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Fluoroalkene chemistry
Part 1. Highly-toxic fluorobutenes and their mode of toxicity: reactions of perfluoroisobutene and polyfluorinated cyclobutenes with thiols

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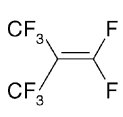
Abstract

The reactions of four highly-toxic fluorobutenes – perfluoroisobutene (PFIB), 1-hydropentafluorocyclobutene (1-H), hexafluorocyclobutene (HFCB) and 3-chloropentafluorocyclobutene (3-Cl)—with propanethiol, 2,6-dimethoxybenzenethiol and *N*-acetylcysteine isopropyl ester were studied. PFIB and HFCB reacted with two molar equivalents of the aliphatic thiols, but with only one molar equivalent of the aromatic thiol (presumably due to steric hindrance) and resembled phosgene in their reactivity. The fluorocyclobutenes 1-H and 3-Cl reacted with one and up to three molar equivalents of the aliphatic thiols, respectively, but with only one molar equivalent of the aromatic thiol. The products of allyl and vinyl substitution were isolated and characterised as fully as possible. The inhalation toxicities of the fluorocyclobutenes to rodents correlated with the number of easily-displaceable fluorine substituents, supporting the contention that toxicity is due to reaction with biological thiols in the lung.

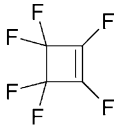
Keywords: Fluorinated alkenes and cycloalkenes; Hexafluorocyclobutene; Perfluoroisobutene; Phosgene; Nucleophilic reactions; Thiol; Toxicity

1. Introduction

Many monofluorinated compounds are highly toxic by metabolism to 2*R*,3*R*-2-fluorocitrate or by inhibition of the enzyme acetylcholinesterase, but some polyfluorinated materials such as highly fluorinated alkenes are also poisonous [1–4]. One of the most toxic is perfluoroisobutene (PFIB),[1] a by-product of Teflon™ manufacture whose toxicity is legendary [8–14]. Other fluorinated alkenes such as hexafluorocyclobutene (HFCB) are also toxic by inhalation. Once inhaled, PFIB and HFCB produce a potentially lethal build up of fluid in the lung 'pulmonary oedema' after a latent period of many hours [15,16].



PFIB
bp 6 °C



HFCB
bp 5 °C

The ability of fluoroalkenes to react easily with nucleophiles distinguishes them from alkenes and is pronounced in the case of PFIB and HFCB [17]. Comparative data on rates of reaction of the fluoroalkenes with nucleophiles are unavailable, although from experience PFIB appears more reactive than HFCB; the reactivity of acyclic fluoroalkenes declines in the order $(R_F)_2C{=}CF_2 > R_FCF{=}CFR_F$ [18].

Addition to the double bond occurs with nucleophiles under acidic or neutral conditions. Under basic conditions, addition is usually accompanied by dehydrofluorination (this distinguishes PFIB and HFCB from less fluorinated alkenes for which addition is to a large extent characteristic). The carbanion intermediates can eliminate fluoride from the carbon bonded to the nucleophile giving the *vinyl substitution* pro-

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[1] PFIB is included in Schedule 2B of the Chemical Weapons Convention (CWC) which entered into force on 29 April 1997 and bans the development, production, stockpiling and use of chemical weapons [5]. PFIB was incorporated into the final text of the CWC after prompting by one delegation during the Conference on Disarmament [6]. Concern was raised over the potential military utility of PFIB [7] and related highly-toxic fluorinated gases.

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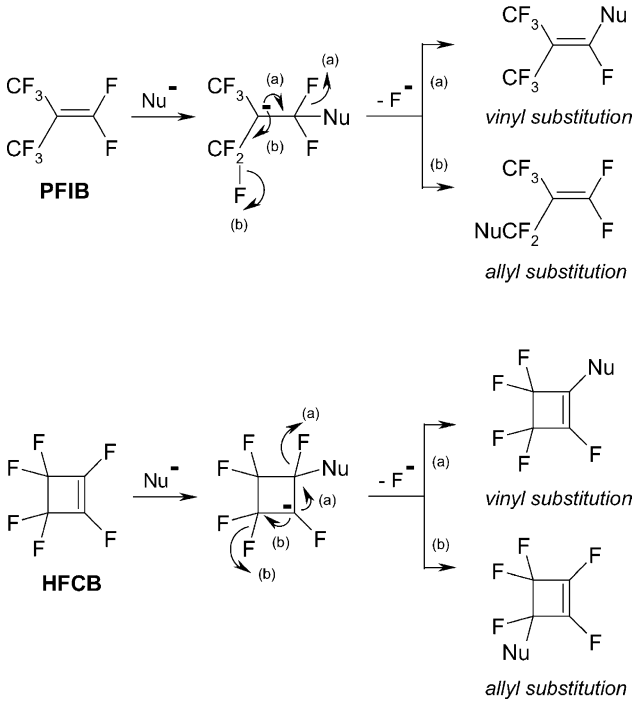


Fig. 1. Carbanions from attack of a nucleophile on PFIB and HFCB and possible products arising from loss of vinylic (a) or allylic (b) fluorine as fluoride.

duct, or from the CF_3 group (PFIB) or the CF_2 group (HFCB) giving the *allyl substitution* product (Fig. 1). The relationship between vinyl and allyl substitution is determined by the nature of the nucleophile and the reaction conditions. Vinyl substitution usually predominates unless the allylic position contains a good leaving group (e.g. a halogen atom other than fluorine). In this case, allyl substitution can occur more easily, sometimes to the exclusion of vinyl substitution. Often vinyl and allyl products can undergo further addition–elimination to give poly-substituted products.

Highly-toxic fluoroalkenes such as PFIB are essentially insoluble in water [19] and have a high affinity for thiols in the lung. A rapid fall in lung cysteine and glutathione levels was observed in rodents exposed to PFIB [20]. Cysteine esters administered as pretreatments increased intracellular thiol levels and protected against lethal doses, presumably by reacting with the fluoroalkene in preference to cellular components [21–23]. Cysteine isopropyl ester was later shown to combine with PFIB in aqueous solution to give a thiazole [24], implicating direct reaction as part of the protective mechanism. We showed that the acute inhalation toxicity towards rodents of PFIB, HFCB and close structural analogues correlated with their reactivities towards thiols in the lung [25]. Inhalation toxicity data appear in Table 1. Several structure-toxicity relationships are evident:

- Vinyl hydro analogues have low toxicity (1-H versus HFCB).
- Vinyl chloro and bromo analogues are less toxic than the perfluoro prototype (1-Cl and 1-Br versus HFCB).

Table 1
Inhalation toxicities of fluorobutene analogues in mice and rats [4,25]

Fluorobutene	Designation	LCt_{50} mice[a] (mg min m^{-3})	LCt_{50} rats[a] (mg min m^{-3})	Toxicity group[b]
F_2C—CH / F_2C—CF	1-H	10,000–20,000	>80,000	I
F_2C—CCl / F_2C—CF	1-Cl	6000	10,630	II
F_2C—CBr / F_2C—CF	1-Br	>6750	6460	II
F_2C—CF / F_2C—CF	HFCB	6000	4410	II
F_2C—CF / ClFC—CF	3-Cl	1930	1910	III
F_2C—CF / BrFC—CF	3-Br	1890	1310	III
$(CF_3)_2C{=}CF_2$	PFIB	880[c]	1200	–
$O{=}CCl_2$	Phosgene	1800	3000	–

[a] The LCt_{50} is the lethal concentration that kills 50% of a group of animals and is expressed in milligrams of fluoroalkene per metre cubed multiplied by the exposure time t in minutes (mg min m^{-3}). It is based on deaths occurring up to 14 days following exposures of 10 min duration. 95% confidence limits can be found elsewhere [25].

[b] For an explanation of the toxicity groups, see Section 2.6.

[c] The preliminary LCt_{50} of PFIB in mice was reported as 980 mg min m^{-3} in an earlier paper [24]; the revised figure is now 880 mg min m^{-3}.

- Vinyl chloro and bromo analogues are less toxic than allyl isomers (1-Cl versus 3-Cl and 1-Br versus 3-Br).
- Allyl chloro and bromo analogues are more toxic than HFCB (3-Cl and 3-Br versus HFCB).
- The most toxic fluoroalkene tested was PFIB, which is more toxic than phosgene.

The purpose of the work described here was to examine the reactions of some toxic fluorobutenes with model biological thiols and to use the results to explain the toxicity order. Few additions of thiols to PFIB and HFCB appear in the literature. Mono or bis-vinyl substitution products have been obtained by treating PFIB with thiophenols in the presence of a tertiary amine [24] or with alkali-metal mercaptides [26,27] or thiophenoxides [28]. Disubstituted products have been obtained from the reaction of HFCB with butanethiol or mercaptoacetic acid with Triton B as base [29] or with toluene-3,4-dithiol with potassium carbonate as base [30]. In this study, the reactions of PFIB and three fluorocyclobutanes (1-H, HFCB, 3-Cl) with propanethiol, 2,6-dimethoxybenzenethiol and *N*-acetylcysteine isopropyl ester were examined. Propanethiol and *N*-acetylcysteine isopropyl ester, with accessible SH groups, have reactivities comparable to those of the lung thiols cysteine and glutathione.[2] Steric hindrance of the thiol

[2] The tripeptide glutathione (γ-glutamylcysteineglycine) is the most common intracellular thiol; it contains a primary SH group and is present in mammalian cells in concentrations between 0.5–10 mM.

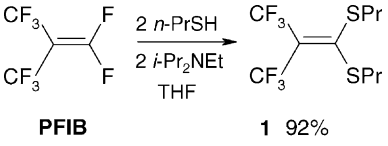
group often lowers reactivity, and 2,6-dimethoxybenzenethiol models a biological thiol that is part of a larger structure such as a protein.

2. Results and discussion

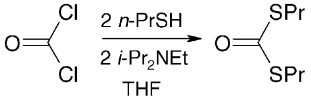
2.1. Perfluoroisobutene and phosgene

The hallmark of acute lung injury caused by PFIB is a breach in the permeability characteristics of the air–blood barrier of the lung that manifests itself as pulmonary oedema. The symptoms are very similar to those caused by inhalation of phosgene [31–33], so it is possible that both PFIB and phosgene share a common mechanism of action. Therefore, both were treated with two molar equivalents of propanethiol to compare their behaviour under the same conditions.[3]

In line with previous results [24], PFIB gave the ketene dithioacetal **1**. The IR stretching frequency of the double bond in **1** (1526 cm^{-1}) was much lower than that in PFIB (1751 cm^{-1}). Phosgene gave the dithiocarbonate **2** whose carbonyl stretch appeared at 1647 cm^{-1}. The $(CF_3)_2C{=}C$ group of PFIB is isoelectronic with the O=C group of phosgene and both gases react similarly with thiols, suggesting a common mechanism of action. Successful use of *N*-acetylcysteine to alleviate the symptoms of both PFIB [20–23] and phosgene poisoning [34] supports this theory.

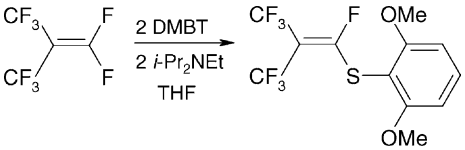


PFIB **1** 92%



phosgene **2** 85%

Treatment of PFIB with two molar equivalents of 2,6-dimethoxybenzenethiol (DMBT) led to the isolation of only the mono-vinyl species **3**. Here a second nucleophilic attack was probably prevented by electron-donation from the 2,6-dimethoxybenzenethio substituent to the double bond and steric hindrance. Allylic substitution was not detected in this case.



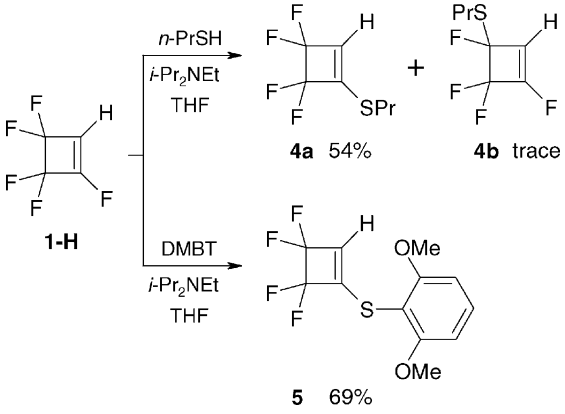
PFIB **3** 58%

[3] Additions of fluoroalkenes to the thiols were carried out at −78 °C. After addition, reaction mixtures were allowed to warm up to room temperature and were left for 12 h prior to work up. This procedure was used throughout.

In the two cases presented, attack on PFIB takes place at the difluoromethylene group as this is the most electrophilic site. Likewise attack by nucleophiles on substituted fluorocyclobutenes occurs on the most positive carbon atom of the double bond, as will now be seen.

2.2. 1-Hydropentafluorocyclobutene (1-H)

1-Hydropentafluorocyclobutene has only one displaceable leaving group on the double bond and reacts with nucleophiles such as alcohols to give mono products arising from displacement of vinyl fluoride [35]. A similar outcome occurred with thiol nucleophiles, with propanethiol reacting to give a mixture of isomers: vinyl sulfide **4a** and a trace of allyl sulfide **4b**, which could not be separated by chromatography or by distillation. Use of 2,6-dimethoxybenzenethiol gave vinyl sulfide **5** in moderate yield; allylic substitution was not detected in this instance.

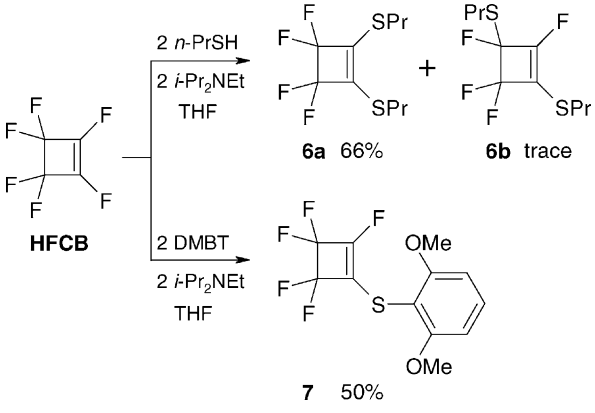


1-H **4a** 54% **4b** trace

5 69%

2.3. Hexafluorocyclobutene (HFCB)

Two equivalents of propanethiol gave the 1,2-bis(sulfide) **6a** (double vinyl substitution) and a trace of its 1,3-isomer **6b** (allyl substitution then either allyl or vinyl substitution). Even with a two molar proportion of 2,6-dimethoxybenzenethiol only the mono-substituted product was obtained. Further reaction was presumably precluded by steric hindrance.



HFCB **6a** 66% **6b** trace

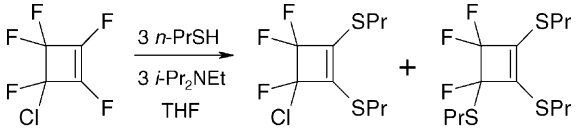
7 50%

Thus, in its behaviour towards thiols, HFCB showed analogous reactivity to PFIB (see Section 2.1) and can

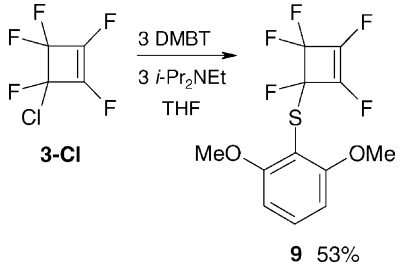
therefore be regarded, in terms of its ability to damage the lung, as an analogue of phosgene, which it also resembles in its toxic effect and symptoms.

2.4. 3-Chloropentafluorocyclobut-1-ene (3-Cl)

3-Chloropentafluorocyclobutene (bp 31–33 °C) was synthesised in 65% yield by heating 3-(fluorosulfato)pentafluorocyclobutene with potassium chloride in diglyme (see Section 3.3). It reacted with an excess of propanethiol to give a mixture of bis vinyl sulfide **8a** and tris sulfide **8b**. The presence of the latter is explained by initial allylic substitution (with loss of chloride), followed by vinyl or allyl substitution, then a final vinyl substitution (with loss of fluoride).



Reaction of 3-chloropentafluorocyclobutene with an excess of 2,6-dimethoxybenzenethiol resulted in displacement of the allylic chlorine, giving sulfide **9**; no evidence was found for further attack at the double bond (a trace of an isomer, presumed to be the vinylic product, was detected in the reaction mixture, but could not be isolated in a pure state by chromatography).[4] The result is useful from a synthetic viewpoint, vinyl sulfide **7** (1674 cm^{-1}) made by treating HFCB with 2,6-dimethoxybenzenethiol is isomeric with allyl sulfide **9** (1784 cm^{-1}) which displays a C=C stretch close to that for HFCB (1798 cm^{-1}) and for 3-Cl (1795 cm^{-1}) confirming that the arylthio group is not attached to the double bond.



2.5. Reactions with N-acetylcysteine isopropyl ester

Perfluoroisobutene, 1-hydropentafluorocyclobutene and hexafluorocyclobutene reacted with *N*-acetylcysteine isopropyl ester under mild conditions to give vinyl substitution products (Fig. 2). The substitution pattern was the same as in previous experiments, 1-H combining with one molar equivalent of thiol, and PFIB and HFCB combining with two. It is likely that some of the protective action of cysteine esters administered as pretreatments in animals prior to fluorobutene exposure will be due to reaction of the thiol with the incoming gas.

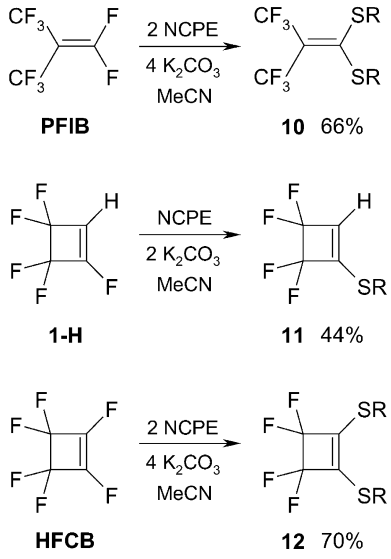
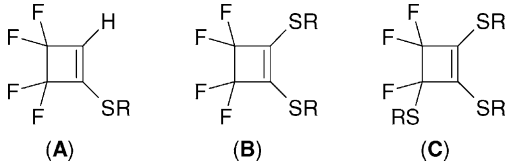


Fig. 2. Products of reaction of fluorobutenes with *N*-acetylcysteine isopropyl ester (NCPE) where R = $CH_2CH(NHAc)CO_2Pr$-*i*.

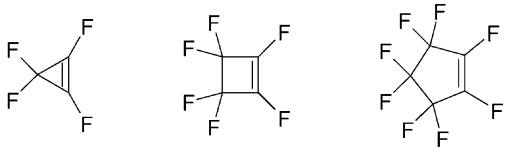
2.6. Discussion

The susceptibility of fluorobutenes towards attack by biological nucleophiles, such as thiols, accounts for their toxicity, and the author has classified them into Toxicity Groups (I-III) according to their observed alkylating abilities. Group I fluoroalkenes can condense with one molar equivalent of thiol, Group II fluoroalkenes with two, and Group III fluoroalkenes with three. In the absence of special effects, toxicity increases on progressing from Group I through Group II to Group III (Table 1). The toxicities of the fluorobutenes correlate with their susceptibilities towards attack by thiols. 1-Hydropentafluorocyclobutene, which reacts with thiols to give mono-substituted products (**A**), is the least toxic compound of the series. The similar toxicities of HFCB and its 1-chloro and 1-bromo analogues can be rationalised on the basis of their similar electrophilicities and the fact that they are all bis-alkylating agents, giving disubstituted products (**B**) with thiols. The greater toxicities of the 3-chloro and 3-bromopentafluorocylobutenes are ascribable to their ability to act as tris-alkylating agents, giving trisubstituted products (**C**).



[4] Other polyfluorocyclobutenes with an allylic leaving group undergo similar reaction with oxygen nucleophiles; methanolysis of 3-(fluorosulfato)pentafluorocyclobutene yielded the corresponding 3-methoxy ether in 80% yield [36].

Further evidence that biological activity correlates with fluorocycloalkene reactivity was provided by a study of the effect of ring size on toxicity. It was found that inhalation toxicity to mice decreased in the order perfluorocyclopropene > HFCB > perfluorocyclopentene [4]. Perfluorocyclopropene is the most toxic cycloalkene examined to date, its toxicity approaching that of PFIB. It is highly electrophilic and reacts violently with nucleophiles, often with ring opening, to give polysubstituted adducts [37].



1000 6000 >100 000

LCt_{50} values in mice (mg min m^{-3}, 10 min exposures)

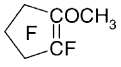
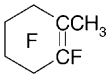
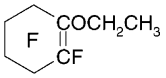
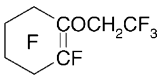
Several cyclic fluoroalkenes previously shown to be toxic are listed in Table 2. They are ranked into toxicity groups according to their projected ability to act as mono- or bis-alkylating agents. Such classification gives rise to the following predictions:

- Group I cycloalkenes having a 1-OCH_2R_F substituent are likely to be more toxic than analogues with a 1-OCH_2R substituent (as vinyl fluoroalkoxy groups can stabilise carbanionic intermediates derived from nucleophilic attack better than alkoxy groups; there is also the possibility that the fluoroalkoxy substituent could be displaced by thiols).
- Group II fluorocyclopentenes should be more toxic than the corresponding Group II fluorocyclohexenes (as they are more reactive).
- Group II fluoroalkenes having a 1,2-difluoro substitution pattern are expected to be more toxic than 1,2-dichloro analogues (as they are more reactive).

3. Experimental

The following were made using literature procedures—*N*-acetylcysteine isopropyl ester (method similar to that for cysteine isopropyl ester [20]), 1-hydropentafluorocyclobutene [40], PFIB [41] and 2,6-dimethoxybenzenethiol [42]. HFCB was obtained from Apollo Scientific Ltd (Derbyshire, UK). *N*,*N*-Diisopropylethylamine was obtained from Aldrich (Gillingham, UK) and used as received. Anhydrous solvents were used for reactions: THF was distilled from sodium/benzophenone. Petroleum ether refers to the fraction with boiling range between 40–60 °C. TLC was performed on MK6F silica gel 60 Å plates (Whatman, USA) with detection by UV light ($\lambda = 254$ nm) and I_2 vapour. Sorbsil C30 40/60 silica was used for column chromatography. Melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Nicolet SP210 instrument using Omnic software. NMR spectra were obtained on a Jeol Lambda 500 instrument (operating at 470 MHz for ^{19}F, 500 MHz for ^{1}H, and 125 MHz for ^{13}C spectra); products were examined as solutions in $CDCl_3$, with $CFCl_3$ and $SiMe_4$ as external references for ^{19}F and ^{1}H, respectively. Data are recorded

Table 2
Previously reported biological activities of toxic fluorocycloalkenes [38,39]

Fluoroalkene	Species	Dose	Biological effects	Toxicity group
	Mice	1–2%	Slow induction and recovery; one out of three mice died	I
	Mice	3–7%	Convulsive movements; all mice died within 6 min	II
	Rats	2 ml	Analgesia and respiratory depression; animals died within 18 h	II
	Mice	0.8–3.4%	No anaesthesia; all mice died	I
	Mice	0.1–0.6%	Poor anaesthesia; one out of two mice died	I
	Mice	1.9–2.8%	All mice died in 3 h after 15 min exposure	I[a]
	Mice	0.8–1.5%	No anaesthesia; all mice died after 20 min	II
	Mice	–	LCt_{50} for mice is 109,622 mg min m^{-3} (2 h exposure)	II

[a] If the 2,2,2-trifluoroethoxy group can act as a leaving group, then this compound will belong to toxicity group II.

as follows—chemical shift in ppm from reference on the δ scale, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, tt = triplet of triplets, q = quartet and m = multiplet), coupling constant (Hz) and assignment. Mass spectra were recorded on a Finnigan MAT GCQ instrument using a direct insertion probe; electron impact (EI) with methane as reagent gas or chemical ionisation (CI) in the presence of ammonia.

Caution. Owing to the high inhalation toxicities of the fluoroalkenes, the chemistry described requires a high level of awareness. Experiments must be performed in an efficient, dedicated fume-cupboard. The safest way to handle the toxic gases is to inflate a polypropylene gas bag with a resealing syringe port via a lecture bottle and a short length of rubber tubing; a known volume of gas can then be removed from the bag, as required, using a large gas-tight syringe. Gas bags of 1 liter capacity supplied by SKC Limited (Unit 11, Sunrise Park, Higher Shaftesbury Road, Blandford Forum, Dorset DT11 8ST, UK; Catalogue No. 232-01) are ideal for this type of work and were used for experiments involving PFIB and HFCB.

3.1. 1,1-Bis(propylthio)-2-(trifluoromethyl)-3,3,3-trifluoroprop-1-ene (*1*)

A solution of propanethiol (2.64 ml, 29.2 mmol) and *N*,*N*-diisopropylethylamine (5.1 ml, 29.2 mmol) in THF (50 ml) and a magnetic stirrer bar were placed in a 250 ml round-bottomed flask fitted with a rubber septum. Approximately 300 ml of air were removed from the headspace using a gas-tight syringe. The mixture was cooled to −78 °C and perfluoroisobutene (328 ml, 14.6 mmol) added via the syringe. A slight precipitate of *N*,*N*-diisopropylethylamine hydrofluoride formed. The reaction was left for 12 h at room temperature to ensure completion. Water (50 ml) was added and the mixture transferred to a separating funnel. The organic layer was separated, the aqueous layer extracted with ether (2 × 50 ml) and the ether extracts combined and dried ($MgSO_4$). The drying agent was filtered off and the filtrate concentrated to give a yellow liquid. Chromatography on silica gel, eluting with 9:1 hexane–acetone, gave the title compound as a colourless liquid (4.23 g, 92%). ^{1}H NMR $\delta = 2.9$ (4H, t, $J = 7$ Hz, SCH_2), 1.15 (4H, m, CH_2), 0.96 (6H, $J = 7$, CH_3). ^{13}C NMR $\delta = 162.3$ (s, *C*-CF_3), 121.43 (q, $J = 277$ Hz, CF_3), 117.91 (s, C-S), 37.99 (SCH_2), 23.13 (CH_2), 15.25 (s, CH_3). ^{19}F NMR $\delta = -56.09$ (6F, s, CF_3). IR (film) $\nu = 2970$, 2937, 2878, 1526 (C=C), 1460, 1412, 1382, 1307, 1228, 1207, 1149, 992, 879, 843, 810, 783, 715, 699 cm^{-1}. CI–MS: $m/z = 312$ ($M + 1$, 32), 293 (M-HF, 100), 269 (45). Calcd. for $C_{10}H_{14}F_6S_2$: C, 38.5; H, 4.5; S, 20.5. Found: C, 38.4; H, 4.5; S, 20.3%.

3.2. S,S-Dipropyl dithiocarbonate (*2*)

A solution of propanethiol (2.64 ml, 29.2 mmol) and *N*,*N*-diisopropylethylamine (5.1 ml, 29.2 mmol) in THF (50 ml) and a magnetic stirrer bar were placed in a 250 ml round-bottomed flask fitted with a rubber septum. Approximately 300 ml of air was removed from the headspace using a gas-tight syringe. The mixture was cooled to −78 °C and phosgene (328 ml, 14.6 mmol) added via the syringe. A heavy precipitate of *N*,*N*-diisopropylethylamine hydrochloride formed. The reaction was left for 12 h at room temperature to ensure completion. Water (50 ml) was added and the mixture transferred to a separating funnel. The organic layer was separated, the aqueous layer extracted with ether (2 × 50 ml) and the ether extracts combined and dried ($MgSO_4$). The drying agent was filtered off and the filtrate concentrated to give a yellow liquid. Chromatography on silica gel, eluting with 9:1 hexane–acetone, gave the title compound as a colourless liquid (2.2 g, 85%). ^{1}H NMR $\delta = 3.58$ (4H, t, $J = 7$ Hz, SCH_2), 2.47 (4H, m, CH_2), 1.17 (6H, $J = 7$, CH_3). ^{13}C NMR $\delta = 189.74$ (C=O), 32.48 (SCH_2), 23.24 (CH_2), 15.28 (CH_3). IR (film) $\nu = 2967$, 2933, 2873, 2799, 1647 (C=O), 1457, 1410, 1379, 1340, 1291, 1239, 1204, 1070, 873, 782, 734 cm^{-1}. CI–MS: $m/z = 179$ ($M + 1$, 100), 150 (22). Calcd. for $C_7H_{14}OS_2$: C, 47.1; H, 7.9; S, 36.0. Found: C, 47; H, 7.7; S, 36.1%.

3.3. Synthesis of 3-chloropentafluorocyclobutene (*3-Cl*)

3-(Fluorosulfato)pentafluorocyclobutene [36] (16 g, 0.07 mol) was added dropwise to a stirred suspension of dried powdered KCl (5.2 g, 0.07 mol) in diglyme (50 ml). When the addition was complete, the mixture was heated to 80–90 °C (external bath temperature) for 2 h. The product was distilled from the mixture and fractionated to give the title compound as a colourless mobile liquid (8 g, 65%); bp 31–33 °C. IR (film): $\nu = 1795$ cm^{-1} (C=C). EI–MS: $m/z = 180$, (M^+ $C_4F_5{}^{37}Cl^+$, 9), 178 (M^+ $C_4F_5{}^{35}Cl^+$, 28), 161 (1), 159 (4), 143 (64), 124 (5), 118 (4), 116 (12), 111 (35), 109 (100).[5] HRMS: calculated C_4ClF_5 178.492, found 178.482 (error 0.3).

3.4. Reactions with propanethiol and 2,6-dimethoxybenzenethiol

Hexafluorocyclobutene (224 ml, 10 mmol) was removed from a gas bag using a gas-tight syringe. In a flask sealed with a septum, a mixture of the appropriate thiol (20 mmol) and *N*,*N*-diisopropylethylamine (20 mmol) in THF (15 ml) was cooled to −78 °C and stirred under argon. The syringe needle was inserted through the septum. Contraction due to cooling caused the syringe plunger to deliver the fluoroalkene into

[5] A gas chromatogram showing the fluoroalkene to be 98% pure (retention time 1.6 min) was obtained using a 2 m × 4 mm internal diameter glass column packed with 10% SE-30 on Chromosorb WHP (80–100 mesh) at 30 °C with 25 ml min^{-1} nitrogen as carrier gas. GC–MS spectra were obtained using the same column at the same temperature and 15 ml min^{-1} helium as carrier gas.

the flask. The liquid fluoroalkenes 1-H and 3-Cl were added dropwise via cannula as a solution in THF (15 ml) to a stirred solution of the thiol (1 M or 3 M equivalents) and tertiary amine (1 M or 3 M equivalents) at −78 °C. Reaction occurred immediately and TLC after 1 h confirmed the disappearance of the thiol. The mixture was allowed to warm to room temperature. Products were isolated by (A) removing the solvent and chromatography of the residue on silica using 4:1 petrol–ethyl acetate or petrol–ether as eluent (except where stated otherwise), or (B) washing with saturated aqueous $NaHCO_3$ (2×5 ml), extracting with dichloromethane (3×10 ml), drying ($MgSO_4$), filtering, removing the solvent and distilling the residue under reduced pressure in a Kugelrohr apparatus (oven temperatures quoted).

3.5. 1,3-Dimethoxy-2-{[1,3,3,3-tetrafluoro-2-(trifluoromethyl)prop-1-en-1-yl]thio}benzene (3)

Work-up A (with hexane, followed by 15:1 hexane–acetone as eluents), gave the title compound as a pale yellow liquid (58%). R_f 0.1 in hexane. ^{1}H NMR $\delta = 7.4$ (1H, dd, each $J = 8$, 4-H), 6.6 (2H, d, $J = 8$ Hz, 3- and 5-H), 3.9 (6H, s, OCH_3). ^{13}C NMR $\delta = 170.9$ (m, CF), 160.9 (s, 2- and 6-C), 132.9 (s, 4-C), 123 (1-C), 104.2 (s, 3- and 5-C), 102.4 (s, C-CF_3), 120.5 (low intensity and complex, CF_3 groups), 56.2 (s, OCH_3). ^{19}F NMR $\delta = -64.7$ (1F, m, CF), −57 (3F, dq, $J = 24$ and 8 Hz, CF_3 *trans* to dimethoxybenzenethio group), −56.3 (3F, dq, $J = 8$ Hz, CF_3 *cis* to dimethoxybenzenethio group). IR (film) $\nu = 2254$, 1622 (C=C), 1583, 1475, 1432, 1348, 1298, 1269, 1257, 1213, 1157, 1111, 987, 908, 862, 775, 735, 704, 650 cm^{-1}. CI–MS: $m/z = 351$ ($M + 1$, 35), 331 (M-F, 100), 168 (82). Calcd. for $C_{12}H_9F_7O_2S$: C, 41.1; H, 2.6; S, 9.2. Found: C, 41.2; H, 2.5; S, 9.1%.

3.6. 3,3,4,4-Tetrafluoro-1-(propylthio)cyclobutene (4a)

Work-up B gave the title compound as a colourless mobile liquid (54%); bp 41 °C/12 mm Hg. ^{1}H NMR: $\delta = 6.23$ (1H, tt, $J = 11$ and 2 Hz, =CH), 2.82 (2H, t, $J = 7$ Hz, SCH_2), 1.68 (2H, qt, each $J = 7$ Hz, CH_2), 0.97 (3H, t, $J = 7$ H, CH_3). ^{13}C NMR: $\delta = 154.5$ (m, =CS), 128.9 (pseudo tt, $J = 13$ Hz, =CH), 118.7 and 119 (each tt, $J = 289$ and 26 Hz, CF_2 groups), 33.3 (SCH_2), 23.4 (CH_2) and 13 (CH_3). ^{19}F NMR: $\delta = -111.8$ (2F, m, 3-CF_2), −107.5 (2F, m, 4-CF_2). IR (film): $\nu = 1543$ (C=C), 1460, 1371, 1335, 1281, 1244, 1167, 1128, 1098, 849, 747 cm^{-1}. EI–MS: $m/z = 200$ (M^+, 100), 181 (3), 171 (7), 158 (83), 151 (5), 139 (12), 125 (6), 107 (87), 100 (4), 94 (23), 87 (8), 75 (30), 69 (11), 63 (9), 58 (20), 45 (16). The product contained a trace of 1,3,4,4-tetrafluoro-3-(propylthio)cyclobutene **4b**. EI–MS: $m/z = 200$ (M^+, 100), 181 (2), 171 (3), 158 (55), 151 (3), 139 (8), 125 (25), 121 (2), 107 (14), 102 (1), 95 (2), 89 (17), 75 (27), 69 (9), 63 (5), 57 (2), 51 (1), 45 (6).

3.7. 1,3-Dimethoxy-2-[(3,3,4,4-tetrafluorocyclobut-1-en-1-yl)thio]benzene (5)

Work-up A gave the title compound as fine white crystals that were recrystallised from 1:1 petrol–ether (69%); mp 63–65 °C. ^{1}H NMR: $\delta = 7.4$ (1H, t, $J = 9$ Hz, 4-H), 6.61 (2H, d, $J = 9$ Hz, 3- and 5-H), 5.95 (1H, tt, $J = 11$ and 2 Hz, =CH), 3.89 (6H, s, OCH_3). ^{13}C NMR: $\delta = 160.7$ (2- and 6-C), 153.6 (m, 1-C), 132.6 (4-C), 128.6 (pseudo tt, $J = 12$ Hz, =CH and =CS), 118.7 and 118.4 (tt, $J = 282$ and 24 Hz, CF_2 groups), 104.3 (3- and 5-C), 56.1 (OCH_3). ^{19}F NMR: $\delta = -112.3$ (2F, m, 4-CF_2), −107.7 (2F, m, 3-CF_2). IR (KBr): $\nu = 1589$ (C=C), 1549, 1476, 1435, 1341, 1277, 1256, 1169, 1096, 843, 770 cm^{-1}. EI–MS: $m/z = 294$ (M^+, 100), 279 (8), 259 (4), 239 (2), 228 (4), 213 (4), 187 (23), 179 (2), 167 (4), 154 (5), 139 (2), 123 (5), 109 (39), 91 (8), 69 (7), 51 (5). Calcd. $C_{12}H_{10}F_4O_2S$: C, 49; H, 3.4; S, 10.9. Found: C, 49.1; H, 3.6; S, 10.8%.

3.8. 3,3,4,4-Tetrafluoro-1,2-bis(propylthio)cyclobutene (6a)

Work-up B gave the title compound as a colourless mobile oil (66%); bp 65 °C/10 mm. ^{1}H NMR: $\delta = 2.9$ (4H, t, $J = 7$ Hz, SCH_2), 1.65 (4H, qt, $J = 7$ Hz, CH_2) and 0.95 (6H, t, $J = 7$ Hz, CH_3). ^{13}C NMR: $\delta = 140.2$ (pseudo quintet, $J = 21$ Hz, =CS), 119.2 (ddt, $J = 17$, 25 and 279 Hz, CF_2), 33.2 (SCH_2), 23.6 (CH_2) and 12.8 (CH_3). ^{19}F NMR: $\delta = -108.6$ (4F, s, CF_2). IR (film) $\nu = 1458$ (C=C), 1310, 1238, 1157, 1098, 860 cm^{-1}. EI-MS: $m/z = 274$ (M^+, 87), 255 (4), 232 (50), 213 (3), 190 (100), 183 (2), 171 (7), 153 (2), 139 (12), 125 (4), 107 (8), 93 (3), 88 (9), 74 (5). The product contained a trace of 3,4,4-trifluoro-1,3-bis(propylthio)cyclobutene **6b**. EI–MS: $m/z = 274$ (M^+, 100), 255 (2), 232 (27), 212 (4), 203 (8), 190 (60), 183 (5), 170 (15), 157 (5), 139 (8), 125 (11), 107 (5), 93 (1), 87 (7), 74 (5), 63 (3), 45 (6).

3.9. 1,3-Dimethoxy-2-[(2,3,3,4,4-pentafluorocyclobut-1-en-1-yl)thio]benzene (7)

Work-up A gave the title as white prisms that were recrystallized from petrol–ether (50%); mp 64 °C. ^{1}H NMR: $\delta = 7.4$ (2H, t, $J = 8$ Hz, 3- and 5-H), 6.6 (1H, d, $J = 8$ Hz, 4-H), 3.92 (6H, s, OCH_3). ^{13}C NMR: $\delta = 160.8$ (2- and 6-C), 150 (m, 1-C), 148 (=CF), 132.4 (4-C), 116 (CF_2 groups), 104.1 (3- and 5-C), 56.2 (OCH_3); one signal obscured in background noise (C-S). ^{19}F NMR (AA'BB'X system): $\delta = -120.1$, −114.8, −114.8, −114.6 (four resonances for CF) and −120.5 (1F, m, =CF). IR (KBr) $\nu = 1674$ (C=C), 1582, 1478, 1456, 1435, 1364, 1287, 1260, 1217, 1113, 1028, 955, 855, 816, 772 cm^{-1}. EI-MS: $m/z = 312$ (M^+, 100), 297 (4), 277 (11), 264 (2), 246 (7), 200 (2), 187 (9), 168 (4), 154 (6), 123 (4), 109 (20), 95 (7), 77 (5), 51 (4). Calcd. for $C_{12}H_9F_5O_2S$: C, 46.2; H, 2.9; S, 10.3. Found: C, 46; H, 3; S, 10.2%.

3.10. 3-Chloro-3,4,4-trifluoro-1,2-bis(propylthio)cyclobutene (**8a**) and 3,3,4-trifluoro-1,2,4-tris(propylthio)cyclobutene (**8b**)

Work-up B gave an inseparable mixture of the title compounds **8a** (20%) and **8b** (60%) as a colourless mobile oil; bp 95 °C/12 mm Hg. ^{1}H NMR: $\delta = 2.3$–2.6 (m, SCH_2), 1.7 (m, CH_2), 1.1 (m, CH_3). ^{19}F NMR (spectra taken as AMX system, *ie*. treated as first order) for adduct **8a**: $\delta = -106.9$ (1F, m, $J = 20$ and 183 Hz, 4-F), -102.2 (1F, m, $J = 23$ and 183 Hz, 4-F) and -101.2 (1F, m, $J = 20$ and 23 Hz, 3-F) and for adduct **8b**: $\delta = -122.3$ (1F, m, $J = 22$ and 27 Hz, 4-F), -105.5 ($J = 22$ and 183 Hz, 3-F) and -102.2 ($J = 27$ and 183 Hz, 3-F). EI–MS for **8a**: $m/z = 290$ (M^+, 100), 271 (1), 248 (75), 206 (100), 183 (6), 171 (29), 155 (4), 139 (6), 125 (11), 107 (7), 87 (12), 74 (7), 63 (3). EI-MS for **8b**: $m/z = 330$ (M^+, 46), 312 (1), 287 (27), 269 (2), 255 (100), 245 (25), 225 (3), 213 (52), 203 (18), 193 (4), 184 (7), 171 (20), 139 (5), 117 (6), 107 (6), 87 (5), 75 (4), 59 (3), 47 (5).

3.11. 1,3-Dimethoxy-2-[(1,2,3,4,4-pentafluorocyclobut-2-en-1-yl)thio]benzene (**9**)

Work-up A gave the title compound as a white solid (53%); mp 66–67 °C. ^{1}H NMR: $\delta = 7.38$ (1H, t, $J = 9$ Hz, 4-H), 6.6 (2H, d, $J = 9$ Hz, 3- and 5-H), 3.9 (6H, s, OCH_3). ^{13}C NMR (some resonances obscured): $\delta = 162.2$ (2- and 6-C), 132.6 (4-C), 104.3 (3- and 5-C), 56.4 (OCH_3). ^{19}F NMR: $\delta = -131.3$ (1F, m, =C*F*-CFS), -130.5 (1F, m, =C*F*-CF_2), –124.3 (1F, m, CFS), -115.7 and -112.4 (both 1F, m, CF_2). IR (KBr) $\nu = 1784$ (C=C), 1582, 1476, 1431, 1381, 1327, 1317, 1294, 1256, 1196, 1134, 1109, 1080, 1030, 1003, 924, 866, 818, 774 cm^{-1}. EI–MS: $m/z = 312$ (M^+, 100), 297 (5), 281 (9), 249 (4), 231 (28), 215 (14), 200 (3), 187 (8), 167 (7), 154 (18), 141 (15), 123 (19), 109 (21), 95 (15), 69 (9), 51 (5). Calcd. for $C_{12}H_9F_5O_2S$: C, 46.2; H, 2.9; S, 10.3. Found: C, 46.1; H, 2.9; S, 10.5%.

3.12. Reactions with N-acetylcysteine isopropyl ester

A solution of *N*-acetylcysteine isopropyl ester (6.15 g, 30 mmol) in acetonitrile (25 ml) containing anhydrous potassium carbonate (8.28 g, 60 mmol) and a magnetic stirrer bar was placed in a 250 ml round-bottomed flask fitted with a rubber septum. Approximately 300 ml of air were removed from the headspce using a gas-tight syringe. The mixture was cooled to −78 °C and PFIB or HFCB (336 ml, 15 mmol) added via the syringe. The suspension was stirred for 12 h. The inorganic solid was removed by filtration and the filtrate concentrated to give a yellow liquid. The experiment with 1-hydropentafluorocyclobutene (2.16 g, 15 mmol) involved dropwise addition of a solution in acetonitrile (25 ml) via cannula to a stirred mixture of the thiol (3.08 g, 15 mmol) and potassium carbonate (4.14 g, 30 mmol). The mixture was worked up as before. Chromatography on silica gel gave the following pure products as white solids.

3.13. 1,1-Bis[2-acetylamino-2-(isopropoxycarbonyl)ethylthio]-2-(trifluoromethyl)-3,3,3-trifluoroprop-1-ene (**10**)

Chromatography eluent: 6:1 hexane–acetone (yield 66%); mp 157–158 °C. ^{1}H NMR (ABX cysteinyl system): $\delta = 6.4$ (2H, d, $J = 6$ Hz, NH), 5.05 (2H, septet, $J = 6$ Hz, OCH), 4.77 (2H, dd, $J = 6$ and 4 Hz, H_X), 3.63 (2H, dd, $J = 14$ and 5 Hz, H_A), 3.42 (2H, dd, $J = 14$ and 3 Hz, H_B), 1.95 (6H, s, $COCH_3$), 1.25 (12H, d, $J = 6$ Hz, CH_3). ^{13}C NMR: $\delta = 170.1$ and 168.7 (C=O), 161.5 (m, $=CS_2$), 124.6 (q, $J_{CF} = 276$ Hz, CF_3), 119 (m, $J_{CF} = 33$ Hz, CF_3C), 70.7 (OCH), 52.8 (NCH), 36.8 (SCH_2), 22.7 (acetyl CH_3), 21.5 (isopropyl CH_3). ^{19}F NMR; $\delta = -56.1$ (6F, s, CF_3). IR (KBr): $\nu = 1734$ and 1654 (C=O), 1536 (C=C), 1532, 1375, 1314, 1245, 1220, 1108, 1092 cm^{-1}. CI–MS: $m/z = 571$ ($M + 1$, 10), 551 (M-F, 3), 400 (10), 358 (16), 206 (32), 172 (46), 164 (74), 149 (28), 130 (62), 122 (24), 91 (32), 73 (28), 60 (47). Calcd. for $C_{20}H_{28}F_6N_2O_6S_2$: C, 42.1; H, 4.9; S, 11.2. Found: C, 41.9; H, 4.9; S, 11.3%.

3.14. 1-[2-Acetylamino-2-(isopropoxycarbonyl)ethylthio]-3,3,4,4-tetrafluorocyclobutene (**11**)

Chromatography eluent: 9:1 hexane–acetone (yield 44%); mp 44–46 °C. ^{1}H NMR (ABX cysteinyl system): $\delta = 6.53$ (1H, tt, $J_{HF} = 11$ and 2 Hz, =CH), 6.51 (1H, br s, NH), 5.1 (1H, septet, $J = 5$ Hz, OCH), 4.84 (1H, ddd, $J = 7$ and 5 Hz, H_X), 3.5 (1H, dd, $J = 14$ and 6 Hz, H_A), 3.38 (1H, dd, $J = 14$ and 4 Hz, H_B), 2.04 (3H, s, $COCH_3$), 1.29 and 1.28 (6H, d, $J = 6$ and 5 Hz, CH_3). ^{13}C NMR: $\delta = 170.3$ and 168.9 (C=O), 153.1 (m, =CS), 129.6 (m, =CH), 118.2 and 118 (m, 3- and 4-CF_2), 70.9 (OCH), 51.9 (NCH), 33.1 (SCH_2), 22.9 (acetyl CH_3), 21.5 (isopropyl CH_3). ^{19}F NMR: $\delta = -112$ (2F, m, 4-CF_2), -108 (2F, m, 3-CF_2). IR (KBr): $\nu = 1737$ and 1661 (C=O), 1543 (C=C), 1376, 1335, 1280, 1216, 1167, 1129, 1101, 847 cm^{-1}. CI–MS: $m/z = 330$ ($M^+ + 1$, 48), 310 (84), 288 (54), 268 (100), 246 (16), 226 (23). EI-MS: $m/z = 329$ (M^+, 8), 296 (2), 287 (6), 270 (M^+-OPr-*i*, 36), 242 (M^+-CO_2*i*-Pr, 16), 228 (40), 200 (100), 180 (12), 160 (27), 133 (14), 113 (21), 87 (37), 74 (31), 60 (18), 43 (*i*-Pr^+, 27). Calcd. for $C_{12}H_{15}F_4NO_3S$: C, 43.8; H, 4.6; S, 9.7. Found: C, 43.9; H, 4.4; S, 9.6%.

3.15. 1,2-Bis[S-(N-acetylcysteinyl isopropyl ester)]-3,3,4,4-tetrafluorocyclobutene (**12**)

Chromatography eluent: 6:1 hexane–acetone (yield 70%); mp 132 °C (dec.). ^{1}H NMR (ABX cysteinyl system): $\delta = 6.85$ (2H, d, $J = 6$ Hz, NH), 5.15 (2H, septet, $J = 6$ Hz, OCH), 5.9 (2H, m, H_X), 3.65 (2H, dd, $J = 14$ and 4 Hz, H_A), 3.45 (2H, dd, $J = 14$ and 5 Hz, H_B), 2.2 (6H, s, $COCH_3$), 1.4 (12H, d, $J = 6$ Hz, CH_3). ^{13}C NMR:

$\delta = 170.6$ and 169.5 (C=O), 142 ('quintet', $J_{CF} = 21$ Hz, C=C), 119 (tt, $J_{CF} = 286$ and 27 Hz, CF_2), 70.8 (OCH), 52.6 (NCH), 33.5 (SCH_2), 23.1 (acetyl CH_3), 21.9 (isopropyl CH_3). ^{19}F NMR: $\delta = -111.9$ (AA'BB' system, 4F, m, CF_2). IR (KBr): $\nu = 1736$ and 1654 (C=O), 1529 (C=C), 1377, 1309, 1231, 1137 and 1126 cm^{-1}. CI–MS: $m/z = 533$ ($M + 1$, 100), 513 (M-HF, 34), 493 (14), 471 (16), 451 (6), 172 (49), 130 (62), 112 (26), 86 (28), 73 (12), 60 (21), 49 (14), 43 (i-Pr^+, 52). Calcd. for $C_{20}H_{28}F_4N_2O_6S_2$: C, 45.1; H, 5.3; S, 12. Found: C, 44.8; H, 5.1; S, 11.7%.

4. Conclusion

Reactions of toxic fluorobutenes with thiols took place rapidly and resulted in vinyl or allyl substitution depending on the fluoroalkene and the thiol. The toxicities of the fluorobutenes correlated with their susceptibility to nucleophilic attack and the number of successive alkylations that occurred with thiols. In future, investigations of the reactions of thiols with volatile fluoroalkenes might be useful for estimating their acute toxicities.

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