

The Synthesis of β -Nitropyridine Compounds

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Pyridine and a number of substituted pyridines have been nitrated by reaction with N_2O_5 followed by reaction with an aqueous solution of $SO_2 \cdot xH_2O$ or $NaHSO_3$. The dependence of the yields on the pH of the aqueous reaction medium, on the concentration of $SO_2 \cdot xH_2O - HSO_3^-$, on addition of methanol to the aqueous phase, and on the reaction temperature were investigated. The yields obtained with $NaHSO_3$ were: 3-nitropyridine 77%, 2-methyl-5-nitropyridine 36%, 3-methyl-5-nitropyridine 24%, 3-acetyl-5-nitropyridine 18%, 5-nitropyridine-3-carboxylic acid 15%, 3-chloro-5-nitropyridine 11%, 4-methyl-3-nitropyridine 39%, 4-acetyl-3-nitropyridine 67%, 4-cyano-3-nitropyridine 45%, 4-phenyl-3-nitropyridine 68%, 4-formyl-3-nitropyridine 62% (from reaction in liquid SO_2), 3-nitropyridine-4-carboxylic acid 48%, methyl 3-nitropyridine-4-carboxylate 75%, 2,3-dimethyl-5-nitropyridine 37%, 2,4-dimethyl-5-nitropyridine 64%, 3-nitroquinoline 10% and 4-nitroisoquinoline 42%.

The pyridine ring system is incorporated into the structure of many natural products, pharmaceutical and agrochemical compounds and other commercial products. A number of synthetic methods have therefore been developed, both for the 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 harsh conditions on this system.¹ This is due to the electron-deficient nature 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,² and even this low yield could not be reproduced by den Hertog *et al.*, who obtained a 6% yield under the same reaction conditions.³

Some time ago we found to our surprise that, in spite of the low partial rate factors referred to above, it was possible to nitrate pyridine in the 3-position with dinitrogen pentoxide (N_2O_5 , DNP) as the nitrating agent and liquid SO_2 as the solvent.⁴ In a preliminary communication we later reported that organic solvents could be used for the reaction between the pyridine and DNP if the formed *N*-nitropyridinium nitrate (**1**) was reacted further with an aqueous solution of a nucleophile. A number of nucleophiles were evaluated for this reaction

and the bisulfite ion was found to give the best results. These reaction conditions were also used for a few substituted pyridine compounds.⁵ The use of an aqueous solution of sodium bisulfite was considerably simpler than the use of liquid SO_2 , but in some cases the yields were lower than those obtained by the use of SO_2 . We have therefore made further investigations of the reaction conditions. These new conditions have been applied to the nitration of pyridine and a number of substituted pyridines. For many compounds, the yields are higher than the ones we obtained earlier. The new conditions make a number of β -nitropyridine compounds readily available.

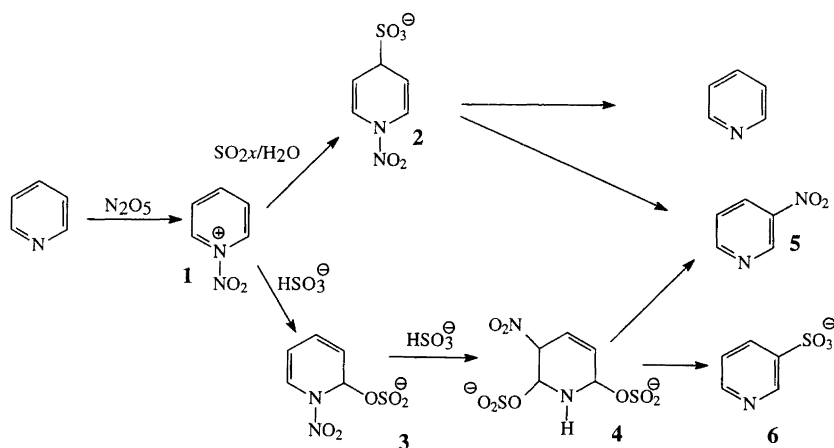
Results and discussion

In the reported procedures for nitration, pyridine was either reacted with DNP in SO_2 and the reaction mixture poured into water before work-up (procedure A),⁴ reacted with DNP in a mixture of SO_2 and an organic solvent and then poured into water (procedure B)⁶ or reacted with DNP and poured into water containing a nucleophile (HSO_3^- gave the best results, procedure C)⁵.

From previous work it was clear that the reaction of the pyridine compounds with DNP in SO_2 or an organic solvent was an *N*-nitration of the pyridine ring, regio-specific and essentially complete in a few minutes.⁵ Improvements of the yields would therefore have to be achieved by changes in the conditions for the reaction in the aqueous phase.

Our investigations on the reaction mechanism of pyri-

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Scheme 1.

dine nitration showed that two unstable compounds were formed on reaction with nucleophiles in the water phase, the 1,4-dihydropyridine derivative **2** and the 1,2-dihydropyridine derivative **3** (Scheme 1).⁷ The ratio [2]:[3] was dependent on the pH of the aqueous solution, apparently reflecting the ratio $[\text{SO}_2 \cdot x\text{H}_2\text{O}]:[\text{HSO}_3^-]$.

Compound **3** reacted rapidly to the tetrahydropyridine derivative **4**. The concentration of both compounds **2** and **4** decreased with time and that of the 3-nitropyridine (**5**) increased. The rate of reaction of **4** was pH dependent. At low pH, compound **2** was the only observable intermediate. In addition to 3-nitropyridine, pyridine was formed as a by-product from **2**. Furthermore, we have now discovered that sodium 3-pyridinesulfonate (**6**) was formed as a by-product when sodium bisulfite was used as the nucleophile and the pH of the water phase was 2–3. We have also studied which reaction conditions make the pyridinesulfonate the major product.⁸ The reaction of both **2** and **3** appeared to be intramolecular or to take place in a solvent cage.⁷ These observations suggest that variations of the reaction conditions could possibly improve the yields of the β -nitropyridine compounds.

The effect of pH. We have earlier shown that the ratio [2]:[3] was dependent on the pH of the aqueous solution of $\text{SO}_2 \cdot x\text{H}_2\text{O} - \text{HSO}_3^-$ during the addition to the *N*-nitropyridinium salt (**1**).³ However, the yield of 3-nitropyridine did not change very much when the pH was varied from ca. 1 to ca. 2.5 **before** the addition to *N*-nitropyridinium nitrate.^{4,5} Pyridine was formed as a by-product when the 1,4-dihydropyridine **2** was the major intermediate and 3-pyridinesulfonate when the 1,2-dihydropyridine derivative **3** was predominant. Therefore, the yield of 3-nitropyridine might be improved if one:

- 1, minimized the formation of **2** to avoid the formation of pyridine;
- 2, decreased the concentration of HSO_3^- to avert the formation of 3-pyridinesulfonate.



To achieve point 1 it would be necessary to react the

N-nitropyridinium ion with an aqueous solution with a low $[\text{SO}_2 \cdot x\text{H}_2\text{O}]:[\text{HSO}_3^-]$ ratio. This would give a solution with a high [3]:[2] ratio. Point 2 might be fulfilled by adjusting the pH of the aqueous solution **after** compound **1** had reacted to form **3** so that excess HSO_3^- is converted into $\text{SO}_2 \cdot x\text{H}_2\text{O}$.⁷ We have tried this protocol (procedure D) for pyridine and a number of substituted pyridines. The reactions were performed by reacting the appropriate *N*-nitropyridinium ion with an aqueous solution of NaHSO_3 at pH 2.5. After ca. 10 min, the pH was adjusted by the addition of a 1 M solution of HNO_3 . The results are given in Table 1 together with the results from the reactions without adjustment of pH. For some substrates, only procedure D, with pH adjustment was applied.

From Table 1 it is evident that this procedure increased the yield of the β -nitropyridine compounds in most cases. For instance, for 2-methylpyridine the yield of 2-methyl-3-nitropyridine was increased from 19% to 46% by application of the pH adjustment, for 4-acetylpyridine from 50% to 67% and for pyridine itself from 68% to 77%.

The effect of concentration of the nucleophile. The pyridinesulfonate by-products were probably formed from reactions with the bisulfite ions present. We therefore attempted to decrease the yield of the pyridinesulfonates by lowering the concentration of HSO_3^- in the aqueous solution. This might also lower the rate of formation of the two intermediates **2** and **3** and thus favour the hydrolysis of the *N*-nitropyridinium ion to give back the starting compound. We have tried this with one compound, 4-methyl pyridinecarboxylate (methyl isonicotinate). The methyl *N*-nitro-4-pyridinium-carboxylate nitrate formed by reaction with DNP was reacted with six and three mole equivalents of NaHSO_3 . The respective yields of 4-methoxycarbonyl-3-nitropyridine were 38 and 55% with a simultaneous decrease in the yield of the pyridinesulfonic acid, indicating that significant improvements may be obtained by variations in the concentrations of the nucleophile. No increase in recovered starting material was observed.

Table 1. Results from nitration of pyridine and substituted pyridines with N_2O_5 . The *N*-nitropyridinium ion formed was reacted with $SO_2-HSO_3^-$ in water or water-methanol mixture as stated in the columns under the Procedure heading.

Substrate 	Product 		Procedure yields (%)			
	X	Y	SO_2-H_2O (procedure A)	$NaHSO_3$ in H_2O (procedure C)	pH adjusted (procedure D)	$NaHSO_3$ in $MeOH-H_2O$ 3:1 (procedure E)
H	H	3-Nitro	63 ⁴	68 ⁵	77	67
2-Methyl	2-Methyl	5-Nitro	42	19 ⁵	36	36
3-Methyl	3-Methyl	5-Nitro	30 ⁴	5	24	20
3-Acetyl	3-Acetyl	5-Nitro	33		18	
3-Carboxy	3-Carboxy	5-Nitro				15 ^a
3-Chloro	3-Chloro	5-Nitro	15		11	
4-Methyl	4-Methyl	3-Nitro	51 ⁴	24 ⁵	33	39
4-Acetyl	4-Acetyl	3-Nitro	75	50 ⁵	67	58
4-Cyano	4-Cyano	3-Nitro	35		26	45
4-Phenyl	4-Phenyl	3-Nitro	37 ⁴		68	
4-Formyl	4-Formyl	3-nitro	62			
4-Carboxy	4-Carboxy	3-Nitro		36	15	48
4-Methoxycarbonyl	4-Methoxycarbonyl	3-Nitro				75
2,3-Dimethyl	2,3-Dimethyl	5-Nitro	46 ⁴	14		37
2,4-Dimethyl	2,4-Dimethyl	5-Nitro	66 ⁴	45		64
	2,4-Dimethyl	3-Nitro				8
3,4-Dimethyl	3,4-Dimethyl	5-Nitro	58 ⁴	14		20
Quinoline	3-Nitroquinoline		16 ⁴	7 ⁵	10	< 10
Isoquinoline	4-Nitroisoquinoline		28 ⁴	29 ⁵	32	42

^aFrom 1H NMR spectroscopy.

The effect of the reaction medium. The reactions of the intermediates **2** and **3** and their analogues to give the β-nitropyridine compounds have been shown to be intramolecular or to take place in a solvent cage.⁴ On the other hand, it appeared reasonable that the formation of the by-products pyridinesulfonates took place by reactions of intermediates and bisulfite ions. It was further speculated that these reactions involving ionic species could be suppressed by lowering the polarity of the reaction medium. Accordingly, we reacted *N*-nitropyridinium nitrate **1** and a number of substituted *N*-nitropyridinium ions with sodium bisulfite in solvent mixtures containing increasing proportions of methanol. The results of the experiments are given in Table 1 for solutions consisting of $MeOH-H_2O$ 3:1. The results were somewhat better with $MeOH-H_2O$ 3:1 than with 1:1. The reaction with $MeOH-H_2O$ 3:1 is called procedure E in Table 1.

For a few compounds, this procedure gave better yields than those obtained by the other procedures, particularly for 4-cyanopyridine (45% yield as compared with 26% by procedure D) and for 4-carboxypyridine (48% vs. 15%). For several other compounds the yields were comparable to those obtained by procedure D. As procedure E, consisting of a reaction of the *N*-nitropyridinium ion with a water-methanol solution of bisulfite ions, is simpler than the adjustment of pH (procedure D), procedure E may be the method of choice in many cases.

The effect of temperature. The use of $MeOH-H_2O$ as the medium for reaction of the *N*-nitropyridinium ion with sodium bisulfite made it possible to study the effect of temperature on the yield of β-nitropyridine compounds over a larger range. Reaction of methyl *N*-nitro-4-pyridiniumcarboxylate with $NaHSO_3$ in $MeOH-H_2O$ 3:1 at three different temperatures, -20, +5 and 25 °C showed that the temperature had no significant influence on the yield of methyl 3-nitro-4-pyridinecarboxylate. Furthermore, at low temperatures the reactions of the dihydropyridine intermediates corresponding to compounds **2** and **3** were so slow that it was necessary to wait for a week to obtain a complete reaction.

In addition to the results reported in Table 1 it should be noted that the following compounds gave yields <2% of β-nitropyridine compounds by the methods in Table 1: 2-acetyl-, 2-chloro-, 2-cyano-, 2-methoxy-, 2-vinyl-, 2-carboxy-, 3-nitro-, 4-amino-, 4-chloro-, 4-hydroxy- and 4-methoxypyridine. These reactions have not been thoroughly investigated. However, in one case, that of 4-chloropyridine, two products were isolated which indicated that hydrolysis reactions competed with migration of the *N*-nitro group: *N*-nitro-4(1*H*)-pyridone and 4-chloro-*N*-nitro-2(1*H*)-pyridone.

Conclusions

We have presented the results of the direct β-nitration of pyridine and a series of substituted pyridines with N_2O_5

in dichloromethane followed by reaction of the *N*-nitropyridinium salt formed with sodium bisulfite in an aqueous phase. Different conditions for the reaction in the aqueous phase were applied. Depending on the substrate, adjustment of pH after addition of the *N*-nitropyridinium salt to the aqueous phase, or addition of the *N*-nitropyridinium salt to a 3:1 mixture of a MeOH–H₂O solution of NaHSO₃, gave the best results (Table 1). The yields were dependent on the substrate, varying from 77% for pyridine to 15% for 3-chloropyridine.

Experimental

All starting materials used for the nitration reactions were commercially available and the methods for their purification have been described.⁵ DNP preparation from N₂O₄ and O₃ has been reported.⁹ The spectroscopic and chromatographic equipment used has been described.⁷

General procedure for the nitration of pyridine and substituted pyridines. DNP (1.35 g, 12.5 mmol) was dissolved in nitromethane¹⁰ (12.5 ml) and the pyridine compound (6.4 mmol) added slowly at 0 °C. After 5 min, the suspension of *N*-nitropyridinium nitrate (substituted or unsubstituted) was poured into water or water–methanol mixture containing NaHSO₃. The solvent compositions and concentrations of NaHSO₃ are given in Table 1. After 2–20 h, this solution was worked up. If it contained methanol this was removed under vacuum and the water solution extracted with diethyl ether, the ether solution dried (MgSO₄) and evaporated to give the product which was recrystallised from the appropriate solvent or distilled in a Kuegelrohr apparatus. The water phase was made basic (pH ca. 8) and treated as the acidic solution to give mainly recovered starting material.

For reactions with pH adjustments, the pH of the water phase after the addition of the *N*-nitropyridinium salt was adjusted to pH ca. 1 with 1 M HNO₃ after 10 min reaction at the original pH (ca. 2.5). After the pH adjustment, the water phase was stirred at room temperature for 2–20 h and then worked up as above. The physical and spectroscopic properties of the β-nitropyridine compounds in Table 1 were identical with those reported.^{1,5,6}

Nitration of 4-chloropyridine. 4-Chloropyridine was nitrated by procedure C in Table 1. Two compounds were isolated by flash chromatography and identified by their spectroscopic data.

4-Chloro-*N*-nitro-2(1*H*)-pyridone: decomp. at 260 °C. ¹H NMR (300 MHz, CDCl₃): δ 6.47 (1 H, d, *J*=8.58 Hz, H⁵), 8.56 (1 H, dd, *J*=3.03, 8.63 Hz, H⁶), 8.84 (1 H, d,

J=3.03 Hz, H²). ¹³C NMR (100 MHz, CDCl₃): δ 115.4, 125.4, 128.1, 129.7, 173.9. IR (KBr): 3128 (w), 3090 (w), 2960 (w), 2927 (w), 2876 (w), 1730 (w), 1642 (s), 1461 (w), 1374 (m), 1330 (m), 1278 (s), 1258 (s), 1130 (m), 1077 (s), 1015 (s), 901 (w), 870 (m), 823 (s), 723 (m), 630 (w) cm⁻¹. MS [*m/z* (% rel. int.)]: 176 (*M*+2, 2), 174 (*M*⁺, 6), 131 (32), 130 (7), 129 (100), 102 (5), 94 (22), 73 (9). Peak matching: measured 173.9829, calculated C₅H₃³⁵CIN₂O₃: 173.9832; measured 128.9976, calculated C₅H₄³⁵CINO: 128.9981.

N-Nitro-4(1*H*)-pyridone: decomp. at 130–131 °C. ¹H NMR (300 MHz, CDCl₃): δ 6.33 (2 H, d, *J*=8.57 Hz, H^{3,5}), 8.54 (2 H, d, *J*=8.62 Hz, H^{2,6}). ¹³C NMR (100 MHz, CDCl₃): δ 117.3, 130.4, 179.8. IR (KBr): 3081 (w), 1641 (s), 1630 (s), 1616 (s), 1594 (s), 1424 (w), 1396 (w), 1343 (m), 1272 (s), 1188 (m), 1102 (w), 1053 (s), 978 (m), 854 (m), 802 (m), 736 (w), 626 (w) cm⁻¹. MS [*m/z* (% rel. int.)]: 141 (*M*+1, 4), 140 (*M*⁺, 46), 110 (28), 96 (7), 95 (100), 94 (11), 68 (23), 67 (16). Peak matching: measured 140.0219, calculated C₅H₄N₂O₃: 140.0222; measured 95.0368, calculated C₅H₅NO: 95.0371.

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