α-Fluorination of Sulfides with *N*-Fluoropyridinium Triflates

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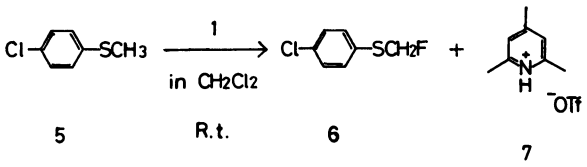
The reaction of sulfides possessing α-hydrogen with various *N*-fluoropyridinium salts was examined. While the fluorinating power increased in the order of *N*-fluoro-2,4,6-trimethylpyridinium triflate **1**<*N*-fluoropyridinium triflate **2**<*N*-fluoro-3,5-dichloropyridinium triflate **3**, the yield of an α-fluoro sulfide decreased in the order of **1**>**2**, and **3** no longer produced the α-fluoro sulfide. Triflate **1** was more reactive than the corresponding tetrafluoroborate **4**. Thus, it was shown that **1** satisfactorily fluorinated various kinds of sulfides under very mild conditions, giving α-fluoro sulfides. A two-step mechanism, oxidative fluorination of sulfur and Pummerer-type rearrangement, was proposed for the fluorination. The corresponding α-fluoro sulfoxide or sulfones were easily prepared from the sulfides by successive fluorination-oxidation procedure.

In recent years, introduction of fluorine into organic molecules is of increasing importance in the biological and pharmaceutical fields because it can alter the biological activity of the molecules or make them specific irreversible enzyme inhibitors with high possibility.[1] Therefore the methodologies for preparing the fluoro-compounds are being investigated actively.[1,2] Among them, α-fluorination of sulfides is of importance since some of sulfides are biologically active compounds such as β-lactam antibiotics[3] and amino acids[4] or since the resulting α-fluoro sulfides can serve as useful synthetic intermediates for the biologically active fluoro-compounds.[5] The reported methods for the preparation of α-fluoro sulfides are as follows; (1) direct fluorination of sulfides with xenon difluoride,[6] (2) replacement reaction of α-chloro sulfides with rigorously dried potassium fluoride and 18-crown-6,[7] and (3) conversion of sulfoxides to α-fluoro sulfides with diethylaminosulfur trifluoride (DAST).[8] However, xenon difluoride is very expensive and difficult to handle, and in order to prepare acid-labile α-fluoro sulfides, the special technique using bis (trimethylsilyl) amine is needed to remove hydrogen fluoride resulting from the reaction.[6b,c] The latter two methods required two steps from sulfides and severe reaction conditions for the fluorination because of the use of very hygroscopic potassium fluoride or thermally unstable and moisture-sensitive DAST.

We developed *N*-fluoropyridinium salts as easily handled fluorinating agents with variable fluorinating power[9] and found that the reaction of sulfides having α-hydrogen with the reagents resulted in the easy formation of α-fluoro sulfides. In this paper, α-fluorination of the sulfides with various *N*-fluoropyridinium salts was examined.

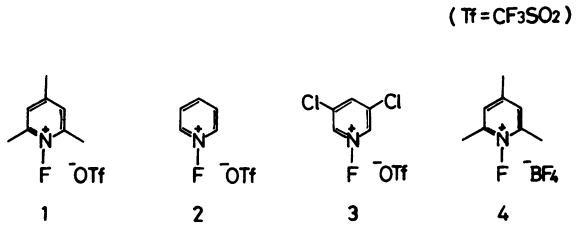
Results and Discussion

The reactivity of *N*-fluoropyridinium triflates **1**—**3** to the sulfide **5** was examined and the results are shown in Table 1. It was found that, while the fluorinating power increased in the order of **1** < **2** < **3**,[9] the yield of an α-fluoro sulfide **6** decreased in the order of **1** > **2** and **3** no longer produced **6**. It has been demonstrated that the fluorinating power is variable depending on the electron density at the positive nitrogen site.[9] The least reactive **1** mildly reacted with **5** in dichloromethane at room temperature to produce the α-fluoro sulfide **6** in a high yield (Eq. 1). On the other hand, the most reactive **3** underwent rapid and exothermic reaction with **5**, but the fluoro sulfide **6** and any other organic fluorides were not detected in



(1)

the ^{19}F-NMR spectrum of the resulting reaction solution. **2** afforded **6** in a moderate yield (48%) under



Scheme 1.

Table 1. α-Fluorination of Sulfide **5** with *N*-Fluoropyridinium Salts

Run[a]	Salt	Temp	Time/h	Yield/%[b] of **6**
1	**1**	R.t.	8	87 (76)
2	**2**	R.t.	7.5	(48)
3[c]	**3**	R.t.	—	0
4	**4**	R.t.	11	No reaction
5	**4**	Reflux	4.5	75

a) Dichloromethane was used as a solvent. b) ^{19}F NMR yields. The values in parentheses are isolated yields. c) An exothermic reaction occurred immediately.

the similar conditions. As seen from Eq. 1, the reaction of **1** proceeded under almost neutral conditions because triflic acid liberated during the reaction was trapped by collidine simultaneously liberated. This is of great benefit to the preparation of acid-labile α-fluoro sulfides. Accordingly, the relatively low Yield and the unproductiveness of the fluoro sulfide **6** using **2** and **3** should be concerned with their relatively acidic conditions because of low and very low basicity of pyridine and 3,5-dichloropyridine liberated, respectively, compared to collidine. Of course, it cannot be excluded that the high oxidation power, particularly, of **3** is reponsible for it.

A tetrafluoroborate **4** which was expected to have the same fluorination power as triflate **1**[9a] exhibited the great difference in the reactivity. **4** did not react with the sulfide **5** under the same conditions as **1**, but **4** reacted at an elevated temperature to give the fluoro sulfide **6** in a 75% yield (Table 1, Run 5). The low reactivity of **4** is probably due to the low solubility compared to **1**. But another reason cannot entirely be excluded that the reactivity is somewhat dependent on the nature of the counter anions.

Furthermore, the reaction of *N*-fluoropyridinium salts was greatly dependent on the solvents. It was found from the ^{19}F NMR spectra of the resulting reaction solutions that no α-fluoro sulfides were produced in the polar solvents such as tetrahydrofuran (THF) and acetonitrile though the reagents were consumed (Table 2, Runs, 6, 11, and 12). The cause of the great solvent dependence is not clear. The *N*-fluoropyridinium salts do not fluorinate THF and acetonitrile.

Table 2 shows the results about α-fluorination of several kinds of sulfides including ones having functional groups such as alkoxycarbonyl and amido with triflate **1** or **2**. Alkyl aryl sulfides were converted to α-fluoroalkyl aryl sulfides in high yields. More acid-labile α-fluoroalkyl alkyl sulfides were also prepared by the present method though their yields were generally moderate. Since the more labile fluoro sulfides decomposed during the post-treatment, they were determined by ^{19}F NMR and their structures were confirmed by oxidizing them to stable α-fluoro sulfones which were characterized.

An unsymmetrical dialkyl sulfide, methyl dodecyl sulfide, afforded fluoromethyl dodecyl sulfide only. Ethyl methylthioacetate gave the product resulting from the fluorination at activated hydrogen site only. Benzyl methyl sulfide gave a mixture of benzyl fluoromethyl sulfide and α-fluorobenzyl methyl sulfide (3:4). Thus, the present method using **1** has been shown to be very useful and broadly applicable to the preparation of α-fluoro sulfides because of stable and nonhygroscopic crystals of **1**, mildness of the reaction conditions, and the simplicity of the procedure.

The above-mentioned selectivity of the α-fluorination with *N*-fluoropyridinium salts is very similar to that of Pummerer rearrangement which converted sulfoxides to α-acetoxy sulfides.[10] We propose the following two-step mechanism, oxidative fluorination of sulfur and Pummerer-type rearrangement, for

Table 2. α-Fluorination of Sulfides

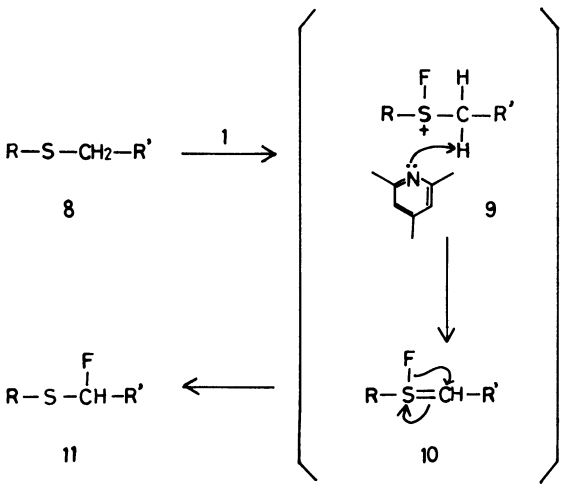
Run	Sulfide	Salt	Solv.	Temp/°C	Time/h	α-Fluoro sulfide	Yield/%[a]	^{19}F NMR[b]
1	$PhSCH_3$	**1**	CH_2Cl_2	R.t.	4	$PhSCH_2F$	85 (49)	180.3 (t, J=54 Hz)
2	$PhSCH_3$	**2**	CH_2Cl_2	R.t.	6	$PhSCH_2F$	56	—
3	Cl-C$_6$H$_4$-SCH_3	**1**	CH_2Cl_2	R.t.	8	Cl-C$_6$H$_4$-SCH_2F	87 (76)	182.8 (t, J=52.5 Hz)
4	Cl-C$_6$H$_4$-SCH_3	**2**	CH_2Cl_2	R.t.	7.5	Cl-C$_6$H$_4$-SCH_2F	48	—
5	n-$C_{12}H_{25}SCH_3$	**1**	CH_2Cl_2	R.t.	17.5	n-$C_{12}H_{25}SCH_2F$	44	184.2 (t, J=52 Hz)
6	n-$C_{12}H_{25}SCH_3$	**1**	CH_3CN	R.t.	18	None[c]	—	—
7	CH_3SCH_2COOEt	**1**	CH_2Cl_2	R.t.	8	$CH_3SCHFCOOEt$	46	167.3 (d, J=54 Hz)
8	$PhSCH_2COOMe$	**1**	CH_2Cl_2	R.t.	23	$PhSCHFCOOMe$	45 (38)	158.4 (d, J=52 Hz)
9	$PhCH_2SCH_3$	**1**	CH_2Cl_2	R.t.	0.5	$PhCHFSCH_3$ 4) $PhCH_2SCH_2F$ 3)	77	152.0 (d, J=56 Hz) 187.2 (t, J=51 Hz)
10	$PhCH_2SCH_3$	**1**	CH_2Cl_2	0	3	$PhCHFSCH_3$ 4) $PhCH_2SCH_2F$ 3)	48	—
11	$PhCH_2SCH_3$	**1**	THF	0→R.t.	50	None[c]	—	—
12	$PhCH_2SCH_3$	**2**	THF	R.t.	11	None[c]	—	—
13	$CH_3SCH_2CH_2CHCOOMe$ $NHCOCF_3$	**1**	CH_2Cl_2	R.t.	7.5	$FCH_2SCH_2CH_2CHCOOMe$ $NHCOCF_3$	39	183.8 (t, J=51 Hz)
14	$CH_3SCH_2CH_2CHCOOMe$ $NHCOCF_3$	**1**	CH_2Cl_2	Reflux	2	$FCH_2SCH_2CH_2CHCOOMe$ $NHCOCF_3$	41	—

a) See b) in Table 1. b) Chloroform-*d* was used as a solvent for Run 1, 2, 8, and 13, and dichloromethane for Runs 5, 7, and 9. c) No α-fluoro sulfides were detected.

the α-fluorination (Scheme 2). Marat and Janzen suggested a similar mechanism for the α-fluorination with xenon difluoride.[5b] McCarthy et al. proposed Pummerer-type rearrangement as the mechanism for the conversion of sulfoxides to α-fluoro sulfides with DAST.[8]

Our attempt to detect intermediate S–F compounds on ^{19}F NMR spectra was unsuccessful. In the α-fluorination of methyl phenyl sulfide, the ^{19}F-peak corresponding to the α-fluoro sulfide appeared with the consumption of triflate **1**, indicating that the intermediates are very unstable. M. Zupan also failed to detect the intermediate S–F compounds by ^{19}F NMR technique in the reaction with xenon difluoride.[6a]

Furthermore, we tried to detect a ^{19}F-peak corresponding to S–F in the reaction of **1** with diphenyl sulfide without α-hydrogen in order to demonstrate the transfer of a fluorine atom from the positive nitrogen to the sulfur site. The reaction of **1** with diphenyl sulfide in dichloromethane was carried out at room temperature in a NMR-tube and followed by



Scheme 2.

NMR measurement. A new singlet peak at −3.25 ppm was definitely observed after 19 h. It was found that the peak slightly shifted to downfield with time and reached to −5.25 ppm after 4 d. The reaction mixture became completely homogeneous in 5 d and addition of water into the solution resulted in immediate disappearence of the peak. The subsequent usual

$$\text{Ph-S-Ph} \xrightarrow{1} \xrightarrow{H_2O} \text{Ph-SO-Ph} \qquad (2)$$

workup gave diphenyl sulfoxide in a 34% yield. Although the slight shift with time cannot be explained at the present stage, the chemical shift of the new peak is very close to the ^{19}F-chemical shift (−5.43 ppm) of diphenylsulfur difluoride[6b] which was easily hydrolyzed to diphenyl sulfoxide. The above results indicated that the new peak corresponded to a S–F compound and supported that the α-fluorination of sulfides occurred via the oxidative fluorination of sulfur followed by the rearrangement of fluorine to α-carbon. But we have no full data for determining the exact structures of the intermediate S–F compounds.

The mechanism is in agreement with that of the other α-halogenation of sulfides with chlorine, bromine, sulfuryl chloride, or *N*-chloro- or bromosuccinimide.[11] However, the present α-fluorination should be essentially different in the mechanism of the initial transfer of fluorine to sulfur site from the case of the other α-halogenation, because the N^+–F bond is very firm[9a] due to extreme difficulty in the formation of a fluorine cation in contrast to the case of the other halogen atoms.[12] Although a stepwise mechanism by a one-electron transfer for the initial fluorine transfer may be suggested, the detailed mechanism is not clear at the present stage.

α-Fluoro sulfoxide[7,8] or sulfones[8] were easily prepared by the fluorination, followed by oxidation with *N*-bromosuccinimide–water or *m*-chloroperbenzoic acid (Table 3). The successive fluorination–oxidation were conveniently carried out by one-pot

Table 3. One-Pot Preparation of α-Fluoro sulfoxide or Sulfones from Sulfides

$$\text{R-S-CH}_2\text{R}' \xrightarrow[\text{R.t. in } CH_2Cl_2]{1} \xrightarrow{[O]} \text{R-S(O)}_n\text{-CHFR}' \ (n=1,\ 2)$$

Run	Sulfide	Oxidation Conditions	Product	Yield/%[a]
1	$PhSCH_3$	NBS[b] (1.5 eq), r.t., 0.5 h in CH_2Cl_2–MeOH–H_2O	$PhSOCH_2F$	66
2	$PhCH_2SCH_3$	MCPBA[c] (2.5 eq), r.t., 2 h in CH_2Cl_2	$PhCHFSO_2CH_3$ (4), $PhCH_2SO_2CH_2F$ (3)	77
3	n-$C_{12}H_{25}SCH_3$	MCPBA[c] (2.5 eq), r.t., 4 h in CH_2Cl_2	n-$C_{12}H_{25}SO_2CH_2F$	37
4	CH_3SCH_2COOEt	MCPBA[c] (2.5 eq), r.t., 10 h in CH_2Cl_2	$CH_3SO_2CHFCOOEt$	48
5	$CH_3SCH_2CH_2CHCOOMe$ (NHCOCF$_3$)	MCPBA[c] (2.5 eq), r.t., 10 h in CH_2Cl_2	$FCH_2SO_2CH_2CH_2CHCOOMe$ (NHCOCF$_3$)	34

a) Isolated yields. b) *N*-Bromosuccinimide. c) *m*-Chloroperbenzoic acid.

method. Since most of α-fluoro sulfides decompose partly or completely during the post-treatment, our one-pot procedure is very advantageous for praparing the α-fluoro sulfoxides or sulfones from sulfides.

Experimental

General. Melting points were uncorrected. ^{1}H NMR spectra were determined with a Varian HA-100 NMR spectrometer or a Varian EM 390 NMR spectrometer. ^{19}F NMR spectra were determined with a Varian XL-100 A NMR spectrometer or a Hitachi R-20 B NMR spectrometer. ^{19}F NMR chemical shifts are given in ppm upfield from trichlorofluoromethane as an internal standard. IR spectra were measured on a Jasco A-202 diffraction grating infrared spectrophotometer. Dichloromethane used was dried by treatment with calcium chloride followed by distillation on calcium hydride.

Materials. *N*-Fluoropyridinium salts **1**—**4** were prepared according to our methods reported previously.[9a]

α-Fluorination of Sulfides. A Typical Procedure: *p*-Chlorophenyl methyl sulfide (158 mg, 1 mmol) was added into a mixture of triflate **1** (290 mg, 1 mmol) and dry dichloromethane (3 ml) at room temperature under argon atmosphere and the reaction mixture was stirred for 8 h. The reaction was followed by checking the oxidation power with aq KI solution. After **1** completely disappeared, anhydrous sodium carbonate (0.5 g) was added and the organic layer was thin-layer chromatographed on silica gel by using a mixture of hexane and triethylamine (100:1) as an eluent to give *p*-chlorophenyl fluoromethyl sulfide as an oily product (133 mg, 76%).

Spectral date of fluoromethyl phenyl sulfide and *p*-chlorophenyl fluoromethyl sulfide are in good agreement with the reported data.[7] Although the products of Runs 5, 7, 9, 10, 13 and 14 in Table 2 were detected by ^{19}F NMR analysis, they completely decomposed during the post-treatment using chromatography on silica gel. Therefore the labile α-fluoro sulfides were converted to the easily isolated fluoro sulfones.

Methyl Phenylthio Fluoroacetate: Oil, ^{1}H NMR ($CDCl_3$) δ=3.70 (3 H, s, CH_3), 6.08 (1 H, d, J_{H-F}=52.5 Hz, CHF), 7.20—7.70 (5 H, m, Ar); ^{19}F NMR ($CDCl_3$) 158.4 (d, J_{H-F}=52.5 Hz); IR (neat, cm^{-1}) 1760 (CO); MS (*m/z*) 200 (M^+). Found: C, 53.97; H, 4.46%. Calcd for $C_9H_9FO_2S$: C, 53.99; H, 4.53%.

One-Pot Synthesis of Fluoromethyl Phenyl Sulfoxide from Methyl Phenyl Sulfide. α-Fluorination of methyl phenyl sulfide (124 mg, 1 mmol) by using **1** (290 mg, 1 mmol) and dry dichloromethane (3 ml) as a solvent was carried out in the same manner as the above. The reaction time was 4 h. After that, methanol (1 ml), water (0.1 ml) and then *N*-bromosuccinimide (270 mg, 1.5 mmol) were added into the resulting reaction mixture under cooling with ice bath and it was stirred at room temperature for 0.5 h. The reaction mixture was washed with aq sodium thiosulfate and the aq layer was extracted with ethyl acetate. The combined organic layer was washed with aq sodium hydrogen carbonate solution, 10% hydrochloric acid, and then aq sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was column-chromatographed on silica gel by using a mixture of hexane and ethyl acetate (2:1) as an eluent to give fluoromethyl phenyl sulfoxide (105 mg, 66%). The spectral data of the sulfoxide was in good agreement with the reported.[7]

One-Pot Synthesis of α-Fluoro Sulfones from Sulfides. A Typical Procedure: α-Fluorination of dodecyl methyl sulfide (216 mg, 1 mmol) by using **1** (290 mg) and dry dichloromethane (2 ml) was carried out in the same manner as the above. The reaction time was 4 h. Then, 80—90%

Table 4. Properties of α-Fluoro Sulfones

α-Fluoro sulfones		Mp θ_m/°C	^{19}F NMR[a]/ppm (CHF)	^{1}H NMR[a]/δ (CHF)	IR/cm^{-1} [Method]	Mass/*m/z*	Anal./% (Calcd)
$PhCHFSO_2CH_3$	**12**	78—79	176.0 (d, J=48 Hz)	5.96 (1H, J=48 Hz)	1320 (SO_2) [KBr]	190 ($M^+-CH_3SO_2$)	C, 51.25 (51.05) H, 4.82 (4.81)
$PhCH_2SO_2CH_2F$	**13**	Oil	212.3 (t, J=47 Hz)	4.86 (2H, t, J=47 Hz)	1320 (SO_2) [Neat]	180 (M^+)	C, 50.76 (51.05) H, 4.83 (4.82)
n-$C_{12}H_{25}SO_2CH_2F$	**14**	62—63	212.6 (t, J=48 Hz)	5.06 (2H, t, J=48 Hz)	1325 (SO_2) [KBr]	266 (M^+)	C, 58.37 (58.61) H, 10.00 (10.22)
$CH_3SO_2CHFCOOC_2H_5$	**15**	Oil	183.4 (d.q, J=48 Hz J=2.4 Hz)	5.53 (1H, d, J=48 Hz)	1760 (CO) 1380 (SO_2) [Neat]	185 (M^++1) 156	C, 32.75 (32.61) H, 5.00 (4.93)
$FCH_2SO_2CH_2CH_2CHCOOCH_3$ (NHCOCF$_3$)	**16**	117—118	213.0 (t, J=46.5 Hz)	5.27 (2H, d, J=46.5 Hz)	3350 (NH) 1750 (CO) 1715 (CONH) 1310 (SO_2) [KBr]	277 (M^+−CHF)	C, 31.01 (31.07) H, 3.35 (3.58) N, 4.44 (4.53)

a) Chloroform-*d* was used as a solvent for α-fluoro sulfones **12**—**15**, and acetonitrile-d_3 for **16**.

m-chloroperbenzoic acid (540 mg, about 2.5 mmol) was added into the resulting reaction mixture under cooling with ice bath and then the mixture was stirred at room temperature for 4 h. The same workup as the above gave dodecyl fluoromethyl sulfone (99.4 mg, 37%). The spectral data and elemental analysis of new α-fluoro sulfones are shown in Table 4.

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