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SYNTHESIS OF β-FLUOROALKYL PHENYL (OR METHYL) THIOETHERS BY SULFUR-ASSISTED HALOGEN EXCHANGE WITH TRIETHYLAMINE TRIS-HYDROFLUORIDE

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SUMMARY

The exchange of chlorine in β-chloroalkyl phenyl (or methyl) thioethers by fluorine, with anchimeric assistance of sulfur, is very easily realized with the almost neutral fluorinating reagent, $Et_3N.3HF$. The 'one-pot' reactions of alkenes with sulfenyl chlorides and subsequently with $Et_3N.3HF$ lead to the corresponding β-fluoroalkyl thioethers in high yields.

INTRODUCTION

In a recent paper [1] we reported that the reaction of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) [2] and triethylamine tris-hydrofluoride ($ET_3N.3HF$) [3] with alkenes leads to β-fluoroalkyl methyl thioethers in high yields. The main disadvantage of this procedure is the relatively difficult preparation of DMTSF, which requires the use of trimethyloxonium tetrafluoroborate [$(CH_3)_3O^+BF_4^-$], which is rather unstable and expensive.

Another way to obtain β-fluoroalkyl phenyl thioethers was proposed by action of phenylsulfenyl chloride on an alkene in

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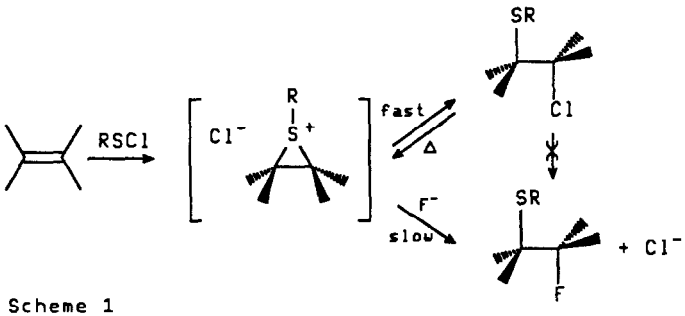
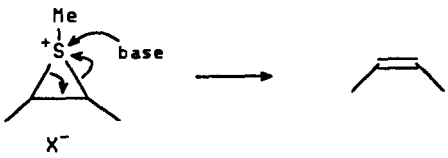
the presence of silver fluoride or mercury difluoride in acetonitrile [4].

We wish to report a new procedure leading to β-fluoroalkyl phenyl (or methyl) thioethers, using halogen exchange between a β-chloroalkyl thioether (easily prepared from an alkene and a sulfenyl chloride [5]) and a fluoride ion according to Scheme 1.



Scheme 1

The success of such an exchange reaction depends on the nucleophilicity of the fluoride ion employed and on whether the fluorination step is reversible or not. The basicity of the fluorinating agent also seems to be an important factor ; for instance, the use of potassium fluoride often leads to elimination instead of exchange of a halogen by fluorine [6]. Likewise, it has been shown [7,8] that an isolated episulfonium ion, which can be opened only with difficulty by cesium fluoride, gives an alkene by the action of some other reagents such as potassium fluoride, thiourea, triethyl-amine or tetramethylammonium iodide by way of direct attack on sulfur rather than on carbon (Scheme 2).



Scheme 2

On the other hand, other authors have reported that chlorine [4] or bromine [9] exchange by fluorine could be readily carried out by the action of silver fluoride on β-chloro (or bromo) thioethers.

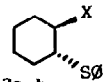
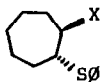
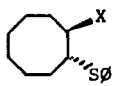
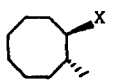
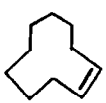
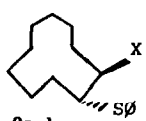
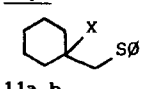
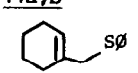
RESULTS AND DISCUSSION

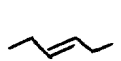
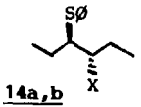
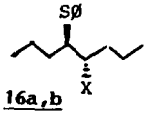
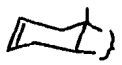
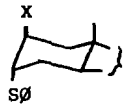
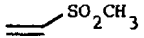
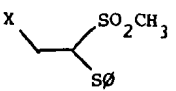
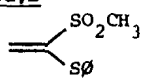
We have previously shown that triethylamine tris-hydrofluoride [3] can be a suitable source of fluoride ion in some reactions involving bromonium [10], aziridinium [11] or episulfonium [1] ions. This reagent can also be used as a fluorine source in electrochemical fluorination [12]. We therefore decided to use this same reagent for halogen exchange reactions because it is cheaper than silver fluoride, very stable (not very hygroscopic), and quite soluble in chlorinated solvents. Triethylamine tris-hydrofluoride is a weak nucleophile but it is not basic, in contrast to other classical fluorides (KF, KHF_2, $Bu_4N^+F^-$, $Et_4N^+F^-$), thus avoiding alkene re-formation (cf. Scheme 2). It is neither very acidic nor aggressive unlike Olah's reagent (pyridine, 9HF) which sometimes leads to side reactions because it favours the formation of carbocations [13]. Since addition of sulfenyl chlorides to alkenes was often carried out in chlorinated solvents [14, 15], we performed the exchange reaction in chloroform at 60°C without isolation of the intermediate β-chloroalkyl thioether obtained starting from alkenes. We report only one example of preparation of β-fluoroalkyl methyl thioether. Taking into account the instability of methanesulfenyl chloride [16], all other reactions were performed with the more stable phenylsulfenyl chloride [15] ; results are summarized in Table 1.

When we added sulfenyl chloride at room temperature to a chloroform solution of cyclooctene and triethylamine tris-hydrofluoride, we obtained only the chloro compound **6a** formed through an episulfonium ion intermediate [19] ; formation of coumpound **6a** proves the better nucleophilicity of chloride ion compared to fluoride one under the reaction conditions. This result is in agreement with the weak nucleophilicity of triethylamine tris-hydrofluoride as fluoride donnor [20]. Hea-

TABLE 1

Phenyl (methyl) thiofluorination of alkenes by halogen exchange reaction in $CHCl_3$ at 60°C

Alkene	Product(s)[A] **a** X = Cl **b** X = F	React. time (hrs)	Overall yield (%)	Fluorination[(A)] yield (%)	b.p. (°C)/torr	Unreacted[(A)] chloride (%)
 **1**	 **2a,b**	26	80	67	85-98 (0,3)	13
 **3**	 **4a,b**	3	96	89	90-105 (0,5)	7
 **5**	 **6a,b**	15	92	89	90-118 (0,3)	3
5	 **7a,b**	15	85	83	62-65 (0,5)	⩽2
 **8**	 **9a,b**	34	83[B]	55	99-123 (0,3)	11
 **10**	 **11a,b**  **12**	14	90[C]	55	95-105 (0,3)	2,5

 **13**	 **14a,b**	21	97	87	D	10
 **15**	 **16a,b**	21	87	84	D	3
 **17** (Δ^2cholestene)	 **18a,b**	21	98[E]	59	-	0
	 **19**					
 **20**	 **21a,b**	20	80[F]	0	-	0
	 **22**					

[A] Structures of products, composition of crude reaction mixtures and yields were determined by ^{1}H, ^{13}C and ^{19}F N.M.R. [B] The crude mixture contains an ethylenic elimination product (17 %). [C] 33.5 % of ethylenic compound **12** is also formed. [D] Decomposes when distilled. [E] Product **19** (39 %) is the result of an already known rearrangement [17]. [F] Only compound **21a** can be isolated [18]. **21b** cannot be detected. The 'one-pot' exchange reaction leads directly to ethylenic compound **22**.

ting of the chloro compound **6a** with triethylamine tris-hydrofluoride leads back to episulfonium ion which is slowly opened, giving irreversibly the fluoro compound **6b**. This assumption was confirmed when heating this latter isolated compound under the reaction conditions (60°C, $CHCl_3$) in presence of an excess of chloride ions ($Et_3NH^+Cl^-$) : no back formation of **6a** was observed. The fluorination step of scheme 1 being therefore irreversible, we were able to displace the equilibrium toward the ß-fluoro thioether formation even with the relatively weak nucleophile used. When trying to realize the exchange reaction starting from isolated **6a**, under the same conditions, while using triethylamine-monofluorohydrate or tetrabutylammonium fluoride trihydrate, no β-fluoro thioether **6b** was formed. We were able, however, after usual workup, to isolate cyclooctene. This means that the reaction of Scheme 2 had taken place.

From a preparative point of view, during these exchange reactions, the complete disappearance of the chloro derivative often needs quite a long reaction time. Nevertheless, we can proceed in two stages as follows : the reaction mixture is worked up while some chloro derivative still remains, allowing us to eliminate the chloride ions formed. After removal of the solvent, the crude mixture is again reacted under the same conditions. Starting, for instance, from chloro compound **6a**, after 7 hours some 9 % of **6a** are still remaining. After workup and reacting the crude mixture again for 5 additional hours we could obtain **6b** in almost a pure form (less than 1 % of compound **6a** remaining) in an 80 % yield.

Such exchange reactions are, because of experimental conditions, only possible with thermally stable molecules. For instance, starting from **10** we obtained around 40 % of the elimination product **12** (its formation is favoured by the axial position of the halogen in the preferred conformation of **11a** : equatorial $CH_2S\phi$), whereas the utilization of DMTSF according to HAUFE *et al.* [1] leads to 1-fluoro-1-(methylthiomethyl)-cyclohexane **23** with a yield of over 90 % without noticeable formation of elimination product. In a similar manner, the exchange reaction with **18a** leads, besides the expected compound

18b (59 %), to **19** (39 %) as a result of thermal isomerisation according to KING *et al.* [17]. On the other hand, starting from vinylic sulfone **20**, we were not able to perform the phenyl (or alkyl) thio fluorination : DMTSF was not electrophilic enough to react with the deactivated double bond and the chloro compound **21a** [18] led to ethylenic compound **22** when heated with triethylamine tris-hydrofluoride.

CONCLUSION

Triethylamine tris-hydrofluoride is a versatile fluorinating reagent for exchange reactions of a chlorine atom by a fluorine atom with anchimeric assistance of the sulfur atom of β-chloro phenyl thioethers. These reactions are restricted to molecules which do not suffer eliminations or rearrangement processes. Another advantage of $Et_3N.3HF$ as compared to other basic fluorinating reagents, is that it does not lead to olefinic compounds by direct attack on the sulfur atom of the intermediate episulfonium ion.

EXPERIMENTAL

^1H and ^{13}C N.M.R. spectra were recorded with a Bruker AM 300 (300,13 MHz for ^1H and 75,47 MHz for ^{13}C) and with a Bruker WP 80 instrument for ^{19}F (75,38 MHz) unless otherwise stated. All samples were run in deuterochloroform. Chemical shifts (δ) are given in ppm relative to tetramethylsilane for ^1H and ^{13}C and to trichlorofluoromethane for ^{19}F. N.M.R. data of new phenylthiochlorinated intermediates are listed in Table 2 and data for fluoro compounds obtained from exchange reaction are listed in Table 3. Data related to aromatic rings are not reported unless otherwise stated. ^{13}C N.M.R. assignments are given using DEPT sequence.

Compounds **2a** and **4a** have already been reported by HOPKINS and FUCHS [21]. Compounds **6a** and **7a** were previously prepared by BURGOINE *et al.* [22] and by GYBIN *et al.* [7] respectively.

Typical procedure for phenyl thiofluorination of olefinic compounds

The olefinic compound, in a polypropylene flask, was dissolved in chloroform (1 mmol/ml). The solution was cooled at -30°C and phenylsulfenyl chloride was then added dropwise (1 equivalent). Stirring was continued for 15 min at -30°C and the mixture was then allowed to reach room temperature. A sample was taken and the β-chloroalkyl phenyl thioether was characterized by the ^1H N.M.R. data (see Table 2). Seven equivalents of triethylamine tris-hydrofluoride were added ; the flask was closed and the reaction mixture was heated to 60°C. The progress of the reaction was followed by the HPLC (Silica Polygosil column 5μ ; eluent : Et_2O/light pet. ether 1:99) or by TLC (same eluent). After completion of the reaction the mixture was cooled to room temperature. Usual workup (pouring into iced water, neutralization, extraction with chloroform, washing with water and diluted hydrochloric acid, drying, evaporation of the solvent) gave the crude reaction mixture which was analysed by the N.M.R before subsequent purification.

1-(Phenylthiomethyl)-cyclohexene **12** : this compound was not isolated in pure form from the crude product of the reaction. ^1H N.M.R. : 3,43 (broad s, 2H, H-7) ; 5,50 (m, 1H, H-2).

Methyl-(1-phenylthiovinyl)-sulfone **22** : ^1H N.M.R. : 2,99 (s, 3H, CH_3) ; 5,72 (d, 1H) and 6,52 (d, 1H, AB system, J_{gem}=1,6). ^{13}C N.M.R. : 41,0 (CH_3) ; 127,3 (C-2) ; 147,4 (C-1) ; aromatic : 129,3 (para), 129,8 (meta), 130,4 (quat.), 132,9 (ortho).

1-Fluoro 1-(methylthiomethyl)-cyclohexane **23** : a solution of 10 mmol (0,96 g) of methylenecyclohexane in 20 ml methylene chloride was treated at 0°C, while stirring, with 11 mmoles (2,16 g) of DMTSF. After 20 min a slight excess of triethylamine tris-hydrofluoride in 10 ml of methylene chloride was added dropwise at 0°C and stirring was continued for 3 hours at room temperature. Usual workup (pouring into ice water, neutralization, extraction, drying, evaporation of the sol-

TABLE 2

N.M.R. spectral data of the phenylthiochlorination products

Compound	^1H
9a	1.50-2.34 (m, 16H, CH_2) ; 3.72 (sex., 1H, J_{HH} 7.6, 5.5, 5.5, H-1) ; 4.53 (oct., 1H, J_{HH} 7.9, 5.8, 4.2, H-2).
11a	1.49-1.94 (m, 10H, CH_2) ; 3.39 (s, 2H, H-7).
14a	0.98 (J_{HH}=7.2) and 1.10 (J_{HH}=7.3) (2t, 6H, CH_3, CH_3) ; 1.59-1.84 (m, 4H, CH_2) ; 3.14 (sex., 1H, J_{HH} 9.3, 6.2, 3.3, H-3) ; 3.92 (sex., 1H, J_{HH} 8.9, 6.3, 3.5, H-4).
16a	0.85 (J_{HH}=7.4) and 0.92 (J_{HH}=7.1) (2t, 6H, CH_3, CH_3) ; 1.29-1.86 (m, 8H, CH_2) ; 3.21 (m, 1H, H-4) ; 4.01 (sex., 1H, J_{HH} 8.9, 6.3, 3.5, H-5).
18a	3.75 (bs, 1H, H-3) ; 4.38 (bs, 1H, H-2)*).
19	3.19 (sex., 1H, J_{HH} 12.3, 11.3, 4.1, H-2) ; 3.68 (sex., 1H, J_{HH} 11.3, 11.3, 5.1, H-3)*.
21a	3.05 (s, 3H, CH_3) ; XAB system respectively : 3.87 (dd, 1H), 4.19 (dd, 1H), 4.31 (dd, 1H), J_{AX}=12.1, J_{BX}=7.4, J_{AB}=4.1.

* Only characteristic values for H-2, H-3 are given.

TABLE 3

N.M.R. spectral data of the phenyl (methyl) thiofluorination products

Compound	^1H	^{13}C ; J_{CF}	^{19}F
2b	1.19-2.17 (m, 8H, CH_2) ; 3.16 (oct., 1H, $J_{H_1H_{6a}}$ $J_{H_1H_2}$ 8.2, J_{H_1F} 9.2, $J_{H_1H_{6e}}$=4.3, H-1) ; 4.38 (dsex., 1H, J_{H_2F}=48.3, $J_{H_2H_{3a}}$ $J_{H_2H_1}$ 8.2, $J_{H_2H_{4e}}$ 4.0, H-2).	22.7 (J=8.3, C-4) ; 24.1 (C-5) ; 30.7 (J=3.5, C-6) ; 31.0 (J=19.3, C-3) ; 50.5 (J=18.7, C-1) ; 92.9 (J=177.7, C-2).	-170.8
4b	1.39-2.09 (m, 10H, CH_2) ; 3.46 (dm, 1H, J_{H_1F}= 16.2, H-1) ; 4.66 (dsex., 1H, J_{H_2F}=46.9, J_{HH} 6.2, 3.5, H-2).	21.1 (J=6.8, C-4) ; 25.6, 28.5 (C-5, C-6) ; 30.2 (J=4.5, C-7) ; 31.9 (J=21.7, C-3) ; 52.9 (J=22.6, C-1) ; 95.8 (J=174.4, C-2).	-163.7
6b	1.26-2.05 (m, 12H, CH_2) ; 3.46 (m, 1H, H-1) ; 4.64 (dsept., 1H, J_{H_2F}=46.8, J_{HH} 9.1, 6.5, 2.6, H-2).	24.2 (J=6.8, C-4) ; 25.2, 25.3, 26.0 (C-5, C-6, C-7) ; 28.5 (J=5.9, C-8) ; 31.7 (J=22.6, C-3) ; 52.7 (J=21.3, C-1) ; 96.5 (J=171.9, C-2).	-159.4
7b	1.2-2.1 (m, 12H, CH_2) ; 2.2 (d, 3H, J_{HF}=2, CH_3) ; 2.3-3.1 (m, 1H, H-1) ; 4.6 (d, 1H, J_{H_2F}=48, H-2)[A] .	15.5 (J=3.9, C-9) ; 24.4 (J=7.1, C-4) ; 25.4, 25.6, 26.2 (C-5, C-6, C-7) ; 28.5 (J=7.0, C-8) ; 32.2 (J=23.2, C-3) ; 50.5 (J=21.5, C-1) ; 99.0 (J=170.4, C-2).	-159.2

9b	1.40-2.27 (m, 16H, CH_2) ; 3.53 (m, 1H, H-1) ; 4.76 (dsept., 1H, J_{H_2F}=46.8, J_{HH} 8.7, 5.8, 3, H-2).	21.7 (J=4.3, C-4) ; 23.7, 23.9, 24.8, 25.1 (C-5, C-6, C-7, C-8, C-9) ; 29.2 (J=4.7, C-10) ; 29.7 (J=22.6, C-3) ; 51.1 (J=19.1, C-1) ; 94.9 (J=172.4, C-2).	-173.2
11b	0.90-1.64 (m, 6H, CH_2) ; 1.88-1.95 (m, 4H, H-2, H-6) ; 3.13 (d, 2H, J_{H_7F}=18.4, H-7).	21.9 (J=2.8, C-3 and C-5) ; 25.3 (C-4) ; 34.6 (J=22.1, C-2 and C-6) ; 44.3 (J=25.4, C-7) ; 95.3 (J=174.4, C-1).	-153.3
14b	0.95 (J_{HH}=7,4) and 1.10 (J_{HH}=7.3)(2t, 6H, CH_3, CH_3) ; 1.47-1.92 (m, 4H, CH_2) ; 3.01 (m, 1H, H-3) ; 4.40 (doct., 1H, J_{H_4F}=49.2, J_{HH}=8.2, 6.7, 3.6, H-4).	9.6 (J=5.4, C-6) ; 11.5 (C-1) ; 23.4 (J=5.2, C-2) ; 25.7 (J=19.9, C-5) ; 54.7 (J=20.7, C-3) ; 96.4 (J=176.5, C-4).	-183.2
16b	0.90 (J_{HH}=7.3) and 0.93 (J_{HH}=7.1) (2t, 6H, CH_3, CH_3) ; 1.31-1.79 (m, 8H, CH_2) ; 3.13 (m, 1H, H-4) ; 4.51 (dm, 1H, J_{H_5F}=48.2, H-5).	13.8, 13.9 (C-1, C-8) ; 18.7 (J=3.5, C-7) ; 20.2 (C-2) ; 32.3 (J=5.0, C-3) ; 34.4 (J=21.3, C-6) ; 53.2 (J=20.5, C-4) ; 95.2 (J=175.9, C-5).	-182.1
18b	3.60 (dbs, 1H, J_{H_3F}=13.6, H-3) ; 4.81 (dm, 1H, J_{H_2F}=48.9, H-2)[B].	13.7 (J=5.2, C-19) ; 28.2 (J=2.3, C-4) ; 35.7 (J=1.5, C-10) ; 38.2 (J=18.5, C-1) ; 41.0 (C-5) ; 47.5 (J=24.3, C-3) ; 91.9 (J=176.1, C-2)[C] .	-163.9

[A] VARIAN EM 360A (60 MHz) ; [B] Only characteristic values for H-2, H-3 are given ; [C] Only ring A data are given.

vent) and subsequent purification of the crude product (95 %) by distillation yielded 1-fluoro 1-(methylthiomethyl)-cyclohexane **23** : bp/15 mm=72-73°C.
^{1}H N.M.R. : 1,10-2,0 (m, 10H) ; 2,16 (s, 3H) ; 2,68 (d, 2H, J_{H-F}=19,76, H-7). ^{13}C N.M.R. : 17,7 (J=2,7, CH_3) ; 21,9 (J=3,0, C-3, C-5) ; 25,3 (C-4) ; 34,5 (J=22,2, C-2, C-6) ; 44,3 (J=24,9, C-7) ; 96,2 (J=173,1, C-1). ^{19}F N.M.R. : ϕ=-153,4 ppm.

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