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PERFLUOROALKYLATION OF 2-MERCAPTOBENZOTHIAZOLE AND ITS ANALOGUES WITH PERFLUOROALKYL IODIDES BY AN $S_{RN}1$ REACTION

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SUMMARY

The thiolates, generated in situ by the reaction of 2-mercaptobenzothiazole (1) and its analogues (2) and (3) with sodium hydride, react under UV irradiation with perfluoroalkyl iodides **(4)**-**(8)** to give the corresponding heteroaromatic perfluoroalkyl sulfides **(9)**-**(18)** in 50-98% yields. The fact that the UV irradiation increases the conversion of perfluoroalkyl iodides and that the radical scavenger di-tert-butylnitroxide suppresses the reaction demonstrates that the reaction proceeds via an $S_{RN}1$ mechanism.

INTRODUCTION

The single electron transfer (SET) process is now well recognised as a fundamental reaction in organic chemistry and in the last two decades it has increased in importance in organofluorine chemistry [1]. The S-perfluoroalkylation of aromatic [2-4], heteroaromatic [5] and aliphatic thiols [2,6] with perfluoroalkyl iodides has been described in a series of papers,but so far,no reports on N-perfluoroalkylation have appeared. Beugelmans et al [7] reported that amino groups (NH) of heterocycles react by an $S_{RN}1$ mechanism with p-nitrobenzyl chloride and gem-halonitroalkanes to give N-alkylation products. Similar heterocycles such as imidazole and benzotriazole react with long

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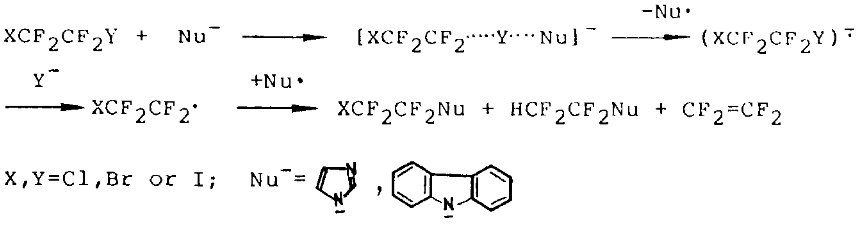
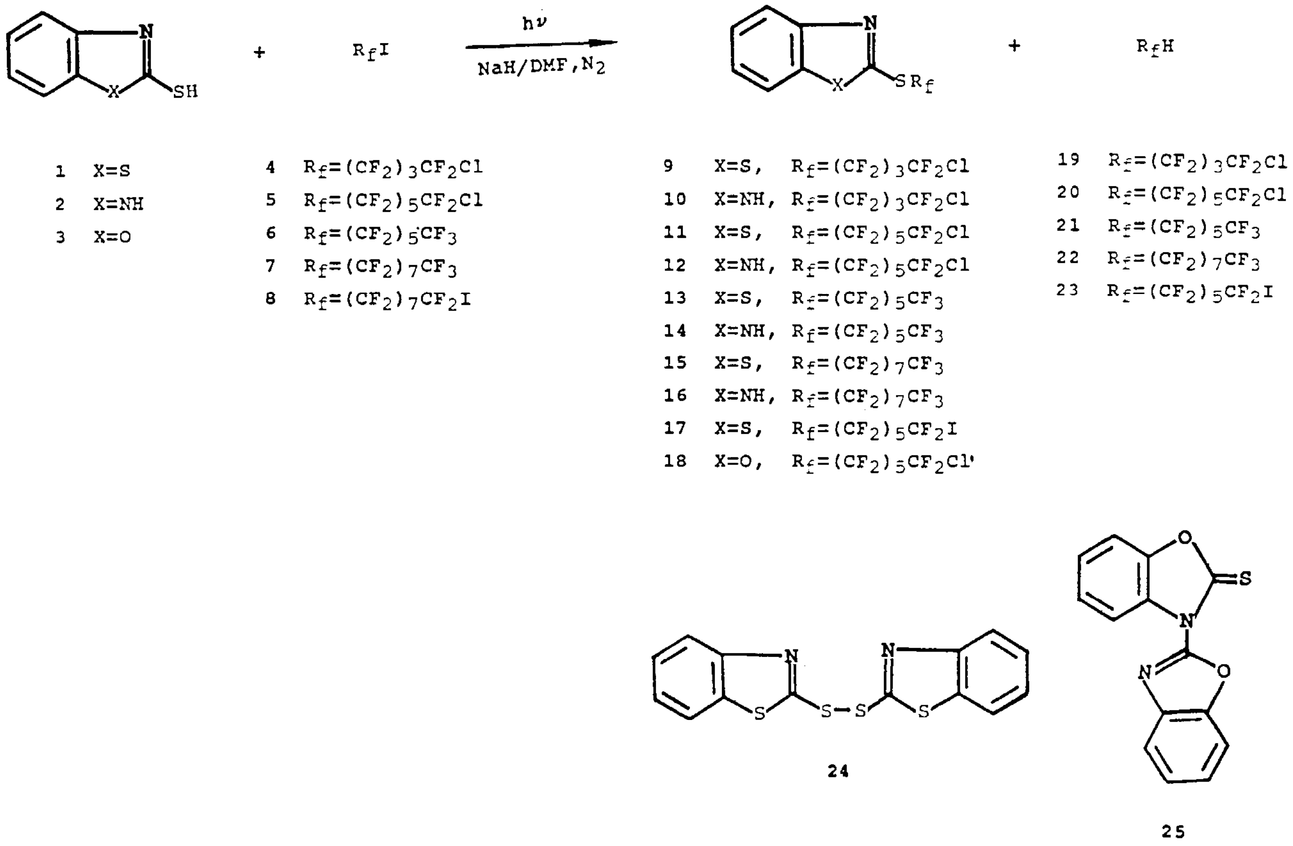
chain perfluoroalkyl iodides, however, to give C-perfluoroalkylation products [8]. Recently, in our laboratory, it was noted that β-halogenperfluoroethyl halides could be successfully used for heterocyclic N-perfluoroalkylation, which was preliminarily thought to proceed via an SET-induced anionic chain mechanism (**Scheme 1**) [9]. We have now extended these studies to 2-mercaptobenzothiazole (**1**) and its analogues 2-mercaptobenzimidazole (**2**) and 2-mercaptobenzoxazole (**3**), in which the N and S atoms, through a tautomeric equilibrium, could both undergo perfluoroalkylation.



Scheme 1.

RESULTS AND DISCUSSION

Treatment of the appropriate perfluoroalkyl iodides (**4**)-(**7**) under ultraviolet (UV) irradiation with the sodium salt, generated in situ from 2-mercaptobenzothiazole (**1**) and sodium hydride in DMF, gave medium to excellent yields of perfluoroalkyl sulfides (**9**),(**11**),(**13**) and (**15**)(see **Scheme 2** and Entries 1,7,13 and 15 in Table 1). The perfluoroalkyl groups were mainly directed to the S atom resulting in the products of S-perfluoroalkylation and partially gave the corresponding hydrogen-abstracted products (**19**)-(**22**).The photochemical product (**17**) may be prepared similarly by treating (**1**) with diiodide (**8**) (2:1, molar ratio), one end of which is attached to the sulfur atom (Entry 17). The use of (**1**) often affords the coupling product(**24**).



1 X=S
2 X=NH
3 X=O

4 $R_f=(CF_2)_3CF_2Cl$
5 $R_f=(CF_2)_5CF_2Cl$
6 $R_f=(CF_2)_5CF_3$
7 $R_f=(CF_2)_7CF_3$
8 $R_f=(CF_2)_7CF_2I$

9 X=S, $R_f=(CF_2)_3CF_2Cl$
10 X=NH, $R_f=(CF_2)_3CF_2Cl$
11 X=S, $R_f=(CF_2)_5CF_2Cl$
12 X=NH, $R_f=(CF_2)_5CF_2Cl$
13 X=S, $R_f=(CF_2)_5CF_3$
14 X=NH, $R_f=(CF_2)_5CF_3$
15 X=S, $R_f=(CF_2)_7CF_3$
16 X=NH, $R_f=(CF_2)_7CF_3$
17 X=S, $R_f=(CF_2)_5CF_2I$
18 X=O, $R_f=(CF_2)_5CF_2Cl$

19 $R_f=(CF_2)_3CF_2Cl$
20 $R_f=(CF_2)_5CF_2Cl$
21 $R_f=(CF_2)_5CF_3$
22 $R_f=(CF_2)_7CF_3$
23 $R_f=(CF_2)_5CF_2I$

24

25

Scheme 2.

TABLE 1

Reaction of Perfluoroalkyl Iodides With Thiolates (DMF,70°C,10h)

Entry	Substrates[a]		NaH (equ.of R_fI)	Reaction Condition[b]	Conversion of R_fI(%)[c]	Products(yield,%)[d]		
	Het.	R_fI				Compound	R_fH[c,e]	Other[f]
1	1	**4**	2.0	A	72.2	**9**(57)[g,h]	**19**(32)	**24**(16)
2	1	**4**	2.0	B	8.5	**9**(53.2)[i]	**19**(46.5)	**24**(trace)
3	1	**4**	2.0	C	30		**19**(41.7)	j
4	2	**4**	1.5	A	67	**10**(60.6)[g,k]	**19**(11)	j
5	**2**	**4**	1.5	B	~3	**10**(100)[i]		
6	**2**	**4**	1.5	C	20	**10**(43)[i]	**19**(57)	
7	**1**	**5**	1.0	A	79	11(78)[g,h]	**20**(17.1)	**24**(14.3)
8	**1**	5	1.0	B	~0			
9	1	5	1.0	C	28	11(66.6)[i]	**20**(33.3)	
10	**2**	5	1.5	A	76.5	**12**(50)[g,k]	20(21)	j
11	2	**5**	1.5	B	~0			
12	2	**5**	1.5	C	16.7		**20**(60)	j
13	1	**6**	1.0	A	54.7	13(98)[g,h]	**21**(trace)	**24**(16)
14	**2**	**6**	1.5	A	89	**14**(87.2)[g,k]	**21**(5.6)	
15	1	**7**	1.0	A	84.3	**15**(85)[g,k]	**22**(trace)	**24**(13)
16	**2**	7	1.5	A	92	**16**(85)[g,k]	**22**(trace)	
17	**1**	**8**	2.0	A	25	**17**(78)[g,h]	**23**(14)	**24**(38.6)
18	**3**	**5**	2.0	A	35	**18**(42.9)[i]	**20**(57.1)	**25**(35.6)[h]

[a] Equimolar ratio except **(1)**:**(8)**=2:1;

[b] A: $h\nu$; B: heat; C: $h\nu$,with addition of 20% mole of $\underline{t}$-$Bu_2N\dot{-}O$;

[c] Determined by ^{19}F NMR,based on reference to $ClCF_2$ moiety (Entries 1-12 and 18) and trifluoroacetic acid (Entries 13-17) respectively;

[d] In ^{19}F NMR,the yield of the fluorinated product plus that of R_fH is 100% except entries 3,4,10 and 12;

[e] Product has a characteristic signal at ~61-62ppm (2F,d,$\underline{J}$=56Hz,HCF_2).Other peaks are near those of the corresponding R_fI;

[f] Isolated yields of **(24)** and **(25)** are based on **(1)** and **(3)** respectively;

[g] Isolated yields;

[h] Isolated by chromatography (silica gel),eluants as follows: ethyl acetate-petroleum (1:1) and (3:7) for **(9)** and **(13)** respectively;toluene-cyclohexane (1:1),(3:7) and (2:5) for **(11)**,**(17)** and **(25)** respectively;

[i] Yield determined by ^{19}F NMR and structure proposed both by ^{19}F NMR and by analogy with the isolated products **(9)**-**(17)**;

[j] A small amount of product detected by ^{19}F NMR has a characteristic signal at ~33 ppm,probably due to the product of aromatic $\underline{C}$-perfluoroalkylation;

[k] Isolated by crystallization from ethanol.

Treatment of perfluoroalkyl iodides (**4**)-(**7**) and (2) rather than (**1**) under UV irradiation afforded similar results (Entries 4,10,14 and 16). The reaction mainly led to the formation of perfluoroalkyl sulfides (**10**),(12),(**14**) and (**16**).

When 2-mercaptobenzoxazole (3) was employed as substrate, aryl sulfide (**18**) was obtained in a lower yield. Instead, a large amount of hydroperfluoroalkane (**20**) was the main product, accomplished with 35.6% isolated yield of heterocycle (25) (Entry 18 in Table 1).

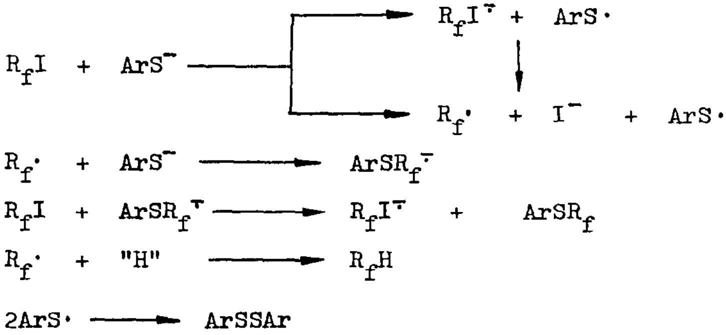
Proofs of structures for the assigned heterocycles are based on elemental analyses, mass, NMR, infrared and ultraviolet spectra (see Table 2 and Table 3).The IR absorption at 1450cm^{-1} reveals the presence of C=N bond. The characteristic fluorine signals of the SCF_2 moiety are observed around δ 8-9.6ppm as a singlet. The ultraviolet spectra contain two characteristic long-wave absorption maxima: one in the region of 217-235 mu, and the other at ~285 mμ, which are attributable to the S-substituted derivatives [10,11].

The formation of S- rather than N-perfluoroalkylation may be because the sulfur anion is more nucleophilic towards carbon than the nitrogen anion, i.e. nucleophilicity is the dominating factor [12].

In order to get further evidence, comparative reactions were carried out in daylight (70°C) instead of under UV irradiation. The conversion of (**4**) in reaction with (**1**) was lowered from 72% to 8%, and in reaction with (**2**) was decreased from 67% to 3% (compare Entry 1 with 2,and Entry 4 with 5). No reactions were observed on treatment of (**5**) with (**1**) and (**2**) (Entry 8 and 11).

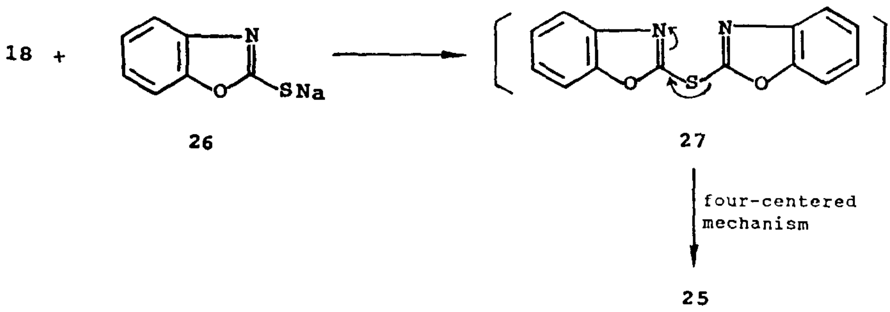
From the results,it was anticipated that addition of a radical inhibitor would suppress the reaction and this has been found to be the case. The repeated reactions under UV light,with addition of 20% molar di-tert-butylnitroxide, an SET scavenger, indicate that the conversion ratios of perfluoroalkyl iodides are noticeably reduced (compare Entry 1 with 3,Entry 4 with 6, Entry 7 with 9 and Entry 10 with 12).

The S-perfluoroalkylation of thiolates is formed via an $S_{RN}1$ mechanism, which was proposed and was well investigated previously [6]. The fact that UV irradiation promotes the reactions and that the inhibitor, in contrast to UV light, suppresses the process plus the known resistance to displacement of halides from perfluoroalkyl halides by S_N1 or S_N2 processes [13,14] supports the proposed $S_{RN}1$ mechanism. The isolation of coupling product **(24)** is a convincing evidence that radicals occur in the reaction system and further confirms the mechanism described in **Scheme 3**.



Scheme 3.

Detailed insight into the formation of **(25)** was not sought, but the literature showed that **(27)** can readily undergo rearrangement to afford (25) [15,16]. It is assumed that (27) is an intermediate, which might be formed by the attack of **(26)** on **(18)** and from which the observed product (25) is offered in a four-centered mechanism as in **Scheme 4**.



Scheme 4.

TABLE 2

Data For Products

Compd (Formula)	m.p.[a] (°C)	MS[b] (m/z,%)	IR[c] (cm^{-1})	UV[d] (mμ)	elemental analysis(Calcd/Found) C	 H	 N	 F	 S	 Cl/I
9	44-46	401(21.9%)	1125,1200(vs,C-F)	217	32.84	1.00	3.48	37.81	15.92	8.95
($C_{11}H_4NClF_8S_2$)		403(7.9)	1450(m,C=N)	285	32.66	1.22	3.38	37.43	15.71	8.60
10	223-224	384(64.3)	1130,1200(vs,C-F)	217	34.33	1.30	7.28	39.53	8.32	9.23
($C_{11}H_5N_2ClF_8S$)		385(52.1)	1420(m,C=N),3060(NH)	287	34.35	1.16	7.14	39.51	8.59	9.12
11	57-58	501(30.5)	1140,1210(vs,C-F)	225	31.08	0.80	2.79	45.42	12.75	7.07
($C_{13}H_4NClF_{12}S_2$)		503(15.2)	1450(m,C=N)	285	31.19	0.60	2.64	45.09	12.95	7.12
12	232-234	484(28.0)	1130,1200(vs,C-F)	230	32.20	1.03	5.78	47.06	6.60	7.33
($C_{13}H_5N_2ClF_{12}S$)		486(10.3)	1420(m,C=N),2930(NH)	287	32.19	1.26	5.65	47.31	6.84	7.12
13	46-47	483(64.0)	1140,1200(vs,C-F)	235	32.16	0.82	2.89	50.93	13.20	
($C_{13}H_4NF_{13}S_2$)		484(18.3)	1460(w,C=N)	285	32.30	0.67	2.98	51.09	13.57	
14	221-222	468(22.2)	1140,1200(s,C-F)	225	33.33	1.07	5.13	52.78	6.84	
($C_{13}H_5N_2F_{13}S$)		469(100)	1400(s,C=N)	288	33.34	0.95	5.26	52.91	6.86	

15	156-157	585(40.6)	1150,1200(vs,C-F)		30.77	0.68	2.39	55.21	10.94	
($C_{15}H_4NF_{17}S_2$)			1465(m,C=N)		31.03	0.65	2.48	55.56	10.81	
16	207-208	568(100)	1140,1200(vs,C-F)		31.69	0.88	4.93	56.87	5.63	
($C_{15}H_5N_2F_{17}S$)		569(99.5)	1400(m,C=N),2950(NH)		31.44	0.65	4.78	56.97	5.76	
17	89-90	592(40.8)	1140,1200(vs,C-F)	233	26.31	0.67	2.36	38.45	10.79	21.42
($C_{13}H_4NF_{12}S_2I$)		593(7.5)	1450(m,C=N)	285	26.42	0.89	2.36	38.11	10.77	21.35
24	179-180^{e,f}									
($C_{14}H_8N_2S_4$)										
25	162-163^{f,g}									
($C_{14}H_8N_2O_2S$)										

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[a] Taken in open capillaries,uncorrected,product recrystallized from ethanol except (**24**);

[b] Recorded on a Finnigan-402 spectrometer;

[c] Measured on a Shimadzu IR-440 spectrophotometer (KCl pellets);

[d] Performed on a Shimadzu Dual-wavelength TLC Scanner CS-910;

[e] Recrystallized from DMF/H_2O,see TCI Catalog,28 (1986) 342;

[f] See ref. [16];

[g] See ref. [15].

TABLE 3

^{1}H and ^{19}F NMR Data

Compd (No.)	NMR(ppm)[a,b]	
	^{19}F	^{1}H
9	-7.5(2F,s,$ClCF_2$),9.3(2F,s,SCF_2), 42.3(2F,s,$ClCF_2$),43.3(2F,s,$SCCF_2$)	(2H,t,ArH),8.3(1H, m,ArH)
10	-8.3(2F,s,$ClCF_2$),8.5(2F,s,SCF_2) 41.3(2F,s,$ClCCF_2$),42.2(2F,s,$SCCF_2$)	7.5(3H,m,ArH,NH), 7.7 (2H,m,ArH)
11	-7.5(2F,s,$ClCF_2$),9.6(2F,s,SCF_2) 42.6(2F,s,$ClCCF_2$),44.3-44.8(6F,m, $SC(CF_2)_3$)	7.4(2H,m,ArH),7.7(1H, m,ArH)
12	-8.0(2F,s,$ClCF_2$),8.6(2F,s,SCF_2), 42.3-44.0(8F,m,$SC(CF_2)_4$)	7.3(2H,m,ArH),7.6(2H, m,ArH),13.6(1H,s,NH)
13	5.3(3F,s,CF_3),9.6(2F,s,SCF_2),43.3 (2F,s,CF_2),45.3(2F,s,$SCCF_2$),47.0 (2F,s,CF_2),50.3(2F,s,CF_2)	7.2(2H,m,ArH),7.7(2H, m,ArH)
14	3.6(3F,s,CF_3),8.0(2F,s,SCF_2),41.6 (2F,s,CF_2),44.0(2F,s,$SCCF_2$) 45.3(2F,s,CF_2),48.6(2F,s,$SCCF_2$)	7.8(2H,m,ArH),8.0(2H, m.ArH),NH was obscured
15	7.0(3F,s,CF_3),9.6(2F,s,SCF_2),42.3-48.6(10F,m,$5CF_2$),50.3(2F,s,CF_2)	7.5(2H,m,ArH),8.1(2H, m,ArH)
16	4.3(3F,s,CF_3),8.5(2F,s,SCF_2),42.3 (2F,s,CF_2),45.0(8F,m,$4CF_2$),49.3 (2F,s,CF_2)	7.2(2H,m,ArH),7.4(2H, m,ArH)
17	-12.0(2F,s,ICF_2),9.5(2F,s,SCF_2), 37.3(2F,S,$ICCF_2$),42.6(2F,s,$SCCF_2$), 44.6(4F,s,middle $2CF_2$)	7.3(2H,m,ArH),7.7(2H, m,ArH)
18	-8.3(2F,s,$ClCF_2$),9.3(2F,s,SCF_2), 42.5-44.5(8F,s,$4CF_2$)	

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[a] Recorded on a Varian EM-360L spectrometer,TMS as internal reference for ^{1}H and except **(13)**-**(16)** TFA as external standard for ^{19}F;

[b] Solvents as follows:CCl_4 for **(9)**;DMSO-d_6 for **(10)**,**(12)**,**(14)**-**(16)**;

EXPERIMENTAL

General procedure: Under a nitrogen atmosphere, 80% pure sodium hydride (10-20 mmole) was added to 10ml DMF solution of 2-mercaptobenzoheterocycle (10 mmole) in a Pyrex flask. After stirring for several minutes, the corresponding perfluoroalkyl iodide was added and was exposed to a high pressure mercury lamp (400w) at a distance of about 15 cm from the flask for 10h (70°C). The conversion rate was determimed and the R_fH was detected by ^{19}F NMR as noted in Table 1. To the reaction mixture was added 2ml ethanol,then 20ml water and 20ml ethyl acetate. Product (24) was collected by filtration.The mixture was extracted with ethyl acetate, washed with water and isolated by chromatographic techniques and/or crystallization from ethanol(see Tables 1 and 2).

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