A New Efficient Synthesis of 3-Nitropyridine and Substituted Derivatives

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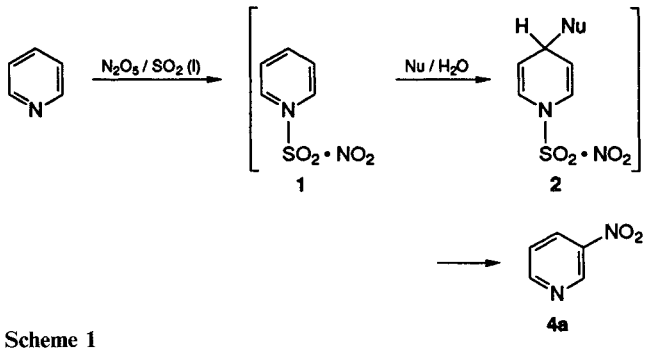
Pyridine and pyridine derivatives have been nitrated in the β-position by reaction with N_2O_5 or $NO_2 \cdot BF_4$ in $MeNO_2$, THF or MeCN to form the *N*-nitropyridinium salt. This was then reacted with an aqueous solution of a nucleophile to give the β-nitro compound in moderate to good yield.

Electrophilic aromatic substitution of the pyridine ring system takes place only under forcing conditions and often with very low yields of the substituted products.[1] This is typical for the nitration of pyridine and its substituted derivatives: nitration of pyridine with HNO_3/H_2SO_4 gave 3% of 3-nitropyridine,[2] the use of KNO_3/H_2SO_4 at 330°C gave 1% of the same compound[3] and nitration of 2-methylpyridine gave 2% of 2-methyl-5-nitropyridine with the same reactants at 160°C.[4] As a result, 3-nitropyridine does not feature in the majority of chemical suppliers' catalogues. New methods for the nitration of pyridine and its substituted derivatives are therefore clearly needed.

We have recently reported the use of a new reagent system for nitration, that is, dinitrogen pentoxide (N_2O_5, DNP) in liquid sulfur dioxide.[5] Later, we found that common organic solvents such as tetrahydrofuran or nitromethane containing a minor proportion of SO_2 could be used for the nitration of pyridine with DNP.[6] However, a certain amount of SO_2, approximately two moles SO_2 per mole of pyridine, was needed to obtain a good yield. For both reaction systems, the workup procedure involved quenching with water/ice and subsequent extraction of the product. From the available evidence the reaction was formulated as depicted in Scheme 1.



Scheme 1

Although this represented the first method for the direct nitration of pyridine, the use of gaseous SO_2 made the method less suitable for preparative work. The role of SO_2 in the reaction could be in the formation of a pyridine-SO_2-NO_2 complex (**1**) or the nucleophile Nu or both (Scheme 1). To test this we reacted pyridine with DNP in organic solvents without SO_2 and quenched the product of this reaction with water containing SO_2. The product was indeed 3-nitropyridine and the yield depended on the concentration of SO_2 in the water phase. This showed that the role of SO_2 was to act as, or to form, the nucleophile which reacted with the complex **1** to give the 1,4-dihydropyridine adduct **2**.

This result has important implications as it indicates that other nucleophiles could be used in the nitration reaction. The nucleophiles Br^-, AcO^-, F^-, Et_3N and pyridine itself gave only traces of the product 3-nitropyridine. With a few other nucleophiles the results were better, as shown in Table 1.

Table 1. Nitration of Pyridine with $NO_2 \cdot X$ in an Organic Solvent and Subsequent Reaction with Nucleophiles in Water[a]

Substrate/ $NO_2 \cdot X$; Ratio	Solvent	Nucleophile	Recovered Pyridine (%)	3-Nitropyridine (%)
Pyr/N_2O_5; 1:2	THF	SO_2[b]	–	33
Pyr/N_2O_5; 1:1	MeCN	SO_2[b]	16	15
Pyr/N_2O_5; 1:2	$MeNO_2$	SO_2[c]	13	56
Pyr/N_2O_5; 1:1.8	$MeNO_2$	$NaHSO_3$	3	65
Pyr/N_2O_5; 1:2	$MeNO_2$	$NaHSO_3$[d]	1	68
Pyr/N_2O_5; 1:2	THF	Na_2SO_3	1	23
Pyr/N_2O_5; 1:0.7	THF	$NaHSO_3$	41	30
Pyr/N_2O_5; 1:2	$MeNO_2$	NaOH	14	12
Pyr/N_2O_5; 2:1	$MeNO_2$	Pyridine[e]	–	1.5
$Pyr/NO_2 \cdot BF_4$	MeCN	$NaHSO_3$	–	22[f]
$Pyr/NO_2 \cdot BF_4$	$MeNO_2$	$NaHSO_3$	–	59[g]
Pyr/N_2O_5; 1:2	$MeNO_2$	$CH_2NO_2^-$	70	25[h]

[a] $[Pyridine]^0 = 0.5$ M, $H_2O = 100$ mL. The nucleophile was present in a 5 fold excess.
[b] Gaseous SO_2 was passed into the water phase for 30 min before the addition of the pyridine/N_2O_5 solution.
[c] Liquid SO_2 (25 mL) added to the water phase immediately after the addition of the pyridine/N_2O_5 solution.
[d] Amount of $NaHSO_3$ used was twice that of the previous experiment.
[e] Pyridine was added to the water phase in large excess.
[f] *N*-Nitropyridinium tetrafluoroborate was formed in 37% yield from pyridine and $NO_2 \cdot BF_4$. Yield of 3-nitropyridine (**4a**) was calculated based on this data. Yield of **4a** based on pyridine was calculated to be 8% from ^1H NMR spectrum.
[g] *N*-Nitropyridinium tetrafluoroborate was formed from pyridine and $NO_2 \cdot BF_4$ in 29% yield. Yield of **4a** was calculated based on this data. Yield of **4a** based on pyridine was calculated to be 17% from ^1H NMR spectrum.
[h] The water phase contained KOH (0.5 M). $[CH_2NO_2]^-$ was formed from the solvent and OH^-. Yield of **4a** calculated from ^1H NMR spectrum.

It is clear from Table 1 that nucleophiles other than SO_2 can be used in the nitration of pyridine to form 3-nitropyridine. One is the sulfite ion (SO_3^{2-}) which gave 23% of 3-nitropyridine, another is $[CH_2NO_2]^-$ (from

CH_3NO_2 and OH^-), the use of which gave 25% of the same product. However, the most useful nucleophile for synthetic purposes is the bisulfite ion (HSO_3^-). The presence of this as its sodium salt in the nitration medium gave 68% of 3-nitropyridine. This is as high as that obtained by using liquid SO_2 as solvent for the reaction.[5] The bisulfite salts are much easier to handle than the noxious gas SO_2 and they are also cheap reagents. This result, therefore, indicates a new, widely-applicable and synthetically useful preparative method for the nitration of pyridine and other compounds containing the pyridine ring.

Accordingly we applied this new method to a range of representative pyridine compounds. The results from these experiments are given in Table 2. The use of sodium bisulfite in these reactions gave yields comparable to those obtained by the use of liquid SO_2 as a solvent.[5] These results therefore strongly suggest that a general nitration method has been found which can be used for the nitration of a number of pyridine derivatives.

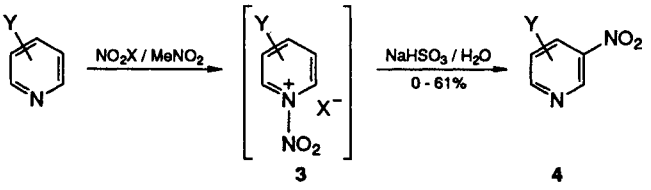
Table 2. Nitration of Pyridine Derivatives with N_2O_5 in $MeNO_2$ and the Subsequent Reaction with Aqueous $NaHSO_3$[a]

Product	Recovered Substrate[b] (%)	Yield[c] (%)
4a	1	68
4b	11	50
4c	10	24
4d	48	19
4e	98	0
4f	50	6.5
4g	11	29

[a] [Substrate]^0 = 0.5 M, N_2O_5 = 1.0 M, $MeNO_2$ = 25 mL, H_2O = 100 mL, $NaHSO_3$ = 1 M.
[b] Recovered substrate from GC analysis.
[c] Yield of isolated product.

The structures of the nitration products in Table 2 were determined from the vicinal proton-proton coupling pattern of their ^1H NMR spectra (experimental section) and comparisons of these with compounds of known substitution pattern.[7] The only exception was the product from the nitration of isoquinoline. In this case, the vicinal coupling pattern showed this to be either 3- or 4-nitroisoquinoline, but not which of these two. However, the correct structure for the product could be assigned from the NOE-experiments (experimental section). The two signals at δ = 9.46 and 9.28 are assigned to the two protons on the pyridine ring as they showed only long range coupling constants. Irradiation at δ = 9.46 resulted in a 3.6% increase in the signal at δ = 8.15 and irradiation at δ = 9.28 gave no observable NOE effect. If the nitro group was in the 3-position, one would expect observable NOE effects from both these experiments, but only from one of these in the case of 4-nitroisoquinoline. From this it follows that the product was 4-nitroisoquinoline, and the signal at δ = 9.46 originating from H-1 and that at δ = 8.15 from H-8. The other assignments for 4-nitroisoquinoline reported in the experimental section follow from these and the other NOE experiments described. This result is also in accordance with the reported long range couplings for isoquinoline.[8]

The results in Table 2 show that the reaction product from DNP and pyridine does not contain the SO_2 group as formulated in **1**. Instead, the evidence from ^1H NMR were in accordance with the structure **3**, *N*-nitropyridinium nitrate (X=NO_3) (Scheme 2).



4	a	b	c	d	e
Y	H	4-Ac	4-Me	2-Me	2-Cl

4f: 3-nitroquinoline; **4g**: 4-nitroisoquinoline

Scheme 2

This indicated that other sources of $[NO_2]^+$ could be used for the nitration of pyridine. We therefore tried nitronium tetrafluoroborate for the reaction. The product formed with pyridine had the same ^1H and ^{13}C NMR spectra as that of the product from pyridine and DNP and, furthermore, gave 3-nitropyridine on reaction with sodium bisulfite in water. Nitronium tetrafluoroborate is commercially available and for nitrations at laboratory scale this may be a convenient reagent. However, for large scale use it has some disadvantages including the price and instability towards humidity.

DNP may therefore be the reagent of choice. It need not be used as the preformed crystalline compound employed in the experiments reported here. We have made a preliminary experiment in which a mixture of N_2O_4 and O_3 was passed into a sulfur dioxide solution of pyridine. A yield of 23% of 3-nitropyridine (**4a**) was obtained by this method, a result that could probably be improved. This method of DNP formation is similar to the Kyodai-nitration.[9] When this method was applied to the nitration of pyridine in dichloromethane but without a subsequent reaction with a nucleophile in water, a combined yield of 3-nitropyridine and 3,5-dinitropyridine in 3–5% was obtained.[10]

Another large scale method for DNP formation is the electrolytic oxidation of N_2O_4 in HNO_3.[11] It is possible to strip DNP from this solution and into an organic solvent. This solution of DNP could then react with a pyridine derivative to give the *N*-nitropyridinium salt which would give the β-nitropyridine compound on reaction with bisulfite ion.

In conclusion, we have presented a new method for the

nitration of pyridine ring systems that gives good yields of nitrated products. Pyridine or substituted pyridines are reacted with the commercially available $NO_2 \cdot BF_4$ or the easily prepared DNP in an organic solvent. The product of this reaction is reacted with a solution of sodium bisulfite in water. The nitrated product is isolated by standard methods.

All starting materials used for the nitration reactions are all commercially available. Pyridine, quinoline and isoquinoline were purified by reflux over BaO for 2 h followed by distillation and stored over molecular sieves (4Å, activated at 400 °C for 3 h). All other compounds were used as received. DNP was prepared from N_2O_4 and O_3.[12] DNP could be stored at −25 °C for two weeks. DNP was weighed into a vial at r.t. and then poured into an appropriate solvent. The solvents were purified by standard methods.[13] The addition of $NO_2 \cdot BF_4$ to the solvent was done in a dry-box under N_2. The $NO_2 \cdot BF_4$ was used as received from Acros. As a purity test,[14] it was reacted with 4-nitrotoluene in $MeNO_2$ to give 2,4-dinitrotoluene in 87% yield.

Nitration of Pyridines; General Procedure:
The pyridine compound (12.5 mmol) was added to a solution of the nitrating reagent, DNP or $NO_2 \cdot BF_4$, in the selected solvent (25 mL) at 0 °C. After ca 1 h, the mixture was poured into water (100 mL) containing the nucleophile and the aqueous layer was allowed to reach r.t. After ca 2 h, the water phase was extracted with CH_2Cl_2 (3 × 80 mL). The pH of the water phase was then adjusted to 7–8 by addition of $NaHCO_3$ and again extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated. The nitro compounds **4** were usually isolated from the first of these extractions and the recovered starting materials from the second one. The solvents, nitrating agents and nucleophiles used are given in Tables 1 and 2. Unless otherwise stated the yields reported are for isolated products, the purities are indicated by mp or bp.

3-Nitropyridine **(4a)**: mp 39.5–40.5 °C (Lit.[15] mp 41.0 °C).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.55 (1 H, dd, J = 4.88, 8.30 Hz, H-5), 8.52 (1 H, ddd, J = 1.46, 2.44, 8.30 Hz, H-4), 8.94 (1 H, dd, J = 1.46, 4.88 Hz, H-6), 9.48 (1 H, d, J = 2.44 Hz, H-2).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 123.8 (C-5), 131.1 (C-4), 145.2 (C-2), 154.9 (C-6).

4-Acetyl-3-nitropyridine **(4b)**: mp 35.0–36.5 °C (Lit.[20] mp 35.0–36.5 °C); 99.6% pure by GC (CP-Sil 5 CB).

^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ = 2.59 (3 H, s, $COCH_3$), 7.34 (1 H, dd, J = 0.62, 4.88 Hz, H-5), 8.96 (1 H, dd, J = 0.36, 4.87 Hz, H-6).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 30.0, 120.6, 140.8, 144.8, 145.9, 155.2, 197.8.

4-Methyl-3-nitropyridine **(4c)**: bp 110 °C/3 Torr (Lit.[16] bp 100 °C/3.5 Torr).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.66 (3 H, s, CH_3), 7.32 (1 H, d, J = 5.87 Hz, H-5), 8.66 (1 H, d, J = 5.87 Hz, H-6), 9.17 (1 H, s, H-2).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 20.0, 122.3, 132.9, 146.4, 153.3, 154.3.

2-Methyl-5-nitropyridine **(4d)**: mp 103–106 °C. (Lit.[17] mp 106–108 °C).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.71 (3 H, s, CH_3), 7.36 (1 H, d, J = 8.79 Hz, H-3), 8.37 (1 H, dd, J = 2.44, 8.79 Hz, H-4), 9.33 (1 H, d, J = 2.44 Hz, H-6).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 24.9, 123.4, 131.2, 142.5, 144.7, 165.5.

3-Nitroquinoline **(4f)**: mp 116–118 °C (Lit.[18] mp 127.0–128.0 °C).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.75 (1 H, br d, J = 7.57 Hz, H-6), 7.96 (1 H, dt, J = 1.3, 7.8 Hz, H-7), 8.05 (1 H, d, J = 8.30 Hz, H-5), 8.25 (1 H, d, J = 8.79 Hz, H-8), 9.05 (1 H, d, J = 2.44 Hz, H-4), 9.67 (1 H, d, J = 2.44 Hz, H-2).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 126.0, 128.8, 129.8, 129.9, 132.3, 133.4, 141.0, 144.1, 150.2.

4-Nitroisoquinoline **(4g)**: mp 54.0–55.0 °C (Lit.[19] mp 63.0 °C).

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 7.79 (1 H, dd, J = 1.01, 7.0 Hz, H-7), 7.99 (1 H, ddd, J = 1.32, 6.98, 8.31 Hz, H-6), 8.15 (1 H, br d, J = 8.25 Hz, H-8), 8.69 (1 H, dd, J = 0.80, 8.80 Hz, H-5), 9.28 (1 H, s, H-3), 9.46 (1 H, d, J = 0.80 Hz, H-2).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$/TMS): δ = 122.6, 127.8, 128.4, 128.9, 129.1, 134.0, 141.1, 141.3.

Nitration of Pyridine to 3-Nitropyridine (4a) Using Dinitrogen Tetroxide and Ozone as Nitrating Agent; Typical Procedure:
Pyridine (1.98 g, 25 mmol) was dissolved in liquid SO_2 (50 mL) at −30 °C and a mixture of N_2O_4 and O_3 was passed through the SO_2 solution for 4 h. The volume of the solution was kept constant by addition of liquid SO_2. The solution was then poured into water/ice (100 g). After 2 h at r.t. the water phase was worked up as described above. Yield of 3-nitropyridine 0.72 g (23%); recovered pyridine 0.83 g (42%).

Nuclear Overhauser Measurements for 4-Nitroisoquinoline **(4g)**: The observed NOE effects are reported from difference NOE spectra.

{H}	Observed NOE
9.46 (H-1)	8.15 (3.6%, H-8)
8.15 (H-8)	9.46 (3.4%, H-1), 7.99 (−2.6%, H-6), 7.79 (2.3%, H-7)
9.28 (H-3)	–
8.69 (H-5)	7.99 (3.3%, H-6)

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