α-Fluorination of Sulfoxides Bearing α-Hydrogens by Molecular Fluorine. A Novel Method for the Synthesis of α-Fluorosulfones

Jun Chiba, Takumichi Sugihara, and Chikara Kaneko*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77

(Received April 19, 1995)

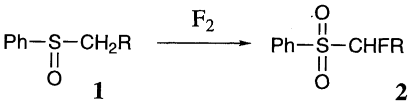
Direct formation of α-fluorosulfones from sulfoxides bearing α-hydrogens merely by reacting molecular fluorine (5% F_2/N_2) is reported and a possible mechanism for this novel α-fluorination reaction is proposed.

α-Fluorination of sulfides and related compounds (sulfoxides and sulfones) is of importance since the resulting α-fluorinated sulfur compounds can serve as useful synthetic intermediates for the synthesis of organofluorine compounds of medicinal importance.[1-3] Among such compounds, fluoromethyl phenyl sulfone[4] and the corresponding sulfoximine (α-fluoromethyl-*N*-methyl-*N*-phenyl sulfoximine)[5] are the reagents which permit direct conversion of a ketone or an aldehyde to fluoromethylene derivatives. Except for the replacement reaction of α-chlorosulfides with potassium fluoride in presence of 18-crown-6,[6] all of the reported methods for the preparation of α-fluorinated sulfides uses α-fluorination reaction of the corresponding sulfides or sulfoxides bearing α-H atoms. These are as follows; (1) direct fluorination of the sulfides with xenon difluoride,[7] (2) conversion of the sulfoxides to α-fluorosulfides with diethylaminosulfur trifluoride (DAST),[8,9] and (3) fluorination of the sulfides with electrophilic fluorinating reagents (such as *N*-fluoropyridinium triflates[10] or *N*-fluorinated derivatives of 1,4-diazabicyclo[2.2.2]octane).[11] However, all of these reagents are expensive and require anhydrous conditions. Furthermore, since most of α-fluorosulfides decompose during the post-treatment, they must be isolated as the corresponding sulfoxides or sulfones by an appropriate oxidation. It is desirable, therefore, to explore an easily handled fluorination reaction using a non-expensive fluorinating reagent in an ordinary organic solvent giving directly the stable α-fluorinated sulfur compounds (e.g. the sulfones or sulfoxides). The fluorination with molecular fluorine has the advantages—apart from the favorable price of the reagent—that the reaction can be performed without difficulty.[1-3,12,13]

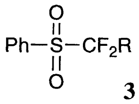
We now report an efficient synthesis of α-fluorinated sulfones merely by reacting sulfoxides bearing α-hydrogens with molecular fluorine (5% F_2/N_2). In a typical experiment using methyl phenyl sufoxide (**1a**) as the substrate, fluorine (5% F_2/N_2: the approximate amounts of fluorine were evaluated by using volumeter) was passed through CH_3CN[14] solution (20 ml) of methyl phenyl sulfoxide (**1**: 1 mmol) for 10-15 min at -20 °C. After the addition of 2.5 mol equiv. of F_2 was completed, N_2 was bubbled through the solution to expel excess fluorine and the reaction was quenched by the addition of water. After basification with aqueous saturated sodium bicarbonate, the products were extracted with dichloromethane and separated by flash chromatography performed on Merck silica gel (240-400 mesh) using *n*-hexane-ethyl acetate (5:1) as the solvent. In general, the sulfones are eluted faster than the sulfoxides and, in each series of compounds, the more fluorinated ones are eluted faster than the less fluorinated ones. Without exception, monofluorinated sulfones are the major product and accompanied with small amounts of difluorinated (and/or trifluorinated) and unfluorinated sulfones. The reactions of methyl phenyl sulfoxide (**1a**) and related compounds (**1b**-**1d**) are summarized in Table 1.

Taking the fluorination of methyl phenyl sulfoxide (**1a**), our results are consistent with initial oxidative fluorination of **1a** to give sulfur(IV) difluoride **6**[15] as the intermediate (Scheme 1). Perhaps HF is lost to give the dehydrofluorinated product **7** followed by fluorine addition to give the precursor **8** of the α-fluorinated product **2a**.[4] Repetition of the similar reaction sequence to **8** leads to **10** (the precursor of **3a**)[16] *via* **9**. Trifluoromethyl phenyl sulfone (**4**)[17] is also formed from **10** in a similar manner.

Formation of the fluorine adduct **6** as the intermediate is supported by the similar difluoride formation from diaryl sulfoxides under comparable conditions (-90 °C in $CFCl_3$) reported by Ruppert.[18] It is also noted that, while ethyl phenyl sulfoxide (**1b**) gave poor yields of the fluorinated product **2b**,

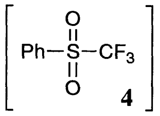


$$\mathrm{Ph{-}\underset{\displaystyle \|\atop O}{S}{-}CH_2R}\ \mathbf{1}\ \xrightarrow{F_2}\ \mathrm{Ph{-}\overset{O\atop \|}{\underset{\| \atop O}{S}}{-}CHFR}\ \mathbf{2}$$



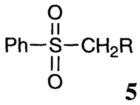
$$\mathrm{Ph{-}\overset{O\atop \|}{\underset{\| \atop O}{S}}{-}CF_2R}$$

3



$$\left[\mathrm{Ph{-}\overset{O\atop \|}{\underset{\| \atop O}{S}}{-}CF_3}\right]$$

4



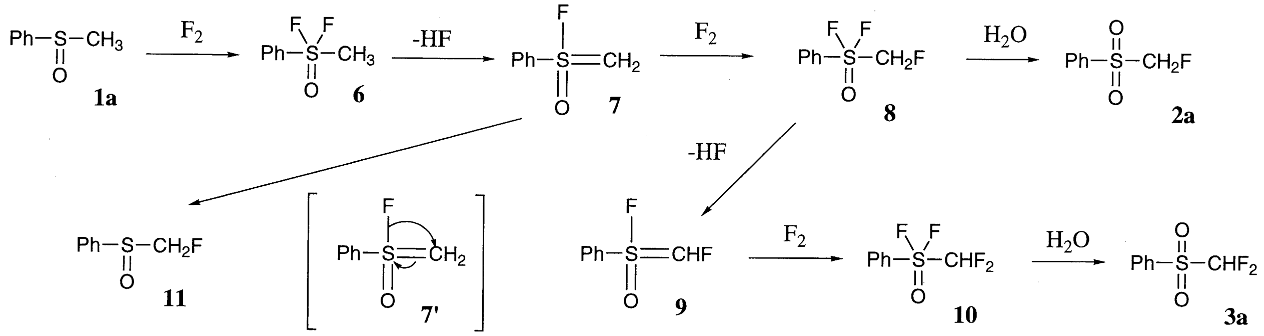
$$\mathrm{Ph{-}\overset{O\atop \|}{\underset{\| \atop O}{S}}{-}CH_2R}$$

5

Table 1. Fluorination of Sulfides with F_2/N_2 in CH_3CN at -20 °C

Entry	Substrate (R)	Product / %[a] 2	3	4	5
1[b,c]	**1a** (H)	21	12	8	23
2[d]	**1b** (CH_3)	11	-	-	8
3[e]	**1c** (Cl)	49	-	-	22
4	**1d** ($CH_2CO_2C_2H_5$)	50	19	-	-

[a] Unless otherwise noted, yields refer to isolated yields. [b] Though all products from **1a** could be separated by flash chromatography (see the text), the yields in this line refer to the ones determined by GLC (5% OV-17, column temp. 175 °C). [c] 3% of **1a** was recovered. [d] 9% of **1b** was recovered. [e] 13% of **1c** was recovered.



Scheme 1.

chloromethyl phenyl sulfoxide (**1c**) and ethyl 2-(phenylsulfoxy)acetate (**1d**) gave high yields of the monofluorinated products **2c** and **2d**. This fact also supports the above mechanism, since the dehydrofluorination step of the difluoride (e.g. **6**) should be accelerated by an increase of acidity of the α-proton. If 1 mol equiv. of F_2 was used in the above reaction, yet **2a** was again obtained as the major products and none of the corresponding sulfoxide **11** was detected. This fact demonstrates that Pummerer reaction (cf. **7**→**7'**→**11**) is not involved in the present α-fluorination reaction.[19]

Remarkably, if the same reaction of **1a** was carried out in a mixture of CH_3CN-H_2O (10:1), the same products **2a**-**5a** were again obtained. The yields of the products [**2a** (20%), **3a** (4%), **4** (5%) and **5a** (26%)] were comparable with those of Entry 1. This fact implies that the reaction can be likewise carried out in the presence of water. Rozen *et al.* reported that, if fluorine was passed through a mixture of CH_3CN-H_2O (10:1), HOF was formed within a few minutes and utilized as a strong oxidation reagent.[20] Actually, if **1a** was added into the above HOF solution [prepared by passing fluorine (2.5 mol equiv.) in the mixture at -20 °C and keeping the whole mixture at -20 °C for 5 min], **5a** was obtained in 85% yield without any detectable formation of the fluorinated product. Hence it is obvious that the reaction of **1a** to give **6** and its subsequent reactions with F_2 (cf. Scheme 1) are much faster than that of fluorine with water to give HOF.

In conclusion, the present study not only provides one-step synthesis of α-monofluorinated sulfones **2a-d** and its further fluorinated ones **3a-d** and/or **4**, but also complements existing methodology for the α-fluorination of sulfides and sulfoxides bearing α-H atoms for which only Pummerer-type rearrangement has so far been utilized as the key step.[7-11] Preliminary experiments carried out on some sulfides were found to give α-fluorinated sulfoxides as the major products.[19] Hence, this novel non-Pummerer-type fluorination may have wide applicability upon further investigation.

References and Notes

1 R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha, Tokyo (1982).
2 J. T. Welch, *Tetrahedron*, **43**, 3123 (1987).
3 J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry," John Wiley & Sons, Inc., New York (1991).
4 M. Inbasekaran, N. P. Peet, J. R. McCarthy, and M. E. LeTourneau, *J. Chem. Soc., Chem. Commun.*, **1985**, 678.
5 M. L. Boys, E. W. Collington, H. Finch, S. Swanson, and J. Whitehead, *Tetrahedron Lett.*, **29**, 3365 (1988).
6 K. M. More and J. Wemple, *Synthesis*, **1977**, 791.
7 M. Zupan, *J. Fluorine Chem.*, **8**, 305 (1976); R. K. Marat and A. F. Janzen, *Can. J. Chem.*, **55** 3031 (1977); A. F. Janzen, P. M. C. Wang, and A. E. Lemire, *J. Fluorine Chem.*, **22**, 557 (1983).
8 J. R. McCarthy, N. P. Peet, M. E. LeTourneau, and M. Inbasekaran, *J. Am. Chem. Soc.*, **107**, 735 (1985).
9 S. F. Wunk and M. J. Robins, *J. Org. Chem.*, **55**, 4757 (1990).
10 T. Umemoto and G. Tomizawa, *Bull. Chem. Soc. Jpn.*, **59**, 3625 (1986).
11 G. S. Lal, *J. Org. Chem.*, **58**, 2791 (1993).
12 S. T. Purrington, B. S. Kagan, and T. B. Patrick, *Chem. Rev.*, **86**, 997 (1986).
13 C. Kaneko, A. Toyota, and J. Chiba, *Yakugaku Zasshi*, **114**, 160 (1994).
14 CH_3CN (special grade, Wako Pure Chemical Industries, Ltd.) was used as such.
15 The most stable geometry of **6** should be a trigonal bipyramidal structure with two fluorine atoms in apical sites. Due to attachment of three electronegative atoms to the sulfur atom, the *d-p* π-bonding between S and O atoms becomes important. J. C. Matin, *Science*, **221**, 509 (1983); T. A. Albright, J. K. Burdett, and M-H. Whangbo, "Orbital Interactions in Chemistry," John, Wiley & Sons, Inc., New York, pp 258-276 (1985).
16 Q-Y. Chen and S-W. Wu, *J. Org. Chem.*, **54**, 3023 (1989).
17 J. B. Hendrickson and K. W. Bair, *J. Org. Chem.*, **42**, 3875 (1977).
18 I. Ruppert, *Angew. Chem., Int. Ed. Engl.*, **18**, 880 (1979).
19 The reaction of $PhSCH_3$ with F_2 (1 mol equiv.) under the same conditions was found to give, in addition to 34% recovery of the sulfide, $PhSOCH_3$ (**1a**, 21%), $PhSOCH_2F$ (**11**, 15%), $PhSOCHF_2$ (6%), and $PhSO_2CH_2F$ (**2a**, 2%). The low ratio of **2a**/**11** indicates that the formation of **2a** from **11** is a minor process, if any.
20 S. Rozen, A. Bar-Haim, and E. Mishani, *J. Org. Chem.*, **59**, 1208 (1994). Experimental details for the oxidation reaction with HOF-CH_3CN: D. Hebel and S. Rozen, *J. Org. Chem.*, **56**, 6298 (1991).