1-Fluoro-2,5-dimethoxy-4-nitrobenzene

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Abstract: 1-Fluoro-2,5-dimethoxy-4-nitrobenzene was synthesized in 90% yield by the reaction of commercial 2-fluoro-1,4-dimethoxybenzene with nitric acid. The structure was confirmed by X-ray crystallography. The new title compound was characterized by 1H and 13C-NMR, elemental analysis, EI-MS and FT-IR.

Keywords: X-ray crystallography; fluorobenzene; nitration; nucleophilic aromatic substitution

1. Introduction

2-Fluoro-1,4-dimethoxybenzene (3) is available from Apollo Scientific (CAS Number: 82830-49-7) and sold by Sigma-Aldrich in the UK at £277.20 for 100 g. Nitration would give a suitably activated aromatic for facile nucleophilic aromatic substitution. Given the reaction of 1,4-dimethoxybenzene with nitric acid is reported to give 2,3-dinitro-1,4-dimethoxybenzene (2) in high yields of 76–90%, depending on the publication source [1–3], the analogous reaction with compound 3 was expected to give some 2-fluoro-1,4-dimethoxy-3-nitrobenzene (4) (Scheme 1). The fluoro-group was expected to direct nitration ortho and para to give 2-fluoro-1,4-dimethoxy-3-nitrobenzene (4) and 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5). The 3-nitro isomer (4) was intended as a substrate for the synthesis of alicyclic ring-fused benzimidazolequinone anti-tumour agents [4–6], however nitration was selective giving only isomer (5) in high yield. Herein, is described the first available preparation and analytical characterization of 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5).

Scheme 1. Expected nitration based upon similar literature reaction [1–3].

2. Results and Discussion

Treating 2-fluoro-1,4-dimethoxybenzene (3) with nitric acid (Honeywell Chemicals, 64–66%) over 10 minutes at 0 °C gave 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5) in 90% yield (Scheme 2). This is the first reported synthesis and characterisation of (5), even though alleged commercial sources exist [7]. X-ray crystallography confirmed the location of the substitution (Figure 1 & Supplementary Materials). There were two chemically identical molecules in the asymmetric unit and there were no significant intermolecular interactions in the solid state.

![Scheme 2. Preparation of 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5).](image)

Figure 1. One of the two molecules in the asymmetric unit of the X-ray crystal structure of 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5), 40% ellipsoids.

The fluoro-substituent was found to be overwhelmingly para-directing, in contrast to the nitro-group of the intermediate 1,4-dimethoxy-2-nitrobenzene (1), which directs the electrophile to the adjacent position to give 2,3-dinitro-1,4-dimethoxybenzene (2) in the analogous nitration of 1,4-dimethoxybenzene (Scheme 1). Nitro-groups are well-known to participate in adjacent group coordination and reactions, especially under strong acidic conditions that also favour their protonation [8].

3. Materials and Methods

3.1. General Information

All of the chemicals were obtained from commercial sources and used without purification. Nitric acid was 64–66% (w/v) in water. Melting point was measured on a Stuart Scientific melting point apparatus SMP1 (Cole-Parmer, Staffordshire, UK). Infrared spectrum was recorded using a Perkin-Elmer Spec 1 with ATR attached. $^1$H-NMR spectra were recorded using a JEOL ECX 400 MHz instrument equipped with a DEC AXP 300 computer workstation (JEOL Ltd., Tokyo, Japan). The chemical shifts were recorded in ppm relative to tetramethylsilane. $^{13}$C-NMR data were collected at 100 MHz with complete proton decoupling. NMR assignment was supported by DEPT and $^1$H-$^{13}$C-NMR correlation. GC-MS analysis was performed on an Agilent 6890 Series GC System.
equipped with an Agilent 5975 Inert Mass Selective Detector (EI) and a DB-1, 30 m, ID 0.25 mm, FD 0.25 μm column (Agilent Technologies, Santa Clara, CA., USA). Helium was used as carrier gas at a flow rate of 2.4 mL/min. The injector was heated to 160 °C and the oven temperature was increased from 150 to 180 °C at the rate of 22 °C/min and was then further increased to 320 °C at 40 °C/min. Elemental analysis was carried out on an Exeter Analytical CE-440 analyzer (Exeter Analytical, Coventry, UK). An Oxford Diffraction Xcalibur system was used to collect X-ray diffraction data at room temperature (Rigaku Oxford Diffraction, Oxford, UK). The crystal structures were solved using ShelXT and refined using ShelXL 2016/6 within the Oscail package (Patrick McArdle, Galway, Ireland) [9–11].

3.2. Synthesis of 1-Fluoro-2,5-dimethoxy-4-nitrobenzene (5)

2-Fluoro-1,4-dimethoxybenzene (3) (16.00 g, 0.10 mol) was slowly added to a stirred solution of HNO₃ (64–66%, 143 mL) at 0 °C. The solution was stirred for 10 min, poured onto ice water (600 mL), and stirred for 30 min. The precipitate was collected, washed with water, and dried to give 1-fluoro-2,5-dimethoxy-4-nitrobenzene (5) (18.63 g, 90%) as yellow solid; mp 116–118 °C; GC-EIMS m/z: 201 [M⁺] (100), 154 (48), 141 (39), 125 (65), 97 (68), 95 (48), 69 (34); vmax (neat, cm⁻¹): 3073, 2974, 2944, 1640, 1506 (NO₂), 1450, 1351 (NO₂), 1285, 1223, 1194, 1081, 1024; δ₁H (400 MHz, CDCl₃) 3.90 (s, 3H, Me), 3.92 (s, 3H, Me), 6.88 (d, J 12.2 Hz, 1H, 6-H), 7.62 (d, J 9.2 Hz, 1H, 3-H); δc (100 MHz, CDCl₃) 57.0, 57.3 (both Me), 103.0 (d, J 294 Hz, 6-CH), 111.4 (d, J 3.8 Hz, 3-CH), 134.4 (4-C), 141.1 (d, J 11.4 Hz, C), 149.0 (d, J 9.5 Hz, C), 155.8 (d, J 255.5 Hz, 1-C). Anal. Calcd for C₈H₈FNO₄: C, 47.77; H, 4.01; N, 6.96. Found: C, 47.67; H, 3.92; N, 6.79.

Crystal Data for C₈H₈FNO₄ (M = 201.15 g/mol): monoclinic, space group Cc, a = 7.9538(6) Å, b = 13.5379(11) Å, c = 16.0790(13) Å, α = 90°, β = 89.983(6)°, γ = 90°, V = 15588.1(3) Å³, Z = 8, T = 298.4(4) K, μ(MoKα) = 0.138 mm⁻¹, Dcalc = 1.543 g/cm³, 6792 reflections measured (−10 ≤ h ≤ 9, −18 ≤ k ≤ 17, −20 ≤ l ≤ 9), 3164 unique (Rint = 0.0214) which were used in all calculations. The structure was refined as an inversion twin. The final R1 was 0.0755 (I > 2σ(I)) and wR2 was 0.1838 (all data).

Supplementary Materials: The following are available online: www.mdpi.com/1422-8599/2018/1/M984/s1. ¹H and ¹³C-NMR spectra, EI-MS, and crystal data and structure refinement of the title compound 5. CCDC 1819149 also contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Author Contributions: M. Sweeney was the only experimentalist, who obtained, and analysed all data, apart from the X-ray crystallography, which was performed by P. McArdle. F. Aldabbagh directed the research and wrote the paper.

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References


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