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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 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 nucleophilic substitution (VNS) method with ammonia and amines 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. The VNS method has also been used in alkylation reactions with 3-nitropyridines to form dichloromethyl- and alkoxycarbomethyl-β-nitropyridines. From the appropriate substituted nitropyridines imidazopyridines and azaindoles have been formed.

J. Heterocyclic Chem., **42**, 463 (2005).

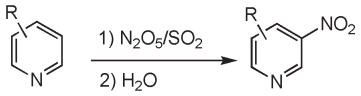
Introduction.

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]. This is due 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 ºC 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.

Preparation of Nitropyridines.

We treated a few pyridines with N_2O_5 dissolved in liquid SO_2 at –11 ºC and then poured the reaction mixture into water [4]. The yields were all better than those reported from nitration with HNO_3/H_2SO_4. For pyridine itself a yield of 56 % 3-.nitropyridine was obtained. From a mechanisitc point of view, the result from the nitration of 4-phenylpyridine was important, a 31% yield of 3-nitro-4-phenylpyridine was obtained, in contrast to the nitration with HNO_3/H_2SO_4 which gave exclusively nitration of the phenyl ring [5]. This suggested that the nitration with N_2O_5/SO_2 did not go by the mechanism of an electrophilic aromatic substitution.

Table 1
Nitration of pyridien and 4-phenylpyridine with N_2O_5/SO_2

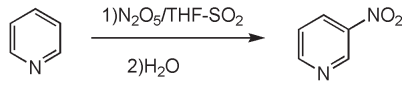


R	Product	Yield/%
H	3-NO_2	56
4-Ph	4-Ph-3-NO_2	31

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.

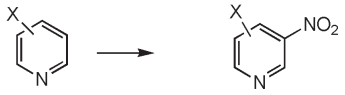


[SO_2]/[Pyridine]	T/°C	Yield/%
24	-20	65
16	-20	57
4	0	68
2	0	69
0.8	0	23
0	0	0

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 series 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 [6].

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
3-Ac	19	19	
4-Ac	75	67	67
4-Ph	31		68
3-Cl	15		
4-CN	35		
4-CHO (protected)	62		
Quinoline	16	12	10
Isoquinoline	28	38	32

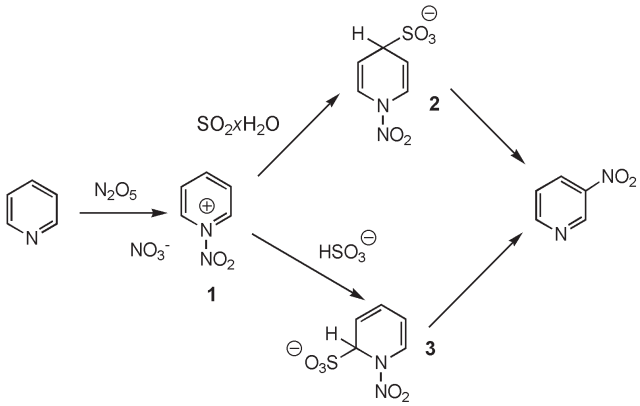
Method A: 1) N_2O_5/SO_2; 2) H_2O
Method B: 1) $N_2O_5/CH_3NO_2/SO_2$; 2)H_2O
Method C: 1) N_2O_5/CH_3NO_2; 2) HSO_3^-/H_2O

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.

Reaction Mechanism.

The results of preliminary crossover experiments suggested that the reaction was intramolecular with respect to the pyridine compound [4]. Furthermore, investigation of the reaction by NMR spectroscopy 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

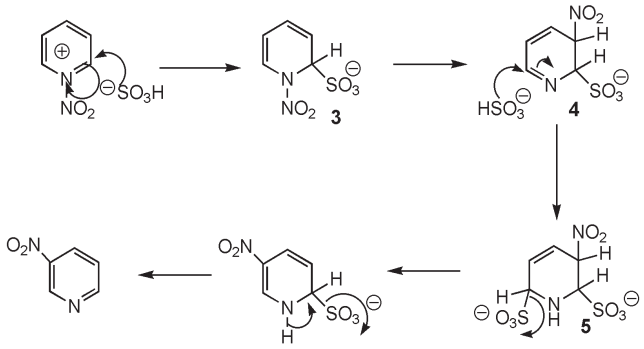


We will first discuss the reaction of the 1,2-dihydropyridine sulfonic acid **3**. We observed compounds **3** and **5** (Scheme 2) by NMR spectroscopy. As the concentration of compound **3** decreased, that of **5** increased and this in turn decreased to give 3-nitropyridine. The kinetics of the reaction 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} [7]. A reaction path in accordance with these data is summarized in Scheme 2.

The hydrogen sulfite ion 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.

Scheme 2



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

To distinguish between these two routes, the rates of reaction of **3** were determined with different solvents and under different ion strengths [7]. 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 [8].

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 were 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 [9].

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 [10].

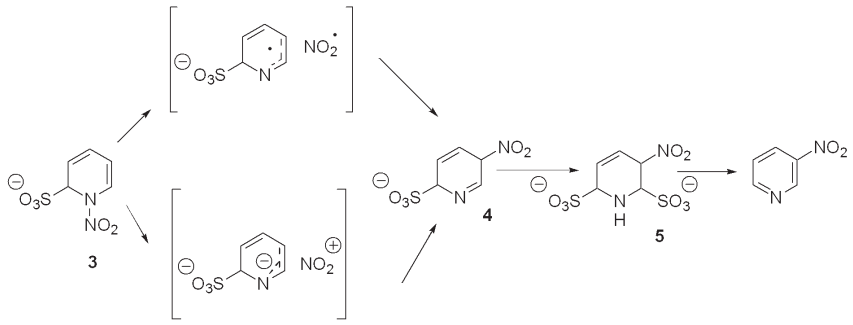
Table 4

Nitration of dimethylpyridines by N_2O_5/SO_2 .

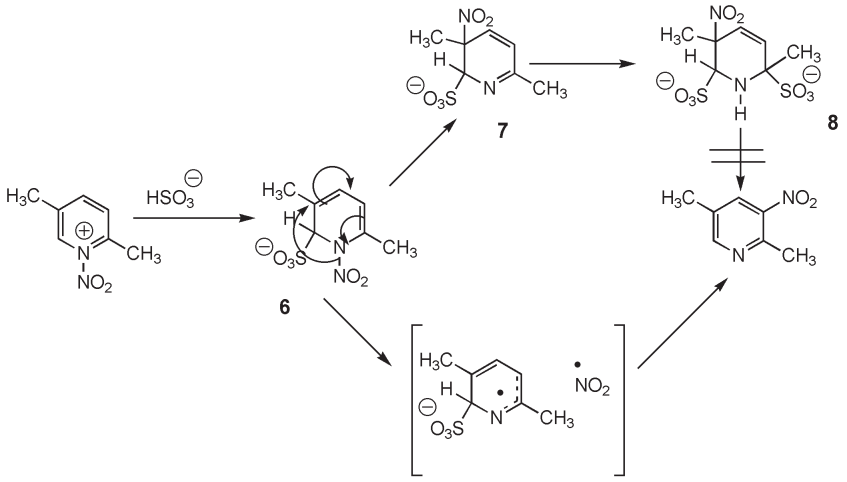
Positions of methyl groups	Position of nitro group	Yield/%
2,3	5	46
2,4	5	66
2,5	3,4 (1:4)	<3
2,6	3	1
3,4	5	58
3,5		0

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 [11]. 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 product from **8**.

Scheme 3



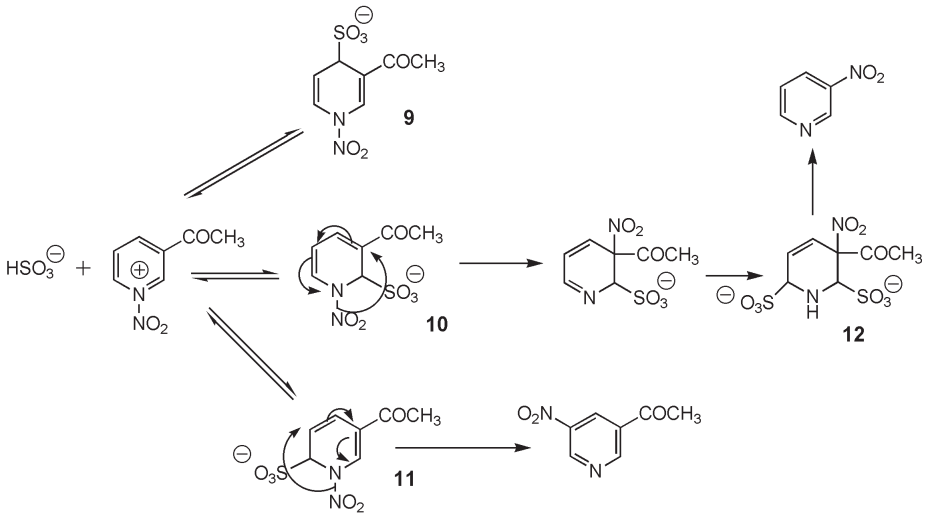
Scheme 4



Further evidence was obtained from the reaction of 3-acetylpyridine (Scheme 5) [7]. Here we observed (NMR) the three intermediates **9**, **10** and **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.

derivative **2** (Scheme 1) was less clear and several reaction paths appeared possible [12]. However, a crossover 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 [12]. The

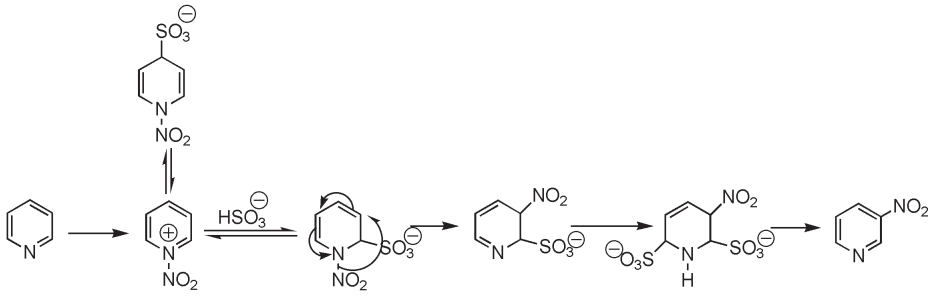
Scheme 5



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

proposed reaction mechanism for the formation of 3-nitropyridine from the *N*-nitropyridinium ion is summarised 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-pyridines. Because of this we have investigated some of their reactions.

Two reactions which would have been very useful are shown in Scheme 7. One is the formation of β-carboline from 3-nitro-4-phenylpyridine (Table 3) in analogy with the formation of carbazole from 2-nitrobiphenyl [13]. The other Diels-Alder reactions with 3-nitropyridine as a diene in reactions with electron rich dienophiles in resemblance with Denmarks work on nitroalkenes [14]. Unfortunately, as shown in Scheme 7, both these attempts failed.

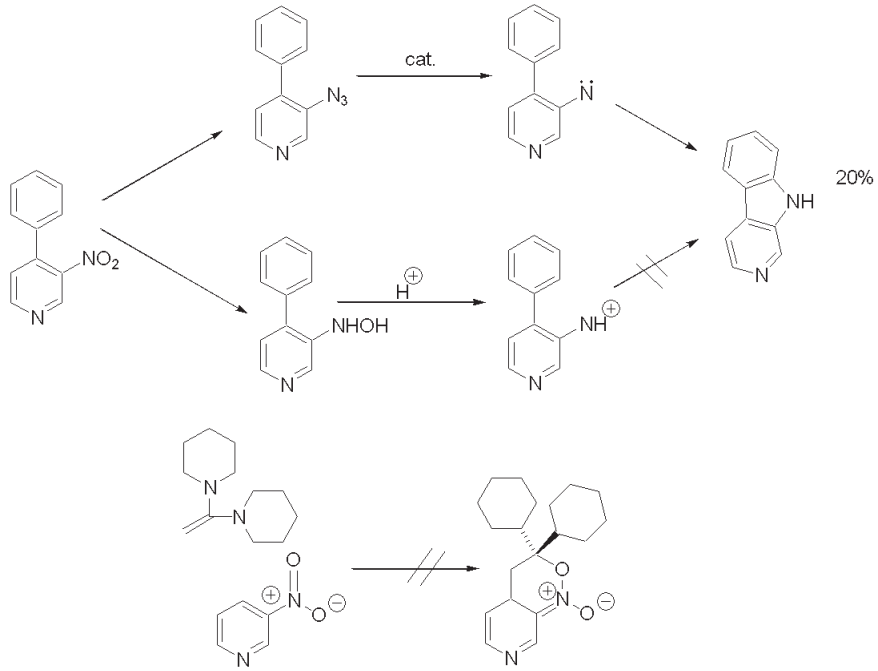
Substitution reactions.

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, a substitution pattern present in many biologically active compounds. New synthetic methods might therefore be welcome [15].

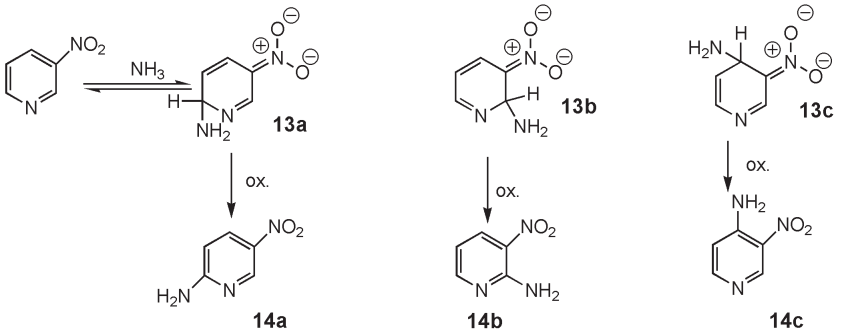
Amination Reactions.

We have obtained the 2,5-substitution pattern by the use the oxidative amination reaction (ONSH) [16] and the Vicarious Nucleophilic Substitution (VNS) method [17].

Scheme 7



Scheme 8



The oxidative amination of aromatic and heteroaromatic compounds is an important reaction for the amination of activated substrates [16]. It is reported that the reaction of 3-nitropyridine in liquid ammonia and $KMnO_4$ gave a mixture of 2-amino-5-nitropyridine (**14a**, relative amount 1), 2-amino-3-nitropyridine (**14b**, relative amount 1.7) and 4-amino-3-nitropyridine (**14c**, relative amount 1.3) [18]. The reaction presumably proceeds *via* a revercible nucleophilic addition to give the three intermediates **13a-c** (Scheme 8). These are then oxidized irreversibly to give the amino-nitro products **14a** – **14c**. If the oxidation step was 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 were slow, the equilibrium might be established before the oxidation and the product mixture would then reflect the equilibrium composition of the addition products, perhaps, for steric reasons, giving more of the product with the amino group *para* to the nitro group (**14a**).

We therefore reacted 3-nitropyridine with ammonia and $KMnO_4$ at room temperature under different conditions. The results are given in Table 5 [19].

Table 5

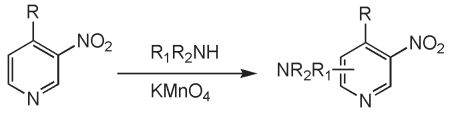
Reaction of 3-nitropyridine in the presence of $KMnO_4$ at 22 °C to give 2-amino-5-nitropyridine (**14a**), 2-amino-3-nitropyridine (**14b**) and 4-amino-3-nitropyridine (**14c**).

Solvent	Conditions	Reaction Time/h	Conversion % GC	Yields (%, GC) **14a**	**14b**	**14c**
Water, 28 % NH_3	Stirring	20	20	7	3	10
Water, 28 % NH_3	Superson. mixing	3	80	68	1	11
DMSO/water 75/25	Stream of NH_3	15	90	98 [a]		2

[a] 66 % isolated yield

Table 6

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$5 [b]	Et	Et	90	86(72 [a])	4	-

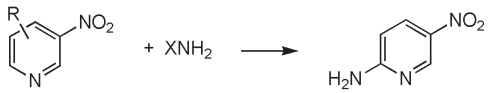
[a] Isolated yield. [b] Protected as dioxolane.

From Table 5 it is clear that by running the reaction at room temperature with ammonia in a solvent, a better regioselectivity was obtained then in liquid ammonia. 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 with a stream of NH_3 both a high conversion (90 %) and high regioselectivity (98 % *para*) were obtained.

We also used this protocol with a few nitropyridines in reactions with butylamine and diethylamine (Table 6) [19]. Both high conversion and high regioselectivity were obtained (Table 6). 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.

Table 7

Amination of pyridine and and substituted pyridines by the vicarious nucleophilic substitution method [20]



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

[a] Protected as dioxolane.

We have also obtained the 2-amino-5-nitropyridine substitution pattern by the use of the Vicarious Nucleophilic Substitution method. The substrates were 3-nitropyridine and some substituted derivatives. Hydroxylamine and 4-amino-1,2,4-triazole were used as aminating agents [20]. The results are give in Table 7.

The VNS 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.

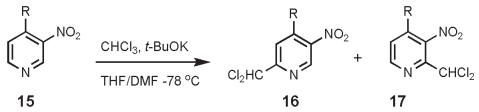
Substitution with carbon nucleophiles.

The VNS methode have also been extensively used for substitution reactions with carbon nucleophiles [21]. Makosza *et al.* have substituted a number of nitropyridines by this method [22]. However, nitration of pyridines has been restricted to those containing electron releasing substituents. We have therefore investigated the VNS alkylation reaction with a number of 3-nitropyridines made available by the N_2O_5/HSO_3^- method [6].

Two types of VNS reagents were investigated, chloroform and α-chlorocarboxylic esters. With chloroform and 3-nitropyridine, 4-(dichloromethyl)-3-nitropyridine was obtained in 80% yield as reported by Makosza. With substituted 3-nitropyridine high regioselectivity was obtained with electron withdrawing substituents but not with electron releasing ones ([23], Table 8).

Table 8

Reaction of nitropyridines (**15**) with $CHCl_3$/*t*-BuOK at –78 °C.



15 **16** **17**

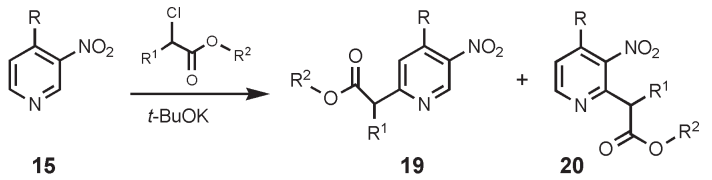
Substrate	Yields/% [a]	
	16	**17**
15a, R = Ph	27 (**16a**)	63 (**17a**)
15b, R = CH_3	51 (**16b**)	21 (**17b**)
15c, R = $CH(OCH_2CH_2O)$	83 [b] (**16c**)	-
15d, R = CH_3CO	60 (**16d**)	-
4-Nitroisoquinoline	1-(Dichloromethyl)-4-nitroisoquinoline 69 %	

[a] Isolated yields. [b] From ^{1}H NMR spectroscopy

With methyl chloroacetate and 3-nitropyridine a high regioselectivity was obtained. The reaction took place in the 4-position with an 80 % yield of 4-methoxycarbomethyl-3-nitropyridine (**18)**. Suprisingly, with some 4-substituted-3-nitropyridines this reagent gave only complex mixtures. On the other hand, with ethyl 2-chloropropionate, regioselective reaction in the *para* position to the nitro group took place with good yields ([23], Table 9).

Table 9

Reaction of 3-nitropyridines (**15**) with ethyl 2-chloropropionate and *t*-BuOK at 0°C.



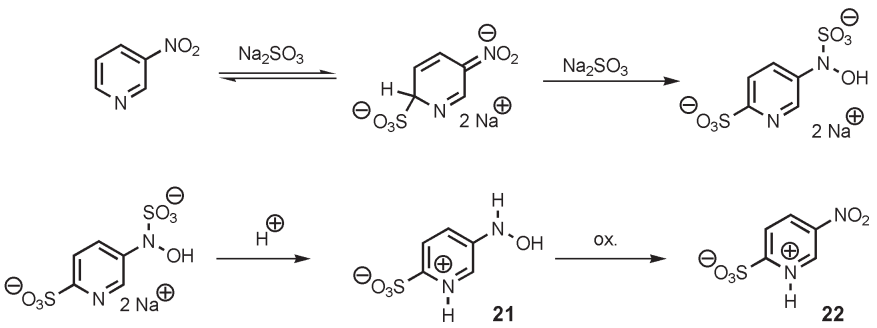
Substrate	R^1	R^2	Solvent	Yield (**19**)/ %
15a, R = Ph	CH_3	C_2H_5	DMF	78 (**19a**)
15b, R = CH_3	CH_3	C_2H_5	DMF	54 (**19b**)
15d, R = CH_3CO	CH_3	C_2H_5	DMF	90 (**19d**)

These products from the VNS substitution with carbon nucleophiles may serve as starting material for syntheses of other pyridine compounds: The dichloro-3-nitropyridines can be hydrolysed to the corresponding aldehydes and the products from the reactions with α-chlorocarboxyl esters may give ring closure products.

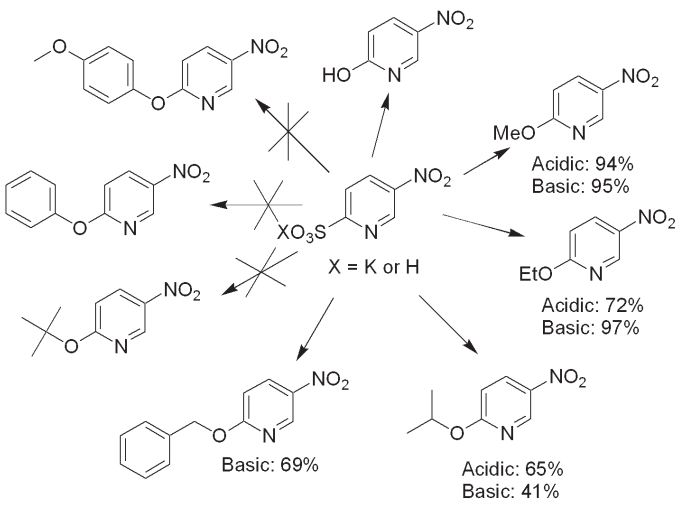
We have investigated one more way of obtaining the 2.5-substitution pattern in pyridines. Some time ago we reported the formation of 5-hydroxylaminopyridine-2-sulfonic acid (**21**, Scheme 9) and its oxidation to the corresponding nitro compound **22.** It was reasoned that the nitro group in the *para* position to the sulfonic acid would make this a better leaving group[24].

We have therefore reacted **22** with a series of alcohols, phenols, amines, anilines and phosphorous pentachloride. The results are given in Schemes 10 and 11 [25]. 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 [25]. This may be of special interest as 2-chloro-5-nitropyridine has served as starting material for a series of 2,5-substitutted pyridines although its synthesis appears to be more complicated than the one presented here [26].

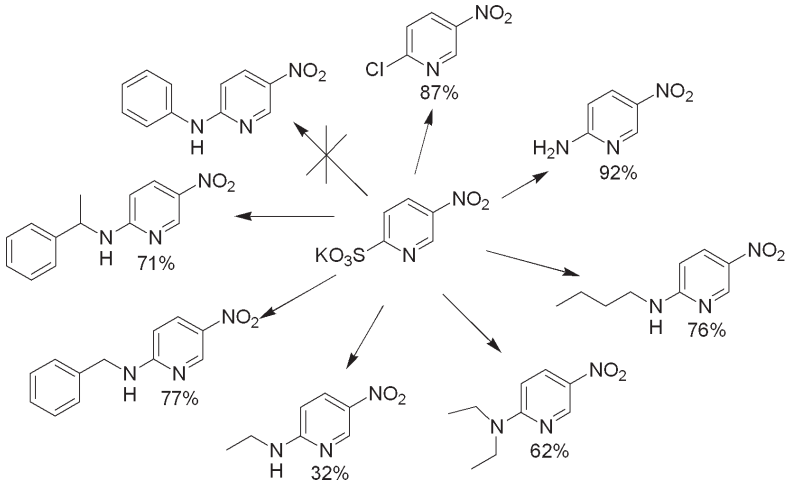
Scheme 9



Scheme 10



Scheme 11



The sulfonic acid **22** or its salt might also act as a substrate in a Vicarious Nucleophilic Substitution reaction. In reaction with methyl chloroacetate under basic conditions two reaction paths appeared possible, a substitution of the sulfonate groupto give compound **23** or a VNS attack in the 4-position to give compound **24**. Only the VNS product **24** was formed (Scheme 12).

Compound **24** contains the *para* relationship between the sulfonate group and the nitro group. The sulfonate group might therefore be substituted by suitable nucleophiles by analogy with the reactions of the starting compound **22** [25]. A few introductory experiments showed this to be the case ([23], Table 10).

Scheme 12

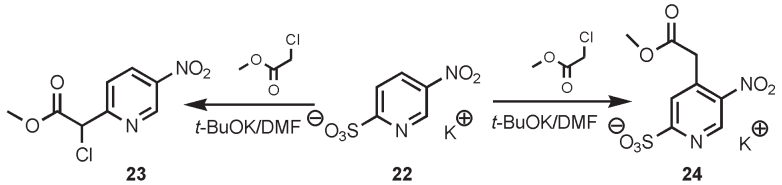
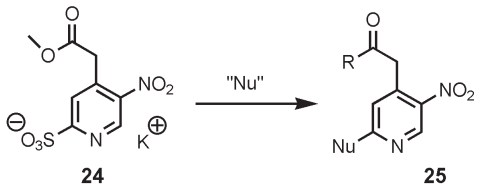


Table 10

Reactions of potassium 4-methoxycarbomethyl-5-nitro-2-pyridinesulfonate (**10**) with nucleophiles.



24 **25**

Nucleophile ("Nu")	Product, Nu / R	Yield (%)
CH_3O	**25a**, CH_3O / CH_3O	63
NH_3	**25b**, NH_2 / NH_2	68
$BuNH_2$	**25c**, BuNH / BuNH and **25d**, BuNH / OH	29 and 45

Ring forming reactions.

The availability of 4-substituted-3-nitropyridines makes new synthetic routes to the [*c*]pyridine bicyclic ring systems possible.

Imidazopyridines.

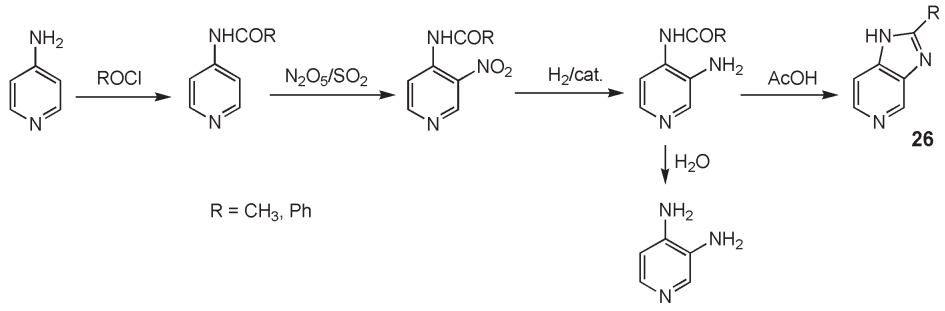
We have investigated the synthesis of the imidazo[4,5-*c*]pyridine system, starting from readily available 4-aminopyridine. In one approach, by the acyl protected amino group, 2-substituted imidazo[4,5-*c*]pyridines (**26**, Scheme 13) were formed [27].

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 (**27**, Scheme 14) [28]. In this 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.

6-Azaoxindoles.

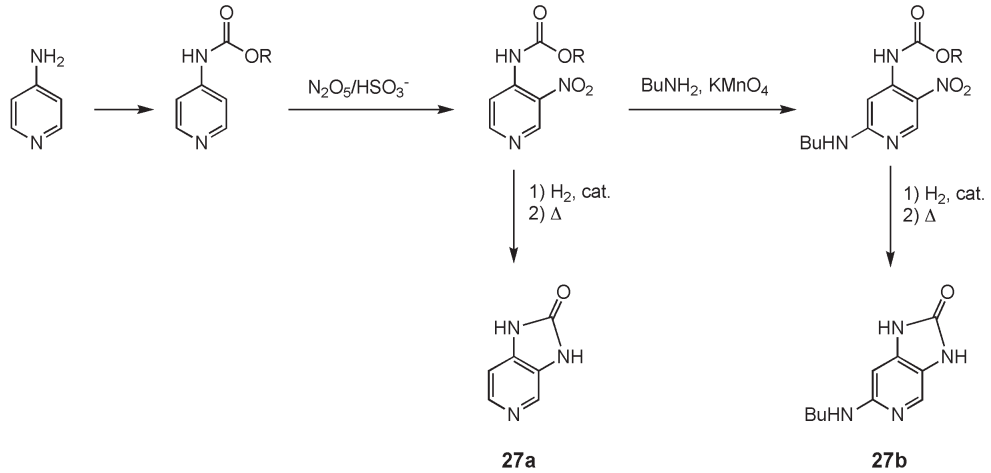
6-Azaindole (**28**) has been made by a reductive ring closure from bis(benzyloxycarbo)methyl-3-nitropyridine

Scheme 13



26

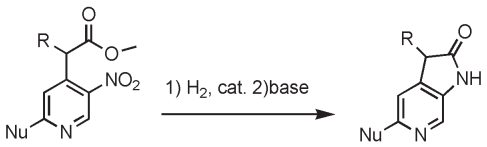
Scheme 14



27a **27b**

[29]. This compound was available only by a multistep synthesis and new syntheses might be of interest. 4-Methoxycarbomethyl-3-nitropyridine (**18**) would be a possible starting material for 6-azaindole. In addition, the methylene group of **18** is activated both by the nitropyridine ring and by the ester group and might therefore be derivatised. Furthermore, the product (**24**) from the VSN reaction with 3-nitropyridine-2-sulfonat could be substituted in the 2-position (Table 10).These points may make it possible to synthesise 6-azaindol itself and also 6-azaindoles with substituents in 3- and 5-position. The results from introductory experiments are given in Table 11 [30].

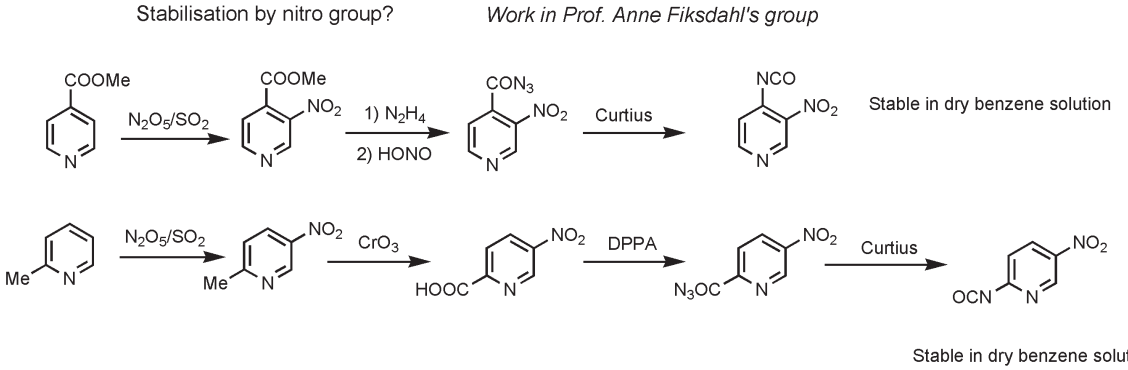
Table 11



R	Nu	Yield/%
H	H	70
Bn	H	50
H	CH_3O	30

Pyridyl Isocyanates.

Pyridyl 2- and 4-isocyanates are very reactive species. Under normal conditions only the dimer (from pyridyl 2-isocyanate) and trimer (from 4-isocyanates) can be isolates. A nitro group in the β-position in these compounds might decrease their reactivity and make it possible to study them. This was indeed the case as shown by the reaction sequence below [31]:



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, 6-azaoxindiles 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.

Acknowledgements.

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 Reference part. The financial support from Norsk Hydro ASA and the Norwegian Research Council is also gratefully acknowledged.

REFERENCES AND NOTES

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

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

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

[4] 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).

[5] F. DeSarlo and J. H. Ridd, *J. Chem. Soc. (B)* 712 (1971).

[6] J. M. Bakke, E. Ranes, J. Riha and H. Svensen, *Act Chem. Scand.* **53**, 141 (1999).

[7] J. M. Bakke, H. Svensen and E. Ranes, *J. Chem. Soc. Perkin Trans. 2*, 2477 (1998).

[8] T. W. Bentley and P. v. R. Schleyer, *J. Am. Chem. Soc.* **98**, 7658 (1976); S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.* **80**, 169 (1958).

[9] W. N. White, in *Mechanisms of Molecular Migrations*, ed.B. S. Thyagarajan,Vol. 3, Wiley. Interscience, New York, 1971; J. H. Ridd, S. Trevellick and J. P. B. Sandall, *J. Chem. Soc., Perkin Trans. 2*, 1073 (1993).

[10] J. M. Bakke and E. Ranes, *J. Chem. Soc. Perkin Trans. 2*, 1919 (1997).

[11] J. W. A. M. Janssen, C. L. Habraken and R. Louw, *J. Org. Chem.*, **41**, 1758 (1976).

[12] J. M. Bakke and J. Riha, *Acta Chem. Scand.* **53**, 356 (1999).

[13] J. I. G. Cadogan, *Synthesis*,11 (1969).

[14] S.E. Denmark and A. Thorarensen, *Chem. Rev*. **96** 137 (1996).

[15] E. F. V. Scriven, in book of abstracts from *17thInternational Congress of Heterocyclic Chemistry*, IL-33, Vienna **1999**; J. E. Macor and E. Newman, *Heterocycles*, **31**, 805 (1990); C. Papageorgiu, G. Camenisch, and X. Borer, *Bioorg. Med. Chem. Lett*, **11** 1549 (2001); D. J. Ager, R. A. Erickson, D. E. Froen, I. Prakash and B. Zhi, *Org. Process Research & Devel.* **8**, 62 (2004).

[16] M.Wozniak and H. C. van der Plas, *Acta Chem. Scand.* **47**, 95 (1993).

[17] O. N. Chupakhin, V. N. Charushin and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, CA, 1994, pp59-64.

[18] M. Wozniak, A. Baranski and B. Szpakiewicz, *Liebigs Ann. Chem.* 875 (1991).

[19] J. M. Bakke and H. Svensen, *Tetrahedron Lett.* **42**, 4393 (2001).

[20] J. M. Bakke and H. Svensen and R. Trevisan, *J. Chem. Soc. Perkin Trans. 1*, 476 (2001).

[21] T. Lemek, M. Makosza, D. S. Stephenson and H. Mayr, *Angew. Chem. Int. ed.*, **42**, 2793 (2003); M. Makosza and K. Wojciechowski, *Liebigs Ann./Recueil*, 1805 (1997); O. N. Chupakhin, V. N. Charushin and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego 1994 and references cited in these publications.

[22] M. Makosza and Z. Owczarczyk, *J. Org. Chem.*, **54**, 5094 (1989); M. Makosza, K. Sienkiewicz and K. Wojciechowski, *Synthesis*, 850 (1990).

[23] E. J. Andreassen, J. M. Bakke, I. Sletvold and H. Svensen, *Org. Biomol. Chem.* **2**, 2671 (2004).

[24] J. M. Bakke, E. Ranes, C. Rømming and I. Sletvold, *J. Chem. Soc. Perkin Trans. 1*, 1241 (2000); J. M. Bakke, H. H. Gautun, C. Rømming and I. Sletvold, http://www.arkat-usa.org/ark/journal/Volum2/Part3/Undheim/undheim_index.htm,2001

[25] J. M. Bakke and I. Sletvold, *Org. Biomol. Chem.*, **1**, 2710 (2003).

[26] T. Endoand and J. Zemlicka, *J. Org. Chem.* **53**,1887 (1998); Y. Effenberger, A. Krebs, and P. Wilrett, *Chem. Ber.* **125**,1131 (1992).

[27] J. M. Bakke and J. Riha, *J. Heterocyclic Chem.* **36**, 1143 (1999).

[28] J. M. Bakke, H.H. Gautun and H. Svensen, *J. Heterocyclic Chem.*, **40**, 585 (2003).

[29] B. A. J. Clark, M. M. S. El-Bakoush and J. Parrick, *J. Chem. Soc. Perkin Trans. 1*, 1531, (1974); R. W. Daisleyand J. R. Hanbali, *Synth. Comm.*, **11**, 7431981.

[30] E. J. Andreassen and J. M. Bakke, *work in progress.*

[31] J. Holt, T. Andreassen, J. M. Bakke and A. Fiksdahl, *Submitted.*