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Short Note

2-(Fluoromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole

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Abstract: Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) substitutes the TEMPO free radical with fluorine on 4,7-dimethoxy-1-methyl-2-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}-1*H*-benzimidazole to give the title compound in a 77% yield. A mechanism is proposed for the formation of this novel methylene fluoride.

Keywords: fluorine; nitrogen heterocycles; nitroxide; radicals; Selectfluor; TEMPO

1. Introduction

Traditionally, an alkoxyamine undergoes homolysis thermally to give the reactive carbon-centered radical and the stable free radical, nitroxide [1]. TEMPO-Vis is one of a new class of alkoxyamines that releases reactive quinone methide radicals and the nitroxide, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) upon exposure to visible-light at room temperature (Figure 1) [2]. Light-insensitive 4,7-dimethoxy-1-methyl-2-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}-1*H*-benzimidazole **1** is the synthetic precursor to TEMPO-Vis and photoactive bis-alkoxyamines.

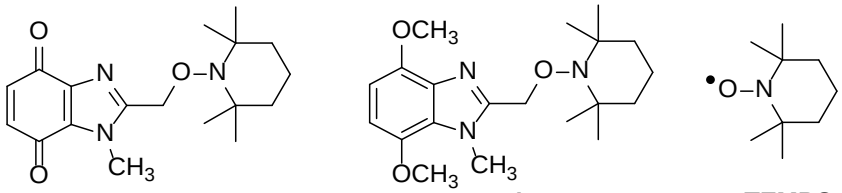
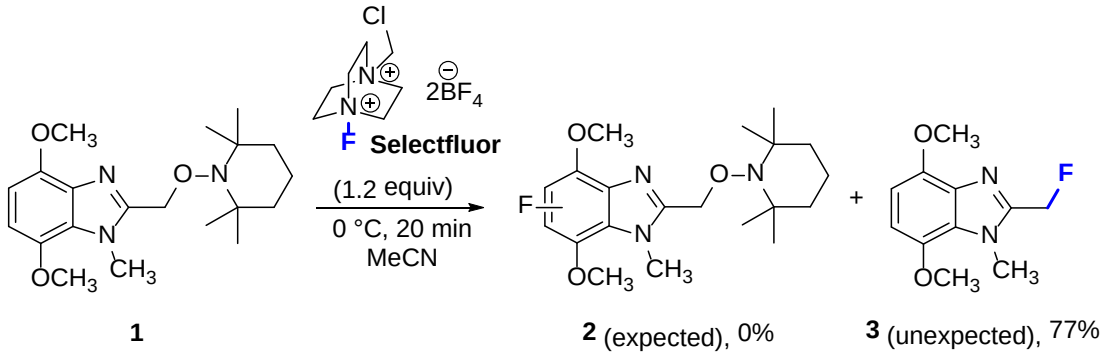


Figure 1. TEMPO-Vis, synthetic precursor **1**, and **TEMPO** free radical.

Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) is an inexpensive and hazard-free source of electrophilic fluorine [3]. Selectfluor is reported to have fluorinated activated aromatic positions on anisoles [4], phenols [4], naphthols [4,5], and benzamides [5,6]. More recently, the enamine-activated position of benzotriazinones was fluorinated using Selectfluor [7]. As part of our attempts to fluorinate at the activated 4,7-dimethoxybenzene part of alkoxyamine **1** to give **2**, an alternative to electrophilic aromatic substitution was discovered, and is now disclosed (Scheme 1).



Scheme 1. Unexpected formation of the title compound **3**.

2. Results and Discussion

Treatment of alkoxyamine **1** with Selectfluor (1.2 equiv) at 0 °C led to the rapid liberation of the TEMPO free radical, as indicated by GC-MS (Figure 2), and benzylic fluorination, to give 2-(fluoromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole **3**. The novel methylene fluoride **3** was isolated in a 77% yield. 2-Fluoromethylbenzimidazole (without the dimethoxy groups) was previously prepared by condensation of 1,2-phenylenediamine with fluoroacetic acid [8]. The expected electrophilic aromatic fluorination at the electron-rich *p*-dimethoxybenzene part of **1** to give **2** was not observed (Scheme 1).

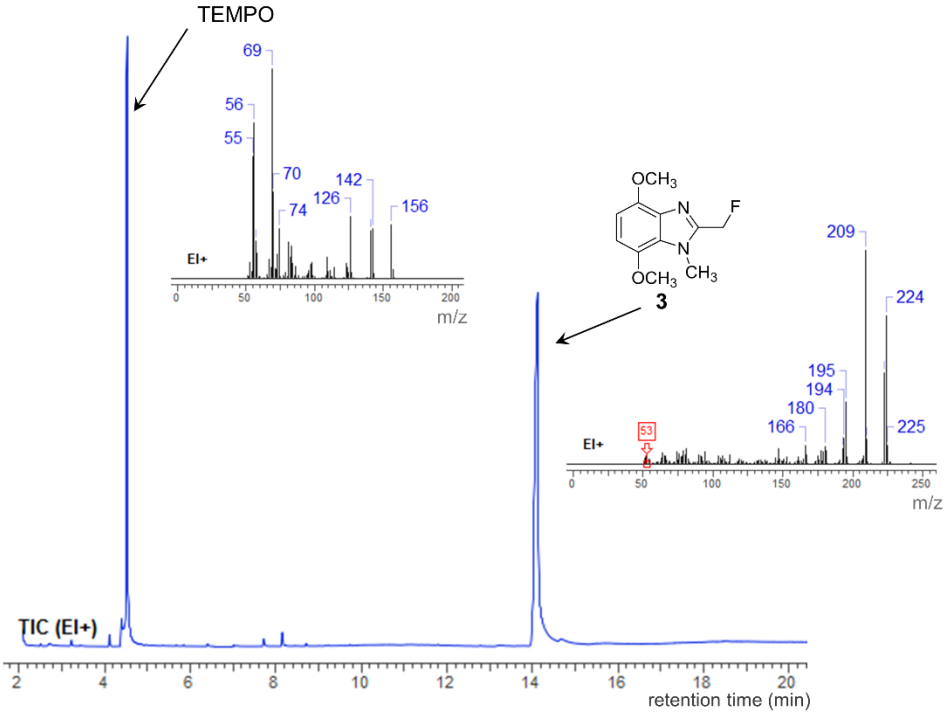


Figure 2. GC-MS analysis of the reaction mixture for the fluorination of alkoxyamine **1**.

The displacement of TEMPO is apparent when comparing the ^{1}H NMR spectra (Figure 3). There are no TEMPO-based peaks in the spectrum of isolated **3**, and the methylene signal shifted downfield to 5.61 ppm with splitting into a doublet ($^{2}J_{H\text{-}F}$ = 48.2 Hz) due to ^{1}H-^{19}F coupling. The location and multiplicity of the methylene signal is in good agreement with signals reported for 2-(fluoromethyl)-1*H*-benzimidazole (5.64 ppm, d, $^{2}J_{H\text{-}F}$ = 47.5 Hz) [8].

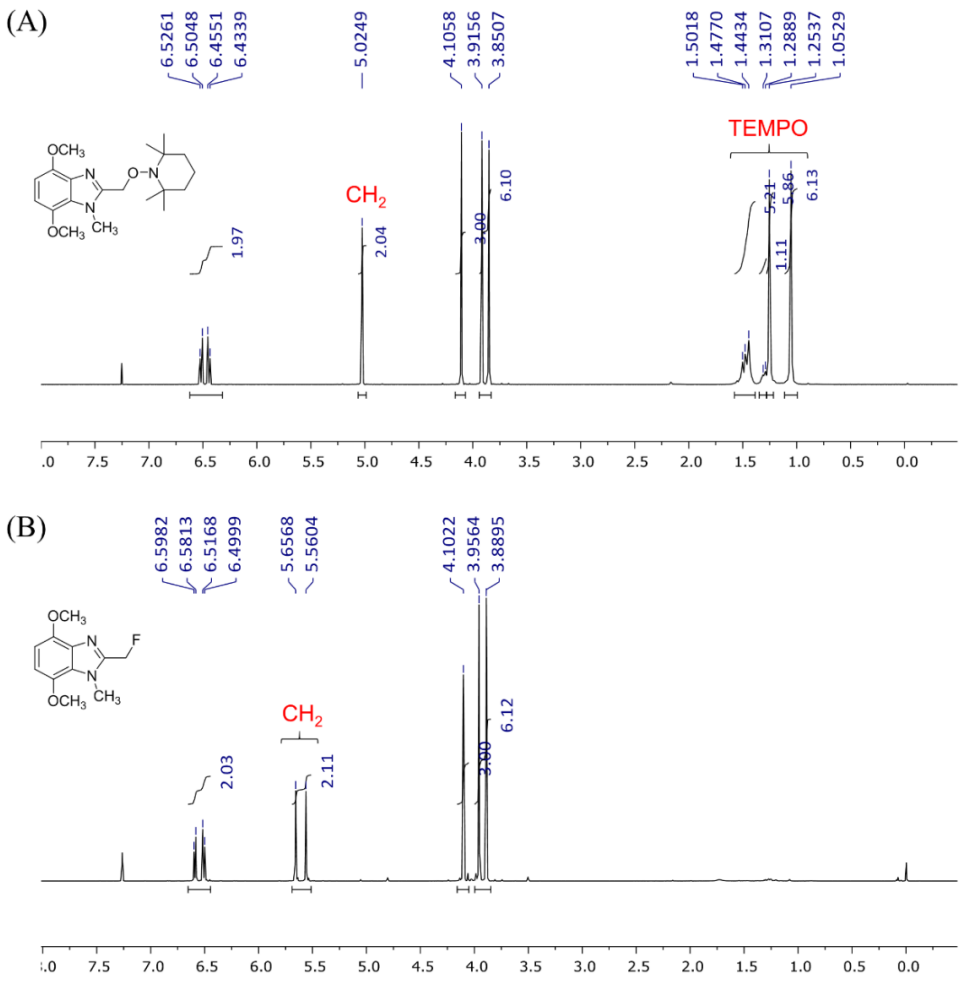
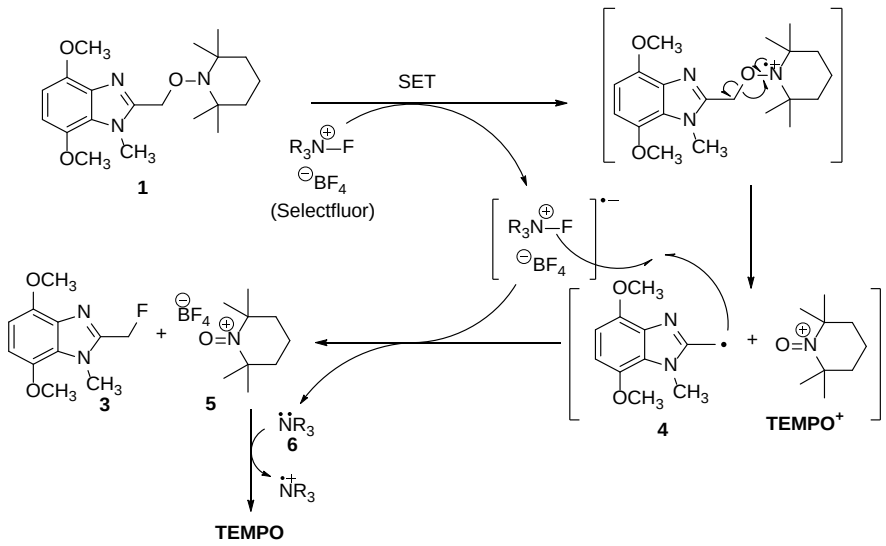


Figure 3. ^{1}H NMR spectra in $CDCl_3$: (**A**) alkoxyamine **1** and (**B**) methylene fluoride **3**.

The methylene signal split into a doublet ($^{1}J_{C\text{-}F}$ = 165.5 Hz) in the ^{13}C NMR spectrum of **3** at 76.8 ppm (see Supplementary Materials for NMR spectra). ^{13}C-^{19}F NMR coupling also gave doublets for benzimidazole-C-2 at 147.1 ppm ($^{2}J_{C\text{-}F}$ = 19.0 Hz), and for the N-CH_3 at 32.6 ppm ($^{4}J_{C\text{-}F}$ = 2.5 Hz). The former is in good agreement with the literature data on 2-(fluoromethyl)-1*H*-benzimidazole C-2 (148.6 ppm, d, $^{2}J_{CF}$ = 19.7 Hz) [8].

The ^{19}F NMR signal for **3** at −214.93 ppm is similar to the literature value of −213.92 ppm for 2-(fluoromethyl)-1*H*-benzimidazole [8]. The signal appeared as a triplet ($^{2}J_{F\text{-}H}$ = 48.0 Hz), due to ^{19}F-^{1}H coupling with the two ^{1}H atoms of the adjacent methylene group.

Alkoxyamine **1** is stable to visible-light and the reaction was performed at 0 °C, therefore ruling out bond homolysis as a pathway to formation of methylene fluoride **3**. Assuming Selectfluor is a source of F^+ or $F^\bullet$ and not fluoride, this rules out S_N2 displacement of the TEMPO residue [3,9]. Incompatible polarization of the alkoxyamine C–O bond also prevents a simple S_H2 mechanism. A single electron transfer (SET) pathway is now proposed, and is supported by the electrochemical oxidations of TEMPO-based alkoxyamines (TEMPO-R) with mesolytic cleavage of the alkoxyamine bond forming $TEMPO^+$ and $R^\bullet$ [10]. In this case (Scheme 2), SET is proposed to induce mesolytic cleavage of 'benzylic alkoxyamine' **1** to produce $TEMPO^+$ and a methylene radical **4**. Abstraction of $F^\bullet$ by **4** gives reaction product **3**, while reduction of the oxoammonium cation **5** by the Selectfluor-derived DABCO derivative **6** gives the TEMPO free radical detected by GC-MS (Figure 2). A plausible alternative to the mesolytic cleavage is initial S_N2 on the fluorine of Selectfluor by the *N*-3 of benzimidazole **1** to give an imidazolium fluoride [9]. The subsequent generation of **3** eliminates a $TEMPO^+$ species that would undergo reduction by **6** (as in Scheme 2) to give a TEMPO free radical.



Scheme 2. Proposed mechanism for the formation of methylene fluoride **3**.

3. Materials and Methods

3.1. Materials and Measurements

4,7-Dimethoxy-1-methyl-2-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}-1*H*-benzimidazole (**1**) was synthesized in an 83% yield by the base-mediated substitution on 2-(chloromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole by TEMPO hydroxylamine (prepared in situ via PtO_2 catalyzed hydrogenation of TEMPO (Sigma-Aldrich, 98%, St. Louis, MO, USA) [11]) [2]. 2-(Chloromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole was prepared in an 85% overall yield by *N*-methylation and chlorination of (4,7-dimethoxy-1*H*-benzimidazol-2-yl)methanol [2,12]. Selectfluor (Sigma-Aldrich, >95% F^+ active), MeCN (Sigma-Aldrich, HPLC Plus, ≥99.9%), CH_2Cl_2 (Fischer Scientific, ≥99%, Hampton, NH, USA) and $MgSO_4$ (Alfa Aesar, 99.5%, Haverhill, MA, USA) were used as received. GC-MS analysis was performed on an Agilent 7890A GC system (Agilent Technologies, Santa Clara, CA, USA), equipped with an Agilent 5975C inert XL Mass Selective Detector (EI) and an RTX-1, 30 m, ID 0.25 mm, FD 0.25 μm column (Restek Corporation, Bellefonte, PA, USA). Helium was used as carrier gas at a flow rate of 0.7 mL/min. The injector was heated to 250 °C, and the oven temperature was increased from 75 to 250 °C at the rate of 10 °C/min, and was then further increased to 350 °C at 50 °C/min. Thin layer chromatography (TLC) was performed on Merck TLC silica gel 60 F_{254} plates using a UV lamp (254 nm) for visualization. Flash chromatography was performed using silica gel, pore size 60 Å, 230–400 mesh, and particle size 40–63 μm (Sigma-Aldrich) using EtOAc (Fischer Scientific, ≥99%) and hexanes (Fischer Scientific, bp 40–60 °C). The melting point was measured on a Stuart Scientific melting point apparatus, SMP3. Infrared spectrum was recorded using a Perkin-Elmer Spec 1 (Perkin-Elmer, Waltham, MA, USA) with ATR attached. $CDCl_3$ (Sigma-Aldrich, 99.8% atom D + 0.03% $Si(CH_3)_4$ v/v) was used as received. NMR spectra were recorded using a Varian 500 MHz instrument (Varian Medical Systems, Palo Alto, CA, USA). The chemical shifts were in ppm relative to $Si(CH_3)_4$. NMR assignments were supported by DEPT and ^1H-^{13}C correlation. ^{13}C NMR with complete proton decoupling and ^{19}F NMR spectra were collected at 125 and 470 MHz, respectively. HRMS was carried out using ESI time-of-flight mass spectrometer (TOFMS) in positive mode using a Waters LCT Mass Spectrometry instrument (Waters, Milford, MA, USA).

3.2. Synthesis of 2-(Fluoromethyl)-4,7-dimethoxy-1-methyl-1H-benzimidazole (**3**)

Selectfluor (0.118 g, 0.33 mmol) was added to alkoxyamine **1** (0.100 g, 0.28 mmol) in MeCN (5 mL) at 0 °C and stirred for 20 min. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the residue purified

by flash chromatography using EtOAc and hexanes, as eluent to yield **3** (48 mg, 77%) as a colorless solid; mp 90–92 °C; R_f 0.33 (1:1 EtOAc:hexanes); ν_{max} (neat, cm^{-1}) 3001, 2936, 2838, 1525, 1465, 1392, 1263, 1238, 1221, 1174, 1100, 1070; δ_H (500 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.10 (3H, s, NCH_3), 5.61 (2H, d, $^2J_{H\text{-}F}$ = 48.2 Hz), 6.51 (1H, d, $^3J_{H\text{-}H}$ = 8.5 Hz), 6.59 (1H, d, $^3J_{H\text{-}H}$ = 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 32.6 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, NCH_3), 55.8, 55.9 (both OCH_3), 76.8 (d, $^1J_{C\text{-}F}$ = 165.5 Hz, CH_2), 101.5, 104.0 (both CH), 127.0, 134.2, 141.8, 146.3 (all C), 147.1 (d, $^2J_{C\text{-}F}$ = 19.0 Hz, C2); δ_F (470 MHz, $CDCl_3$) − 214.93 (t, $^2J_{F\text{-}H}$ = 48.0 Hz); HRMS (ESI) *m/z* $[M + H]^+$, $C_{11}H_{14}N_2O_2F$ calcd. 225.1039, observed 225.1040.

Supplementary Materials: The following are available online: ^1H, ^{13}C, and ^{19}F NMR spectra for compound **3**.

Author Contributions: P.K. was the only experimentalist, who obtained and analyzed all data. P.K. wrote the manuscript with research director and supervisor, F.A. D.A.S. advised on GC-MS and obtained the research funding with F.A. P.F. became the supervisor of this Ph.D., when F.A. departed NUI Galway for Kingston University. All authors checked and approved the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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