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Short Communication

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

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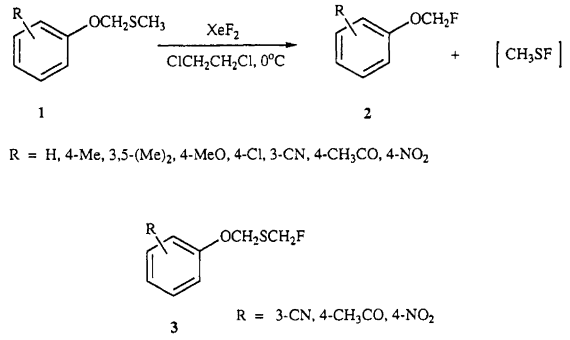
As a part of our studies in the synthesis and reactivity of α-halo ethers,[1] we have become interested in α-fluoro ethers.

The synthetic utility of α-fluoro ethers has been well documented in the carbohydrate series.[2] 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(difluoroiodo)benzene,[5] with *N*-bromosuccinimide–diethylaminosulfur trifluoride[6] 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 function[10] 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]



Scheme 1

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% (^{1}H 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 methanesulfenyl fluoride (Scheme 1), which is an anticipated cleavage product in the reaction, has

Table 1. Reaction of the *O,S*-acetals **1** with xenon difluoride.

Entry	Product 2/3	R	Product distribution[a] 2	3	Yield (%)[b] 2
1	**a**	H	100	—	80[c]
2	**b**	4-Me	100	—	72[c]
3	**c**	3,5-(Me)$_2$	100	—	78[c]
4	**d**	4-CH$_3$O	100	—	83[d]
5	**e**	4-Cl	100	—	70[d]
6	**f**	3-CN	69	31	—
7	**g**	4-CH$_3$CO	93	7	84[d]
8	**h**	4-NO$_2$	96	4	85[d]

[a] From the crude ^{1}H NMR spectrum. [b] Isolated yields. [c] Crude product. [d] Purified by flash chromatography.

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not been investigated. It probably decomposes immediately if formed.[15]

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 ^{13}C NMR spectra at 50 MHz and the ^{19}F 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.[16] Compounds **1a**,[17] **1f**[18] and **1g**[17] have previously been described.

*1-Methyl-4-[(methylthio)methoxy]benzene (**1b**).* Oil. ^1H NMR ($CDCl_3$): δ 2.26 (CH_3S), 2.33 (4-CH_3Ar), 5.13 (OCH_2S), 6.89 (ArH, d, *J* 8.6 Hz), 7.13 (ArH, d, *J* 8.1 Hz).

*1,3-Dimethyl-5-[(methylthio)methoxy]benzene (**1c**).* Oil. ^1H NMR ($CDCl_3$): δ 2.25 (CH_3S), 2.30 [1,3-$(CH_3)_2Ar$, 6 H], 5.11 (OCH_2S), 6.59 (ArH, 2 H), 6.66 (ArH, 1 H).

*1-Methoxy-4-[(methylthio)methoxy]benzene (**1d**).* Oil. ^1H NMR ($CDCl_3$): δ 2.22 (CH_3S), 3.75 (OCH_3), 5.08 (OCH_2S), 6.85 (Ar), 6.88 (Ar).

*1-Chloro-4-[(methylthio)methoxy]benzene (**1e**).* Oil. ^1H NMR ($CDCl_3$): δ 2.22 (CH_3S), 5.10 (OCH_2S), 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 ($CDCl_3$): δ 2.25 (CH_3S), 5.21 (OCH_2S), 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 XeF_2 (0.5 mmol) in dichloroethane (7 ml) in a polypropylene bottle at 0 °C under N_2. 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 ($MgSO_4$) was evaporated. The α-fluoro ethers were purified by flash chromatography on silica gel using hexane–ethyl acetate 4:1 for elution.

*Fluoromethoxybenzene (**2a**).*[10] Oil. ^1H NMR ($CDCl_3$): δ 5.71 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −148.8 (CH_2F, t, *J* 54.7 Hz).

*1-Fluoromethoxy-4-methylbenzene (**2b**).* Oil. ^1H NMR ($CDCl_3$): δ 5.68 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −148.4 (CH_2F, t, *J* 54.9 Hz).

*1-Fluoromethoxy-3,5-dimethylbenzene (**2c**).* Oil. ^1H NMR ($CDCl_3$): δ 5.67 (CH_2F, d, *J* 54.8 Hz), 6.70 (ArH, 2 H, s), 6.73 (ArH, 1 H, s,). ^{19}F NMR ($CFCl_3$): δ −148.2 (CH_2F, t, *J* 54.9 Hz).

*1-Fluoromethoxy-4-methoxybenzene (**2d**).* Oil. ^1H NMR ($CDCl_3$): δ 5.63 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −147.7 (CH_2F, t, *J* 55.0 Hz). ^{13}C NMR ($CDCl_3$): δ 55.83 (CH_3), 101.68 (CH_2F, d, *J* 218.2 Hz), 114.18, 117.67, 149.97, 154.87 (Ar).

*1-Chloro-4-fluoromethoxybenzene (**2e**).* Oil. ^1H NMR ($CDCl_3$): δ 5.68 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −149.4 (CH_2F, t, *J* 54.4 Hz). ^{13}C NMR ($CDCl_3$): δ 100.45 (CH_2F, d, *J* 216.9 Hz), 117.51, 128.02, 128.99, 154.42 (Ar).

*1-Cyano-3-fluoromethoxybenzene (**2f**).* Oil. ^1H NMR ($CDCl_3$): δ 5.69 (CH_2F, d, *J* 53.9 Hz), 7.30 (ArH). ^{19}F NMR ($CFCl_3$): δ −150.7 (CH_2F, t, *J* 54.0 Hz).

*1-Acetyl-4-fluoromethoxybenzene (**2g**).* M.p. 52 °C. ^1H NMR ($CDCl_3$): δ 2.54 (CH_3CO), 5.74 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −150.7 (CH_2F, t, *J* 53.4 Hz). ^{13}C NMR ($CDCl_3$): δ 27.05 (CH_3), 99.5 (CH_2F, 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 ($CDCl_3$): δ 5.77 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −151.95 (CH_2F, t, *J* 53.2 Hz). ^{13}C NMR ($CDCl_3$): δ 99.54 (CH_2F, d, *J* 222.4 Hz), 116.31, 125.81, 143.35, 161.04 (Ar).

*1-Acetyl-4-[(fluoromethylthio)methoxy]benzene (**3g**).* Oil. ^1H NMR ($CDCl_3$): δ 2.51 (CH_3CO), 5.32 (CH_2S, d, *J* 1.4 Hz), 5.58 (CH_2F, 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). ^{19}F NMR ($CFCl_3$): δ −190.1 (CH_2F, t, *J* 52.1 Hz). ^{13}C NMR ($CDCl_3$): δ 26.41 (CH_3), 68.07, 84.13 (CH_2F, d, *J* 216.9 Hz), 115.28, 130.46, 131.38, 160.19 (Ar).

References

1. (a) Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B 37* (1983) 93; (b) Benneche, T., Strande, P. and Undheim, K. *Synthesis* (1983) 762; (c) Antonsen, Ø., Benneche, T., Hagelin, G. and Undheim, K. *Acta Chem. Scand. 43* (1989) 56.
2. Collins, P. M. and Ferrier, R. J. *Monosaccharides*, Wiley, New York 1995.
3. Benneche, T. *Synthesis* (1995) 1.
4. Lockhoff, O. *Methoden der Organischen Chemie*, Thieme, Stuttgart 1992, Vol. E14a/3, p. 627ff.
5. Caddick, S., Motherwell, W. B. and Wilkinson, J. A. *J. Chem. Soc., Chem. Commun.* (1991) 674.
6. Nicolaou, K. C., Dolle, R. E., Papahatjis, D. P. and Randall, J. L. *J. Am. Chem. Soc. 106* (1984) 4189.
7. Blomberg, L. and Nordberg T. *J. Carbohydr. Chem. 11* (1992) 751.
8. (a) Mason, C. T. and Allain, C. C. *J. Am. Chem. Soc. 78* (1956) 1682; (b) Kokesh, F. C. and Hine, J. *J. Org. Chem. 41* (1976) 1976; (c) Zavgorodny, S., Polianski, M., Besidsky, E., Kriukov, V., Sanin, A., Pokrovskaya, M., Gurskaya, G., Lönnberg, H. and Azhayev, A. *Tetrahedron Lett. 32* (1991) 7593.

9. Lucas, H., Basten, J. E. M., van Dinther, Th. G., Meuleman, D. G., van Aelst, S. F. and van Boeckel, C. A. A. *Tetrahedron 46* (1990) 8207.
10. Patrick, T. B., Johri, K. K., White, D. H., Bertrand, W. S., Mokhtar, R., Kilbourn, M. R. and Welch, M. J. *Can. J. Chem. 64* (1986) 138.
11. Stavber, S. and Zupan, M. *Tetrahedron Lett. 34* (1993) 4355.
12. Antonsen, Ø., Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B 42* (1988) 515.
13. Tius, M. A. *Tetrahedron 51* (1995) 6605.
14. Eberson, L. *Electron Transfer Reactions in Organic Synthesis*, Springer, Berlin 1987.
15. Seel, F. *Adv. Inorg. Chem. Radiochem. 16* (1974) 297.
16. Corey, E. J. and Bock, M. C. *Tetrahedron Lett.* (1975) 3269.
17. Holton, R. A. and Davies, R. G. *Tetrahedron Lett.* (1977) 533.
18. Benneche, T., Strande, P. and Undheim, K. *Acta Chem. Scand., Ser. B 41* (1987) 448.

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