# The reaction of 3-nitropyridine with sulfite ions; a pathway to 2,5-disubstituted pyridines

**Jan M. Bakke,[a] Eli Ranes,[a] Christian Rømming[b] and Ingrid Sletvold[a]**

[a] *Department of Chemistry, The Norwegian University of Science and Technology, Sem Sælandsvei 8, NO-7491 Trondheim, Norway*
[b] *Department of Chemistry, University of Oslo, PO 1033 Blindern, NO-0315 Oslo, Norway*

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The reaction of 3-nitropyridine with an aqueous solution of sodium sulfite gave the disodium salt of 5-(*N*-sulfohydroxyamino)pyridine-2-sulfonic acid (**2**) which on treatment with an acidic ion exchange resin gave 5-hydroxyaminopyridine-2-sulfonic acid (**3**). The yield of **3** from 3-nitropyridine was 63%. The structures of the products were verified by X-ray analysis.

## Introduction

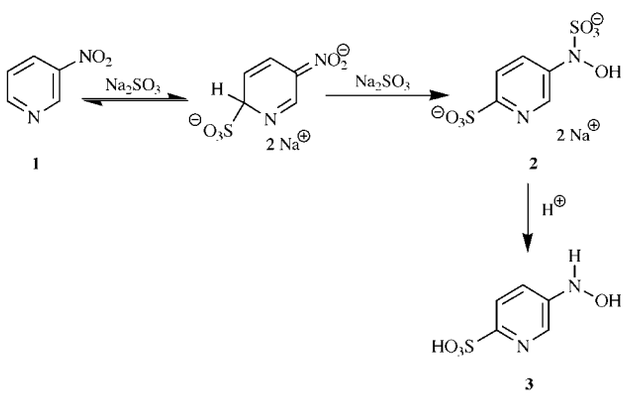
We have reported the successful nitration of pyridine and a number of substituted pyridines by first reacting the pyridine compound with dinitrogen pentaoxide in an organic solvent and then reacting the formed *N*-nitropyridinium nitrate with an aqueous solution of $NaHSO_3$–$SO_2$.[1] As β-nitropyridines have not been readily available before, their chemistry has not been as thoroughly studied as that of nitroarenes.[2] However, pyridine compounds are important substances in natural products and agrochemical and pharmaceutical compounds. New reactions for the preparation of substituted pyridines are therefore of general interest.

Pyridine is an electron-deficient aromatic compound and the 3-nitro group enhances this property. We have therefore carried out reactions of these compounds with a series of nucleophiles and now report the reaction with sulfite ion. In addition to being a very active nucleophilic reagent, the sulfite ion is also a reducing agent.[3] Several outcomes of the reaction were therefore possible.

## Results and discussion

The product from the reaction of 3-nitropyridine with sodium sulfite was a 2,5-disubstituted pyridine compound (as shown by $^1$H NMR spectroscopy) and it demanded two equivalents of sodium sulfite per equivalent of 3-nitropyridine; with equimolar amounts, only half of the 3-nitropyridine reacted. The IR spectrum of the product indicated that one of the substituents was a sulfonic acid and also that the other was not a nitro group. On treatment of this substance with an acidic ion exchange resin a new compound was obtained that was also a 2,5-disubstituted pyridine and was clearly an acid as it could be reversibly deprotonated. However, treatment of this compound with base did not give back the first compound isolated. Analysis of the IR spectrum indicated that one of the substituents was a sulfonic acid but, again, the identity of the second substituent could not be determined with certainty.

The structures of these two compounds were eventually established by X-ray crystallography, the first was the disodium salt of 5-(*N*-sulfohydroxyamino)pyridine-2-sulfonic acid (**2**, Scheme 1). On treatment with the acidic resin this gave 5-hydroxyaminopyridine-2-sulfonic acid (**3**). The structures of these two compounds are shown in Fig. 1. This is the first time the preparation and structures of these compounds have been reported.




**Scheme 1**

Proton NMR spectroscopy showed the reaction of 3-nitropyridine with sodium sulfite to be virtually quantitative as only signals from **2** were observed. Compound **2** was normally not isolated and the crude product was treated directly with the acidic ion exchange resin. This gave compound **3** in a 63% yield from 3-nitropyridine.

The results show the unique power of the nitro group to act both as an activating group for a nucleophilic substitution reaction and as an electron sink. As two equivalents of sulfite ion were necessary and as no intermediates were observed, the first steps in the reaction were probably reversible and involved a low concentration of an intermediate. A plausible pathway is shown in Scheme 1. After addition of the first sulfite ion to the activated 2-position, loss of a proton and rearomatisation of the pyridine ring would lead to a reduction of the nitrogen atom of the nitro group to the oxidation level of that in a nitroso group. A reaction with a second equivalent of sulfite ion then gave the *N*-sulfohydroxyamine **2**. Treatment of this with the acidic ion exchange resin hydrolysed the *N*-sulfohydroxyamino group to give the hydroxyamine **3**.

This reaction is reminiscent of the Piria reaction in which nitroaromatic compounds on treatment with sulfite ion give sulfonated aryl amines together with several other compounds.[4] However, the result of the reaction of 3-nitropyridine differed from that of the Piria reaction on several points. From a preparative point, the most important one was that only one product was formed, not the complex mixture reported from the Piria reaction.[5] Another point was that the reduction of the nitro group stopped at the hydroxylamine stage; a full reduction to the amine did not take place as in the Piria reaction. It was

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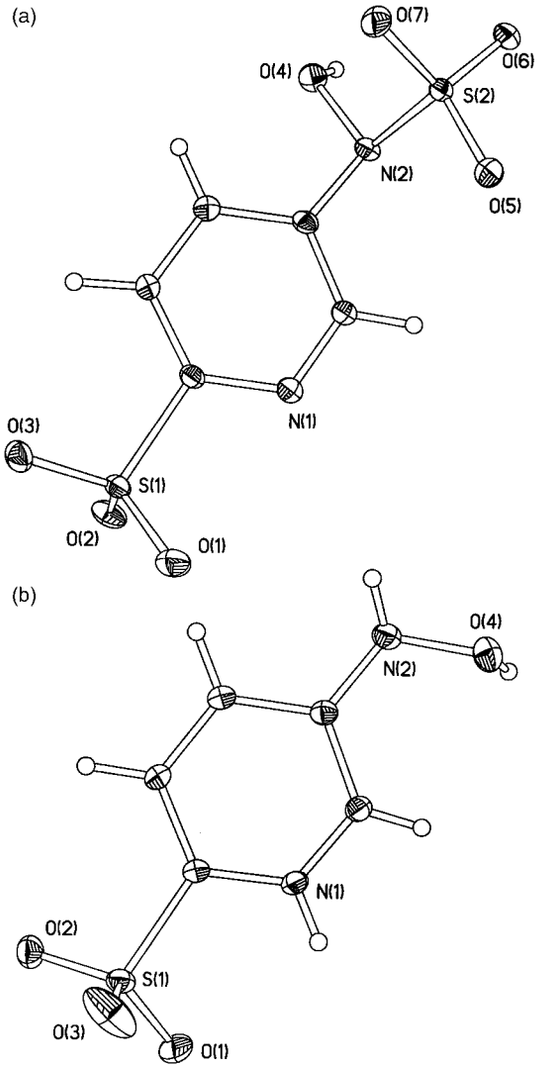


**Fig. 1** ORTEP plots of (a) **2** (only the anion is shown) and (b) **3**. Ellipsoids are drawn at 50% probability.

also suprising that only one regioisomer was formed. Normally, in nucleophilic aromatic substitutions a mixture of isomers is formed with the activating group *ortho* and *para* to the substituting group.

5-Hydroxyaminopyridine-2-sulfonic acid (**3**) may serve as a starting material for other 2,5-disubstituted pyridines, many of which are important, for instance, in pharmaceutical agents.[5] It is well known that sulfonic acids can be transformed to the corresponding phenols or cyanides. The substitution reactions of the sulfonic acid group usually take place at elevated temperatures. However, for the substitution of the sulfonic acid group of **3**, it appears possible to increase its reactivity by transforming the hydroxyamino group into the strongly electron-withdrawing nitro group. Investigation of this is now in progress.

On the other hand, the hydroxyamino group may be reduced to an amino group, which, in turn can be transformed by the use of the Sandmeyer reaction. In this way, compound **3** may serve as a new, versatile starting compound for 2,5-disubstituted pyridines as both the sulfo group and the hydroxyamino group may be replaced by a number of other substituents.

## Experimental

The spectroscopic and analytical equipment used have been reported elsewhere.[1] Elemental analyses were carried out by Dr L. Helesic, Vysoká Škola Chemicko-Technologická (VSCHT), Prague, Czech Republic.

**Table 1** Crystal data and structure refinement for compounds **2** and **3**

| | **2** | **3** |
|---|---|---|
| Empirical formula | $C_5H_4N_2O_7S_2^{2-}\cdot 2Na^+\cdot 4H_2O$ | $C_5H_6N_2O_4S$ |
| Formula weight | 386.76 | 190.18 |
| Temperature/K | 150(2) | 150(2) |
| Crystal system | Triclinic | Orthorhombic |
| Space group | $P\bar{1}$ | $P2_12_12_1$ |
| Unit cell dimensions | | |
| $a$/Å | 5.402(1) | 5.034(1) |
| $b$/Å | 11.558(1) | 11.922(1) |
| $c$/Å | 12.666(1) | 12.089(1) |
| $\alpha$/° | 66.52(1) | |
| $\beta$/° | 79.97(1) | |
| $\gamma$/° | 88.06(1) | |
| Volume/Å$^3$, $Z$ | 713.8(3), 2 | 725.49(2), 4 |
| Absorption coefficient/mm$^{-1}$ | 0.495 | 0.420 |
| Reflections collected | 10834 | 12316 |
| Independent reflections | 5016 [$R_{int}$ = 0.026] | 4296 [$R_{int}$ = 0.012] |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1$ = 0.033, $wR_2$ = 0.079 | $R_1$ = 0.022, $wR_2$ = 0.060 |
| $R$ indices (all data) | $R_1$ = 0.046, $wR_2$ = 0.084 | $R_1$ = 0.024, $wR_2$ = 0.066 |

### Disodium salt of 5-(*N*-sulfohydroxyamino)pyridine-2-sulfonic acid (2)

3-Nitropyridine (5.0 g, 40.3 mmol) was dissolved in water (250 ml) and $Na_2SO_3$ (10.2 g, 80.6 mmol) was added. The reaction was run at room temperature and monitored by $^1$H NMR spectroscopy. All the 3-nitropyridine had reacted after 20 hours. The product, the disodium salt of 5-(*N*-sulfohydroxyamino)-pyridine-2-sulfonic acid (**2**) was usually not isolated but reacted further to produce **3** (see below).

**Isolation of 2.** When the reaction was complete, the reaction mixture was concentrated. A portion (1.5 g) was heated with 80% ethanol (20 ml). This gave two liquid phases, one red and one yellow. These were separated, and the red, denser one dissolved in 80% ethanol (80 ml). At −20 °C crystals of **2** were formed (decomp. 140 °C). These were used for the X-ray analysis (Fig. 1) which showed the crystals to contain four molecules of water. $^1$H NMR (300 MHz, $D_2O$): $\delta$ 7.95 (d, H$^3$, $J$ = 8.6 Hz), 8.13 (dd, H$^4$, $J$ = 8.6, 2.4 Hz), 8.72 (d, H$^6$, $J$ = 2.4 Hz). IR (KBr): $\nu$/cm$^{-1}$ 3736 (w), 3700–3100 (s, br), 3000–2000 (w, br), 1630 (m), 1577 (w), 1463 (m), 1417 (w), 1379 (w), 1299 (s), 1263 (s), 1244 (s), 1227 (s) 1192 (s), 1168 (m), 1120 (m), 1067 (s), 1035 (s), 990 (w), 918 (w), 892 (m), 854 (m), 762 (w), 751 (w), 680 (m), 642 (w), 622 (s), 592 (m), 569 (m), 556 (m).

### 5-Hydroxyaminopyridine-2-sulfonic acid (3)

The reaction mixture from the reaction of 3-nitropyridine (5.0 g, 40.3 mmol) with $Na_2SO_3$ was concentrated to about 100 ml and passed through a column of Ion Exchanger Amberlite® IR-120 (28 cm long, 2.5 cm id). The eluate was concentrated and the product recrystallised from 80% ethanol (160 ml). This gave 5-hydroxyaminopyridine-2-sulfonic acid (**3**) (4.8 g, 25.3 mmol, 63% yield from 3-nitropyridine) as yellow crystals (decomp. 203 °C). $^1$H NMR (300 MHz, $D_2O$): $\delta$ 7.83 (dd, H$^4$, $J$ = 8.7, 2.6 Hz), 8.02 (d, H$^3$, $J$ = 8.7 Hz), 8.29 (d, H$^6$, $J$ = 2.5 Hz). $^{13}$C NMR (300 MHz, $D_2O$): $\delta$ 127.2 (C$^3$), 130.0 (C$^4$), 130.4 (C$^6$), 147.6, 153.4. IR (KBr): $\nu$/cm$^{-1}$ 3736 (w), 3296–1800 (br), 1707 (w), 1612 (s), 1542 (s), 1484 (w), 1445 (w), 1410 (m), 1371 (w), 1326 (m), 1221 (s, br), 1161 (s) 1135 (s), 1054 (s), 1008 (s), 843 (s), 710 (s), 635 (s), 571 (s) 556 (s), 473 (m). Elemental analysis: calculated: C 31.6, H 3.2, N 14.7, S 16.9; found: C 31.1, H 3.2, N 14.6, S 16.6%.

### X-Ray crystallographic analysis of compounds 2 and 3†

X-Ray data were collected on a Siemens SMART CCD diffractometer[6] using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[6] Absorption corrections were applied by the use of the SADABS program.[7] The structure was determined and refined using the SHELXTL program package.[8] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions were found from difference Fourier maps and refined with isotropic thermal parameters. Crystal and refinement data are given in Table 1. Disorder was observed in one of the water sites in the crystals of compound **2**.

## Acknowledgements

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† CCDC reference number 207/402. See http://www.rsc.org/suppdata/p1/a9/a909875e for crystallographic files in .cif format.

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