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Catalytic Activities of Salicylaldehyde Derivatives. III. An Improved Synthesis of 6-Nitrosalicylaldehyde

Makoto Ando and Sakae Emoto
The Institute of Physical and Chemical Research, Wako-shi, Saitama 351

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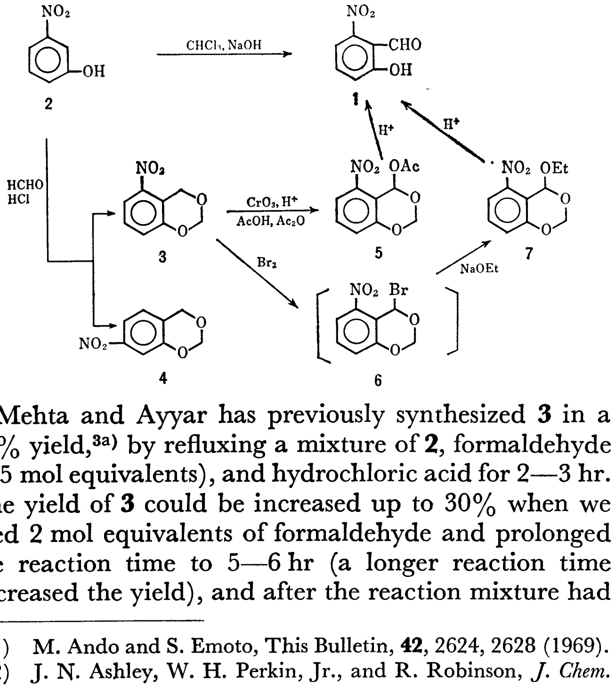
In connection with our studies of the catalytic activities of salicylaldehyde derivatives,[1] it was necessary to synthesize 6-nitrosalicylaldehyde (**1**). Although **1** had been prepared from *m*-nitrophenol (**2**) by the Reimer-Tiemann reaction in a 3—4% yield,[2,3] our reinvestigation showed that the yield was still poor and variable. The methyl ether of **1** has been obtained in a 19% yield from 3-nitro-*o*-cresol,[4] which, in turn, is prepared from 2,6-dinitrotoluene, but this method is unsuitable for preparing a large quantity of **1**. In this paper, we wish to describe an improved synthesis of **1** *via* 5-nitro-1,3-benzodioxane (**3**); it is shown in the scheme.



Mehta and Ayyar has previously synthesized **3** in a 13% yield,[3a] by refluxing a mixture of **2**, formaldehyde (1.5 mol equivalents), and hydrochloric acid for 2—3 hr. The yield of **3** could be increased up to 30% when we used 2 mol equivalents of formaldehyde and prolonged the reaction time to 5—6 hr (a longer reaction time decreased the yield), and after the reaction mixture had been treated according to the Mehta method, a non-crystalline residue was purified by the use of a silica gel column. A small amount of 7-nitro-1,3-benzodioxane (**4**), which had been prepared from **2**, formaldehyde, and sulfuric acid at 40 °C in a poor yield,[5] was also obtained from the non-crystalline residue. 6-Nitrosalicylic acid had previously been prepared by the oxidation of **3** with chromic anhydride and sulfuric acid in acetic acid,[3a] but when we attempted the oxidation in a mixture of acetic acid and acetic anhydride, a product (**5**), into which one acetoxy group was introduced was obtained. Because, by the acidic hydrolysis of **5**, **1** was synthesized, **5** was confirmed to be 4-acetoxy-5-nitro-1,3-benzodioxane. In carbon tetrachloride, **3** was brominated with 1 mol of bromine under the light of a tungsten lamp to give a monobrominated product (**6**); this product was very unstable and decomposed in air, so, after the bromination had been completed, a solution of **6** in carbon tetrachloride was used immediately in the next step. The solution of **6** in carbon tetrachloride was added to a solution of an excessive amount of sodium ethoxide in ethanol to convert the bromo compound into an ethoxy one (**7**), which was then hydrolyzed to **1** by acid. Consequentlyl **6** and **7** were confirmed to be 4-bromo- and 4-ethoxy-5-nitro-1,3-benzodioxanes respectively. The total yield of **1** by this route was 24% based on **2**; as compared with the synthesis by means of the Reimer-Tiemann reaction, the total yield was very much increased, and so **1** can be prepared in a large quantity.

Experimental

All the mps and bp are uncorrected.

5-Nitro-1,3-benzodioxane (3). A mixture of **2** (250 g), a 37% formaldehyde aqueous solution (375 ml), and concd hydrochloric acid (750 ml) was boiled under reflux with vigorous stirring for 5 hr. After being cooled, a clear supernatant was poured off and the residue was stirred with a

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3) a) D. R. Mehta and P. R. Ayyar, *J. Univ. Bombay*, **8**, 176 (1939); *Chem. Abstr.*, **34**, 2814 (1940). b) S. Yoshikawa, K. Kuga, Y. Ueda, M. Goto, and H. Sugiyama, *Kogyo Kagaku Zasshi*, **70**, 331 (1967).

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5) C. A. Buehler, G. F. Deebel, and R. Evans, *J. Org. Chem.*, **6**, 216 (1941).

hot 3 M sodium hydroxide aqueous solution (1 l). After this mixture had then been cooled, the insoluble material was separated by filtration and extraction (1 M sodium hydroxide, 1 l) was repeated twice. After the residue had been dried, it was dissolved in hot ethanol (2 l); an insoluble, oily product was filtered off with charcoal, and then the solution was allowed to stand overnight at room temperature. The resultant turbid solution was treated again with charcoal, after which the solvent was removed under diminished pressure until the solid **3** deposited, whereupon the **3** was separated by filtration. The separation of **3** was repeated until an oily product resulted. The solvent of the oily product was removed *in vacuo*; the residue was dissolved in benzene and then purified by silica gel-column chromatography (*ca.* 50 fold in weight). At first **3** was eluted by benzene; elution was then continued by the use of a mixture of benzene and ethyl acetate, and then ethyl acetate. The second fraction was collected and was confirmed to be 7-nitro-1,3-benzodioxane (**4**) by studies of the mp and by elemental analyses. Mp 91—92 °C (lit,[5] 90.5 °C); yield, 5.3 g (1.6%). The total yield of **3** was 98.5 g (30%). Mp 73—74 °C (lit,[3a] 78 °C). It was recrystallized from ethanol (mp 75 °C), but crude **3** was used in the next step.

4-Acetoxy-5-nitro-1,3-benzodioxane (5). Into a solution of **3** (65 g) in acetic acid (650 ml) and acetic anhydride (650 ml), sulfuric acid (50 ml) was stirred below 10 °C. Solid chromic anhydride (50 g) was then added to the solution in small portions at 0—5 °C; about 30 min was required for the addition. Stirring was continued for another 90 min after the chromic anhydride had been added at the same temperature; the reaction mixture was then poured into ice water and allowed to stand for several hours. A precipitate was then collected on a filter and recrystallized from methanol. Mp 98 °C; yield, 46.0 g (54%); IR (KBr) 1760 cm^{-1} (C=O).

Found: C, 50.24; H, 3.79; N, 5.94%. Calcd for $C_{10}H_9O_6N$: C, 50.21; H, 3.79; N, 5.86%.

6-Nitrosalicylaldehyde (1) from 5. A mixture of **5** (14.3 g), ethanol (75 ml), water (75 ml), and concd sulfuric acid (15 ml) was boiled for 3 hr with stirring. The cooled mixture was then diluted with water and extracted with benzene. The benzene layer was dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. The residue was dissolved in benzene and extracted with a dil sodium hydroxide aqueous solution. The aqueous solution was then acidified with hydrochloric acid and extracted with benzene. The solution was dried over anhydrous magnesium sulfate and concentrated under diminished pressure. Crude **1** was purified by reprecipitation with alkali-acid. Mp 51—52 °C (lit, 54—55 °C,[2] 50—51 °C[3a]); yield, 8.3 g (83%). IR of **1**, prepared from **5**, agreed with that of the authentic sample.

4-Ethoxy-5-nitro-1,3-benzodioxane (7). Under the light of a tungsten lamp, a solution of bromine (22.4 g) in carbon tetrachloride (25 ml) was added to a boiling solution of **3** (25.4 g) in carbon tetrachloride (250 ml) over a period of 1 hr, after which boiling was continued for 3 hr. After the mixture had been cooled, an insoluble product was filtered off with celite. A clear solution which contained some fuming hydrogen bromide was stirred, drop by drop, into a solution of sodium ethoxide in ethanol (prepared from 4.4 g of sodium and 90 ml of ethanol; 1.3 mol equivalents) at 10—15 °C. This required 15 min; stirring was then continued for 3 hr at room temperature. A precipitate was dissolved by the addition of water, and the carbon tetrachloride layer was separated. The aqueous solution was extracted with carbon tetrachloride, and the combined carbon tetrachloride solution was washed well with water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was distilled in a vacuum. Bp 123—127 °C/4 mmHg; yield, 29.3 g (93%).

Found: C, 53.51; H, 4.98; N, 6.18%. Calcd for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.92; N, 6.22%.

6-Nitrosalicylaldehyde (1) from 7. A mixture of **7** (10 g), ethanol (100 ml), water (100 ml), and concd sulfuric acid (20 ml) was reacted as has been described in the hydrolysis of **5**. Mp 52 °C; yield, 6.6 g (89%).

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