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C-Nitration of Pyridine by the *kyodai*-Nitration Modified by the Bakke Procedure. A Simple Route to 3-Nitropyridine and Mechanistic Aspect of its Formation.

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Abstract: *N*-Nitropyridinium nitrate was generated *in situ* from pyridine, nitrogen dioxide and ozone in an inert organic solvent and subsequently treated with aqueous sodium hydrogen sulfite to afford 3-nitropyridine in good yield, together with sodium pyridine-4-sulfonate as a water-soluble by-product.

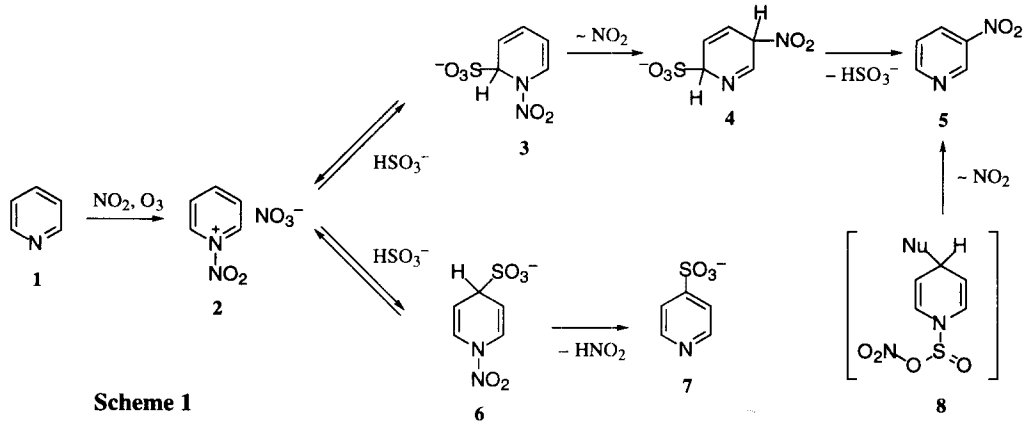
Direct *C*-nitration of pyridine **1** is very difficult to effect. Pyridine can be *C*-nitrated with nitric acid in sulfuric acid at 25 °C 10^{-8} times more slowly as compared with benzene.[1] Thus, the *C*-nitration of pyridine has been effected only under extremely drastic conditions;[2-4] treatment of pyridine with an alkali metal nitrate in fuming sulfuric acid at 300 °C is reported to afford 3-nitropyridine **5** in a 14% yield.[2] The action of a powerful nitrating agent such as nitronium tetrafluoroborate on pyridine only leads to *N*-nitropyridinium salt, with no *C*-nitro compound being obtained.[5] The formation of the pyridinium salt deactivates the pyridine ring and prevents further reaction.

We have recently found that a wide variety of aromatic compounds can be smoothly nitrated with nitrogen dioxide in the presence of ozone under neutral conditions at low temperature to give the corresponding nitro compounds in good yield (*kyodai*-nitration).[6] However, this novel methodology proved to be disappointing with pyridine; the attempted *kyodai*-nitration of compound **1** led to a mixture of **5** and 3,5-dinitropyridine only in 2–5% combined yield under the conditions employed.[7]

Recently, Bakke and co-workers have reported that pyridine can be efficiently nitrated by dinitrogen pentaoxide in liquid sulfur dioxide to give the *C*-nitration product **5** in 68% isolated yield.[8] They explained their successful result by assuming the intermediate formation of an adduct **8** from pyridine, dinitrogen pentaoxide and sulfur dioxide, wherein the nitro moiety migrates intramolecularly to the 3-position of the pyridine nucleus to afford **5**.[9]

Intrigued by the unique lateral to nuclear migration mode of the proposed mechanism, we have carried out our own experiment to gain closer insight into the reaction pathway as well as the role of sulfur dioxide involved therein. First, we prepared *N*-nitropyridinium nitrate **2** by the combined action of nitrogen dioxide and ozone on pyridine in dichloromethane at low temperature. Pyridine is known to react readily with dinitrogen pentaoxide to form **2**.[10] When the resulting white suspension was poured into iced water saturated with sulfur dioxide, much to our delight, we obtained 62% of 3-nitropyridine **5** together with 24% of

unchanged pyridine. Furthermore, treatment with aqueous sodium hydrogen sulfite was found to afford 62% of **5**, 9% of **1** and sodium pyridine-4-sulfonate **7**. These results strongly suggest the role of sulfur dioxide as precursor to a nucleophile rather than an electrophile as has previously been suggested for the nitration of pyridine using dinitrogen pentaoxide in liquid sulfur dioxide.[9] Upon aqueous workup of the reaction mixture, sulfur dioxide should form H_2SO_3 and HSO_3^- which supposedly make a nucleophilic attack on *N*-nitropyridinium salt **2** to form adducts **3** and **6**, eventually leading to the final products **5** and **7** via the sequences shown in Scheme 1. Several nucleophiles were examined to ascertain this hypothesis and the results obtained are summarized in Table 1.



Scheme 1

Table 1 Effect of different nucleophiles on the yield of 3-nitropyridine **5**. [a]

Nucleophile [b]	Equiv	**5** (%) [c]	**1** (%) [c]
SO_2	15	62.0	24.0
$NaHSO_3$	1	44.0	19.2
	2	62.4	8.8
	4	63.8	6.3
	6	55.8	3.0
Na_2SO_3	6	16.0	2.9
$Na_2S_2O_3$	6	24.2	70.2
Na_2SO_4	6	0.5	89.4
$NaNO_2$	6	0.2	83.8
NaI	6	0.1	82.7
none	—	0.1	66.0

[a] All reactions were carried out using pyridine (5 mmol), nitrogen dioxide (1 cm^3), ozone (15 mmol) and dichloromethane (30 cm^3). [b] Dissolved in water (30 cm^3). [c] Determined by HPLC using 3-cyanopyridine as an internal standard.

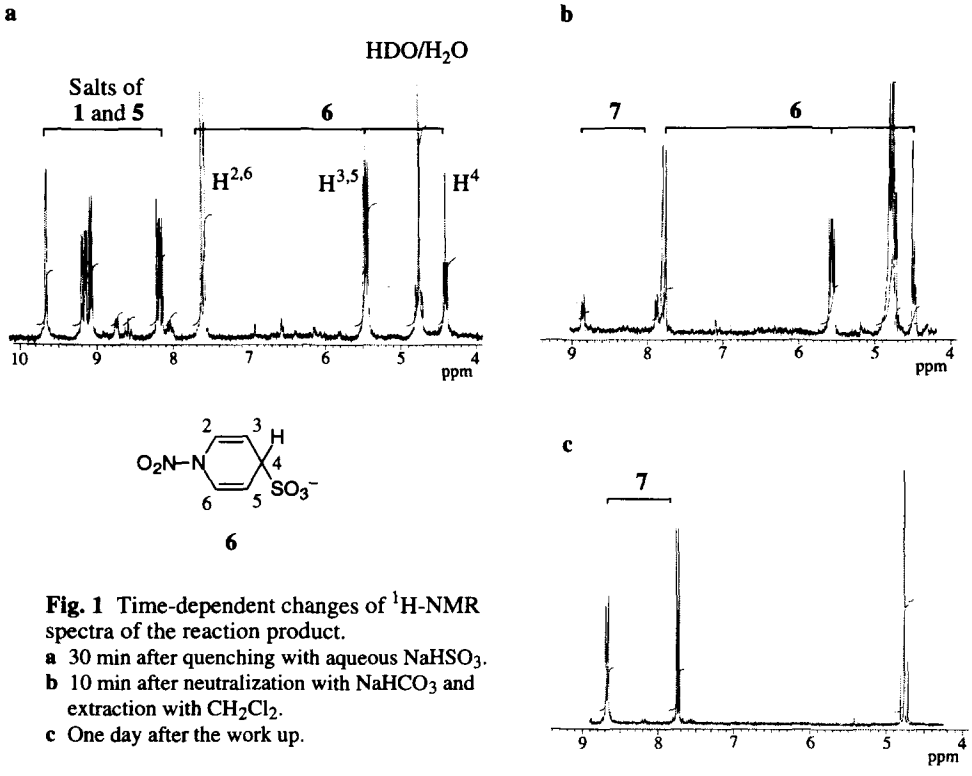


Fig. 1 Time-dependent changes of ^{1}H-NMR spectra of the reaction product.
a 30 min after quenching with aqueous $NaHSO_3$.
b 10 min after neutralization with $NaHCO_3$ and extraction with CH_2Cl_2.
c One day after the work up.

The formation of pyridine-4-sulfonate **7** was monitored by ^{1}H-NMR (Fig. 1). The upper left spectrum (**a**) shows the original products in aqueous phase obtained by quenching with $NaHSO_3$ in deuterium oxide 30 min after the start of the reaction. The upper right (**b**) shows the aqueous phase 10 min after the usual workup (neutralization with $NaHCO_3$ followed by extraction with CH_2Cl_2), and the lower spectrum (**c**) shows the same aqueous phase one day after. In the spectrum (**a**), the peak clusters due to the pyridinium compounds are observed at 8~10 ppm. Another set of signals observed at 7.6 (2H), 5.5 (2H) and 4.4 ppm (1H) suggests the presence of 1,4-dihydropyridine compound **6**. After the usual workup, pyridines **1** and **5** were removed by extraction from the aqueous phase and hence their peaks disappeared (spectrum **b**). However, the peaks of a presumed intermediate **6** were still observed while a set of new signals of a second product began to appear. One day after (spectrum **c**), all peaks of the initial product **6** disappeared and only those of the final product could be observed, which was identified as the sulfonate **7** by direct comparison with the authentic specimen.[11]

The attack of a nucleophile on pyridinium salt **2** would be favored at C-2 and C-6 over C-4 due to the higher positive charge on the carbon atoms at the 2- and 6- positions. The cross-conjugated 1,4-dihydropyridine structure in **6** is more stabilized than the linearly conjugated 1,2-dihydropyridine structure in **3**. Therefore, the nitro compound **5** is most likely to be derived from the unstable adduct **3** via the allylic rearrangement of the nitro group followed by the elimination of HSO_3^- although no 2,5-dihydropyridine

derivative **4**, which should result from the adduct **3**, could be detected (Scheme 1).

The typical preparative procedure was as follows; ozonized oxygen gas was slowly introduced (feeding rate of O_3, 10 mmol h^{-1}) into a mixture of liquid nitrogen dioxide (1 cm^3) and dichloromethane (30 cm^3) at −78 ℃ for 1.5 h. To the resulting solution, pyridine (5 mmol) was added in one portion to obtain a suspension of white crystalline solids. The cooling bath was removed and the suspension was stirred for 1 h at room temperature and then poured into aqueous sodium hydrogen sulfite. After 1 h the mixture was neutralized with $NaHCO_3$ and the organic phase was extracted with dichloromethane (30 cm^3). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave 3-nitropyridine **5** as colorless crystals, which can be further purified by recrystallization from hexane.

In summary, 3-nitropyridine **5** can be obtained in good yield via the *kyodai*-nitration of pyridine to *N*-nitropyridinium nitrate **2**, followed by treatment with aqueous sodium hydrogen sulfite.

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References and Notes

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