

## Short Communication

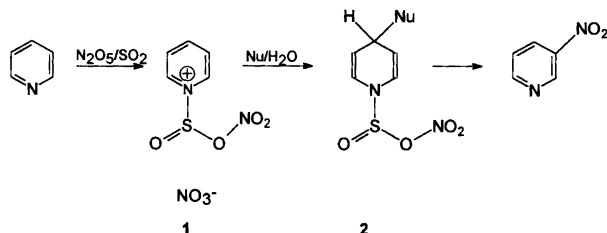
# Direct Nitration of Pyridine and Substituted Pyridines

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We have reported the first direct nitration of pyridine and substituted pyridines in liquid sulfur dioxide with dinitrogen pentoxide (DNP) as the nitrating agent.<sup>1</sup> By that method it was possible to obtain good yields of mononitrated pyridine compounds. We have also proposed a mechanism for the reaction with the formation of a pyridine-SO<sub>2</sub>-DNP complex (1) in the SO<sub>2</sub> solution. This complex was suggested to react with a nucleophile (Nu) to form an 1,4-dihydropyridine compound (2) in the water phase.<sup>2</sup>



The use of liquid SO<sub>2</sub> as the reaction medium for these nitrations made it necessary to run the reactions at low temperature (b.p. of SO<sub>2</sub> –11°C at 760 mmHg). Also, the large amount of SO<sub>2</sub> used might present a problem for preparative scale experiments. We have therefore investigated the possibility of using standard laboratory solvents for the reactions and also determined the minimum amount of SO<sub>2</sub> necessary for acceptable yields. The results from the nitrations of pyridine are given in Table 1.

Table 1 clearly shows that liquid SO<sub>2</sub> was not necessary as solvent for the DNP nitration of pyridine. Several of the standard organic solvents tested gave good yields of 3-nitropyridine even if the reaction medium contained only a minor proportion of sulfur dioxide. Nitrations of pyridine in tetrahydrofuran (THF) and nitromethane gave as good yields as did the nitration in liquid SO<sub>2</sub>.<sup>1</sup> Entries 8–12 demonstrate the effect of SO<sub>2</sub> concentration

on the yields of 3-nitropyridine for the reaction in THF. These were approximately constant down to a 2:1 ratio of SO<sub>2</sub>:pyridine. Even at a ratio of 0.8 a yield of 23% of 3-nitropyridine was obtained. Entry 12 shows an important result: SO<sub>2</sub> was necessary for the successful nitration of pyridine with DNP.

It was thus possible to nitrate pyridine in organic solvents with DNP in the presence of ca. 2 mol SO<sub>2</sub> per mol pyridine.

We have tested this new system on the nitration of a series of pyridine derivatives. In Table 2 the results of these experiments are given together with the yields obtained from nitrations in liquid SO<sub>2</sub>.<sup>1</sup>

The results in Table 2 show that for many pyridine derivatives the yields were comparable to and in some cases better than those obtained from the nitrations in liquid SO<sub>2</sub>. This new nitration system is thus applicable to the same types of compounds as liquid SO<sub>2</sub>-DNP<sup>1</sup> and has the advantages of not using the large amounts of SO<sub>2</sub> and the low temperatures reported earlier. This may have important implications for the nitration of pyridines on a preparative scale.<sup>3</sup> In addition, the use of organic solvents will make new mechanistic investigations possible, such as into the role of SO<sub>2</sub> in both the initial reaction of pyridine with DNP and in the reaction of this product in the water phase. For instance, from the results of the experiments in liquid SO<sub>2</sub> we formulated the complex from pyridine and DNP as 1. As the results in Table 1 show (entries 10 and 11), SO<sub>2</sub> needs only to be present in low concentrations and it may therefore not be a part of the pyridine-DNP complex. These points are now under investigation.

## Experimental

The solvents used were purified by standard methods.<sup>4</sup> DNP was prepared from 100% HNO<sub>3</sub> and P<sub>2</sub>O<sub>5</sub>.<sup>5</sup> The solvent mixtures for the nitration reaction were made by

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Table 1. Nitration of pyridine to 3-nitropyridine with dinitrogen pentaoxide in organic solvents and sulfur dioxide,  $[\text{pyridine}]_0 = 0.5 \text{ M}$ ,  $[\text{N}_2\text{O}_5]_0 = 1.0 \text{ M}$ .

Entry	Solvent	$[\text{SO}_2]/\text{M}$	$T/^\circ\text{C}$	Yield (%)
1	Diethyl ether	12	-20	53
2	Diethyl ether	8	-20	38
3	Diethyl ether	4	-20	48
4	Diethyl ether	2	-20	8
5	Tetrahydrofuran	12	-20	65
6	Tetrahydrofuran	8	-20	57
7	Tetrahydrofuran	4	-20	68
8	Tetrahydrofuran	4	0	68
9	Tetrahydrofuran	2	0	60
10	Tetrahydrofuran	1	0	69
11	Tetrahydrofuran	0.4	0	23
12	Tetrahydrofuran	0	0	0
13	Chloroform	4	0	30
14	Nitromethane	4	0	58
15	1,2-Dimethoxyethane	4	0	32
16	N-Methyl-2-pyrrolidone	4	0	26

Table 2. Nitration of pyridine and pyridine derivatives with dinitrogen pentaoxide and  $\text{SO}_2$ ,  $[\text{substrate}]_0 = 0.5 \text{ M}$ ,  $[\text{N}_2\text{O}_5]_0 = 1 \text{ M}$ ; solvent:  $\text{SO}_2(\text{liq})$  4:1; reaction temperature  $0^\circ\text{C}$ .

Entry	Substrate	Solvent	Position of $\text{NO}_2$	Yield (%)	Yields in $100\% \text{ SO}_2^1$
1	Pyridine	$\text{CH}_3\text{NO}_2$	3	58	63
2	2-Methylpyridine	$\text{CH}_3\text{NO}_2$	5	41	70
3	3-Methylpyridine	$\text{CH}_3\text{NO}_2$	5	37	30
4	4-Methylpyridine	$\text{CH}_3\text{NO}_2$	3	54	51
5	2,3-Dimethylpyridine	$\text{CH}_3\text{NO}_2$	5	16	46
6	3,4-Dimethylpyridine	$\text{CH}_3\text{NO}_2$	5	37	58
7	2,4-Dimethylpyridine	$\text{CH}_3\text{NO}_2$	5	52	66
8	Quinoline <sup>a</sup>	THF	3	12	16
9	Isoquinoline <sup>a</sup>	THF	4	38	28
10	3-Acetylpyridine	THF	5	19	23
11	4-Acetylpyridine	THF	3	67	75

<sup>a</sup> Indole as internal standard.

mixing the organic solvent with the appropriate volume of liquid  $\text{SO}_2$ . This mixture was taken to the reaction temperature, crystalline DNP was added and then the substrate. The reaction mixture was stirred for 2 h and then poured over ice. The work up procedure has been reported.<sup>1</sup> The product mixture was analysed by GC and with 2,4,6-trimethylpyridine as an internal standard. The chromatographic equipment has been reported.<sup>1</sup>

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