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*Short Note*

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

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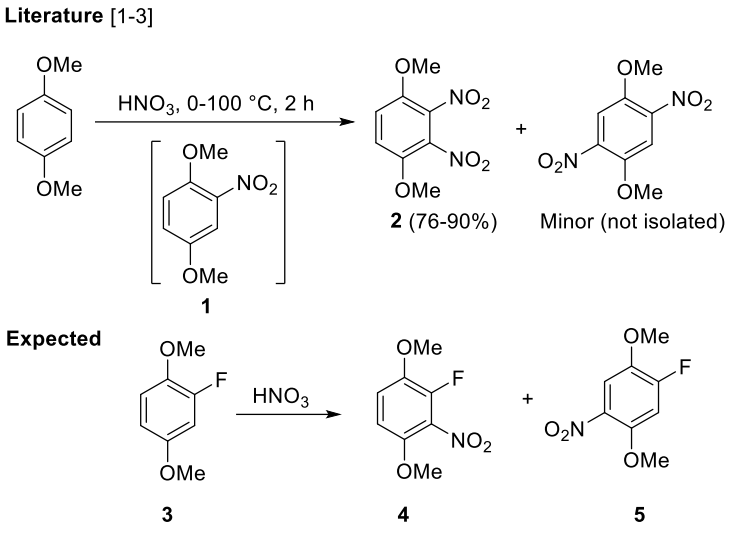
Received: 31 January 2018; Accepted: 18 February 2018; Published: 20 February 2018

**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 $^{1}$H and $^{13}$C-NMR, elemental analysis, EI-MS and FT-IR.

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

## 1. Introduction

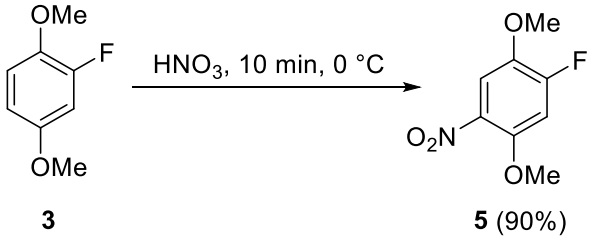
2-Fluoro-1,4-dimethoxybenzene (**3**) is available from Apollo Scientific (CAS Number: 82830-49-7) and sold by Sigma-Aldrich in the UK at £277.20 for 100 g. Nitration would give a suitably activated aromatic for facile nucleophilic aromatic substitution. Given the reaction of 1,4-dimethoxybenzene with 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**).

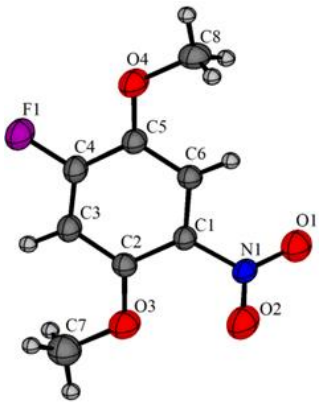



**Figure 1.** One of the two molecules in the asymmetric unit of the X-ray crystal structure of 1-fluoro-2,5-dimethoxy-4-nitrobenzene (**5**), 40% ellipsoids.

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 a 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 $HNO_3$ (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); $\nu_{max}$ (neat, $cm^{-1}$) 3073, 2974, 2944, 1640, 1506 ($NO_2$), 1450, 1351 ($NO_2$), 1285, 1223, 1194, 1081, 1024; $\delta_H$ (400 MHz, $CDCl_3$) 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); $\delta_C$ (100 MHz, $CDCl_3$) 57.0, 57.3 (both Me), 103.0 (d, *J* 24.8 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 $C_8H_8FNO_4$: C, 47.77; H, 4.01; N, 6.96. Found: C, 47.67; H, 3.92; N, 6.79.

Crystal Data for $C_8H_8FNO_4$ (M = 201.15 g/mol): monoclinic, space group Cc, a = 7.9538(6) Å, b = 13.5379(11) Å, c = 16.0790(13) Å, $\alpha$ = 90°, $\beta$ = 89.983(6)°, $\gamma$ = 90°, V = 15588.1(3) $Å^3$, Z = 8, T = 298.4(4) K, $\mu$(MoK$\alpha$) = 0.138 $mm^{-1}$, Dcalc = 1.543 $g/cm^3$, 6792 reflections measured ($-10 \leq h \leq 9$, $-18 \leq k \leq 17$, $-20 \leq l \leq 9$), 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 ($I > 2\sigma(I)$) 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 $^{13}C$-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.

**Acknowledgments:** We thank the Irish Research Council (IRC) for a Government of Ireland Postgraduate Scholarship for M. Sweeney.

**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.

**Conflicts of Interest:** The authors declare no conflict of interest. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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