Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 23 Sep 2006.

To cite this article: M del Mar Blanco , Carmen Avendaño , Nieves Cabezas & J. Carlos Menéndez (1993): Re-examination of the Synthesis of 3,5-Dimethoxy-2-nitrobenzaldehyde, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:10, 1351-1356

To link to this article: http://dx.doi.org/10.1080/00397919308011222

SYNTHETIC COMMUNICATIONS, 23(10), 1351-1356 (1993)

RE-EXAMINATION OF THE SYNTHESIS OF 3,5-DIMETHOXY-2-NITROBENZALDEHYDE

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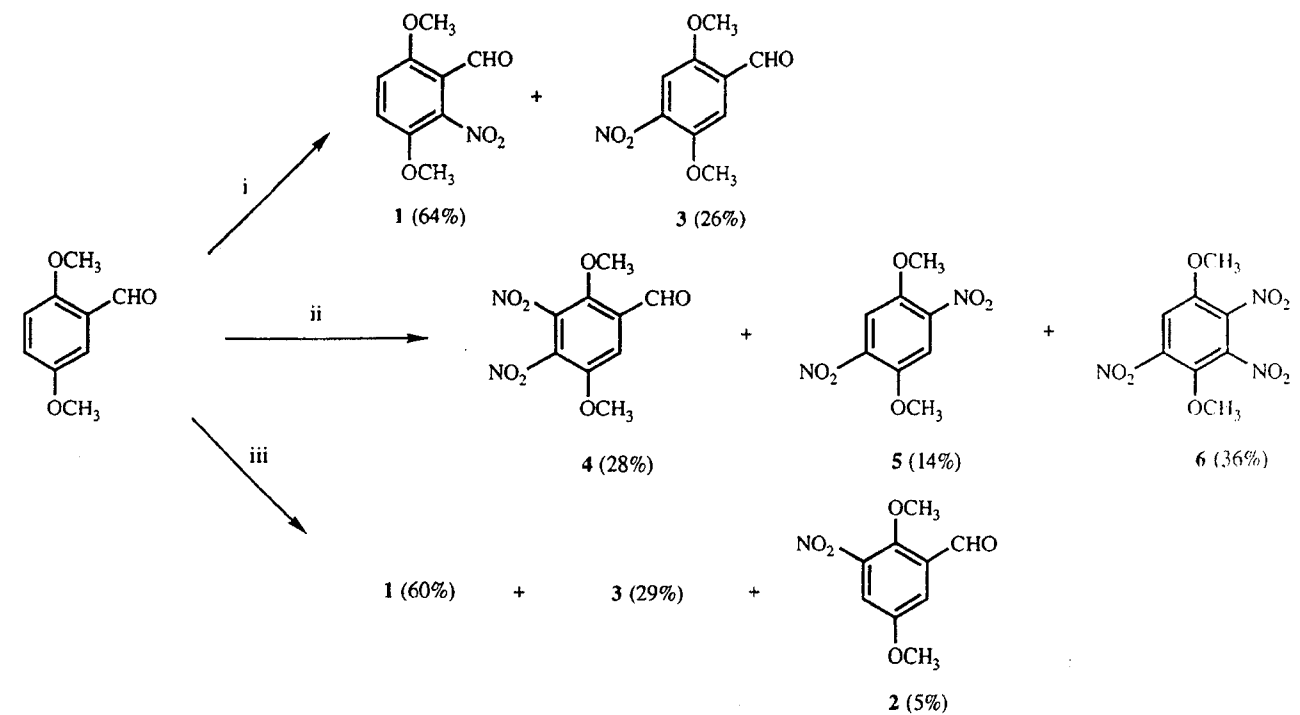
Abstract: An efficient and reproducible synthetic method is proposed for the preparation of 2-nitro-3,6-dimethoxybenzaldehyde.

In connection with our studies on the synthesis of diazaquinomicin A analogues through an hetero Diels-Alder approach[1], using 2,5,8-(1*H*)-quinolinetriones as dienophiles, we planned the use of the Friedländer quinoline synthesis[2,3] for the preparation of 3-substituted derivatives of the above system. An obvius starting material is 2-amino-3,6-dihydroxybenzaldehyde which should be available from the corresponding nitro derivative. However, attempts to nitrate 2,5-dihydroxybenzaldehyde (gentisaldehyde), following literature procedures described for methyl 2,5-dihydroxybenzoate[4] or 2-trifluoroacetamido-5-hydroxybenzaldehyde[5] were unsuccessful. Therefore, attention was turned towards the preparation of 2-nitro-3,6-dimethoxybenzaldehyde (**1**). The studies carried out are summarized in Scheme 1.



Reagents and conditions: i. 70 % HNO_3, r.t., 3 h ii. Fuming HNO_3, r.t., 3 min iii. 70 % HNO_3-AcOH-Et_2O (1:4:4), r.t., 30 h

SCHEME 1

Selective nitration of 2,5-dimethoxybenzaldehyde in either of its three free positions is an interesting problem, which still attracts the attention of synthetic chemists[6,7]. To our knowledge, the only literature procedure for the preparation of compound (**1**) is described in an early report by Rubinstein[8], which lacks several crucial experimental details, including the yield of the desired compound. According to Rubinstein, treatment of 2,5-dimethoxybenzaldehyde with nitric acid at room temperature gives a mixture of **1** and 2,5-dimethoxy-3-nitrobenzaldehyde (**2**). Re-examination of this reaction led to different results. Thus, in our hands, it gave **1** in 64% yield, together with 26% of 2,5-dimethoxy-4-nitrobenzaldehyde (**3**). Furthermore, the melting point described for **1**[8] is not correct, being 17 °C lower than the one found by us, and the method is not easily reproducible, since the yield and the isomeric ratio **1**:**3** strongly depend on the quality of the concentrated nitric acid employed. As the more concentrated reagent afforded the best yield of **1**, it was decided to examine the reaction with fuming nitric acid. However, only polynitrated compounds were observed, including derivatives **5** and **6**, presumably formed through oxidation of the aldehyde group and subsequent decarboxylation.

Finally, we found that the reaction of 2,5-dimethoxybenzaldehyde with nitric acid in acetic acid-ethyl ether, although slow, is an efficient procedure (60% of **1** and 29% of **3**), more easily reproduced and scaled-up than Rubinstein's. The small amount of the third isomer (**2**, 5%) also formed under these conditions is easily separated by column chromatography.

EXPERIMENTAL

Melting points are uncorrected and were determined with a Büchi capillary apparatus. Combustion analyses were obtained by Servicio de Microanálisis, Universidad Complutense, using a Perkin Elmer 2400 CHN microanalyzer. IR spectra were obtained with Perkin Elmer 577 and Buck Scientific 500 instruments. NMR spectra were recorded using a Varian VXR-300 spectrometer (300 MHz for ^{1}H, 75.4 MHz for ^{13}C). "Petrol" refers to the fraction boiling at 40-60°C.

Nitration of 2,5-Dimethoxybenzaldehyde with 70 % Nitric Acid. A solution of finely powdered 2,5-dimethoxybenzaldehyde (1 g, 6.02 mmol) in 70 % nitric acid (12 ml) was stirred at room temperature for 3 h, and was then poured on water (50 ml). The yellow precipitate was filtered, washed with water (4 x 5 ml) and dried *in vacuo* over phosphorous pentoxide. Flash column chromatography (silicagel), eluting with a gradient of petrol-ethyl acetate (4:1) - net ethyl acetate afforded 0.42 g (26 %) of **3** and 1.03 g (64 %) of **1**.

Data for **1**: Mp 176 °C (ethanol); lit[8], 159 °C. Analysis: Calc. for $C_9H_9NO_5$: C, 51.18; H, 4.26; N, 6.63. Found: C, 51.14; H, 4.47; N, 6.64. IR (KBr): 1710, 1530, 1350, 1255 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 10.30 (s, 1H, CHO); 7.28 (d, 1H, J = 9.3 Hz, C_5-H); 7.11 (d, 1H, J = 9.3 Hz, C_4-H); 3.95 (s, 3H, C_3-OCH_3); 3.87 (s, 3H, C_6-OCH_3). ^{13}C-NMR ($CDCl_3$) δ ppm: 186.11 (CHO); 155.20 (C_6); 130.80 (C_2); 119.94 (C_5); 116.02 (C_1); 114.39 (C_3); 114.08 (C_4); 57.13 and 56.69 (OCH_3).

Data for **3**: Mp 161 °C (ethanol). Analysis: Calc. for $C_9H_9NO_5$: C, 51.18; H, 4.26; N, 6.63. Found: C, 50.95; H, 4.35; N, 6.96. IR (KBr): 1690, 1510, 1380, 1340, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 10.50 (s, 1H, CHO); 7.54 (s, 1H, C_3-H); 7.43 (s, 1H, C_6-H); 3.96 and 3.95 (2 s, 6H, 2 OCH_3). ^{13}C-NMR ($CDCl_3$) δ ppm: 187.87 (CHO); 154.87 (C_2); 146.49 (C_5); 143.50 (C_4); 127.53 (C_1); 112.86 (C_6); 109.20 (C_3); 56.96 and 56.45 (OCH_3).

Nitration of 2,5-Dimethoxybenzaldehyde with Fuming Nitric Acid. A solution of 2,5-dimethoxybenzaldehyde (1 g, 6.02 mmol) in fuming nitric acid (5 ml) was stirred at room temperature for 3 min and poured on water (50 ml). The precipitate was washed with 0.5 % aqueous ammonium hydroxide (4 x 5 ml) and was then dissolved in a small amount of refluxing acetic acid, from where it was precipitated again by addition of cold water (50 ml). The yellow precipitate was dried *in vacuo* over phosphorous pentoxide and purified by column chromatography (silicagel), eluting with a gradient of petrol-ethyl acetate (3:1) - net ethyl acetate, yielding 432 mg (28 %) of **4**, 194 mg (14 %) of **5** and 592 mg (36 %) of **6**.

Data for **4**: Mp 120 °C (chloroform). Analysis: Calc. for $C_9H_8N_2O_7$: C, 42.19; H, 3.12; N, 10.94. Found: C, 42.23; H, 3.19; N, 11.02. IR (KBr): 1700, 1550, 1350, 1250 cm^{-1}. ^1H-NMR ($CDCl_3$) δ ppm: 10.25 (s, 1H, CHO); 7.75 (s, 1H, C_5-H); 3.95 and 3.90 (2 s, 6H, OCH_3).

Data for **5**: Mp 66 °C (methanol). Analysis: Calc. for $C_8H_8NO_6$: C, 42.10; H, 3.50; N, 12.28. Found: C, 42.09; H, 3.49; N, 12.15. IR (KBr): 1560, 1340, 1270 cm^{-1}. ^1H-NMR ($CDCl_3$) δ ppm: 7.20 (s, 2H, C_3-H and C_6-H); 3.50 (s, 6H, OCH_3).

Data for **6**: Mp 188 °C (chloroform). Analysis: Calc. for $C_8H_7N_3O_8$: C, 35.16; H, 2.56; N, 15.38. Found: C, 35.49; H, 2.73; N, 14.99. IR (KBr): 1535, 1350, 1270 cm^{-1}. ^1H-NMR ($CDCl_3$) δ ppm: 7.22 (s, 1H, C_6-H); 3.55 and 3.53 (s, 6H, OCH_3).

Nitration of 2,5-Dimethoxybenzaldehyde with Nitric Acid in Acetic Acid-Ethyl Ether. 70 % Nitric acid (13.5 ml) was dropwise added to a solution of finely powdered 2,5-dimethoxybenzaldehyde (5 g, 30 mmol) in ethyl ether (50 ml) and glacial acetic acid (50 ml). The mixture was stirred at room temperature for 30 h, evaporated to dryness, dissolved in ethyl ether (100 ml) and washed with water (3 x 25 ml). The organic phase was dried (sodium sulphate) and evaporated, and the residue was chromatographed on silicagel, eluting with petrol-ethyl ether (3:2) to yield 0.3 g (5 %) of **2** (data identical to those described in reference 6), 1.77 g (28 %) of **3** and 3.63 g (60 %) of **1**.

ACKNOWLEDGEMENT

Financial support from CICYT (project FAR-553/90) is gratefully acknowledged.

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(Received in the UK 02 December 1992)