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PERFLUOROALKYLATION OF THIOLS. EVIDENCE FOR A RADICAL CHAIN PROCESS

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SUMMARY

Perfluoroalkyl sulfides are formed from primary or secondary perfluoroalkyl iodides and aromatic or aliphatic thiolates without UV irradiation. Perfluoroalkyl radicals are intermediates as demonstrated by inhibition and trapping studies.

INTRODUCTION

The perfluoroalkylation of aromatic, heteroaromatic ,and aliphatic thiols by perfluoroalkyl iodides has been described in a series of papers [1]. The reactions were generally conducted in liquid ammonia under UV irradiation. Although the yields were generally quite good, the somewhat inconvenient experimental procedure prompted this study of the perfluoroalkylation reaction under different reaction conditions including the use of phase transfer procedures. After completing this work, a separate report appeared on the phase transfer catalyzed perfluoroalkylation of thiols [2]. In contrast to the earlier reports, I find that the perfluoroalkylation reactions proceed satisfactorily in organic solvents or under phase transfer conditions without UV irradiation. I also describe radical trapping studies which support a radical chain mechanism for this process.

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RESULTS

The perfluoroalkyl sulfides **3a**-**d** were prepared by reaction of the perfluoroalkyl iodides **1a**-**1c** with the sodium salt of benzene or *n*-butane thiol in DMF under normal laboratory lighting. Alternatively, the same sulfides **3** were prepared by vigorously stirring a solution of the thiols in 40% aqueous tetrabutyl ammonium hydroxide with a benzene or methylene chloride solution of the perfluoroalkyl iodide. Results are summarized in Table 1.

$$R_fI \quad + \quad RS^-M^+ \longrightarrow R_fSR$$

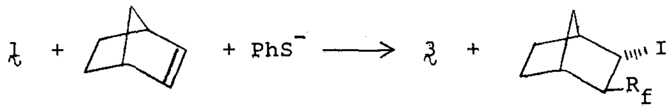
1a $R_f = n\text{-}C_6F_{13}$ **2a** $R = Ph$ **3a**, $R = Ph$, $R_f = n\text{-}C_6F_{13}$
1b $R_f = n\text{-}C_8F_{17}$ **2b** $R = n\text{-}C_4H_9$ **3b**, $R = Ph$, $R_f = n\text{-}C_8F_{17}$
1c $R_f = i\text{-}C_3F_7$ **3c**, $R = Ph$, $R_f = i\text{-}C_3F_7$
3d, $R = n\text{-}C_4H_9, R_f = nC_8F_{17}$

Using either procedure, good yields of the aryl sulfides **3a** and **3b** could be achieved without resorting to UV irradiation (entries 2,5). The phase-transfer catalyzed procedure gave much better results using benzene rather than methylene chloride as cosolvent (entries 1,2). Yields of the alkyl perfluoroalkyl sulfide **3d** were distinctly lower with substantial amounts of unreacted perfluoroalkyl iodide and di-*n*-butyldisulfide isolated using either procedure. Here the DMF conditions appeared to give better results (entries 8,9).

Reactions of the secondary perfluoroalkyl iodide **1c** were studied only with benzenethiol. The product **3c** was obtained in modest yield together with substantial amounts of diphenyldisulfide and the unsaturated sulfide **4**. Again the DMF procedure gave consistently higher yields of **3c** than the phase transfer procedure.

$$\underset{\mathbf{1c}}{(CF_3)_2CFI} + PhS^- \longrightarrow \underset{\mathbf{3c}}{(CF_3)_2CFSPh} + (PhS)_2 + \underset{\mathbf{4}}{CF_3CF{=}CFSPh}$$

Addition of three equivalents of styrene to the reaction of the primary iodides with benzenethiolate in DMF or under phase transfer conditions resulted in complete inhibition of the perfluoroalkylation process. Both the perfluoroalkyl iodide and styrene could be recovered unchanged. In contrast, addition of norbornene to the reaction resulted in the formation of the 2-iodo-3-perfluoroalkylnorbornane **5a** in addition to the normal product **3**. A control experiment established that **5** was not formed from **1** and norbornene under the reaction conditions in the absence of thiolate. Similarly, reaction of the secondary iodide **1c** with benzenethiolate gave **3c**, **4**, and the norbornene adduct **5b**.



5a $R_f = n\text{-}C_8F_{17}$
5b $R_f = i\text{-}C_3F_7$

To compare these results with my earlier work on the perfluoroalkylation of the 2-nitropropyl anion [7], perfluorooctyl iodide (**1b**) was allowed to react with an excess equimolar mixture of sodium benzenethiolate and lithium 2-nitropropanide in DMF. The product mixture was the perfluorooctyl phenyl sulfide (**3b**) plus a small amount of the unreacted iodide **1b**. No 2-perfluorooctyl-2-nitropropane (**6**) was detected.

Table 1.

Reaction of Perfluoroalkyl Iodides with Thiolates

Entry	R_fI(mole)	Thiolate(mole)	Solvent	Additive(mole)	Conditions	Product (gc yield)[isolated yield]
1	$C_6F_{13}I$ (0.02)	PhS $N(Bu)_4$ (0.02)	CH_2Cl_2/H_2O	-	40°C/4 hr	$PhSC_6F_{13}$ (48) [44] $(PhS)_2$ (11) $C_6F_{13}I$ (41)
2	$C_6F_{13}I$ (0.02)	PhS $N(Bu)_4$ (0.02)	C_6H_6/H_2O	-	25°C/2.5 hr	$PhSC_6F_{13}$ [76]
3	$C_6F_{13}I$ (0.02)	PhS $N(Bu)_4$ (0.02)	C_6H_6/H_2O	Styrene (0.06)	25°C/17 hr	NO REACTION
4	$C_8F_{17}I$ (0.02)	PhS $N(Bu)_4$ (0.02)	C_6H_6/H_2O	Norbornene(0.1)	25°C/5 hr	$PhSC_8F_{17}$ (30) $(PhS)_2$ (7) 2-Iodo-3-Perfluorooctyl-norbornane (7) $C_8F_{17}I$ (46)
5	$C_8F_{17}I$ (0.02)	PhS Na(0.025)	DMF	-	25°C/17 hr	$PhSC_8F_{17}$ (92) [90] $C_8F_{17}I$ (5)
6	$C_8F_{17}I$ (0.02)	PhS Na(0.031)	DMF	Styrene (0.075)	25°C/17 hr	NO REACTION
7	$C_8F_{17}I$ (0.02)	PhS Na(0.025)	DMF	Norbornene(0.1)	25°C/17 hr	$PhSC_8F_{17}$ (77) 2-Iodo-3-Perfluorooctyl-norbornane (6) $C_8F_{17}I$ (16)
8	$C_8F_{17}I$ (0.02)	C_4H_9S $N(Bu)_4$(0.023)	C_6H_6/H_2O	-	25°C/4 hr	$C_8F_{17}SC_4H_9$ (12) $(C_4H_9S)_2$ (35) $C_8F_{17}I$ (47)

9	$C_8F_{17}I$ (0.04)	C_4H_9S Na(0.046)	DMF	-	25°C/17 hr	$C_8F_{17}SC_4H_9$ (36) [35] $(C_4H_9S)_2$ (15) $C_8F_{17}I$ (47)
10	$(CF_3)_2CFI$ (0.025)	PhS N(Bu)$_4$(0.025)	C_6H_6/H_2O	-	25°C/4 hr	$PhSCF(CF_3)_2$ (14) $(PhS)_2$ (71) $CF_3CF{=}CFSPh$ (15)
11	$(CF_3)_2CFI$(0.025)	PhS N(Bu)$_4$(0.025)	C_6H_6/H_2O	Norbornene(0.1)	25°C/4 hr	$PhSCF(CF_3)_2$ (3) $(PhS)_2$ (57) $CF_3CF{=}CFSPh$ (10) 2-Iodo-3-(perfluoroisopropyl)-norbornane (30)
12	$(CF_3)_2CFI$(0.025)	PhS Na(0.025)	DMF	-	25°C/17 hr	$PhSCF(CF_3)_2$ (76) [40] $(PhS)_2$ (16) $CF_3CF{=}CFSPh$ (6)
13	$(CF_3)_2CFI$(0.025)	PhS Na(0.025)	DMF	Norbornene(0.1)	25°C/17 hr	$PhSCF(CF_3)_2$ (27) $(PhS)_2$ (31) $CF_3CF{=}CFSPh$ (16) 2-Iodo-3-(perfluoroisopropyl)-norbornane (24)
14	$(C_8F_{17}I$ (0.010)	PhS Na(0.024)	DMF	$(CH_3)_2C{=}NO_2Li$(0.024)	25°C/17 hr	$PhSC_8F_{17}$ [89] $O_2NC(CH_3)_2C_8F_{17}$ [0]

DISCUSSION

The perfluoroalkylation of thiols, involving a facile nucleophilic displacement reaction on a substrate considered [3] to be quite resistant to such processes, is likely to proceed by an $S_{RN}1$ mechanism [1,2]. The $S_{RN}1$ process [4] as applied here is described in Scheme 1. This chain process is initiated by one electron transfer from the thiolate to the perfluoroalkyl iodide. Decomposition of the anion radical generates a perfluoroalkyl radical which adds to the thiolate anion giving a new anion radical. Electron transfer from this species to the perfluoroalkyl iodide gives the product and a new perfluoroalkyl iodide anion radical to continue a chain process.

$$R_fI + PhS^- \longrightarrow R_fI^{\overline{\cdot}} + PhS^\cdot$$

$$R_fI^- \longrightarrow R_f\cdot + I^-$$

$$R_f + PhS^- \longrightarrow R_fSPh^{\overline{\cdot}}$$

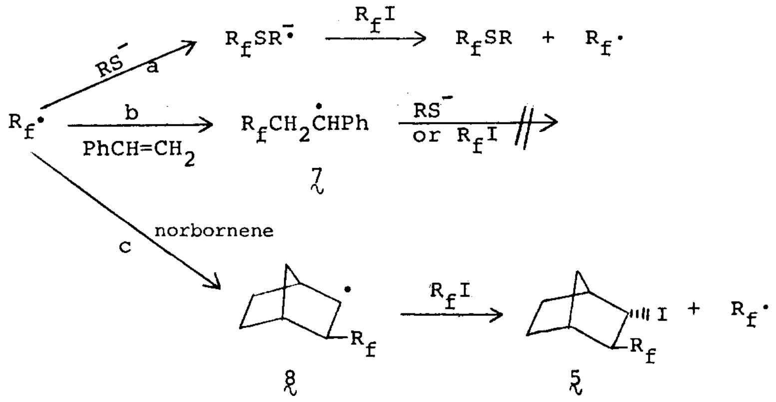
$$R_fI + R_fSPh^{\overline{\cdot}} \longrightarrow R_fI^{\overline{\cdot}} + R_fSPh$$

Scheme 1

The involvement of primary perfluoroalkyl radicals in the substitution process of the 1-iodoperfluoroalkanes is clearly supported by the results with added olefins (Scheme 2). Styrene inhibits the process by efficiently scavenging the perfluoroalkyl radicals formed in the initiation step. The resulting benzyl radical 7 is not sufficiently reactive to abstract an iodine atom from R_fI or add to RS^- to continue an efficient chain process. Norbornene addition of the perfluoroalkyl radical to the olefin generates a reactive secondary alkyl radical 8. This species can abstract an iodine atom from R_fI to form 5 and a new perfluoroalkyl radical. Addition of R_fI to norbornene is known to proceed readily using traditional radical initiators [5]. It is interesting to note that the overall reaction of R_fI with benzenethiolate in the presence of norbornene involves two simultaneous chain processes, one involving electron transfer, the second involving atom transfer in the chain carrying steps. With the primary perfluoroalkyl iodide ,the sulfide 3 is the major product even in the presence of excess norbornene. Thus the primary radical prefers pathway a rather than pathway c in Scheme 2.

INITIATION: $R_fI + RS^- \longrightarrow R_f\cdot + RS^\cdot + I^-$

PROPAGATION:



Scheme 2

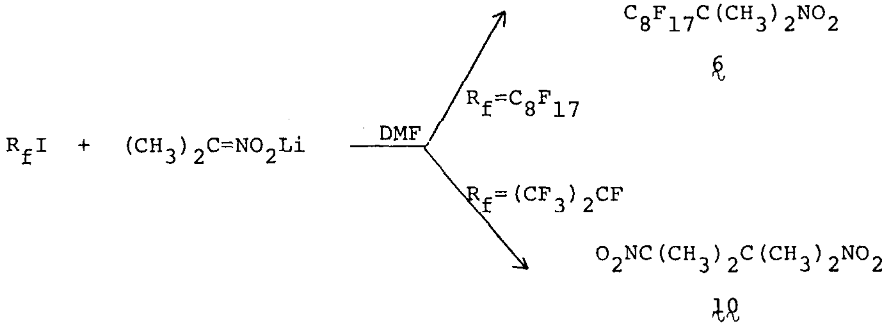
The chemistry of the secondary iodide **1c** is somewhat more complex. The secondary iodide in general gave more diphenyldisulfide. In the presence of norbornene,the secondary iodide gave relatively more of the norbornene adduct **5** than did the primary iodide. The vinyl sulfide **4** was detected as a byproduct from the secondary iodide. Formation of the latter product suggests the involvement of an ionic intermediate, namely the perfluoroisopropyl anion **9** (Scheme 3). Loss of fluoride ion would generate hexafluoropropene which is known to react [6] with the benzenethiolate anion to give the observed vinyl sulfide **4**. The relatively poor material balances in the experiments with the secondary iodide could be due to the undetected loss of the very volatile hexafluoropropene.

$$(CF_3)_2CFI \xrightarrow{PhS^-} \underset{\mathbf{9}}{(CF_3)_2CF^{\ominus}} \longrightarrow CF_3CF{=}CF_2 \xrightarrow{PhS^-} \mathbf{4}$$

Scheme 3

The mechanism of formation of **9** is an interesting question. A direct S_N2 displacement by thiolate anion on the iodine atom of the substrate would generate **9** and phenylsulfenyl iodide. The latter compound would certainly give diphenyldisulfide with excess PhSNa. Alternatively, electron transfer to an intermediate perfluoroalkyl radical could be involved. The perfluoroisopropyl radical is certainly an intermediate in the formation of **3c** and **5b**. Whether it is also an intermediate in the formation of the anion **9** has not been determined.

It is interesting to compare these results to the earlier work [7] on reactions of the 2-nitropropanide ion with perfluoroalkyl iodides. In DMF solution, 1b reacts with lithium 2-nitropropanide giving 2-perfluorooctyl-2-nitropropane (6). Styrene inhibits the process. The secondary iodide 1c gave only the nitronate dimer 10 and volatile fluorocarbons. No product corresponding to 6 was detected.



With both the primary and secondary iodides 1b and 1c, reaction with the nitronate salt in the presence of excess norbornene gave the norbornene adducts 5a or 5b plus 6 or 10 [8]. However, the yields of the norbornene adducts were substantially higher with the nitronate compared to the thiolate. Thus under conditions of experiment 7 using lithium 2-nitropropanide instead of sodium benzenethiolate, the product mixture was 78% norbornene adduct 5a and 23% nitropropane 6. With the secondary iodide 1c, a 55% yield of the norbornene adduct 5b was isolated. The higher yields of the norbornene adducts in the nitronate reactions are consistent with the competition experiment, described above, where thiolate was found to be a better trap than nitronate for perfluorooctyl radical.

Clearly perfluoroalkyl radicals are generated by electron transfer from a variety of organic electron donors [1,2, 7,8,9]. The electron transfer processes can be initiated spontaneously or be catalyzed by UV light as has been observed in non-fluorinated cases [4]. The ultimate fate of the radical depends on the nature of the radical, the nucleophile, solvent [7],and the presence or absence of other radical traps in a finely balanced and not yet fully understood way. Studies along these lines are continuing.

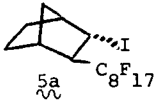
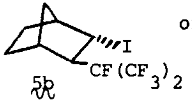
EXPERIMENTAL

Benzenethiol, butanethiol,and styrene were commercial samples, freshly distilled and stored under argon. Norbornene was used as received. The sodium thiolate salts were either prepared as dried solids [10] or generated *in situ* by dropwise addition of the thiol to a suspension of sodium hydride in DMF. The tetrabutylammonium thiolates were generated by addition of the thiol to a carefully deoxygenated solution of commercial 40% tetrabutylammonium hydroxide in water. The perfluoroalkyl iodides were obtained from the Chemicals & Pigments Department, E. I. du Pont de Nemours & Company, or from PCR, Inc. The iodides were washed with dilute aqueous sodium thiosulfate to remove traces of iodine, dried over $MgSO_4$,and stored in the dark.

Proton NMR spectra were obtained on an IBM NR-80 spectrometer at 80 MHz using TMS as internal standard. Fluorine NMR spectra were obtained on a Varian XL-100 spectrometer at 94.1 MHz using fluorotrichloromethane as internal standard. Negative chemical shift values are upfield from the standard.

Table 2.

Product Properties

Structure	bp	Proton NMR	Fluorine NMR	Mass Spectrum	Reference
$PhSC_6F_{13}$ **3a**	103-105°(20 mm)	7.1-7.7 (m)	-81.6(3F); -126.7(2F); -123.1(2F); -121.7(2F) -119.0(2F); -87.6(2F)	Calcd for $C_{12}H_5SF_{13}$ m/e=427.9904 found m/e=427.9861	11
$PhSC_8F_{17}$ **3b**	65-67° (0.4 mm)	7.1-7.7 (m)	-81.7(3F); -126.7(2F); -123.1(2F); -122.2(4F); -121.9(2F); -119.5(2F); -87.1(2F)	Calcd for $C_{14}H_5SF_{17}$ m/e=527.9840 found m/e=527.9821	n.c.
$PhSCF(CF_3)_2$ **3c**		7.1-7.7 (m)	-74.4(6F,d); -157.5(1F,heptet)	m/e=278	1,12
$\underline{n}BuSC_8F_{17}$ **3d**	92-94° (20 mm)	0.93(3H,t); 1.1-1.9(4H,m); 2.93(2H,t)	-81.5(3F); -126.7(2F); -123.2(2F); -122.3(4F) -121.5(2F) -120.23(2F); -87.96(2F)	Calcd for $C_{12}H_9F_{17}S$: m/e=508.0153 found m/e=508.0092	n.c.
$CF_3CF{=}CFSPh$ **4**	oil	7.1-7.7 (m)	-68.11(3F,dd,J=11,22 Hz) -120.25(1F,dq,J=146,11 Hz) -155.88(1F,dq,J=146,22 Hz)	m/e=240	6
 **5a**	mp 40-42°	1.0-2.5(9H,m); 4.31(1H,m)	-81.6(3F); -126.7(2F); -123.2(2F) -122.3(4F) -121.5(2F); -117.7(2F,AB quartet,J=280 Hz)	Calcd for $C_{15}H_{10}F_{17}(M-I)^+$ m/e=513.0510 found m/e=513.0461	n.c.
 **5b**	oil	1.0-2.5(9H,m); 4.50(1H,m)	-183.96 (1F,heptet) -73.66 (3F,dq) -72.55 (3F,dq)		5,13

GLPC data was obtained on a Hewlett-Packard 5700A instrument using a 6 ft x 1/8 in 10% SP-2100 column. Retention times and peak areas were obtained from a HP 3390A digital recording integrator.

PROCEDURE

Reactions in DMF were conducted by adding the perfluoroalkyl iodide in one portion to a stirred DMF solution of the thiolate salt and olefin, if used, under argon. The colorless solution immediately turned bright yellow. After stirring for times indicated in Table 1, the solutions were diluted with several volumes of ether. The ether solutions were washed several times with water, dried over $MgSO_4$,and analyzed by GLPC. In some cases,the products were isolated by concentration of the ether solution and distillation of the residue under reduced pressure.

The phase transfer reactions were conducted by adding a deoxygenated benzene or methylene chloride solution of the perfluoroalkyl iodide and olefin, if used, to the aqueous thiolate solution. The bright yellow solutions were vigorously stirred by magnetic stirring bars for the times indicated in Table 1, then worked up and analyzed as above.

Product properties are summarized in Table 2.

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