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A Facile Method for the Fluorine Substitution of Phenylthio Group *via* Sulfonium Salts Using Cesium Fluoride

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Monofluorinated compounds are easily prepared in good yields by treating phenyl sulfides with methyl fluorosulfonate and cesium fluoride in refluxing dichloromethane, successively. This reaction proceeds under so mild conditions as not to affect the coexisting bromine substituent.

Introducing fluorine substituents at specific sites in a molecule is one of the most important problems in the synthetic field of organic fluorine chemistry. Although quite a few methods have been developed for fluorination, most of them require highly toxic reagents and/or rather severe reaction conditions.[1] It is still desired, therefore, to explore milder and easier fluorination reactions which are readily carried out in ordinary laboratory equipments.

Metal fluorides are convenient sources of fluoride ion in substitution reactions in respect of their easy acquisition and handling. However, owing to their poor solubilities in organic solvents, the fluorine substitution with these reagents requires elevated temperatures in polar solvents,[2] or the addition of crown ether[3] or quaternary onium salts,[4] to replace only good leaving groups such as halogens and sulfonyloxy groups in the substrates.

These difficulties in using metal fluorides prompted us to investigate the fluorination reaction starting from the substrate with a suitable onium moiety as a leaving group in the molecule as shown in Eq. 1. According to this scheme, it was expected that i) the onium part (Z^+) in the substrate molecule would function also as a lipophilic counter cation to dissolve fluoride ion (F^-) into less polar reaction media ("solid-liquid substrate phase-transfer"[5]), and ii) the cationic center would attract fluoride ion to the close neighborhood of the reaction site to promote the expected S_N2 reaction ("substrate-reagent ion-pair reaction"[5]).

$$\text{R-Z}^+\text{X}^-\text{(liq.)} \xrightarrow[-\text{MX}]{\text{MF(solid)}} \text{R-Z}^+\text{F}^-\text{(liq.)} \longrightarrow \text{R-F} + \text{Z} \quad (\text{M = metal ion}) \qquad (1)$$

Sulfides are stable to nucleophilic attack, while easily alkylated *in situ* to

generate sulfonium salts, which readily undergo various substitution reactions; that is, sulfides can be selectively activated as leaving groups by their alkylation. In accordance with these considerations, we took sulfides as the starting substances for the above mentioned fluorination reaction. In this letter we report a facile method for the fluorodesulfurization of sulfides using cesium fluoride under mild conditions.

$$\text{R-SR}' \xrightarrow{\text{R''X}} \text{X}^-[\text{R-S}^+(\text{R''})\text{R}'] \xrightarrow[-\text{MX}]{\text{MF}} \text{F}^-[\text{R-S}^+(\text{R''})\text{R}'] \longrightarrow \text{R-F} + \text{R'SR''} \qquad (2)$$

In the first place, benzyl methyl sulfide was employed as a model compound. Fluorination was performed by the alkylation with methyl fluorosulfonate followed by the addition of cesium fluoride in dichloromethane. After refluxing for 40 h, the expected product, benzyl fluoride, was obtained only in a 10% yield. Then, several sulfide groups to be displaced were examined (See Table 1). The yields varied with the substituent groups of the sulfides. As shown in Entries 2 and 3, phenylthio and *p*-chlorophenylthio groups are found to be satisfactory to attain high yields in the fluorodesulfurization reaction.

Table 1. Effect of Sulfide Groups on Fluorodesulfurization of Eq. 2, where, R = $PhCH_2$-, R"X = FSO_3Me, MF = CsF[a)]

Entry	R'S-	Time/h	Yield/%
1	methylthio-	40	10[b)]
2	phenylthio-	45	98[c)]
3	*p*-chlorophenylthio-	30	quant.[b)]
4	*p*-tolylthio-	37	31[b)]
5	2-pyridylthio	24	5[b)]

a) Reaction was carried out in refluxing CH_2Cl_2, where molar ratio of substrate : FSO_3Me : CsF = 1 : 2-3 : 3-5. b) Yield was determined by ^{19}F-NMR. c) Yield was determined by GLC.

Next, we examined other sulfonium generating reagents and fluoride sources in the same reaction of benzyl phenyl sulfide. Screening of these reagents, as summarized in Table 2, reveals that i) the methylation of sulfides with methyl fluorosulfonate was the most favorable (Entry 4 *vs.* Entries 1, 2, and 3), while the bromination gave a poor result (Entry 5); ii) as a fluoride source cesium fluoride gave the best result among the fluorides so far as examined (Entry 4 *vs.* Entries 6, 7, 8, and 9). Thus, the optimal reaction process was shown as Eq. 3.

$$\text{R-SPh} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{FSO}_3\text{Me}} [\text{R-S}^+\text{PhMe}]\text{FSO}_3^- \xrightarrow[\text{reflux}]{\text{CsF}} \text{R-F} \qquad (3)$$

It should be pointed out that the reaction was unsuccessful with 1,3-dibromo-5,5-dimethylhydantoin (DBH)-HF/Pyridine system, which was recently reported to be effective in the fluorodesulfurization of thioacetals,[6)] and orthothioesters.[7)]

Table 2. Effect of Sulfonium Generating Reagents and Fluorides on Fluorodesulfurization of Eq. 2, where R = $PhCH_2$, R' = Ph[a]

Entry	R"X	MF	Time/h	Yield/%
1	MeI	CsF	20	0[b]
2	Me_2SO_4	CsF	20	15[b]
3	$Et_3O^+BF_4^-$	CsF	24	42[b]
4	FSO_3Me	CsF	45	98[c]
5	DBH[d]	CsF	18	3[b]
6	FSO_3Me	KF	37	22[c]
7	FSO_3Me	CuF_2	37	0[c]
8	FSO_3Me	n-$Bu_4N^+F^-$	40	0[c]
9[e]	FSO_3Me	HF/Pyridine	21	5[c]

a) Reaction was carried out in refluxing CH_2Cl_2, where molar ratio of $PhCH_2SPh$: R"X : MF = 1 : 1-3 : 1-4. b) Yield was determined by ^{19}F-NMR. c) Yield was determined by GLC. d) 1,3-Dibromo-5,5-dimethylhydantoin. e) Reaction was carried out at room temperature.

Table 3. Fluorination of Sulfides[a]

Entry	Substrate	Time/h	Product	Yield/%[b]
1	$PhCH_2SPh$	45	$PhCH_2F$	80(98)[c]
2	p-Cl-$C_6H_4CH_2SPh$	40	p-Cl-$C_6H_4CH_2F$	91(quant.)[c]
3	1-NaphthylCH_2SPh	38	1-NaphthylCH_2F	50
4	$PhCH=CHCH_2SPh$	35	$PhCH=CHCH_2F$	52
5[d]	n-$C_8H_{17}SPh$	27	n-$C_8H_{17}F$	87[e]
6	p-$PhOCH_2$-$C_6H_4CH_2SPh$	32	p-$PhOCH_2$-$C_6H_4CH_2F$	57[f]
7	p-$BrCH_2$-$C_6H_4CH_2SPh$	39	p-$BrCH_2$-$C_6H_4CH_2F$	79[f]
8	$(CH_2)_4S$	25	$MeS(CH_2)_4F$	70
9	$(CH_2S)_2CHPh$	26	$PhCHF_2$	25[e]

a) Reaction was carried out according to Eq. 3, and molar ratio of substrate : FSO_3Me : CsF = 1 : 1-4 : 3-7. b) Isolated yield. All samples gave satisfactory ^{1}H- and ^{19}F-NMR spectra. c) Yield in parentheses was determined by GLC. d) In the presence of CsF (4.4 equiv.), an excess of FSO_3Me (2.6 equiv.) was added to the substrate and not removed.[8] e) Yield was determined by ^{19}F- NMR. f) No difluorinated products were detected.

The reactions of several other phenyl sulfides were examined as shown in Table 3. The substitution reaction with cesium fluoride proceeded enough even at a rather low temperature such as in refluxing dichloromethane, to afford fluorinated products in good yields. Furthermore, the reaction converted selectively the phenyl sulfides into the corresponding fluorides without affecting the coexisting

phenoxy and even bromine substituents (Entries 6 and 7). These reactivity and chemoselectivity may be attributed to the selective activation of sulfides and the sulfonium-fluoride ion-pair reaction in a less polar organic medium. When tetrahydrothiophene, a cyclic sulfide, was treated in a similar manner, ring opening occurred to give 4-methylthiobutyl fluoride (Entry 8), and from the thioacetal geminal difluorination took place though in a lower yield (Entry 9).

A typical reaction procedure is as follows: To a solution of *p*-chlorobenzyl phenyl sulfide (222 mg, 0.946 mmol) in dichloromethane (2 ml) was added methyl fluorosulfonate (326 mg, 2.86 mmol) at room temperature under an argon atmosphere. After stirring for 30 min, the mixture was evaporated off *in vacuo* to remove an excess of methyl fluorosulfonate. Then, dichloromethane (10 ml) and cesium fluoride (533 mg, 3.51 mmol) were added to the residue, and the reaction mixture was refluxed for 40 h and filtered. The filtrate was treated with *m*-chloroperbenzoic acid (533 mg, 3.09 mmol) for the easy isolation of the product, followed by chromatography on a silica-gel column (dichloromethane eluant) to give *p*-chlorobenzyl fluoride (124 mg, 91% yield).

In addition, this fluorination reaction is of great synthetic use when combined with organosulfur chemistry.[9] For example, preceded by phenylthiomethylation,[10] it affords a convenient two-step process for fluoromethylation.

$$\text{R-Br} \xrightarrow{\text{LiCH}_2\text{SPh}} \underset{88\%}{\text{R-CH}_2\text{SPh}} \xrightarrow[\text{CsF}]{\text{FSO}_3\text{Me}} \underset{87\%}{\text{R-CH}_2\text{F}} \quad (\text{R} = n\text{-C}_7\text{H}_{15}) \qquad (4)$$

In conclusion, this reaction provides a convenient method for fluorination by the substitution of phenylthio group, which is stable under various reaction conditions, and yet can be easily introduced into substrates in several ways.

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