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# The oxidative amination of 3-nitropyridines

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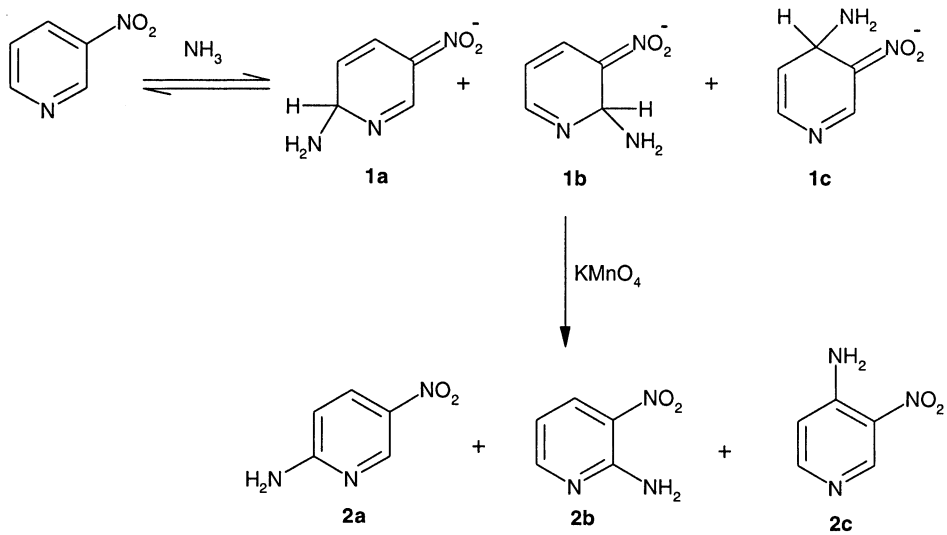
**Abstract**—3-Nitropyridine was reacted with ammonia or alkylamines and $KMnO_4$ under several different conditions. Substitutions in the *para* position to the nitro group were obtained with high regioselectivity: with ammonia, 2-amino-5-nitropyridine (66%), with butylamine, 2-butylamino-5-nitropyridine (92%), with diethylamine, 2-diethylamino-5-nitropyridine (49%). Under the same conditions, with methyl-3-nitroisonicotinoate and diethylamine/$KMnO_4$, methyl 2-diethylamino-5-nitroisonicotinoate (48%), with 4-acetyl-3-nitropyridine (protected by ethylene glycol) 2-diethylamino-4-acetyl-5-nitropyridine (72%, protected) and with 4-cyano-3-nitropyridine, 2-amino-4-cyano-5-nitropyridine (41%) were obtained. All yields are isolated. 

As β-nitropyridines have recently become readily available, we have been interested in studying their chemistry.[1] Recently we reported the successful amination in the position *para* to the nitro group by a vicarious nucleophilic substitution. The reaction proceeded with good to acceptable yields and high regioselectivity for a number of 3-nitropyridines.[2] Another important amination method for electron deficient aromatic and heteroaromatic compounds is oxidative amination.[3] This is usually carried out in liquid ammonia at low temperature, typically at the boiling point of ammonia at –33°C with $KMnO_4$ as oxidant. Although the reaction usually proceeds with acceptable to good overall yields, the low regioselectivity is a problem for some substrates. This is, perhaps, most pronounced for the amination of 3-nitropyridine which gave a mixture of 2-amino- (33%), 4-amino- (24%) and 6-amino-3-nitropyridine (19%).[4]

Recently we have studied nucleophilic substitution reactions with a number of substituted 3-nitropyridine compounds by which hydrogen was substituted with sulfo or amino groups.[2,5] In contrast to the results from the oxidative amination reactions, these reactions pro-

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ceeded with high regioselectivity, the 2-substituted-5-nitropyridine compounds were the only detected products. The oxidative amination reactions were carried out at low temperature in contrast to ours which were carried out at temperatures between 20 and 50°C. It occurred to us that this might be the reason for the observed difference in regioselectivity. These reactions probably proceed by a pathway in which the first step is the reversible addition of ammonia and formation of the intermediates **1a**–**c**.[3,4]

These intermediates are then oxidised by $KMnO_4$ to the products **2a**–**c**. If the irreversible oxidation is faster than the thermodynamic equilibration of the three intermediates, the product composition would reflect the kinetic composition of the intermediates **1a**–**c**. At low temperature in liquid ammonia with $KMnO_4$ well dissolved, this may be the case. Therefore, if the reaction could be carried out at higher temperature so that the equilibration reaction would compete more successfully with the oxidation, we would expect a higher yield of the presumably thermodynamically more stable *para* isomer (**2a**). At the same time it would be of convenience if the reactions could be run at ambient temperature. Recently, Wozniak has reported results which indeed indicate that this may be the case: from the reaction of 3-nitropyridine with methylamine at −7°C, 2-methylamino-5-nitropyridine was the dominant product, in contrast to the results from the reaction with ammonia at −33°C.[6]

We have therefore studied the reactions of 3-nitropyridine with three different amino compounds, ammonia, butylamine and diethylamine in different solvents and under various reaction conditions. The results of the reactions with ammonia are given in Table 1.

These show the strong influence of the reaction conditions, both on the rate of reaction and on the regioselectivity. The change from stirring with a magnetic bar to supersonic mixing not only greatly increased the rate of reaction, but also gave an increase in the relative yield of the *para* product (**2a**). The reaction in pure DMSO gave an increase in the yield of 3-nitro-4-aminopyridine (**2c**), presumably because the high activity of the permanganate anion in this solvent gave rapid oxidation of the σ-adduct before equilibrium was obtained. On changing to a DMSO/water mixture, this solvent effect would be expected to disappear and the results confirmed this with a high regioselectivity for the *para* isomer **2a**. In the reaction run with DMSO/water 75/25 with an initial concentration of 7% $NH_3$, di-2-(5-nitropyridyl)amine (**2d**) was formed in higher yield than that of 2-amino-5-nitropyridine (**2a**). In this reaction the initially low concentration of ammonia (7%) was reduced substantially by reaction with 3-nitropyridine as well as oxidation with $KMnO_4$, thus allowing the already formed **2a** to compete effectively as a nucleophile giving **2d**. However, by bubbling $NH_3$ into the solution, a constant concentration of ammonia was maintained, this side reaction was suppressed and a high yield of 2-amino-5-nitropyridine (**2a**) was obtained.

With these results in hand, we tried the reaction with primary and secondary amines. Wozniak reacted several nitropyridines in liquid methylamine at −7°C and obtained a 65% yield of 2-methylamino-5-nitropyridine together with a 3% yield of the di-aminated product 2,6-dimethylamino-3-nitropyridine.[6] In a similar experiment, we reacted 3-nitropyridine in butylamine with $KMnO_4$ and obtained a 92% yield (isolated) of 2-butylamino-5-nitropyridine together with 2-butylamino-3-nitropyridine (2%, GC area) and 4-butylamino-3-nitropyridine (2%, GC area). Thus, the oxidative amination of 3-nitropyridine in the alkylamine itself gave a high yield of the *para* product both for methyl- and butylamine.

We also tried the reaction of 3-nitropyridine with diethylamine (DEA) and $KMnO_4$ under different conditions. In DEA itself no reaction took place, and the same was the case for a 25/75 mixture of DEA and water. In DEA/diglyme 25/75 the regioselectivity was low, giving 45% of the *para* isomer (corresponding to **2a**) and 55% of the two *ortho* isomers (corresponding to **2b** and **2c**). However, in DEA/DMSO 25/75 with 5 mol equivalents $KMnO_4$, a good isolated yield (60%) and very high regioselectivity (98% *para* product) were

**Table 1.** Reaction of 3-nitropyridine with ammonia in the presence of $KMnO_4$ (5 mol equivalents) at 22°C to give 2-amino-5-nitropyridine (**2a**), 2-amino-3-nitropyridine (**2b**) and 4-amino-3-nitropyridine (**2c**) and di-2-(5-nitropyridyl)amine (**2d**)

| Solvent | Conditions | Reaction time (h) | Conversion (%) GC | Composition (%) (GC) | | | |
|---|---|---|---|---|---|---|---|
| | | | | **2a** | **2b** | **2c** | **2d** |
| Water $NH_3$ 28% | Stirring | 20 | 20 | 7 | 3 | 10 | – |
| Water $NH_3$ 28% | Supersonic mixing | 3 | 80 | 68 | 1 | 11 | – |
| DMSO, $NH_3$ Atmosphere | | 3 | 80 | 43 | 0.2 | 37 | – |
| DMSO/Water 75/25, $NH_3$ 7% | | 15 | 85 | 44 | – | 1 | 55 |
| DMSO/Water 75/25, $NH_3$ 7%, | Stream of $NH_3$ passed through | 15 | 90 | 98(66[a]) | – | 2 | – |

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

**Table 2.** Reaction of 3-nitro-4-X-pyridines with diethylamine/DMSO 25/75 and $KMnO_4$ (5 mol equiv.) at 22°C[7]

| X | Product | Yield (%) |
|---|---|---|
| CN | 2-Diethylamino-4-cyano-5-nitropyridine | 41 |
| $COOCH_3$ | 2-Diethylamino-4-methoxycarbonyl-5-nitropyridine | 48 |
| $COCH_3$[a] | 4-Acetyl-2-diethylamino-5-nitropyridine[a] | 72 |

[a] Protected with ethylene glycol.

obtained, the same conditions which gave the best results for the amination reaction (Table 1). We have also reacted DEA with a few 4-substituted-3-nitropyridines under the same conditions as used for 3-nitropyridine and diethylamine. The results are given in Table 2.

The results above present an easy way of aminating and alkylaminating 3-nitropyridine and 4-substituted-3-nitropyridines in the position *para* to the nitro group with acceptable to good yields and with high regioselectivity. The last point is important, as the separation of regioisomers in these systems is not always trivial. The best result for the amination (Table 1) was comparable with that from vicarious substitution.[2] However, the results for the 4-substituted-3-nitropyridines (Table 2) were better than those from that reaction.

## Acknowledgements

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7. All compounds were characterised spectroscopically. Some representative data follow: **2-diethylamino-4-cyano-5-nitropyridine**: mp: 116.5–118°C; IR (KBr): 1597, 1551, 1482, 1448, 1330, 1278, 1096 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 9.92 (s), 6.75 (s), 3.65 (br s, 4H), 1.28 (t, $J=7.1$); $^{13}C$ NMR ($CDCl_3$): 159, 149, 132, 117, 115, 110, 43, 13; HRMS: calcd for $C_{10}H_{12}N_4O_2$: 220.09603, obs. 220.09617. **2-diethylamino-4-methoxycarbonyl-5-nitropyridine**: mp: 84.5–86.5°C; IR (KBr): 3444, 1736, 1604, 1553, 1525, 1492, 1451, 1335, 1287, 1267, 1079 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 8.97 (s), 6.46 (s), 3.97 (s, 3H) 3.63 (br s, 4H), 1.25 (t, $J=7.1$); $^{13}C$ NMR ($CDCl_3$): 167, 159, 148, 139, 132; HRMS: calcd for $C_{11}H_{15}N_3O_4$ 253.10626, obs 253.10587. **2-diethylamino-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine**: mp: 108–109.5°C; IR (KBr): 1596, 1546, 1506, 1436, 1340, 1273, 1190, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 8.56 (s), 6.64 (s), 4.03 (t, 2H, $J=4.9$) 3.72 (t, 2H, $J=4.9$), 3.67 (q, 4H, $J=7.1$), 1.26 (t, $J=7.1$); $^{13}C$ NMR ($CDCl_3$): 159, 148, 147, 136, 108, 102, 65, 44, 27, 13; HRMS: calcd for $C_{13}H_{19}N_3O_4$ 281.13756, obs 281.13801.