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Ion–radical perfluoroalkylation. Part 11★. Perfluoroalkylation of thiols by perfluoroalkyl iodides in the absence of initiators★★

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Abstract

Perfluoroalkylation of aliphatic, aromatic and heterocyclic thiols by perfluoroalkyl iodides in the presence of Et_3N appears to occur spontaneously under daylight or the usual laboratory lighting conditions at 20–22 °C and is complete in 10–15 min to 2–3 h. An exception to this rule are thiols with a low nucleophilicity. The reaction is accompanied by thiol oxidation (2%–3%) and depends directly on the temperature, lighting, solvent polarity and electronic properties of the perfluoroalkylating agents and of the thiol substituents. At the same time, formation of diaryl disulphides frequently occurs contrary to above rules. The reaction mechanism is discussed.

Keywords: Ion–radical perfluoroalkylation; Thiols; Perfluoroalkyl iodides; Reaction mechanism; Nucleophilicity; NMR spectroscopy

1. Introduction

Because of their opposite polarization to the hydrocarbon analogues [2], perfluoroalkyl iodides have been considered as not displaying alkylating properties. Thus, the reactions of CF_3I with alkali give only fluoroform and the corresponding hypoiodite [3]. Similarly, interactions of polyfluoroiodoalkanes with CH_3SNa, carried out at high temperature in the presence of Me_2S_2 or Me_2S, yield methyl polyfluoroalkyl sulphides together with a number of by-products [4].

For the more successful perfluoroalkylation of thiols, it is necessary to apply various methods of initiation: UV irradiation [1,5–8], phase-transfer catalysis [8,9] or electrochemical activation [10]. In the absence of initiators the process is slow (17 h) [9], requires heat [11] or a repeated increase in the concentration of perfluoroalkylating agent [12].

We have found that interaction of perfluoroalkyl iodides with triethylammonium thiolates in polar organic solvents and at room temperature proceeds quite effectively without activation to yield the corresponding perfluoroalkyl sulphides (**II**). Under usual laboratory or daylight conditions, from 10–15 min to 2–3 h is required for completion of the reaction. The exceptions are thiols with low nucleophilicity containing electron-withdrawing groups. Unlike the various initiated reactions in which the process does not depend on the thiol or perfluoroalkyl iodide structure and the restrictions relate only to tertiary perfluoroiodoalkanes [6], *p*-nitrothiophenol [5] and some carbonyl containing heterocyclic thiols [7], the spontaneous reaction described in the present paper depends on many factors and displays some specific features which can be readily studied.

2. Results and discussion

Two conversion routes are almost always obtained: (a) *S*-perfluoroalkylation which gives $ArSR_F$ (**II**) and (b) the formation of diaryl disulphides (**III**) (Scheme 1).

In order to study the influence of the reaction conditions and reactant structure on the process, three types of species were investigated: the perfluoroalkyl sulphides (**II**), diaryl disulphides (**III**) and the initial

★Part 10, see Ref. [1].

★★Dedicated to Professor L.M. Yagupolskii on the occasion of his 70th birthday.

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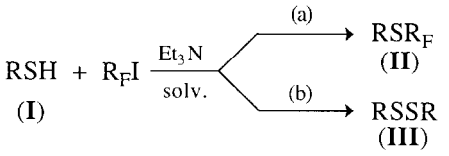


[R = XC_6H_4 (X = H, 2-NH_2, 4-$NHCOOCH_3$, 4-Cl, 4-OCH_3, 4-COOH, 4-$COOCH_3$, 4-NO_2), CH_2COOH, 2-benzothiazole, 8-quinoline; R_F = CF_3, C_3F_7]

Scheme 1.

unreacted thiols (**I**). The results are listed in Tables 1–4.

The usual laboratory or daylight conditions appear to have an essential effect in stimulating thiol perfluoroalkylation. Thus, under the usual conditions, interaction of thiol (**I**, R = $C_6H_4NHCOOCH_3$) with C_3F_7I in DMF or CH_3CN at 20–22 °C proceeded rapidly (for 20–30 min) and produced the corresponding sulphide **II** in quantitative yield (Runs 5 and 8). However, undertaking the reaction in the dark (Run 6) moderated the whole process (12% of the thiol remained after 1 h) and product **II** was formed only in 60% yield. On the other hand, the absence of light had no noticeable effect on the formation of the disulphide **III**.

Lowering the temperature to 0–5 °C also had an inhibitory effect on the perfluoroalkylation process (Table 2). As a result, the rate of consumption of thiol and the yields of **II** were greatly reduced. At the same time, the parallel process, i.e. formation of disulphide **III**, was not inhibited but rather slightly accelerated with an increase in the yield to 11%–12%.

The reaction studied was also dependent on the solvent used. A decrease in the solvent polarity caused total inhibition and reduced the RSR_F yield (Runs 5, 8–11). With poorly reactive *p*-chlorothiophenol, changing the solvent from DMF to CH_3CN (Runs 15 and

Table 1
The reaction of arenethiolates $XC_6H_4S^-$ $^+NHEt_3$ with C_3F_7I

Run No.	X	Solvent	Temp. (°C)	Time (h)	Yield of products (%)[a]		
					II	III	I[b]
1	H	DMF	19–20	2	83[c]	3[c]	–
2	4-$NHCO_2CH_3$	DMF	0–5	3	17	12	30
3	4-$NHCO_2CH_3$	HMPA	0–5	3	0	12[b]	50
4[d]	4-$NHCO_2CH_3$	DMF	0–22	5	30	7	54
5	4-$NHCO_2CH_3$	DMF	21–22	0.5[e]	89	3	–
6[f]	4-$NHCO_2CH_3$	DMF	21–22	1	60	4	12
7[d]	4-$NHCO_2CH_3$	DMF	21–22	1	70	9	–
8	4-$NHCO_2CH_3$	CH_3CN	21–22	0.5	98[b]	trace	–
9	4-$NHCO_2CH_3$	dioxan	21–22	2	82	2	–
10	4-$NHCO_2CH_3$	HMPA	21–22	3[g]	75	3	–
11	4-$NHCO_2CH_3$	THF	21–22	1.5	64	10	–
12	2-NH_2	CH_3CN	21–30[h]	0.5[i]	84[b]	–	–
13[d]	2-NH_2	DMF	23–24	1.5[j]	66	7	–
					52[b]	8[b]	–
14	4-OCH_3	CH_3CN	22–40[h]	2[i]	88	6	–
					87[b]		
15	4-Cl	DMF	22	2	72[b]	3[b]	–
16	4-Cl	CH_3CN	21–22	4[k]	40[b]	12[b]	9
17	4-COOH	DMF	22–30[h]	0.5[i]	72[b]	trace	trace
18	4-$COOCH_3$	DMF	20	3	39[l]	13	trace
					18[b]	12[b]	
19	4-NO_2[m]	DMF	50–55	5	trace	6[b]	80

[a]Determined by ^1H NMR spectroscopy unless noted otherwise; not detected by TLC.
[b]Isolated yield.
[c]Determined by GLC.
[d]Reaction with CF_3I.
[e]Thiol absent after 20 min.
[f]Reaction conducted in the dark.
[g]Thiol absent after 2 h.
[h]Spontaneous short heating.
[i]TLC unchanged after 10 min.
[j]TLC unchanged after 1 h.
[k]TLC unchanged after 3 h.
[l]Resin formation observed.
[m]Na thiolate.

Table 2
Temperature effect on the reaction of I ($R=C_6H_4NHCOOCH_3$-*p*) with C_3F_7I

Run No.	Solvent	Temp. (°C)	Time (h)	Yield of products (%)		
				II	III	I
5	DMF	21	0.5	89.2	3.4	–
2	DMF	0–5	3	16.8	12.0	29.9
10	HMPA	21–22	3	74.5	2.7	–
3	HMPA	0–5	3	0	11.5	49.9

16) slowed down the reaction to such an extent that almost 9% of thiol remained even after 4 h. It should be noted that a decrease in the yield of sulphide **II** occured with simultaneous increase in disulphide **III** formation (Runs 11 and 16).

HMPA is the odd one out in the series. This highly polar solvent unexpectedly slowed the reaction down to 2–3 h (Run 10) whereas in DMF and CH_3CN only 20–30 min were required with the same reagents for completion. In contrast with DMF, perfluoroalkylation (path a) did not occur at 0–5 °C (Table 2). At the same time, oxidation (path b) was not retarded.

In contrast to thiol perfluoroalkylation under UV irradiation [5], the spontaneous nature of the reaction depended on the substituents associated with the arenethiol. Electron-donating groups promote the reaction but electron-withdrawing ones caused a decrease in the yield of aryl perfluoroalkyl sulphides **II** and a retardation of the whole interaction. In the latter case (X=4-Cl and 4-$COOCH_3$, Runs 16 and 18), an increase in the yields of diaryl disulphides **III** up to 12%–13% was observed. Nitro groups deactivate the thiols to such an extent that under the conditions studied there was no reaction with C_3F_7I (Run 19).

The spontaneous interaction of aromatic thiols with perfluoroalkyl iodides also depends upon the structure of the perfluoroalkyl fragment (Table 3). Reaction proceeded more easily and the products of perfluoroalkylation (**II**) were formed in higher yield when heptafluoropropyl iodide was employed instead of CF_3I. At the same time, in spite of the fact that the former is a stronger oxidizer [10,13], a larger yield of disulphide **III** occurred with CF_3I.

Aliphatic and heterocyclic thiols also react with perfluoroalkyl iodides without activation (Table 4). The low yields of heptafluoropropylthioacetic acid observed are probably due to its high solubility in water and also to the ease of oxidation of the initial thioglycolic acid. It is curious that this oxidation (route b) occurs more readily in DMF whereas in CH_3CN it occurs to a lesser extent. At the same time, the perfluoroalkylation process (route a) is noticeably decreased (Runs 20 and 21). There is a similar dependence in the case of substituted thiophenols containing electron-donating (NH_2) or neutral ($NHCO_2CH_3$) groups but not electron-withdrawing (Cl) groups (compare Run 5 with Run 8 and Run 12 with Run 13).

In contrast to aromatic and aliphatic thiols, 2-mercaptobenzothiazole and 8-mercaptoquinoline reacted much more slowly with C_3F_7I both with regard to perfluoroalkylation and to disulphide (**III**) formation. Such low reactivity for heterocyclic thiols is perhaps due to their higher oxidation potentials.

The present investigation leads to the conclusion that temperature, light, solvent polarity and also the electronic properties of perfluoroalkyl iodide and thiol substituents have a direct influence on the perfluoroalkylation process (route a), whereas disulphide formation (route b) is either unaffected, or, more frequently, affected adversely by these effects.

Thiol perfluoroalkylations are considered by many researchers [5,9,12,14] to proceed by $S_{RN}1$ mechanisms:

$$RS^- + R_FI \longrightarrow RS^{\bullet} + R_FI^{\bullet -} \quad (1)$$

$$R_FI^{\bullet -} \longrightarrow R_F^{\bullet} + I^- \quad (2)$$

$$R_F^{\bullet} + RS^- \longrightarrow RSR_F^{\bullet -} \quad (3)$$

$$RSR_F^{\bullet -} + R_FI \longrightarrow RSR_F + R_FI^{\bullet -} \quad (4)$$

Scheme 2.

Two steps in this mechanism, i.e. the very fast fragmentation of the radical anion $R_FI^{\bullet -}$ [Eq. (2)] and the coupling of the electrophilic radical $R_F^{\bullet}$ with the anion RS^- [Eq. (3)] both of which apparently occur at ionic reaction speed, are not limiting. If the radical anion $R_FI^{\bullet -}$ is not formed in polar solvents and appears only as its fragments ($R_F^{\bullet}$ and I^-) as is assumed in Ref. [15], it is not possible to consider stage (2) at all.

Table 3
Reaction of R_FI with aromatic thiols XC_6H_4SH at room temperature

Run No.	R_F	X	Solvent	Time (h)	Yield of products (%)	
					II	III
5	C_3F_7	4-$NHCO_2CH_3$	DMF	0.5	89.2	3.4
7	CF_3	4-$NHCO_2CH_3$	DMF	1	69.9	9.5
12	C_3F_7	2-NH_2	CH_3CN	0.5	84.1	–
13	CF_3	2-NH_2	DMF	1.5	66.4	6.8

Table 4
Interaction of C_3F_7I with aliphatic and heterocyclic thiols at 20–22 °C

Run No.	Thiol	Solvent	Time (h)	Yield of products[a] (%)		
				II	III	I
20	thioglycolic acid	CH_3CN	3	50.9	6.6	[b]
21	thioglycolic acid	DMF	2	41.2	17.1	[b]
22	2-SH-benzothiazole	DMF	48	trace	trace	87
23	2-SH-benzothiazole	DMF	120[c]	58.8[d]	trace	20
24	8-mercaptoquinoline[e]	DMF	24	72.2[d]	3.8[d]	–

[a]See footnote a in Table 1.
[b]Not determined.
[c]First 3 h at 55–60 °C.
[d]Isolated yield.
[e]Na salt.

The radicals RS$^{\cdot}$ which appear in the first step are the source of disulphide **III** formation. Since many of the factors studied in this work do not directly affect the yield of disulphides **III**, it must be concluded that the first step is not limiting. Nevertheless, as shown above, perfluoroalkyl iodides take part in the rate-determining step. In our opinion such a step could be the single electron transfer from $RSR_F^{\cdot -}$ to the initial molecule R_FI [Eq. (4) in Scheme 2]. All the factors studied influence this stage and when it is slowed down, accumulation of radical RS$^{\cdot}$ (and, as a result, an increase in disulphide **III** yield) takes place.

The above hypothesis allows us to explain why thiol perfluoroalkylation (route a) but not path (b) is inhibited in such solvents as HMPA (Run 10) and DMF (Run 21). When in contact with solvent, perfluoroalkyl iodides are known to form donor–acceptor complexes [16,17]. The extent to which a shift in electron density occurs correlates with the donor ability of the solvent. High donor solvents such as HMPA (*DN* 38.8) and DMF (*DN* 26.6) in combination with R_FI apparently reduce the electrophilic properties of R_FI. This undoubtedly initially affects the limiting stage [Eq. (4)] by slowing down the perfluoroalkylation process and by lowering the yield of its product.

3. Experimental details

Analytical TLC plates (Silufol) and silica gel (L 100/160) were purchased from Cavalier and Chemapol (Czechoslovakia), respectively. GC analyses were carried out on a Chrom-5 chromatograph (Prague). ^1H and ^{19}F NMR spectra were obtained on Varian Gemini-200 (200 MHz) and Bruker WP-200 (188.28 MHz for ^{19}F) spectrometers with CD_3COCD_3 as the solvent. ^1H and ^{19}F chemical shifts are reported in δ (ppm) values relative to hexamethyl disiloxane (^1H) and trichlorofluoromethane (^{19}F) as internal standards. Some of the aryl heptafluoropropyl sulphides (**II**) with H, 4-Cl [6,8], 4-$COOCH_3$ [8,18], 4-COOH [18] and 4-NO_2 [19] substituents and 2-aminophenyl trifluoromethyl sulphide [5] are already known. All experiments were carried out under pure argon in molybdenum or Pyrex glass flasks under daylight or normal laboratory lighting. Reaction completion was judged by disappearance of the thiol (by TLC).

3.1. Thiol perfluoroalkylation. General procedure

To a solution of thiol (1–20 mmol) and Et_3N (10–15 mol% excess) in chosen organic solvent (1–2 ml for 1 mmol of thiol) under argon and with stirring was added the perfluoroalkyl iodide (2 equiv.). The reaction mixture was maintained under the chosen conditions until the thiol had disappeared. The reaction solution was then diluted with water and extracted with ether. The ether solution was washed with alkali and then with acidified water, dried with $MgSO_4$ and the residue obtained after solvent removal studied by ^1H NMR spectroscopy (see Table 5). In some cases the reaction products were separated by vacuum distillation following precipitation of the disulphide (**III**) by hexane (Runs 15 and 16) and also by silica gel column chromatography using the following eluents: benzene (Run 13); hexane followed by benzene (Run 18) and hexane followed by

Table 5
Characteristic chemical shifts (δ, ppm) of compounds **II** and **III** used for ^1H NMR analysis of reaction mixtures

Proton of substituent X	Chemical shifts δ (ppm)	
	II	III
4-NHCOOC*H*$_3$	3.66	3.63
4-N*H*COOCH$_3$	9.02	8.78
4-OC*H*$_3$	3.81	3.74
2-N*H*$_2$	5.34	5.03
4-COOC*H*$_3$	3.86	3.80
C*H*$_2$COOH[a]	3.90	3.61

[a]In derivatives of thioglycolic acid.

acetone (Run 24). If necessary, the starting thiols were separated from alkaline solution by acidification. Reagents, solvents, temperature, reaction time and yields of products are given in Tables 1–4.

The characteristic properties of new compounds obtained by this procedure (or its modification), are given below.

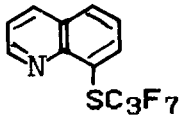
$C_3F_7SCH_2COOH$: b.p. 103–104 °C/18 mmHg; m.p. 8–9 °C; n_D^{25} 1.3590. Analysis: Found (Calc.): F, 51.11 (51.12)%.

4-$CH_3OC_6H_4SC_3F_7$: b.p. 98 °C/19 mmHg; n_D^{21} 1.4382. ^1H NMR δ: 3.81 (s, CH_3); 7.29 (2d, C_6H_4) ppm. Analysis: Found (Calc.): C, 38.99 (38.96); H, 2.35 (2.29); F, 43.05 (43.15); S, 10.44 (10.40)%.

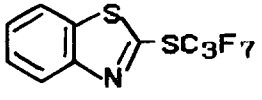
2-$H_2NC_6H_4SC_3F_7$: b.p. 95–97 °C/15 mmHg. Analysis: Found (Calc.): C, 36.79 (36.86); H, 2.10 (2.06); F, 45.43 (45.36)%.

4-$CH_3OCONHC_6H_4SCF_3$: m.p. 129–131 °C (from benzene). ^1H NMR δ: 3.66 (s, CH_3); 7.62 (2d, C_6H_4); 9.00 (s, NH) ppm. ^{19}F NMR δ: −43.57 ppm. Analysis: Found (Calc.): C, 42.85 (43.02); H, 2.98 (3.20); F, 22.69 (22.68)%.

4-$CH_3OCONHC_6H_4SC_3F_7$: m.p. 75–76 °C (from benzene with hexane, 1:9). ^1H NMR δ: 3.66 (s, CH_3); 7.62 (2d, C_6H_4); 9.02 (s, NH) ppm. ^{19}F NMR δ: −80.01 (s, CF_3); −88.11 (s, CF_2); −123.32 (s, CF_2) ppm. Analysis: Found (Calc.): C, 37.70 (37.61); H, 2.24 (2.29); F, 37.73 (37.86)%.



m.p. 31–32 °C (from pentane). ^{19}F NMR δ: −79.81 (s, CF_3); −85.97 (s, CF_2); −123.06 (s, CF_2) ppm. Analysis: Found (Calc.): C, 35.58 (35.81); H, 1.13 (1.20); F, 39.65 (39.66); N, 4.15 (4.17)%.



The mixture of products (5.24 g) was separated by silica gel column chromatography. Using hexane as eluant, 3.9 g (72.2%) of 8-heptafluoropropylthioquinoline was obtained; b.p. 127 °C/16 mmHg. Analysis: Found (Calc.): C, 43.08 (43.77); H, 1.81 (1.80); F, 40.42 (40.39)%. The diquinolyl disulphide (0.4 g, 3.8%) was then washed with acetone to give a solid, m.p. 205 °C. This showed no mixed melting-point depression with an authentic sample. ^{19}F NMR δ: −79.88 (s, CF_3); −85.62 (s, CF_2); −123.44 (s, CF_2) ppm.

$C_3F_7SC_6H_4COOH$-*p*: To the solution of (*p*-$CH_3OCOC_6H_4S-)_2$ (1 g, 2.99 mmol) in 30 ml of liquid ammonia at −50 °C to −30 °C was added with stirring small pieces of Na metal (0.14 g) until a stable blue colour was formed. After removal of ammonia, the residue was dissolved in DMF (10 ml) with C_3F_7I (2.64 g, 8.97 mmol), the reaction mixture stirred for 0.5 h and diluted with acidified water. The resulting precipitate was filtered off and, after drying, 1.4 g of crystals was obtained; m.p. 171–172 °C (from ether) (lit. value [18], 175–177 °C). This product was oxidized with CrO_3 in CH_3COOH to yield $C_3F_7SO_2C_6H_4COOH$. A mixture with a known sample [18] showed no melting-point depression.

$C_3F_7SC_6H_4COOCH_3$-*p*: The solution of (*p*-$CH_3OCOC_6H_4S-)_2$ (2 g, 5.98 mmol), Ph_3P (1.64 g, 6.25 mmol) and three drops of conc. HCl in 18 ml of dioxan and 4.5 ml of water was stirred for 3 h at 40 °C. After 16 h, the reaction mixture was diluted with water (pH 8–10), extracted with ether, the aqueous layer acidified and the thiol extracted with ether and dried. To the residue (0.6 g) after vacuum removal of solvent were added DMF (5 ml), Et_3N (0.54 g, 5.3 mmol) and C_3F_7I (2.1 g, 7.1 mmol), and the solution was stirred for 3 h at 20 °C. The mixture of products (0.77 g) after usual treatment was analyzed by ^1H NMR spectroscopy and then separated by silica gel column chromatography. Hexane, as the first eluant, washed out the fluorinated product (0.22 g, 18.4%). ^{19}F NMR δ: −80.7 (s, CF_3); −87.5 (s, CF_2); −123.9 (s, CF_2) ppm. Benzene, as second solvent, gave the initial disulphide (0.3 g, 15%), m.p. 125 °C. This showed no mixed melting-point depression.

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