Improved Synthesis of 3-Nitrosalicylic Acid

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IMPROVED SYNTHESIS OF 3-NITROSALICYLIC ACID

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Nitration of salicylic acid using 2-propyl nitrate / sulfuric acid / tetrabutylammonium hydrogensulfate / dichloromethane / water yielded a mixture of 3-nitro and 5-nitrosalicylic acids in the ratio 56:44. Pure potassium 3-nitrosalicylate was crystallized and converted to 3-nitrosalicylic acid in 30% overall yield.

Keywords: 3-Nitrosalicylic acid; potassium 3-nitrosalicylate; 2-propyl nitrate

INTRODUCTION

3-Nitrosalicylic acid is a very useful synthetic intermediate for 3-aminosalicylates or 3-aminosalicylamides, which are of wide interest and relevance for pharmaceutical and agrochemical products, as reflected in the literature.[1] The compound has been prepared from salicylic acid by various nitration methods. Typical procedures involve dilute nitric acid,[2] nitric acid / acetic acid mixtures,[3] sodium nitrite / hot sulfuric acid in an extremely violent reaction,[4] and toxic or expensive reagents such as transition-metal nitrates, like zinc nitrate / dinitrogen tetroxide[5] or cerium ammonium nitrate.[6] All the known methods suffer from a lack of regioselectivity. The undesired 5-nitro isomer is preferentially formed, accompanied by decarboxylation and dinitration products, as detailed studies have shown.[3] However, no protocols allowing for a reliable isolation of a pure product have been disclosed in all these published methods. In addition, violent runaway reactions have been observed.

No matter how the nitration is performed, the subsequent separation of the isomers is obviously necessary to obtain pure 3-nitrosalicylic acid. Meldrum’s classic method via the monopotassium salts is well suited for this purpose.[2] Unfortunately, in Meldrum’s original publication, no experimental details of the crystallization are given.

3-Nitrosalicylic acid is now commercially available, but the price is relatively high. Also no satisfactory process has been published. For these reasons, we assessed a new method of nitration and optimized the separation of the isomers.
RESULTS AND DISCUSSION

Several known methods of nitration were checked. In an attempt to reproduce Meldrum's original nitration/workup recipe, we were not able to reach the reported yield (25% given). The procedure described used dilute nitric acid and gave a viscous paste that was difficult to stir. The reaction was very slow when cooling was applied, and without cooling a runaway reaction occurred. The use of more acid facilitated stirring and temperature control (20 °C). Nevertheless, in our hands only 12% of the pure 3-nitro product was obtained.

In another attempt by microwave-assisted nitration of salicylic acid using cerium ammonium nitrate (in analogy to a published method), a violent explosion occurred and completely wrecked our microwave equipment.

Several known methods for ortho-nitration of phenolic compounds fail in the presence of electron-withdrawing groups such as a carboxylic acid. A new method that favors the desired ortho-nitration has recently been described in a patent. It involves phase-transfer catalysis and the use of 2-propyl nitrate/sulfuric acid in dichloromethane, where the 3-nitro isomer is claimed to precipitate exclusively from the reaction mixture. However, in our hands no pure product was obtained following the instructions. On the other hand, isopropyl nitrate is indeed a safe and inexpensive nitration agent that is easy to handle and gives preferentially the 3-nitro isomer. Therefore, a more detailed investigation was undertaken. We found that the use of less than 2.5 equivalents of nitration reagent led to incomplete conversion, whereas prolongation of the reaction time did not increase the yield. NMR spectra revealed that the crude product was a mixture of 3- and 5-nitrosalicylic acid in the ratio of 56:44 (mean value of 10 runs). After addition of potassium carbonate, pure potassium 3-nitrosalicylate precipitates, but the solution of the salts must not be cooled below 20 °C. Cooling by means of an ice bath, as one might be tempted to do, provokes precipitation of unwanted potassium 5-nitrosalicylate. Liberation of the acid and subsequent crystallization is straightforward. As previously reported, the colorless primary product is a hydrate, whereas the anhydrous acid is yellow. Finally, it should be noted that this optimized nitration

![Scheme 1. Synthesis of 3-nitrosalicylic acid.](image-url)
procedure has also been carried out on double the scale specified, with similar yield and without any problem.

This procedure represents a combination of the most ortho-selective nitration method of salicylic acid with the optimized classic separation of the isomers by crystallization of the monopotassium salts.[2] The described three-step synthesis (Scheme 1) is superior to all previous ones with respect to safety, yield, convenience, and overall costs.

**EXPERIMENTAL**

Chemicals were obtained from commercial sources (Sigma-Aldrich) and were used as received. NMR spectra were recorded using a Bruker AC 300 spectrometer. Infrared (IR) spectra were obtained with a Nicolet 5700 FT spectrometer in attenuated total reflection (ATR) mode.

**Preparation of a Mixture of 3-Nitrosalicylic Acid (2) and 5-Nitrosalicylic Acid (3)**

A 500-mL, two-necked, round-bottomed flask equipped with a 50-mL pressure-equalizing addition funnel, a thermometer, and a magnetic stirrer is charged with salicylic acid ([1]; 20.7 g, 0.150 mol) and 300 mL of dichloromethane. The suspension is cooled by means of an ice bath. Subsequently, tetrabutylammonium hydrogensulfate (2.55 g, 7.5 mmol, 0.05 equivalents) and 2-propyl nitrate (38 mL, 0.38 mol, 2.5 equivalents) are added. Then, concentrated sulfuric acid (21 mL) is added dropwise from the funnel over a period of 40 min (the temperature does not exceed 10°C). In the course of addition, a yellow precipitate is formed. After the addition is completed, the reaction mixture is stirred for an additional 10 min with cooling and then for another hour without cooling (the temperature rises to 35°C). The suspension is poured into a 3-L beaker filled with 1500 mL of distilled water and stirred rapidly by means of a magnetic stirrer. After 10 min, the precipitate is filtered through a Büchner funnel, washed with water (3 × 20 mL), and predried by suction. The crude product is finally dried in a vacuum desiccator over phosphorus pentoxide (P2O5) to yield 17.7 g (64% of theory) of a mixture of 3- and 5-nitrosalicylic acid in the ratio of 56:44 (mean value of 10 runs).

**Purification of Potassium 3-Nitrosalicylate (4)**

The mixture of isomeric 3- and 5-nitrosalicylic acid (17.7 g, 0.097 mol) is placed in a 1000-mL round-bottomed flask equipped with a magnetic stirring bar, and a 1.45 M solution of potassium carbonate (270 mL) is added carefully under vigorous stirring, followed by 180 mL of distilled water. The flask is fitted with a reflux condenser, and the dark-orange suspension is heated by means of an oil bath (110°C). After complete dissolution, the solution is allowed to cool to 20°C. The yellow precipitate is filtered through a glass frit (porosity 3), washed with ice-cold water (2 × 50 mL), and predried by suction. The solid is finally dried in a vacuum desiccator over phosphorus pentoxide (P2O5) to yield 10.2 g of potassium 3-nitrosalicylate (4) as fine yellow needles (31% overall yield). NMR spectra show less than 1% of
potassium 5-nitrosalicylate. An even purer product can be obtained by a second recrystallization. Mp 296 °C (dec); 1H NMR (300 MHz, DMSO-d6): δ 6.52 (t, J = 7.7 Hz, 1H), 7.86 (dd, J = 8.1, 1.9 Hz, 1H), 7.95 (dd, J = 7.5, 1.9 Hz, 1H) ppm; 13C NMR (75.5 MHz, DMSO-d6): δ 112.0, 122.2, 129.0, 135.6, 138.1, 162.6, 169.6 ppm; IR (neat): 1578, 1522, 1451, 1401, 1346, 1281, 1073, 912, 854, 778, 739, 600, 456 cm⁻¹.

3-Nitrosalicylic Acid (5)

A 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, an addition funnel, and a reflux condenser is charged with the purified potassium 3-nitrosalicylate (4; 10.0 g, 0.045 mol) and deionized water (240 mL). The mixture is heated to boiling (bath temperature 115 °C) under vigorous stirring until a clear solution is obtained. Concentrated hydrochloric acid (37%, 3.8 mL) is added dropwise from the funnel. A precipitate forms, which dissolves again on stirring and heating for another 5 to 10 min. The hot solution is allowed to cool with stirring to room temperature and then is refrigerated at 5 °C. After standing for 30 min, the precipitated 3-nitrosalicylic acid is filtered with suction and washed with ice-cold water until it is free of chloride. The off-white product is dried in a vacuum desiccator over phosphorus pentoxide (P₂O₅) and then at 60 °C in high vacuum to a constant weight to yield 8.1 g (30% overall yield) of yellow, anhydrous 3-nitrosalicylic acid (5). Mp 148 °C; 1H NMR (300 MHz, DMSO-d6): δ = 7.05 (t, J = 8.0 Hz, 1H), 8.11 (dd, J = 8.0, 1.7 Hz, 1H), 8.15 (dd, J = 8.0, 1.7 Hz, 1H) ppm; 13C NMR (75.5 MHz, DMSO-d6): δ = 116.3, 118.4, 130.8, 135.6, 138.2, 155.1, 171.2 ppm; IR (neat): 3096, 2824, 2548, 1667, 1596, 1519, 1441, 1357, 1251, 1130, 1097, 900, 848, 771, 743, 693, 597 cm⁻¹; HRMS (EI⁺) m/z calcd. for C₇H₅NO₅: 183.0162, found 183.0175 (M⁺).

Spectral Data of Potassium 5-Nitrosalicylate

1H NMR (300 MHz, DMSO-d6): δ = 6.64 (d, J = 9.2 Hz, 1H), 8.01 (dd, J = 9.2, 3.1 Hz, 1H), 8.49 (d, J = 3.1 Hz, 1H) ppm.

Spectral Data of 5-Nitrosalicylic Acid

1H NMR (300 MHz, DMSO-d6): δ = 7.12 (d, J = 9.2 Hz, 1H), 8.30 (dd, J = 9.2, 2.9 Hz, 1H), 8.53 (d, J = 2.9 Hz, 1H) ppm.

REFERENCES


