially for large-scale preparations.

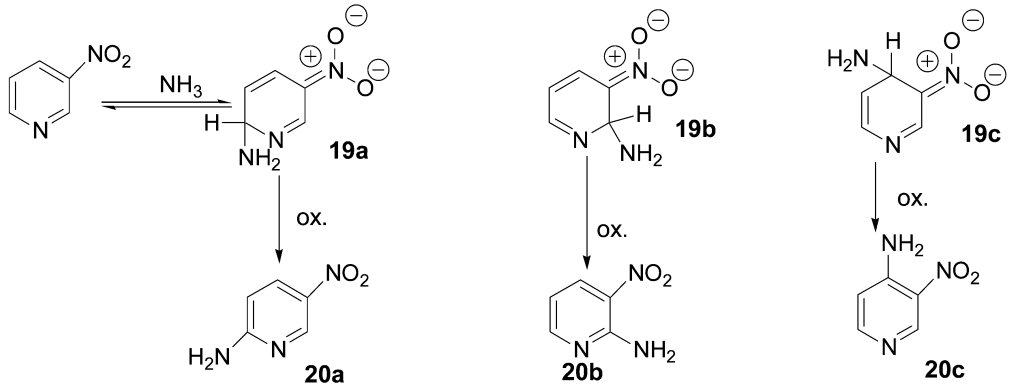
Table 5 Amination of pyridine and and substituted pyridines by the vicarious nucleophilic substitution method [27].



R	Yield/%		Product
	X = OH	X = 	
H	54	76	2-amino-5-nitro
4-CH_3	42	61	2-amino-4-methyl-5-nitro
5-CH_3	56	59	2-amino-3-methyl-5-nitro
4-CO_2CH_3	30	11	methyl 2-amino-5-nitroisonicotinate
4-CHO[a]	47	47	2-amino-4-(1,3-dioxolan-2-yl)-5-nitro
4-$COCH_3$[a]	63	65	2-amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitro
4-Ph	64	79	2-amino-4-phenyl-5-nitro
5-Ph	35	66	2-amino-3-phenyl-5-nitro
4-nitroisoquinoline	23	65	1-amino-4-nitroquinoline

[a]Protected as dioxolane.

The oxidative amination of aromatic and heteroaromatic compounds is an important reaction for the amination of activated substrates [26]. It is reported that the reaction of 3-nitropyridine in liquid ammonia and $KMnO_4$ gave a mixture of 2-amino-5-nitropyridine (**20a**, relative amount 1), 2-amino-3-nitropyridine (**20b**, relative amount 1.7), and 4-amino-3-nitropyridine (**20c**, relative amount 1.3) [28]. The reaction presumably proceeds via a reversible nucleophilic addition to give the three intermediates **19a**–**c** (Scheme 13). These are then oxidized irreversibly to give the amino-nitro products **20a**–**c**. If the oxidation step is faster than the establishment of the equilibrium in the first (addition) step, the product mixture would reflect the rate of formation of the three addition products (kinetic control). On the other hand, if the oxidation was slow, the equilibrium might be established before the oxidation and the product mixture would then reflect the equilibrium composition of the addition products, perhaps giving more of the product with the amino group para to the nitro group (**20a**).



Scheme 13

Therefore, we reacted 3-nitropyridine with ammonia and $KMnO_4$ at room temperature under different conditions. The results are given in Table 6 [29].

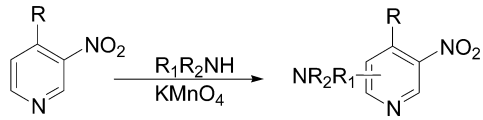
Table 6 Reaction of 3-nitropyridine in the presence of $KMnO_4$ at 22 °C to give 2-amino-5-nitropyridine (**20a**), 2-amino-3-nitropyridine (**20b**), and 4-amino-3-nitropyridine (**20c**).

Solvent	Conditions	Reaction time/h	Conversion % GC	Yields (%, GC)		
				20a	**20b**	**20c**
Water, 28 % NH_3	Stirring	20	20	7	3	10
Water, 28 % NH_3	Superson. mixing	380	68	1	11	
DMSO/water 75/25	Stream of NH_3	15	90	98[a]	2	

[a]66 % isolated yield.

From Table 6, it is clear that by running the reaction at room temperature with ammonia in a solvent, a better regioselectivity was obtained. In water, only a low conversion was obtained and in DMSO high conversion, but low regioselectivity was the result. However, in DMSO/water75/25 and a stream of NH_3, both a high conversion (90 %) and high regioselectivity (98 % para) were obtained.

Table 7 Oxidative amination of 3-nitropyridine and 4-substituted-3-nitropyridines.



R	R_1	R_2	Conversion (%, GC)	Composition (%, GC)		
				2-NR_1R_2-5-NO_2	2-NR_1R_2-3-NO_2	4-NR_1R_2-3-NO_2
H	H	H	90	98(66[a])	–	2
H	*n*-Bu	H	96	92[a]	2	2
H	Et	Et	95	93(60[a])	–	2
CN	Et	Et	99	93(41[a])	6	–
CO_2CH_3	Et	Et	99	96(48[a])	3	–
$COCH_3$[b]	Et	Et	90	86(72[a])	4	–

[a]Isolated yield.
[b]Protected as dioxolane.

We also used this protocol with a few nitropyridines in reactions with butylamine and diethylamine (Table 7) [29]. Both high conversion and high regioselectivity were obtained (Table 7). By the oxidative nucleophilic substitution protocol, we have, thus, discovered a general method for amination of β-nitropyridines in the position para to the nitro group.

SUMMARY

We have presented a general method for the nitration of pyridine compounds in the 3-position and discussed the mechanism for this nitration. Many of these 3-nitropyridines have been made available for general use for the first time by this method. We have investigated their reactions and presented syntheses to give imidazopyridines and nitropyridines further substituted in the position para to the nitro group. By this protocol, a series of compounds has been made available, which hitherto were either inaccessible or accessible only by multistep reactions.

ACKNOWLEDGMENTS

It is a great pleasure to acknowledge the work of my students. Their enthusiasm and expertise are documented by the list of publications in the references. The financial support from Norsk Hydro ASA and the Norwegian Research Council is also gratefully acknowledged.

REFERENCES

1. E. F. V. Scriven and G. Jones. In *Comprehensive Heterocyclic Chemistry*, Vol. 2, A. J. Boulton and A. McKillop (Eds.), Pergamon, Oxford (1984); D. L. Commins, S. P. Joseph, G. Jones. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5, A. McKillop (Ed.), Pergamon, Oxford (1996).
2. A. R. Katritzky and B. J. Ridgewell. *J. Chem. Soc.* 3753–3764, 3882–3883 (1963).
3. H. J. den Hertog, Jr. and J. Overhoff. *Recl. Trav. Chim. Pays-Bas* **49**, 552–556 (1930).
4. J. M. Bakke and I. Hegbom. *Acta Chem. Scand.* **48**, 181–182 (1994); J. M. Bakke, I. Hegbom, E. Øvreeide, K. Aaby. *Acta Chem. Scand.* **48**, 1001–1006 (1994).
5. E. Plazek. *Chem. Ber.* **72B**, 577–581 (1939).
6. F. DeSarlo and J. H. Ridd. *J. Chem. Soc. (B)* 712–715 (1971).
7. J. M. Bakke, E. Ranes, J. Riha, H. Svensen. *Act Chem. Scand.* **53**, 141–144 (1999).
8. J. M. Bakke and E. Ranes. *J. Chem. Soc., Perkin Trans. 2* 2477–2481 (1998).
9. T. W. Bentley and P. v. R. Schleyer. *J. Am. Chem. Soc.* **98**, 7658–7666 (1976); S. Winstein and G. C. Robinson. *J. Am. Chem. Soc.* **80**, 169–181 (1958).
10. W. N. White. In *Mechanisms of Molecular Migrations*, Vol. 3, B. S. Thyagarajan (Ed.), Wiley Interscience, New York (1971); J. H. Ridd, S. Trevellick, J. P. B. Sandall. *J. Chem. Soc., Perkin Trans. 2* 1073–1079 (1993).
11. J. M. Bakke and E. Ranes. *J. Chem. Soc., Perkin Trans. 2* 1919–1923 (1997).
12. J. W. A. M. Janssen, C. L. Habraken, R. Louw. *J. Org. Chem.* **41**, 1758–1762 (1976).
13. J. M. Bakke and J. Riha. *Acta Chem. Scand.* **53**, 356–359 (1999).
14. J. I. G. Cadogan. *Synthesis* 11–17 (1969).
15. J. Riha. Ph.D. Thesis, NTNU (2000).
16. J. M. Bakke and E. J. Andreassen. Unpublished results.
17. S. E. Denmark and A. Thorarensen. *Chem. Rev*. **96**, 137–165 (1996).
18. J. M. Bakke and H. H. Gautun. Unpublished results.
19. J. M. Bakke and J. Riha. *J. Heterocyclic Chem.* **36**, 1143 (1999).
20. J. M. Bakke and H. H. Gautun. *J. Heterocyclic Chem.* In press.
21. E. F. V. Scriven. In book of abstracts from 17th International Congress of Heterocyclic Chemistry, IL-33, Vienna 1999; J. E. Macor and E. Newman. *Heterocycles* **31**, 805–809 (1990); C. Papageorgiu, G. Camenisch, X. Borer. *Bioorg. Med. Chem. Lett*. **11** 1549–1552 (2001).
22. J. M. Bakke, E. Ranes, C. Rømming, I. Sletvold. *J. Chem. Soc., Perkin Trans. 1* 1241–1243 (2000); J. M. Bakke, H. H. Gautun, C. Rømming, I. Sletvold. <http://www.arkat-usa.org/ark/journal/Volum2/Part3/Undheim/undheim_index.htm,2001>
23. J. M. Bakke and I. Sletvold. *Org. Biomol. Chem.* **1**, 2710 (2003).
24. T. Endo and J. Zemlicka. *J. Org. Chem.* **53**, 1887–1894 (1998); Y. Effenberger, A. Krebs, P. Wilrett. *Chem. Ber.* **125**, 1131–1140 (1992).
25. O. N. Chupakhin, V. N. Charushin, H. C. van der Plas. *Nucleophilic Aromatic Substitution of Hydrogen*, pp. 59–64, Academic Press, San Diego (1994).
26. M. Wozniak and H. C. van der Plas. *Acta Chem. Scand.* **47**, 95–101 (1993).
27. J. M. Bakke, H. Svensen, R. Trevisan. *J. Chem. Soc., Perkin Trans. 1* 476–378 (2001).
28. M. Wozniak, A. Baranski, B. Szpakiewicz. *Liebigs Ann. Chem.* 875–878 (1991).
29. J. M. Bakke and H. Svensen. *Tetrahedron Lett.* **42**, 4393–4395.