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Monofluorination of α-Dichlorosulfides : A Short Access to α-Fluoro Polyfunctionalised Thioethers

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Abstract : α-Chlorinated-α-fluorinated thioethers were synthesized in good yields by nucleophilic fluorination of their corresponding dichlorinated thioethers. A complete conversion of dihalosulfides **2** into α-fluoro-α-chlorosulfides **3** was achieved with $Et_3N.3HF$ in refluxing acetonitrile.

INTRODUCTION

Fluoroorganic compounds are today of particular interest to the organic chemist.[1] The introduction of a fluorine atom very often enhances the biological properties of active molecules.[2] Examples of compounds bearing a trifluoromethyl or a gem-difluoromethylene group are numerous. There are, however, fewer examples of molecules containing only one fluorine.

Fluorine as an isostere of hydrogen is equivalent to the hydroxyl group in terms of its electronic effects in that it strongly modifies the electron density of the molecule. The ability of fluorine to act as an oxygen surrogate and hydrogen bond acceptor has been widely discussed.[3]

Fluorinated sulfur compounds often serve as useful intermediates for the synthesis of the active component of drugs[4] and so the monofluorination of thioethers and their oxidized analogues (sulfoxides and sulfones) has become of great importance. Nevertheless, owing to their relative instability, the extraction of fluorothioethers from the reaction mixture in which they are formed is a delicate process.[5,6]

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The synthesis of α-fluoro sulfides from sulfoxides was reported by J. R. McCarthy[7] and we have similarly developed the fluorination of thioethers to give particularly interesting synthons bearing a tetrafunctionalised carbon atom.[8] We described here in the results of a new methodology applicable to α-chlorinated thioethers bearing, amongst other groups, a carbonyl, ester or nitrile α- to the sulfur.

In principle, two approaches can be imagined which could lead to α-fluorinated sulfides. The first consists of using synthons which already contain fluorine, Y. Takeuchi *et al*[9] synthesized α-bromo-α-fluoro thioethers from ethyl bromofluoroacetate in this manner.

The second method consists of the direct introduction of a fluorine atom into the thioether using an electrophilic or nucleophilic fluorinating agent, T. Umemoto *et al.* synthesized a series of fluorinated sulfides by substituting a hydrogen atom α- to the sulfur using different N-fluoropyridinium salts.[6] This method gave only moderate yields of purified product and in addition the electrophilic fluorinating agents used are costly.

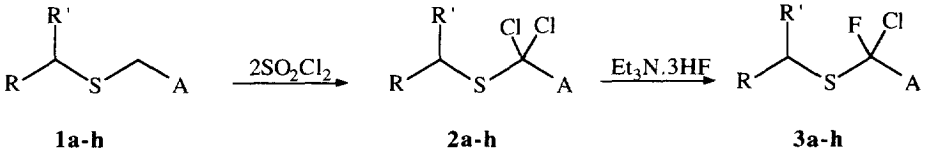
Methods which use a fluoride ion as the nucleophilic fluorinating agent consist of two types. The first replaces a hydrogen by a fluorine atom : this supposedly involves the attack of a fluoride ion on a sulfenium intermediate obtained either chemically from the corresponding sulfoxide,[7,10] or by oxidation of the sulfur, electrochemically[11] or not,[12] in the presence of the fluorinating agent. The second type consists in nucleophilic substitution of a mesylate or a halogen (chlorine or bromine) by a fluoride ion. The most frequently used reagent in this case is potassium fluoride in the presence of 18-crown-ether-6,[13] but substitution can equally be accomplished by dihydrogentrifluoride polymer-supported ($P^+H_2F_3^-$) reagent, developed by J. Cousseau.[14]

We have recently described the monofluorination of thioethers by the reaction of potassium fluoride on the corresponding α-dichlorosulfides, or by diethylaminosulfur trifluoride (DAST) on sulfoxides,[8] however these reactions require rigorously anhydrous conditions since both reagents and substrates (dichlorosulfides) are very sensitive to traces of acid or moisture.

We have now, therefore, developed new conditions which allow the synthesis of activated α-chloro-α-fluoro sulfides in good isolated yields, the fluorinating nucleophile being non-toxic and inexpensive : commercial triethylamine trihydrofluoride ($Et_3N.3HF$).

RESULTS AND DISCUSSION

The synthesis of the α-dichlorosulfides **2a-h**, previously described,[15] can be achieved in two high yielding steps : first step, reaction of a thiolate on an activated alkyl chloride or bromide (A = CO_2Me, COR", CN) leading to thioethers **1a-h**, which were then chlorinated in the second step with two equivalents of sulfuryl chloride (Scheme 1).



1a-h **2a-h** **3a-h**

A = CO_2Me, COMe, COPh, CN

Scheme 1

Initial fluorination attempts were carried out with $Et_3N.2HF$ under conditions previously employed by D. Picq et al.[16] for substituting a mesylate group by a fluoride ion. McClinton has described in a recent report that the relative strengths of this type of reagent for fluorination decrease in the following order : $Et_3N.2HF > Et_3N.3HF > Et_3N.HF$.[17]

Contrary to these conclusions, we found that for the α-dichlorosulfides **2a-h**, $Et_3N.3HF$ was a much more efficient reagent than $Et_3N.2HF$. In fact, the latter gives no trace of the expected fluoro compound **3** ; whatever the molar excess of reagent or the experimental conditions used, only partial degradation of the starting material **2** was observed. Initial experiments with **2a** and $Et_3N.3HF$ in acetonitrile showed clear exchange of chlorine by fluorine, even at room temperature. Thioether **2a** was entirely transformed into fluorothioether **3a** in the presence of 12 equivalents of $Et_3N.3HF$ over 17 hours and **3a** was isolated after purification by Kügelrohr distillation in 67% yield. The reaction was then shown to be general, other activated dichlorothioethers **2b-f**, were transformed to **3b-f** under the same conditions in less than 17 hours. Only the cyano derivative **2g** is recovered unchanged after a day. The isolated yields of the fluorothioethers **3a-f** after purification are given in Table 1 (yields : 46-78%).

Table 1. Preparation of α-chloro-α-fluorothioethers **3a-f** by treatment of **2a-f** with 12 eq. of $Et_3N.3HF$ at room temperature.

substrat **2**	R	R'	A	T°C	t (h)	yields (%) **3**
a	Ph	H	CO_2Me	25	17	67
b	CH_3	H	CO_2Me	25	15	78
c	CO_2Me	H	CO_2Me	25	15	56
d	Ph	H	$COCH_3$	25	15	46,5
e	CH_3	H	COPh	25	15	67
f	CH_3	CH_3	COPh	25	15	54,5
g	Ph	H	CN	25	24	(a)

(a) The thioether **2g** was recovered unchanged after 24 hours at 25°C.

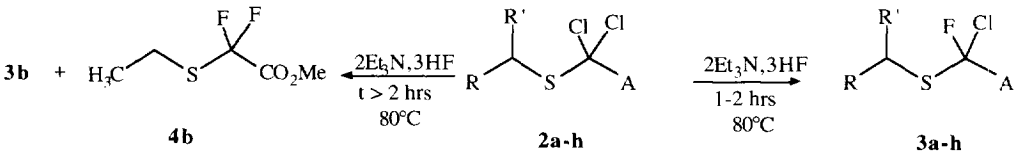
These results followed similar observations made on the substitution of a chlorine atom by a fluorine in a series of aryl trichloromethylsulfides using the same fluorinating reagent.[18]

We then sought to optimise the experimental conditions by varying both the reaction temperature and also the proportion of $Et_3N.3HF$ relative to the thioethers **2** introduced initially in acetonitrile. The most striking results are shown in Table 2.

Table 2. Preparation of α-chloro-α-fluoro thioethers **3a-h** by treatment of **2a-h** with $Et_3N.3HF$ at 80°C.

substrat **2**	R	R'	A	No. eq.	t (h)	yields (%) **3**
a	Ph	H	CO_2Me	2	2	77,5
b	CH_3	H	CO_2Me	2	1	70
d	Ph	H	$COCH_3$	2	1	65
e	CH_3	H	COPh	2	1	70
f	CH_3	CH_3	COPh	2	1	57
g	Ph	H	CN	8	36	50
h	CH_3	CH_3	CO_2Me	2	1	57

A reduction in the amount of reagent used can be compensated by an enhancement of the reaction temperature : the conversion of sulfide **2a** into monofluorinated thioether **3a** was complete in 2 hours in refluxing acetonitrile with 2 equivalents of $Et_3N.3HF$, and the conversion of sulfides **2b-g** was carried out in one hour under the same conditions (Table 2).



A = CO_2Me, COMe, COPh, CN

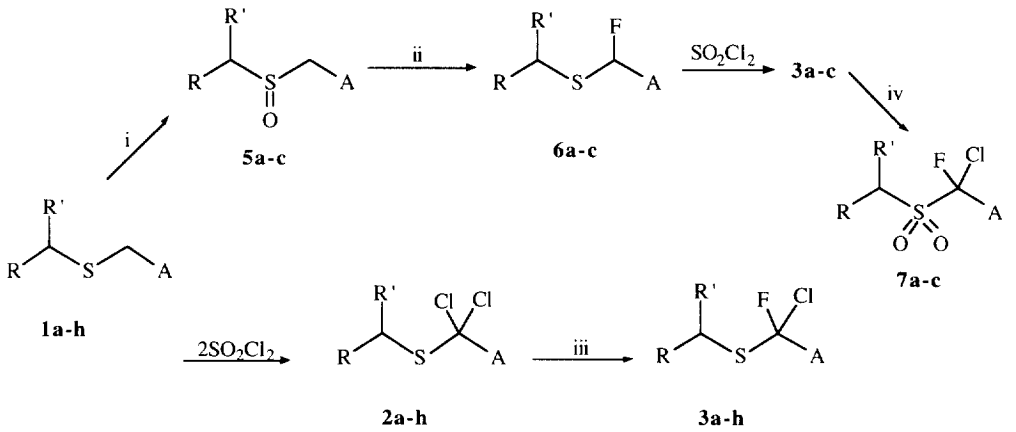
Scheme 2

It should be noted that at 80°C an increase in the reaction time can lead to the substitution of both chlorine atoms. For example, after seventy minutes, we obtained a mixture of difluorinated derivative **4b** (10%) and monofluorinated thioether **3b** (90%). In addition **2b** was partly converted (less than 50%) into the fluorinated derivative **4b** when five equivalents of $Et_3N.3HF$ were used in refluxing acetonitrile for 48 hours. Interestingly only the monofluorinated compound was present after one hour (Scheme 2).

The reaction of monofluorination of dichlorosulfides **2a,b,d-f,h**, when carried out under the optimal conditions described here (2 eq. of $Et_3N.3HF$, 80°C) gives comparable yields with those initially obtained with 12 equivalents of reagent at 25°C (Table 1 and Table 2), which demonstrates the reliability of this reaction. Furthermore, the cyano dichlorosulfide **2g** was converted to the α-chloro-α-fluoro

cyanosulfide **3g** when subjected to 8 equivalents of $Et_3N.3HF$ (Table 2), thus confirming that the speed of the reaction that substitutes a chloride by a fluoride ion is much slower when the activating group, carbonyl or ester, is replaced by a nitrile.

In our preliminary article,[8] we synthesized α-chloro-α-fluoro thioethers **3a-c** using DAST as the fluorinating agent. This required the conversion of sulfides **1a-c** into sulfoxides **5a-c**, the replacement of hydrogen by fluorine, followed in the third step by the chlorination of the monofluorinated sulfides **6a-c** (Scheme 3). Attempts to fluorinate the monochloro sulfoxides, obtained from the sulfides **1a-c**, with DAST proved negative.



i : MCPBA ; ii : DAST, $SbCl_3$; iii : $Et_3N.3HF$; iv : MCPBA

Scheme 3

The use of $Et_3N.3HF$ appears to be a superior method since it allows direct fluorination of dichloro sulfides **2a-c** in very satisfactory yields. Furthermore, the reagent $Et_3N.3HF$ is less expensive than DAST, and requires nearly equivalent proportions to the substrate. It also makes for easier extraction of the isolated product as a sulfide rather than as the sulfones **7a-c** (Scheme 3). The fluoro sulfides **3a-h** are relatively unstable and must be stored in a freezer.

In conclusion, starting from sulfide **1**, the desired polyfunctionalised fluorosulfur compound can be isolated in four steps when DAST is used, while only two steps are required when $Et_3N.3HF$ is employed as the fluorinating agent, and yields were as good if not superior.

ACKNOWLEDGEMENT

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EXPERIMENTAL SECTION

Drying of organic layers during the work up was performed over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotary evaporator. ^1H NMR were recorded at 250 MHz and ^{13}C NMR at 62 MHz on a *Brucker AC-250 MHz* instrument using TMS as reference ; ^{19}F NMR were recorded at 75.3 MHz on a *Brucker WP-80 MHz* instrument using fluorotrichloromethane as reference. IR spectra were recorded on a *Perkin -Elmer 16 PC FT-IR* spectrometer and peaks are given in cm^{-1}. Mass spectra were performed on a *Nermag Riber R10*. All solvents were purified by strandard methods.
Sulfides **1a-h** were prepared by the usual procedure.[19]

Methyl 2-(benzylthio)-2,2-dichloroacetate (2a)[19]
To a solution of sulfide **1a** (2 g, 10.2 mmol) in dichloromethane (10 ml) was added dropwise a solution of sulfuryl chloride (1.63 ml, 20.4 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for two hours. After completion the reaction mixture was concentrated and the product was distilled. Yield : 2.6 g (96.5%) ; bp 98°C/0.02 Torr.
^1H NMR ($CDCl_3$) : δ = 3.85 (s, 3H) ; 4.25 (s, 2H) ; 7.35 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 38.8 (CH_2Ph) ; 55.1 (OCH_3) ; 87 (CCl_2) ; 128-128.9-129.6 (aromatic-5C) ; 134.2 (aromatic-$C_{quater.}$) ; 164.5 (CO). MS : m/z (%) = 266 ($M^{+\cdot}$, 0.03) ; 264 ($M^{+\cdot}$, 0.05) ; 123 (6.53) ; 91 (6.4) ; 65 (25.3) ; 59 (22.8) ; 51 (26.9) ; 45 (100). IR (NaCl) : ν = 3086, 3064, 3030, 2956, 2844, 1752, 1496, 1454, 1434, 1246, 1006, 832, 798, 750, 704. Anal. Calcd. for $C_{10}H_{10}O_2Cl_2S$: C, 45.46 ; H, 3.82 ; S, 12.11. Found : C, 45.16 ; H, 3.77 ; S, 12.00.

Methyl 2,2-dichloro-2-(ethylthio)acetate (2b)
To a solution of thioether **1b** (4 g, 29.8 mmol) was added a solution of sulfuryl chloride (4.75 ml, 59.6 mmol) in dichloromethane. The product was distilled *in vacuo*. Yield : 5.33 g (88.5%) ; bp 40°C/0.06 Torr.
^1H NMR ($CDCl_3$) : δ = 1.36 (t, 3H, *J* = 7.5 Hz) ; 3.07 (qd, 2H) ; 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ = 12.9 (CH_3CH_2) ; 28,1 (CH_2) ; 55.1 (CH_3O) ; 87.6 (CCl_2) ; 164.7 (CO). MS : m/z (%) = 204 ($M^{+\cdot}$, 2.80) ; 202 ($M^{+\cdot}$, 3.5) ; 167 (10.7) ; 143 (10.1) ; 142 (8.4) ; 115 (10.1) ; 103 (21.9) ; 79 (100) ; 59 (67.4) ; 45 (21.5). IR (NaCl) : ν = 2974, 2958, 2934, 1752, 1436, 1380, 1244, 1056, 1004, 838, 814, 750.

Methyl 2,2-dichloro-2-(methoxycarbonylmethylthio)acetate (2c)
To a solution of thioether **1c** (2 g, 11.3 mmol) was added a solution of sulfuryl chloride (1.8 ml, 22.6 mmol)in dichloromethane. The product was distilled in vacuo. Yield : 2.26 g (81.5%) ; bp 95°C/0.06 Torr.
^1H NMR ($CDCl_3$) : δ = 3.78 (s, 3H, CH_3OCOCH_2) ; 3.84 (s, 2H) ; 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ = 36.2 (CH_2S) ; 53 (CH_3OCOCH_2) ; 55.3 (CH_3O) ; 86.4 (CCl_2) ; 164.2 (CO) ; 168.5 (CO). MS : m/z (%) = 250 ($M^{+\cdot}$, 3.8) ; 248 ($M^{+\cdot}$, 19) ; 246 ($M^{+\cdot}$, 28) ; 213-211 (10.7-26.4) ; 191-189-187 (12.5-65-100) ; 146-144-142 (3.7-20.8-29.8) ; 137 (33.8) ; 105 (39.5) ; 88 (55) ; 79 (99.4) ; 74 (81.6) ; 59 (92.6) ; 45 (35.2). IR (NaCl) : ν = 3006, 2956, 2846, 1744, 1436, 1302, 1252, 1198, 1158, 1006, 838, 816. Anal. Calcd. for $C_6H_8O_4Cl_2S$: S, 13.0. Found : S, 13.40.

1-(Benzylthio)-1,1-Dichloroacetone (2d)
To a solution of sulfide **1d** (2 g, 11.1 mmol) was added a solution of sulfuryl chloride (1.77 ml, 22.2 mmol). The product was distilled under reduced pressure. Yield : 2 g (72.5%) ; bp 91°C/0.03 Torr.

^1H NMR ($CDCl_3$) : δ = 2.53 (s, 3H) ; 4.1 (s, 2H) ; 7.32 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 22.9 (**CH_3**) ; 38.2 (**CH_2**) ; 93.4 (**CCl_2**) ; 128-128.9-129.6 (aromatic-5C) ; 134.2 (aromatic-$C_{quater.}$) ; 191.9 (**CO**). MS : m/z (%) = 248 ($M^{+\cdot}$, 0.12) ; 123 (9.2) ; 105 (7.2) ; 91 (100) ; 77 (6.6) ; 65 (7.7) ; 51 (4.8) ; 43 (67.3). IR (NaCl) : ν = 3086, 3064, 3030, 2932, 1732, 1496, 1454, 1356, 1172, 798, 772, 704. Anal. Calcd. for $C_{10}H_{10}OCl_2S$: S, 12.89. Found : S, 13.05.

2,2-Dichloro-2-(ethylthio)-1-phenylethanone (2e)

To a solution of thioether **1e** (2 g, 11.1 mmol) was added a solution of sulfuryl chloride (1.77 ml, 22.2 mmol) in dichloromethane. The product was distilled under reduced pressure. Yield : 2.25 g (81.5%) ; bp 90°C/0.04 Torr.

^1H NMR ($CDCl_3$) : δ = 1.37 (t, 3H, *J* = 7.5 Hz) ; 3.08 (qd, 2H) ; 7.47 (m, aromatic-2$H_{méta}$) ; 7.60 (m, aromatic-H_{para}) ; 8.29 (m, aromatic-2H_{ortho}). ^{13}C NMR ($CDCl_3$) : δ = 12.9 (**CH_3CH_2**) ; 27.7 (**CH_2CH_3**) ; 93.4 (**CCl_2**) ; 128.3-130.9-133.9 (aromatic-6C) ; 185.4 (**CO**). Anal. Calcd. for $C_{10}H_{10}OCl_2S$: S, 12.89. Found : S, 12.64.

2,2-Dichloro-2-(isopropylthio)-1-phenylethanone (2f)

To a solution of sulfide **1f** (2 g, 10.3 mmol) was added a solution of sulfuryl chloride (1.65 ml, 20.6 mmol). The product was distilled under reduce pressure. Yield : 2.40 g (89%) ; bp 91°C/ 0.03 Torr.

^1H NMR ($CDCl_3$) : δ = 1.43 (d, 6H, *J* = 6.9 Hz) ; 3.6 (sept, 1H) ; 7.46 (m, aromatic-2$H_{méta}$) ; 7.59 (m, aromatic-H_{para}) ; 8.29 (m, aromatic-2H_{ortho}). ^{13}C NMR ($CDCl_3$) : δ = 24 ((**CH_3**)$_2$CH) ; 40.2 (**CHS**) ; 93.4 (**CCl_2**) ; 128.2-131.4-133.8 (aromatic-5C) ; 135.3 (aromatic-$C_{quater.}$) ; 185.3 (**CO**). MS : m/z (%) = 262 ($M^{+\cdot}$, 0.12) ; 105 (100) ; 77 (16.8) ; 51 (6.8) ; 43 (6) ; 41 (9.4). IR (NaCl) : ν = 2966, 2926, 2866, 1702, 1596, 1578, 1448, 1222, 1186, 854, 688. Anal. Calcd. for $C_{11}H_{12}OCl_2S$: S, 12.0. Found : S, 12.36.

2-(Benzylthio)-2,2-dichloroacetonitril (2g)

To a solution of thioether **1g** (4.23 g, 25.9 mmol) was added a solution of sulfuryl chloride (4.14 ml, 51.9 mmol) in dichloromethane. The product was distilled under reduced pressure. Yield : 5.54 g (92.5%) ; bp 72°C/0.02 Torr.

^1H NMR ($CDCl_3$) : δ = 4.31 (s, 2H) ; 7.37 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 40.5 (**CH_2S**) ; 68.7 (**CCl_2**) ; 113.9 (**CN**) ; 128.7-129.2-129.8 (aromatic-5C) ; 132.3 (aromatic-$C_{quater.}$). MS : m/z (%) = 235 ($M^{+\cdot}$, 0.5) ; 233 ($M^{+\cdot}$, 2.6) ; 231 ($M^{+\cdot}$, 3.8) ; 123 (2.5) ; 91 (100) ; 45 (13.7). IR (NaCl) : ν = 3088, 3064, 3032, 2238, 1496, 1456, 1244, 1072, 1022, 796, 752, 696.Anal. Calcd. for $C_9H_7SCl_2N$: C, 46.76 ; H, 3.05 ; N, 6.06 ; S, 13.84. Found : C, 46.17 ; H, 3.03 ; N, 5.80 ; S, 13.91.

Methyl 2,2-Dichloro-2-(isopropylthio)acetate (2h)[19]

To a solution of sulfide **1h** (2.51 g, 16.9 mmol) was added a solution of sulfuryl chloride (2.72 ml, 33.8 mmol) in dichloromethane. The product was distilled under reduced pressure. Yield : 2.97 g (81%) ; bp 36°C/0.02 Torr.

^1H NMR ($CDCl_3$) : δ = 1.43 (d, 6H, *J* = 7 Hz) ; 3.57 (sept., 1H) ; 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ = 23.9 ((**CH_3**)$_2$CH) ; 40 (**CH**) ; 55.2 (**OCH_3**) ; 87.5 (**CCl_2**) ; 164.9 (**CO**). IR (NaCl) : ν = 2958, 2928, 2868, 1752, 1436, 1244, 1006, 750.

Methyl 2-(benzylthio)-2-chloro-2-fluoroacetate (3a)

To a solution of **2a** (1.61 g, 6.1 mmol) in MeCN was added dropwise $Et_3N.3HF$ (1.98 ml, 12.2 mmol). This was stirred at reflux under nitrogen for 2 hours. After cooling to room temperature, the mixture was poured into a saturated aqueous sodium bicarbonate solution and diluted with CH_2Cl_2/Et_2O. The organic layers were washed with water, dried and concentrated. The remaining residue was distilled with a Kügelrohr apparatus. Yield : 1.17 g (77.5%) ; bp 75°C/0.02 Torr

^{19}F NMR ($CDCl_3$) : δ = -86.8 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 3.8 (s, 3H) ; 4.10 and 4.16 (syst. AB, J_{AB} = 12.8 Hz, 2H) ; 7.33 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 35.8 (CH_2Ph) ; 54.4 (CH_3O) ; 109 (d, J_{CF} = 258 Hz, CClF) ; 127.9-128.7-129.4 (aromatic-5C) ; 134.8 (aromatic-$C_{quater.}$) ; 163.8 (CO). MS : m/z (%) = 250 ($M^{+\cdot}$, 1.44) ; 248 ($M^{+\cdot}$, 2.9) ; 229 (1.92) ; 123 (87.5) ; 91 (100) ; 65 (35.9) ; 63 (49.2) ; 59 (68.3) ; 45 (18.9). IR (NaCl) : ν = 3088, 3064, 3062, 2956, 1760, 1496, 1456, 1436, 1268, 990, 700. HRMS for $C_{10}H_{10}O_2SClF$: calcd. 248.0074, found 248.0060. Anal. Calcd. for $C_{10}H_{10}O_2SClF$ (248.00) : S, 12.89. Found S, 12.80.

Methyl 2-chloro-2-(ethylthio)-2-fluoroacetate (3b)

To a solution of **2b** (1.2 g, 5.94 mmol) in MeCN was added $Et_3N.3HF$ (1.93 ml, 11.9 mmol). This was stirred at reflux under nitrogen for 1 hour. The product was distilled with a Kügelrohr apparatus. Yield : 778 mg (70%) ; bp 30°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) : δ = -84.8 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 1.36 (t, J = 7.5 Hz, 3H) ; 2.96 (m, 2H) ; 3.94 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ = 14.3 (CH_3CH_2) ; 25.7 (CH_2) ; 54.5 (CH_3O) ; 109.5 (d, J_{CF} = 286 Hz, CClF) ; 164.1 (d, J_{CF} = 30 Hz, CO). MS : m/z (%) = 186 ($M^{+\cdot}$, 100) ; 151 (63.5) ; 150 (38.3) ; 123 (20.6) ; 60 (18.7) ; 47 (13). IR (NaCl) : ν = 2960, 2936, 2876, 1762, 1456, 1438, 1264, 1070, 1022, 876, 778, 752, 688. Anal. Calcd. for $C_5H_8O_2SClF$ (185.99) : C, 32.26 ; H, 4.33 ; S, 17.19. Found C, 32.19 ; H, 4.35 ; S, 17.15.

Methyl 2-chloro-2-fluoro-2-(methoxycarbonylmethylthio)acetate (3c)

To a solution of **2c** (0.89 g, 3.65 mmol) in MeCN was added $Et_3N.3HF$ (7.1 ml, 43.8 mmol). This was stirred at room temperature for 15 hours. This product was distilled with a Kügelrohr apparatus. Yield : 472 mg (56%) ; bp 85°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) : δ = -88.4 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 3.76 (s, 3H, CH_3OCOCH_2) ; 3.83 (s, 2H, CH_2) ; 3.94 (S, 3H, CH_3O). ^{13}C NMR ($CDCl_3$) : δ = 41.3 ($\mathbf{C}H_2$) ; 52.9 ($\mathbf{C}H_3OCOCFCl$) ; 54.7 ($\mathbf{C}H_3O$) ; 108.2 (d, J_{CF} = 288.7 Hz, CFCl) ; 166.5 and 168.6 (**C**O). MS : m/z (%) = 232 ($M^{+\cdot}$, 5.4) ; 230 ($M^{+\cdot}$, 16.6) ; 213-211 (3.3-6.3) ; 200-198 (6.7-16.4) ; 173-171 (5.1-14.7) ; 127-125 (14.5-13.3) ; 105 (100) ; 59 (15.6) ; 45 (10.9). IR (NaCl) : ν = 2958, 1744, 1436, 1302, 1198, 1162, 1010, 908, 804. Anal. Calcd. for $C_6H_8O_4SFCl$ (229,98) : C, 31.31 ; H, 3.51 ; S, 13.9. Found C, 30.61 ; H, 3.58 ; S, 14.56.

1-(Benzylthio)-1-chloro-1-fluoroacetone (3d)

To a solution of **2d** (357 mg, 1.44 mmol) in MeCN was added dropwise $Et_3N.3HF$ (467 µl, 2.88 mmol). This product was distilled with a Kügelrohr apparatus. Yield : 218 mg (65%) ; bp 70°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) : δ = -90.8 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 2.39 (d, J_{HF} = 2.1 Hz, 3H) ; 4.03 and 4.09 (syst. AB, J_{AB} = 12.6 Hz, 2H) ; 7.31 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 23.3 (CH_3) ; 33 (CH_2) ; 113.1 (d, J_{CF} = 291.3 Hz, CFCl) ; 128-129.1-129.4 (aromatic-5C) ; 134.9 (aromatic-$C_{quater.}$) ;

193.7 (d, J_{CF} = 26.6 Hz, CO). MS : m/z (%) = 234 ($M^{+\cdot}$, 0.9) ; 232 ($M^{+\cdot}$, 2.6) ; 123 (43.7) ; 91 (100) ; 77 (42.7) ; 65 (16.9) ; 51 (13.6) ; 43 (64.8). IR (NaCl) : ν = 3064, 3030, 2934, 1724, 1496, 1454, 1358, 1072, 892, 702. HRMS for $C_{10}H_{10}OSClF$: calcd. 232.0125, found 232.0083. Anal. Calcd. for $C_{10}H_{10}OSClF$ (232.01) : C, 51.72 ; H, 4.34 ; S, 13.79. Found C, 52.0 ; H, 4.41 ; S, 13.59.

2-Chloro-2-(ethylthio)-2-fluoro-1-phenylethanone (3e)

To a solution de **2e** (150 mg, 0.6 mmol) in MeCN was added $Et_3N.3HF$ (196 µl, 1.2 mmol). The remaining residue was distilled with Kügelrohr. Yield : 98 mg (70%) ; bp 70°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) : δ = -79.8 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 1.38 (t, J = 7.5 Hz, 3H) ; 3.01 (m, 2H) ; 7,48 (m, aromatic-$H_{méta}$) ; 7.63 (m, aromatic-H_{para}) ; 8.22 (m, aromatic-H_{ortho}). ^{13}C NMR ($CDCl_3$) : δ = 14.3 (CH_3) ; 25.5 (CH_2) ; 114.6 (d, J_{CF} = 288.7 Hz, CClF) ; 128.5-131 (aromatic-5C) ; 134.7 (aromatic-$C_{quater.}$) ; 186.1 (CO). MS : m/z (%) = 234 ($M^{+\cdot}$, 0.16) ; 232 ($M^{+\cdot}$, 0.5) ; 172 (1.4) ; 105 (67.6) ; 77 (100) ; 51 (21.8). IR (NaCl) : ν = 3064, 2974, 2934, 1702, 1598, 1448, 1256, 1186, 1072, 1002, 874, 832, 690. Anal. Calcd. for $C_{10}H_{10}OSClF$ (232.01) : S, 13.79. Found S, 13.63.

2-Chloro-2-fluoro-2-(isopropylthio)-1-phenylethanone (3f)

To a solution of **2f** (150 mg, 0.57 mmol) in MeCN was added $Et_3N.3HF$ (185 µl, 1.14 mmol). After one hour in reflux, the residue was distilled with a Kügelrohr apparatus. Yield : 80 mg (57%) ; bp 60°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) : δ = -78,45 (s, 1F). ^1H NMR ($CDCl_3$) : δ = 1.38 (d, J = 6.8 Hz, 3H) ; 1.44 (d, J = 6.8 Hz, 3H) ; 3.57 (m, 1H) ; 7.48 (m, aromatic-$2H_{méta}$) ; 7.60 (m, aromatic-H_{para}) ; 8.22 (m, aromatic-$2H_{ortho}$). ^{13}C NMR ($CDCl_3$) : δ = 24.5 ($2CH_3$) ; 37.9 (CH) ; 115 (d, J_{CF} = 279 Hz, CFCl) ; 128.5-130.7 (aromatic-5C) ; 134.7 (aromatic-C_{quater}) ; 186.8 (CO). MS : m/z (%) = 248 ($M^{+\cdot}$, 0.2) ; 246 ($M^{+\cdot}$, 0.6) ; 210 (4.9) ; 172 (6) ; 156 (14.4) ; 105 (85.4) ; 77 (100) ; 51 (24.3) ; 43 (31.2). IR (NaCl) : ν = 3064, 2968, 2930, 2868, 1704, 1598, 1578, 1450, 1250, 1002, 986, 874, 688. Anal. Calcd. for $C_{11}H_{12}OSClF$ (246.03) : C, 53.65 ; H, 4.92 ; S, 12.99. Found C, 54.48 ; H, 5.06 ; S, 13.01.

2-(Benzylthio)-2-chloro-2-fluoroacetonitril (3g)

To a solution of **2g** (0.5 g, 2.2 mmol) in MeCN was added dropwise $Et_3N.3HF$ (2.8 ml, 17.6 mmol). The product was distilled with a Kügelrohr apparatus. Yield : 240 mg (50%) ; bp 65°C/0.04 Torr.

^{19}F NMR ($CDCl_3$) δ = -75.5 (s, 1F). ^1H NMR ($CDCl_3$) δ = 4.26 and 4.27 (syst.AB, 2H) ; 7.35 (m, aromatic-5H). ^{13}C NMR ($CDCl_3$) : δ = 38.2 (CH_2) ; 97.6 (d, CFCl, J_{CF} = 278.8 Hz) ; 112.6 (CN) ; 129.1-129.3-133.3 (aromatic-6C).

Methyl 2-chloro-2-fluoro-2-(isopropylthio)acetate (3h)

To a solution of **2h** (0.5 g, 2.3 mmol) in MeCN was added dropwise $Et_3N.3HF$ (0.75 ml, 4.6 mmol). The product was distilled with Kügelrohr. Yield : 264 mg (57%) ; bp 40°C/0.02 Torr.

^{19}F NMR ($CDCl_3$) δ = -83.3 (s, 1F). ^1H NMR ($CDCl_3$) δ = 1.37 (d, J = 6.9 Hz, 3H) ; 1.41 (d, J = 6.8 Hz, 3H) ; 3.50 (sept., 1H) ; 3.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ = 24-24.2 (CH_3) ; 37.8 (CH) ; 54.5 (OCH_3) ; 109.5 (d, J = 278.7 Hz, CFCl) ; 164.5 (d, J = 18.6 Hz, CO). MS : m/z (%) = 202 ($M^{+\cdot}$, 14.2) ; 200 ($M^{+\cdot}$, 30.1) ; 183 (7.6) ; 181 (19.3) ; 165 (67.4) ; 162 (100) ; 59 (21.3). IR (NaCl) ν = 2966, 2932,

2870, 1762, 1438, 1266, 1068, 1028, 870. Anal. Calcd. for $C_6H_{10}O_2SFCl$ (200.00) : C, 36.0 ; H, 5.04 . Found C, 36.9 ; H, 5.24.

Methyl 2,2-difluoro-2-(ethylthio)acetate (4b)

^{19}F NMR ($CDCl_3$) δ = -83.4 (s, F). ^1H NMR ($CDCl_3$) δ = 1.32 (t, J = 7.5 Hz, 3H) ; 2.9 (qd, 2H). ^{13}C NMR ($CDCl_3$) δ = 15.0 (CH_3) ; 23.4 (CH_2) ; 53.9 (OCH_3) ; 120.8 (t, $^1J_{CF}$ = 283.5 Hz, CF_2) ; 162.4 (t, $^2J_{CF}$ = 33 Hz, CO).

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