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Synthesis of α-Fluorinated-α,α-diFunctionalized Sulfides and Sulfones

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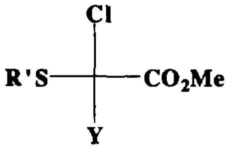
Abstract : *The highly functionalized organofluorine compounds* ***3a-c*** *were prepared from the activated dichlorinated sulfides* ***2a-c*** *by displacement of a chlorine atom using nucleophilic fluorination agents such as dihydrogenfluoride polymer-supported. Fluorination of sulfoxides* ***5a-c*** *with diethylaminosulfur trifluoride gives monofluoro sulfides* ***6a-c****, subsequently transformed into α-chloro-α-fluoro sulfides* ***3a-c*** *and sulfones* ***7a-c****.* Copyright © 1996 Elsevier Science Ltd

A fluorine atom is very often introduced to modify both the chemical reactivity or the physical and biological properties of organic compounds.[1-3] If the functionalized fluoro compounds are well known, only a few examples of compounds containing a carbon atom bearing a fluorine atom and two or three functional groups have been described.[4] Among these compounds, the α-fluorinated sulfides and sulfones have attracted attention[5] because the aryl- and alkylsulfonyl groups exert an electron withdrawing effect. These compounds are usually prepared from halo-fluorinated compounds by nucleophilic displacement of a chlorine or bromine atom by a thiolate anion.[6,7] A few studies of direct fluorination of sulfides by nucleophilic agents (F^-) have been published.

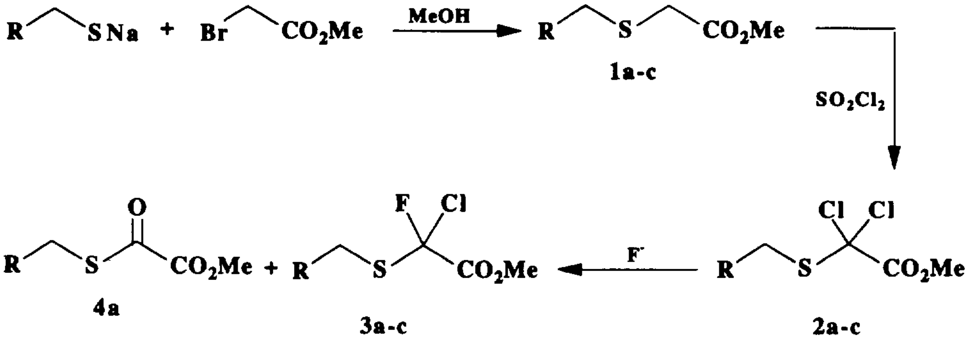
We report here a new route to produce with moderate to good yields α-fluorinated-α,α-difunctionalized sulfides by nucleophilic displacement of a chlorine atom of **2** by naked fluoride anion. The fluorination agents differ from the tetrabutylammonium dihydrogentrifluoride (TBADTF) recently used.[8]



$$R'S-\overset{\displaystyle Cl}{\underset{\displaystyle Y}{C}}-CO_2Me$$

2 : Y = Cl ; 3 : Y = F

Our initial attempts have been realized with dichloro thioethers **2a-c**, the fluorine atom being introduced at the end of the synthesis (Scheme 1). Halogensulfides **2a-c** were prepared in two steps[9] (73-90 % yields) : addition of thiolate on the methyl bromoacetate followed by treatment of thioethers **1a-c** with sulfuryl chloride.



a : R = Ph ; b : R = CH_3 ; c : R = CO_2Me

Scheme 1

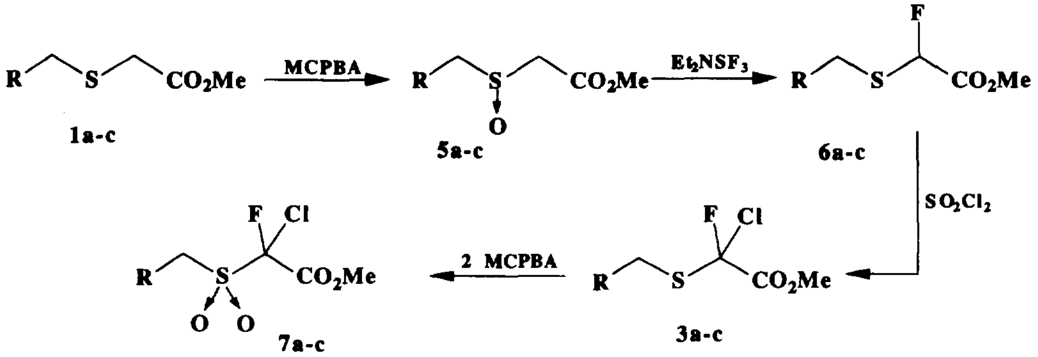
Several fluorination agents have been tested with **2a** (R = Ph). When fluorination agent was potassium hydrogenfluoride (KHF_2) or tetrabutylammoniumfluoride (TBAF), we exclusively obtained the ketone **4a** from **2a**, very sensitive to hydrolysis, whatever experimental precautions used.[10] Treatment of **2a** with potassium fluoride (KF)[11] and 18-Crown-6 gave **3a** in addition to the hydrolysis product **4a**. The highest percentages of expected product **3a** were obtained with dihydrogentrifluoride polymer-supported ($P^+H_2F_3^-$)[12] (Table 1). This later reacted with sulfides **2b** (R = CH_3) and **2c** (R = CO_2Me) to yield **3b** and **3c** in more than 70 %, and hydrolysis products **4b,c** are never observed.[13]

Table 1. Ratio[a] of the different compounds in the reaction mixture.

Reagents	Dichlorosulfides	**2a-c** (%)	**3a-c** (%)	**4a-c** (%)
KHF_2[b]	**2a**	0	0	100
TBAF[b]	**2a**	0	0	100
KF[c]	**2a**	11	32	57
$P^+H_2F_3^-$ [d]	**2a**	46	42	12
$P^+H_2F_3^-$ [d]	**2b**	30	70	0
$P^+H_2F_3^-$ [d]	**2c**	25	75	0

[a] % estimated by ^1H NMR [b] in MeCN, room temperature [c] in MeCN, reflux [d] in CCl_4, reflux.

A complete conversion of **1** into α-fluorinated sulfides **3** or **6** can be achieved via the sulfoxides **5a-c** using Pummerer type fluorination with diethylaminosulfur trifluoride (DAST). Antimony (III) chloride ($SbCl_3$)[14] was prefered as catalyst to zinc (II) iodide (ZnI_2)[5b], the reaction being cleaner, more reproducible and rapid (Scheme 2). Thus sulfoxides **5a-c** quantitatively led to α-fluorothioethers **6a-c**.[15]



a : R = Ph ; **b** : R = CH_3 ; **c** : R = CO_2Me

Scheme 2

The structure of new compounds **6a-c** were assigned on spectroscopic data ; chemical shifts in ^{13}C NMR and ^{19}F NMR are presented in Table 2.

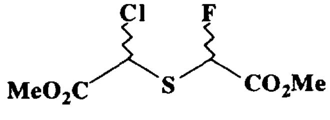
Table 2. Chemical shifts in ^{13}C and ^{19}F of sulfides **3** and **6**

Compounds	3a	3b	3c	6a	6b [a]	6c
δ_F (ppm)[b]	- 86.8	- 84.8	- 88.4	- 165.3	- 162.8	- 166.7
J_{HF} (Hz)	—	—	—	52.4	52.1	50.9
δ_C (ppm)[c]	109	109.5	108	91.1	92.2	90.6
J_{CF} (Hz)	258	286	272	226	225	228

[a] ref(7) : δ_F = - 162.8 ppm ; J_{HF} = 52 Hz ; J_{CF} = 229 Hz ; δ_{CF} = 92.3 ppm

[b] ref = $CFCl_3$, solvent = $CDCl_3$ [c] ref = TMS, solvent = $CDCl_3$.

The chlorination of **6a,b** by sulfuryl chloride only produced the thioethers **3a,b** ; with **6c** we observed a mixture of the thioether **3c** and the products of α' chlorination **3c'**. Fluorinated thioethers **3a-c** were characterized by chemical shifts ^{19}F ($\delta_F \approx$ - 86 ppm) and ^{13}C ($\delta_C \approx$ 109 ppm). Sulfides **3a-c** were decomposed during the purification attempts[16] ; consequently they were transformed into the corresponding sulfones which were isolated after column chromatography with 67 % (**7a**) and 45 % (**7b**) yields from **5a-b**.



3c'

^{19}F NMR Data of Diastereoisomers **3c'**

δ_F (ppm)	-166.6	-165.1
J_{HF} (Hz)	51	53

In summary, dihydrogentrifluoride polymer-supported ($P^+H_2F_3^-$) produced direct conversion of dichlorinated derivatives **2** into fluorinated chlorinated thioethers **3**. Di and trifunctional thioethers **6a-c** and **3a-c**, synthons of high synthetic potentiality, were synthesized via Pummerer type fluorination of **5a-c** with diethylaminosulfur trifluoride. We are currently investigating the reactivity of these compounds.

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13 Typical experiment procedure for fluoration of **2a-c** with $P^+H_2F_3^-$
To a solution of **2a-c** (1.8mmol) in CCl_4 (6ml) under nitrogen was added $P^+H_2F_3^-$ (3.6mmol). After stirring at 60°C for 24 hrs (**2a**) or 5 days (**2b,c**), the reaction mixture was cooled to room temperature, the resin was filtered and washed with CCl_4. The combined organic layers were dried, the solvent removed to give **3a-c**.

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15 General procedure for conversion of sulfoxides **5a-c** to α-fluoro thioethers **6a-c**
To a solution of **5a-c** (9mmol) and $SbCl_3$ (4.6mmol) in anhydrous $CHCl_3$ (16ml) was added dropwise at 4°C under nitrogen 15.8mmol of DAST. After 15 min, the ice bath was removed and the mixture stirred at room temperature for two and three days. The resulting mixture was poured into saturated $NaHCO_3$. The mixture was extracted with $CHCl_3$ and the combined organic phases were washed with $NaHCO_3/H_2O$, H_2O, $NaCl/H_2O$, dried and the solvent removed to give **6a-c**.

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