Short Communication

Synthesis of α-Fluoro Ethers by Cleavage of O,S-Acetals with Xenon Difluoride

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As a part of our studies in the synthesis and reactivity of α-halo ethers, we have become interested in α-fluoro ethers.

The synthetic utility of α-fluoro ethers has been well documented in the carbohydrate series. In the aliphatic series they have hardly been used in synthesis.3

The synthesis of glycosyl fluorides has been intensively studied and a number of methods for their preparation have appeared.4 From thioglycosides as starting material, glycosyl fluorides have been synthesized by reaction with 4-methyl(difluorooiido)benzene,5 with N-bromosuccinimide-diethylyaminosulfur trifluoride6 or with dimethyl(methylthio)sulfonium tetrafluoroborate.7 In the aliphatic series α-fluoro ethers are usually prepared by halide exchange.8 An acetoxy group can also be exchanged for a fluorine.9 Xenon difluoride has been used to make α-fluoro ethers by replacement of a carboxylic acid function10 or from benzyl alcohols by a rearrangement reaction.11

We herein report the synthesis of the fluoromethoxybenzenes 2 by cleavage of the O,S-acetals 1 with xenon difluoride (Scheme 1). The O,S-acetals 1 are readily prepared from phenols by reaction with chloromethyl methyl sulfide under basic conditions.12

The cleavage reaction is clean when the aromatic ring is unsubstituted or contains an electron-donating group (Table 1, entries 1–4) or a weak electron-withdrawing group (Table 1, entry 5). With stronger electron-withdrawing groups α-fluorination is seen to give the products 3 (Table 1, entries 6–8). The amount of α-fluorination is dependent on the reaction conditions. For instance in a 0.125 M solution, the O,S-acetal 2g gives ca. 35% (1H NMR) of the α-fluoro sulfide 3g, while in a more dilute solution i.e. 0.07 M, the crude product contains less than 7% of the α-fluoro sulfide. α-Fluorination is the reaction usually seen between ordinary sulfides with xenon difluoride.13

Since xenon difluoride is a potent one-electron oxidant,14 an electron transfer mechanism may be operating in the reactions above.

The fate of methanesulfonyl fluoride (Scheme 1), which is an anticipated cleavage product in the reaction, has

![Chemical Structure](image)

**Scheme 1**

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Product distribution</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>a</td>
<td>H</td>
<td>100 –</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>4-Br</td>
<td>100 –</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>3,5-(Me)_2</td>
<td>100 –</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>4-Cl</td>
<td>100 –</td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>4-Cl</td>
<td>100 –</td>
<td>70%</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>3-CN</td>
<td>69 31 –</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>4-CH_3CO</td>
<td>93 7 –</td>
<td>84%</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>4-NO_2</td>
<td>96 4 –</td>
<td>85%</td>
</tr>
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</table>

not been investigated. It probably decomposes immediately if formed.  

We are currently investigating the reactivity of α-fluoro ethers and the results will be published in due course.

Experimental

The 1H NMR spectra were recorded at 200 or 300 MHz, the 13C NMR spectra at 50 MHz and the 19F at 188 MHz.

O,S-Acetals 1a–1h were prepared by the reaction of chloromethyl methyl sulfide with the sodium salt of the phenol in the presence of sodium iodide in dimethylformamide according to the literature procedure. Compounds 1a,17 H18 and 1g17 have previously been described.

1-Methyl-4-[(methylthio)methoxy]benzene (1b). Oil. 1H NMR (CDCl3): δ 2.26 (CH3S), 2.33 (4-CH3Ar), 5.13 (OCH3S), 6.89 (ArH, d, J 8.6 Hz), 7.13 (ArH, d, J 8.1 Hz).

1,3-Dimethyl-5-[(methylthio)methoxy]benzene (1e). Oil. 1H NMR (CDCl3): δ 2.25 (CH3S), 2.30 [1,3-(CH3)2Ar, 6 H], 5.11 (OCH3S), 6.59 (ArH, 2 H), 6.66 (ArH, 1 H).

1-Methoxy-4-[(methylthio)methoxy]benzene (1d). Oil. 1H NMR (CDCl3): δ 2.22 (CH3S), 3.75 (OCH3), 5.08 (OCH3S), 6.85 (ArH), 6.88 (Ar).

1-Chloro-4-[(methylthio)methoxy]benzene (1e). Oil. 1H NMR (CDCl3): δ 2.22 (CH3S), 5.10 (OCH3S), 6.87 (ArH, d, J 9.0 Hz), 7.24 (ArH, d, J 9.1 Hz).

1-[(Methylthio)methoxy]-4-nitrobenzene (1h). Oil. 1H NMR (CDCl3): δ 2.25 (CH3S), 5.21 (OCH3S), 7.00 (ArH, d, J 9.3 Hz), 8.20 (ArH, d, J 9.3 Hz).

General procedure for the preparation of the α-fluoro ethers (2a–2h). The O,S-acetal (0.5 mmol) in dichloroethane (4 ml) was added with a syringe to a solution of XeF2 (0.5 mmol) in dichloroethane (7 ml) in a polypropylene bottle at 0 °C under N2. The reaction mixture was stirred for 0.5 h at 0 °C and then for 2 h at ambient temperature. Water was added and the product extracted into dichloroethane. The organic layer was separated and the dried solution (MgSO4) was evaporated. The α-fluoro ethers were purified by flash chromatography on silica gel using hexane–ethyl acetate 4:1 for elution.

Fluoromethoxybenzene (2a). Oil. 1H NMR (CDCl3): δ 5.71 (CH3F, d, J 54.8 Hz), 7.10 (ArH, 3 H, t, J 7.9 Hz), 7.33 (ArH, 2 H, t, J 7.4 Hz). 19F NMR (CFCl3): δ −148.8 (CH3F, t, J 54.7 Hz).

1-Fluoromethoxy-4-methylbenzene (2b). Oil. 1H NMR (CDCl3): δ 5.68 (CH3F, d, J 55.0 Hz), 6.98 (ArH, 2 H, d, J 8.6 Hz), 7.13 (ArH, 2 H, d, J 8.2 Hz). 19F NMR (CFCl3): δ −148.4 (CH3F, t, J 54.9 Hz).

1-Fluoromethoxy-3,5-dimethylbenzene (2e). Oil. 1H NMR (CDCl3): δ 5.67 (CH3F, d, J 54.8 Hz), 6.70 (ArH, 2 H, s), 6.73 (ArH, 1 H, s). 19F NMR (CFCl3): δ −148.2 (CH3F, t, J 54.9 Hz).

1-Fluoromethoxy-4-methoxybenzene (2d). Oil. 1H NMR (CDCl3): δ 5.63 (CH3F, d, J 55.1 Hz), 6.84 (ArH, 2 H, d, J 9.2 Hz), 7.02 (ArH, 2 H, d, J 9.1 Hz). 19F NMR (CFCl3): δ −147.7 (CH3F, t, J 55.0 Hz). 13C NMR (CDCl3): δ 55.83 (CH3), 101.68 (CH3F, d, J 218.2 Hz), 114.18, 117.67, 149.97, 154.87 (Ar).

1-Chloro-4-fluoromethoxybenzene (2e). Oil. 1H NMR (CDCl3): δ 5.68 (CH3F, d, J 54.5 Hz), 7.01 (ArH, 2 H, d, J 9.1 Hz), 7.29 (ArH, 2 H, d, J 9.0 Hz). 19F NMR (CFCl3): δ −149.4 (CH3F, t, J 54.4 Hz). 13C NMR (CDCl3): δ 100.45 (CH3F, d, J 216.9 Hz), 117.51, 128.02, 128.99, 154.42 (Ar).

1-Cyano-3-fluoromethoxybenzene (2f). Oil. 1H NMR (CDCl3): δ 5.69 (CH3F, d, J 53.9 Hz), 7.30 (ArH). 19F NMR (CFCl3): δ −150.7 (CH3F, t, J 54.0 Hz).

1-Acetyl-4-fluoromethoxybenzene (2g). M.p. 52 °C. 1H NMR (CDCl3): δ 2.54 (CH2CO), 5.74 (CH3F, d, J 53.9 Hz), 7.08 (ArH, 2 H, d, J 8.5 Hz), 7.93 (ArH, 2 H, d, J 9.0 Hz). 19F NMR (CFCl3): δ −150.7 (CH3F, t, J 53.4 Hz). 13C NMR (CDCl3): δ 27.05 (CH3), 99.5 (CH3F, d, J 218.2 Hz), 115.51, 129.92, 131.92, 159.16 (Ar).

1-Fluoromethoxy-4-nitrobenzene (2h). M.p. 62 °C. 1H NMR (CDCl3): δ 5.77 (CH3F, d, J 53.0 Hz), 7.15 (ArH, 2 H, d, J 9.2 Hz), 8.21 (ArH, 2 H, d, J 9.1 Hz). 19F NMR (CFCl3): δ −151.95 (CH3F, t, J 53.2 Hz). 13C NMR (CDCl3): δ 99.54 (CH3F, d, J 222.4 Hz), 116.31, 125.81, 143.35, 161.04 (Ar).

1-Acetyl-4-[(fluoromethylthio)methoxy]benzene (3g). Oil. 1H NMR (CDCl3): δ 2.51 (CH2CO), 5.32 (CH3S, d, J 1.4 Hz), 5.58 (CH2F, d, J 52.2 Hz), 6.94 (ArH, 2 H, d, J 8.8 Hz), 7.88 (ArH, 2 H, d, J 9.0 Hz). 19F NMR (CFCl3): δ −190.1 (CH3F, t, J 52.1 Hz). 13C NMR (CDCl3): δ 26.41 (CH3S), 68.07, 84.13 (CH3F, d, J 216.9 Hz), 115.28, 130.46, 131.38, 160.19 (Ar).

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