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Fluoroalkene chemistry
Part 3. Reactions of arylthiols with perfluoroisobutene, perfluoropropene and chlorotrifluoroethene

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Dedicated to Professor R.E. Banks in honour of his enormous contribution to fluorine chemistry.

Abstract

Reactions of perfluoroisobutene (PFIB), perfluoropropene (PFP) and chlorotrifluoroethene (CTFE) with benzenethiol and 2-methoxybenzenethiol in acetonitrile, with potassium carbonate as base, were compared. PFIB reacted with benzenethiol to give ketene thioacetal $(CF_3)_2C{=}C(SAr)_2$ and with 2-methoxybenzenethiol to give mono- and bis-vinyl species $(CF_3)_2C{=}CFSAr$ and $(CF_3)_2C{=}C(SAr)_2$. PFP reacted with both thiols to give the addition product CF_3CFHCF_2SAr and vinyl isomers $CF_3CF{=}CFSAr$ (6:1 *E*/*Z* ratio). CTFE reacted with several methoxy-substituted arylthiols to give addition products of structure $CFClHCF_2SAr$. The arylthiols used throughout the study imitate biological thiols. Inhalation toxicities of the fluoroalkenes decrease in the order PFIB > PFP > CTFE and correlate with their reactivities towards the model thiols, supporting the current view that their toxicity relates to their ability to react with biological thiols.

Keywords: Chlorotrifluoroethene; Perfluoroisobutene; Perfluoropropene; Thiol; Toxicity

1. Introduction

Interest in the reactions of fluoroalkenes with sulfur nucleophiles was prompted by the discovery that the high inhalation toxicities of perfluorobutenes correlated with their reactivities towards biological thiols [1–6]. This study compares the reactions of perfluoroisobutene (PFIB), perfluoropropene (PFP) and chlorotrifluoroethene (CTFE) with selected arylthiols (Fig. 1).

The fluoroalkenes are low-boiling colourless gases that are insoluble in water. PFIB is a by-product of Teflon™ production, PFP is used in polymer synthesis and CTFE in the manufacture of anaesthetics. Inhalation of the fluoroalkenes in large doses can cause fatal lung damage [7–10] and small doses of PFP [11] and CTFE [12,13] can cause kidney damage. Acute inhalation toxicity decreases in the order PFIB > PFP > CTFE (Table 1) mirroring their electrophilicity and reactivity to nucleophiles.

In contrast to alkenes, polyfluorinated alkenes invite nucleophilic attack and resist electrophilic attack because the electronegative fluorine substituents deplete the electron-density at the double bond.[1] Nucleophilic attack occurs at the difluoromethylene group – the most positive site – and three products can arise, the first from addition of NuH to the double bond (Fig. 2). Dehydrofluorination follows when the nucleophile or conditions are appreciably basic and the intermediate carbanion is unstable (stability order: tertiary > secondary > primary). The carbanion can eliminate fluoride from the CF_2Nu group (*vinyl substitution*) or from

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[1] This profile determines the toxicology of alkenes and fluoroalkenes. Isobutene $(CH_3)_2C{=}CH_2$ is excreted from the lungs, the retained portion slowly being metabolised to the toxic epoxide, which can alkylate biological nucleophiles [14]. In contrast, a large proportion of inhaled perfluoroisobutene $(CF_3)_2C{=}CF_2$ is immobilised through rapid reaction with cellular nucleophiles. Perfluoroisobutene cannot be metabolised to an epoxide because of its low reactivity to cytochrome oxidase enzymes present in the lung [15].

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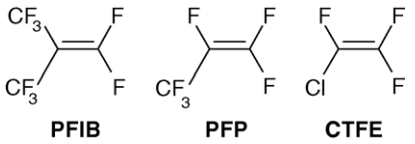


Fig. 1. The three fluoroalkenes studied.

Table 1
Comparative toxicity data for the three fluoroalkenes [9]

Fluoroalkene	Boiling point (°C)	LC_{100} mice[a] (mg/l, 2 h exposure)	LC_{50} rats[b] (ppm, 2 h exposure)
PFIB	6	0.015	<0.18
PFP	−28	9–20	4000–4466
CTFE	−28	36	5040

LC_{100} is the concentration that causes 100% mortality.
[a] Data taken from reference 10.
[b] LC_{50} is the lethal concentration of fluoroalkene that causes 50% mortality.

the CF_3 group (*allyl substitution*). The relationship between the two substitution modes depends on the nucleophile and conditions, but has not yet been studied systematically, and is poorly understood. Vinyl substitution predominates in reactions of PFIB with little or no allyl product forming. Substitution products often undergo further addition–elimination sequences to give geminal sulfides.

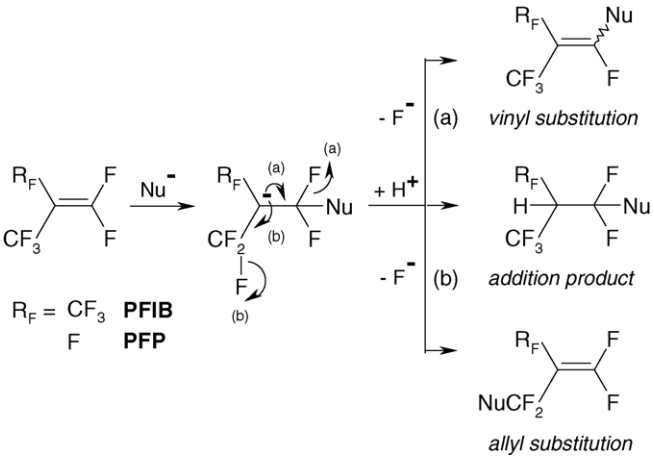


Fig. 2. Carbanion from attack of a nucleophile on perfluoroisobutene (PFIB) and perfluoropropene (PFP) and possible products from protonation or loss of vinylic (a) or allylic (b) fluoride.

PFIB reacts with sodium ethanethiolate and butanethiolate in ether to give mono- or bis-vinyl product **A** or **B** (Fig. 3). The second substitution is suppressed at −30 °C, aiding isolation of mono products [16]. Mono and bis products are also obtained with arylthiols in THF in the presence of Hünig's base (diisopropylethylamine) [1]. PFP gives addition or substitution products, or a mixture of the two. Sodium methane-, ethane- and 2-hydroxyethane-thiolate in an autoclave (130 °C) give addition product **C** [17]. Lithium benzenethiolate and 4-chlorobenzenethiolate in dioxane in an open vessel or autoclave (120 °C) give addition and vinyl products **C** and **D** [18]. CTFE yields addition or substitution products. Ethanethiol or butanethiol (Triton B catalyst),[2] 2-mercaptoacetic acid (Et_3N catalyst) or 2-mercaptoethanol (NaOH catalyst) in an autoclave (23–45 °C) give product **E** [19]. Sodium 1- and 2-propanethiolate react similarly [20]. Sodium benzenethiolate in ethanol in an autoclave also gives addition product **E** [21,22] yet sodium *n*-butane- or benzene-thiolate in THF in an open vessel give substitution product **F** [23].

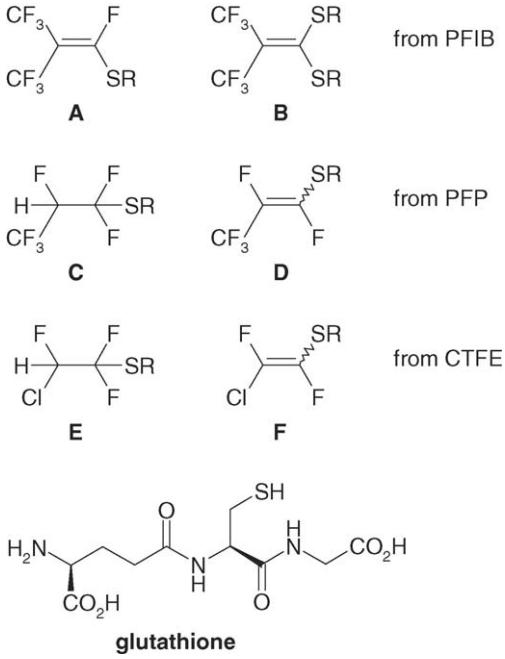


Fig. 3. Products from reactions of the fluoroalkenes with thiols (**D** and **F** can exist as *E*- or *Z*-isomers) [16–27] and the structure of glutathione.

In the body, the tripeptide glutathione protects cells by reacting with toxic electrophiles via a central cysteinyl thiol group; the resulting sulfides are usually metabolised to less toxic products [24]. Glutathione reacts with PFIB in neutral phosphate buffer to give a ketene thioacetal **B** [25]. Glutathione sodium salt reacts with PFP to give products **C** and **D** [26] and with CTFE in alkaline aqueous ethanol to give addition product **E** [27]. These products also form in vivo [26,27].

Selectivity of the fluoroalkenes towards thiols in preference to other nucleophiles, such as amines, water or alcohols, governs their interaction with biomolecules. Fluoroalkenes can be classed as soft acids on Pearson's scale [28] and react more favourably with soft bases (e.g. RSH) than with hard bases (e.g. ROH). PFP and CTFE react selectively with the thiol groups of 2-mercaptoethanol [19], *N*-acetylcysteine [26] and L-cysteine [29].

Elsewhere it has been shown that arylthiols are good models for biological thiols such as cysteine esters [1–4]. In this study, reactions of PFIB, PFP and CTFE with a 10% molar excess of benzenethiol and 2-methoxybenzenethiol were compared. The fluoroalkene was added to a stirred solution of the thiol in

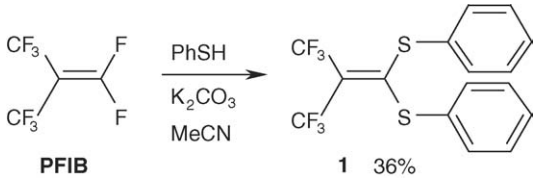
[2] Triton B is a 40% aqueous solution of benzyltrimethylammonium hydroxide.

acetonitrile containing anhydrous potassium carbonate, and the products separated and characterised by the usual techniques.

2. Results and discussion

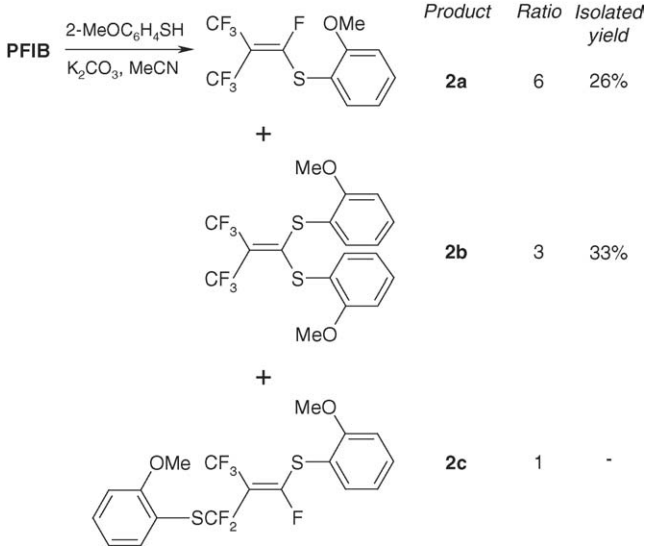
2.1. Perfluoroisobutene

PFIB reacted with two benzenethiol molecules despite the thiol being present in only 10% molar excess. Compound **1** was the only significant product in the GC–MS spectrum and was isolated in modest yield by chromatography on silica gel as a low-melting white solid (Scheme 1).[3]



Scheme 1.

Treatment of PFIB with 2-methoxybenzenethiol gave, from comparison of integrals in a gas chromatogram of the reaction mixture, a 6:3:1 mixture of mono-vinyl product **2a** and bis-vinyl products **2b** and **2c** (Scheme 2).



Scheme 2.

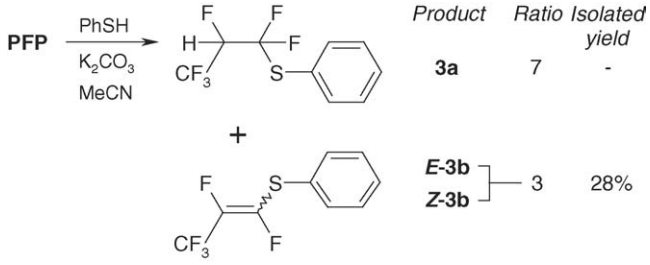
Whereas products **2a** and **2b** were isolated and characterised, product **2c**, whose structure is assumed, but which is isomeric with **2b** by comparison of mass spectra, was isolated in insufficient quantity to allow full characterisation. It presumably arose from allylic then vinylic substitution, the last dehydrofluorination yielding the *E*-isomer for steric reasons. Precedent for structure **2c** comes from experiments with perfluoropropene and sodium ethanethiolate that gave in addition to the main product CF_3CFHCF_2SEt, some bis-sulfide $EtSCF_2CFHCF_2SEt$ [17]. Formation of the latter must have occurred by allylic substitution followed by addition of the thiol across the newly generated double bond.

It is interesting to compare the products from reaction of PFIB with benzenethiol and 2-methoxybenzenethiol: the former thiol yielded no mono-vinyl product, reacting further, whereas the latter thiol yielded mono-vinyl product as the major component. The difference can be rationalised by considering the reactivity of the intermediate/product $(CF_3)_2C{=}C(SR)F$ towards the respective thiols. The *S*-phenyl group is smaller and more electronegative than the *S*-(2-methoxyphenyl) group and renders the carbon atom of the $=C(SR)F$ group more electrophilic. Also, the small size of benzenethiol allows it to react again, yet 2-methoxybenzenethiol cannot due to steric hindrance.

The threefold predominance of the 1,1-diaryl product **2b** over the 1,3-diaryl product **2c** reflects the greater ease of fluoride loss from the $–CF_2SAr$ group than from the $–CF_3$ group of the initial addition product (the trifluoromethyl group is usually a chemically stable unit). This explains why vinyl substitution dominates over allylic substitution.

2.2. Perfluoropropene

Treatment of PFP with benzenethiol gave addition product **3a** and mono-vinyl product **3b** in a 7:3 ratio (Scheme 3). The *E* and *Z* diastereomers of **3b** appeared as one peak by GC–MS analysis and as one spot by TLC analysis using different solvent systems. Column chromatography of the reaction mixture led to apparent decomposition of compound **3a** (it failed to elute) and isolation of *E*/*Z* mixture **3b**.

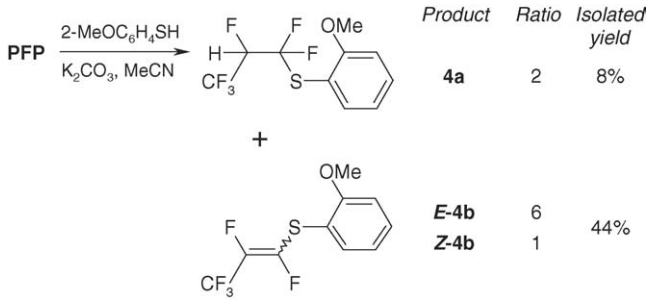


Scheme 3.

Treatment of PFP with 2-methoxybenzenethiol gave addition product **4a** and diastereomeric mono-vinyl product **4b** in a 2:7 ratio (Scheme 4). Column chromatography caused apparent decomposition of compound **4a** (it was however obtained in low yield) and permitted isolation of the *E*/*Z* mixture **4b**.

Multinuclear NMR analysis revealed each pair of diastereomers, **3b** and **4b**, to comprise a 6:1 *E*/*Z* mixture with the *E*-isomers dominating. Diastereomers were easily differentiated

[3] Compound **1** has been made before in 68% yield by treating $(CF_3)_2C{=}CCl_2$ with two molar equivalents of benzenethiol in THF in the presence of Hünig's base [1] and has been detected in distillation residues after treating PFIB with sodium benzenethiolate [30]. It has a rare structure and is related to compounds $CF_3CH{=}C(SR_2)$ formed as by-products from the reactions of the fluoroalkynes $CF_3C{\equiv}CCl$ and $CF_3C{\equiv}CBr$ with sodium alkanethiolates [31]. The chemistry of fluorinated alkyl (and aryl) vinyl sulfides has recently been reviewed [32].



Scheme 4.

by ^{19}F NMR spectroscopy, the values of the F–F coupling constants being particularly diagnostic (Fig. 4). For fluoroalkenes with the FC=CF fragment, the *trans* $^{3}J_{FF}$ is usually much greater than the *cis* $^{3}J_{FF}$, typical values being 106–148 and 0–58 Hz, respectively [33]. The *E*- and *Z*-isomers of **3b** and **4b** had $^{3}J_{FF}$ values of 146 and 3–9 Hz, respectively. For fluoroalkenes with the $CF_3CF{=}CF$ fragment, the geminal $^{3}J_{FF}$ is typically 7–14 Hz, the *cis* $^{4}J_{FF}$ 17–25 Hz and the *trans* $^{4}J_{FF}$ 6–13 Hz [33]. In both isomers of **3b** and **4b**, the geminal $^{3}J_{FF}$ remained constant (11 Hz) and *cis* $^{4}J_{FF}$ equalled 21 Hz (*E*-isomers) and *trans* $^{4}J_{FF}$ equalled 11 Hz (*Z*-isomers). Chemical shifts of the fluorine atoms connected to the double bond of the *E*-isomers also differed significantly from those of the *Z*-isomers (Fig. 4).

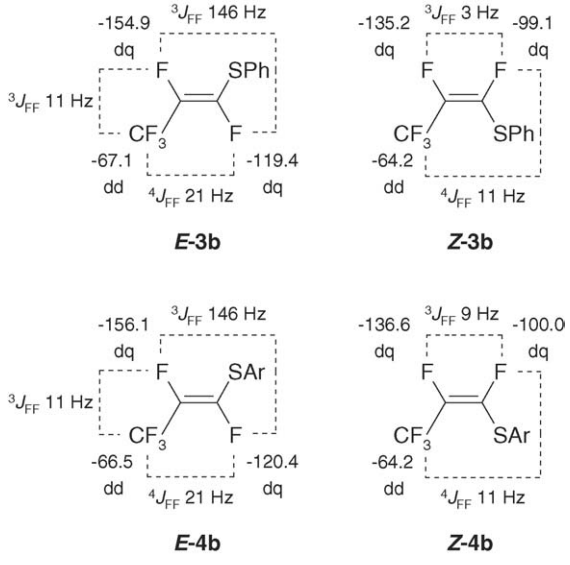
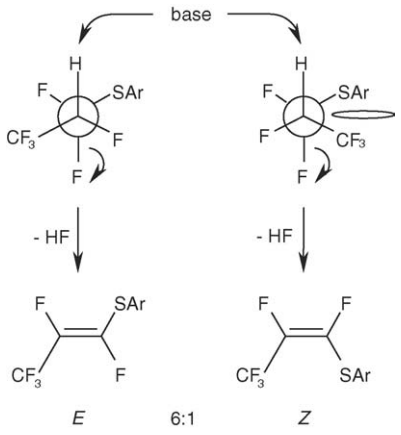


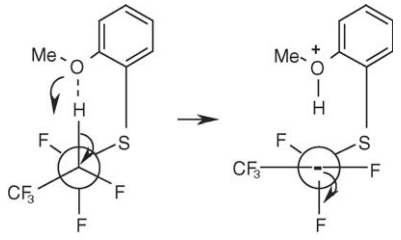
Fig. 4. ^{19}F NMR assignments and coupling constants for *E*- and *Z*-isomers of **3b** (top pair) and **4b** (bottom pair).

The 6:1 *E*/*Z* isomer ratio found for **3b** and **4b** can be rationalised by considering the transition states during the reaction (Scheme 5). In the one leading to the *E*-isomer (left) the arylthio and trifluoromethyl groups are *anti*, whereas in the one leading to the *Z*-isomer (right) the groups are *syn*. The left transition state will be lower energy than the right one where the SAr and CF_3 groups are aligned unfavourably, and a greater proportion of the *E*-isomer therefore forms from dehydrofluorination.



Scheme 5.

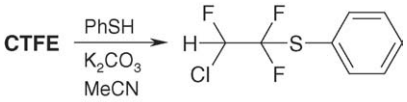
Schemes 3 and 4 show that the ratio of addition product to mono-vinyl product shifts from 7:3 to 2:7 in changing the nucleophile from benzenethiol to 2-methoxybenzenethiol. This difference cannot be convincingly attributed to the effect of the SAr group on the acidity of the CF_3CFH proton of each addition product. Something unusual must account for the product reversal. One possibility is dehydrofluorination assisted by the OMe group hydrogen-bonded to the acidic proton (Scheme 6). Such an effect would not affect the ratio of diastereomers: their relative proportions would be the same in mono-vinyl products derived from benzenethiol and 2-methoxybenzenethiol (as observed).



Scheme 6.

2.3. Chlorotrifluoroethene

Treatment of CTFE with benzenethiol and methoxybenzenethiols gave the addition products **5**–**8** (Scheme 7) and traces of the diaryl disulfide (data not shown). The addition products were isolated after chromatography as colourless liquids.



R group	*Product*	*Yield*
Ph	**5**	58%
2-$MeOC_6H_4S$-	**6**	64%
3-$MeOC_6H_4S$-	**7**	57%
4-$MeOC_6H_4S$-	**8**	68%

Scheme 7.

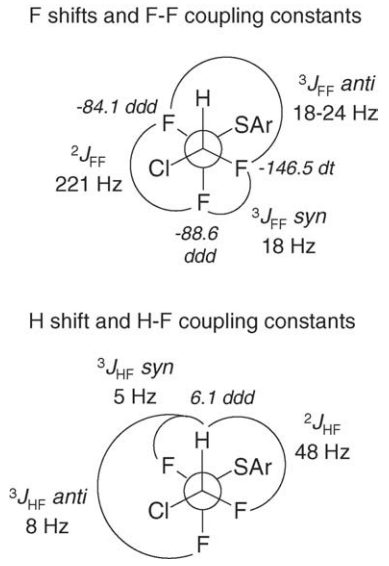


Fig. 5. Representative ^{19}F NMR (top) and ^1H NMR (bottom) shifts for compounds **5–8** and typical values of the F–F and H–F coupling constants.

In each case, the ^{19}F NMR spectrum comprised two zones of absorption: one at low field due to the CF_2Ar group and one at high field due to the CHFCl group (Fig. 5). The $^3J_{HF}$ coupling was in the region of 5–8 Hz and much smaller than the $^2J_{HF}$ coupling (48 Hz) as expected. These NMR parameters agree with data for related fluorinated species [34,35].

2.4. Comparison of the reactivity of the fluoroalkenes

To summarise, PFIB gave bis-vinyl products, PFP gave addition and mono-vinyl products and CTFE gave addition products. These different behaviours can be rationalised by consideration of the relative acidities of the protons in the respective addition products (Fig. 6).

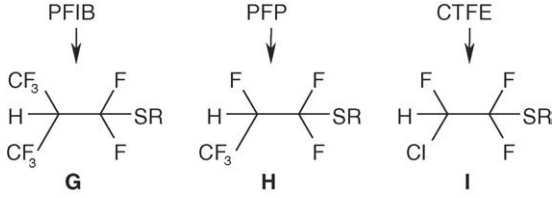


Fig. 6. Products of addition of RSH to PFIB, PFP and CTFE.

The proton acidity decreases in the order **G** > **H** > **I** in line with the relative electronegativities of the flanking groups ($2 \times CF_3 > F + CF_3 > F + Cl$). Therefore, in the presence of potassium carbonate, compound **G** loses HF readily, compound **H** only partially, and compound **I** not at all. The use of a stronger base would be expected to increase the ratio of unsaturated products derived from PFP and CTFE, and from the limited studies available, this appears to be the case (see Section 1).

3. Conclusion

In Parts 1 and 2, the toxicities of fluorocyclobutenes were shown to correlate with the number of aliphatic thiol molecules they could react with, supporting the contention that toxicity was due to reaction with biological thiols in the lung [2,3]. Fluoroalkenes were classified into groups according to their alkylating ability. Group I fluoroalkenes reacted with one molar equivalent of thiol, Group II fluoroalkenes with two molar equivalents of thiol, and so on. Members of Group I were less toxic than members of Group II. If this system is applied to the acyclic fluoroalkenes studied here, then CTFE belongs to Group I, PFP to Group I/II, and PFIB to Group II. This order mirrors their relative toxicities (refer to Table 1). A further refinement of this classification would take into account the relative electrophilicities of the fluoroalkenes: toxicities of fluoroalkenes in the same groups, all other biological factors being equal, should parallel their electrophilicity, the most electrophilic fluoroalkene being the most toxic. An increase in electrophilicity increases the proportion of vinyl substitution and this results in the greatest toxicity.

We have demonstrated that an autoclave or an open vessel and a large excess of fluoroalkene for aryl vinyl sulfide preparation are unnecessary, despite being widely practised in the past (see Section 1). In our work, mixtures of products were quantified and the products wherever possible separated by column chromatography and their stereochemistry deduced. Separation of products is not easily accomplished by distillation which is advocated in studies from other research groups, and such an approach has led to a paucity of stereochemical information.

4. Experimental

PFIB was prepared at Dstl Porton Down using a known procedure [36]. PFP and CTFE were from Apollo Scientific Ltd. (Stockport, UK) and anhydrous solvents from Aldrich Ltd. (Gillingham, UK). 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 ^1H and 125 MHz for ^{13}C spectra) as solutions in $CDCl_3$, with internal references $CFCl_3$ for ^{19}F and $SiMe_4$ for ^1H spectra. Mass spectra were recorded on a Finnigan MAT GCQ instrument using chemical ionisation (CI) in the presence of ammonia. Microanalysis data were obtained from Warwick Analytical Service Ltd. (Coventry, UK).

Caution: Owing to the high inhalation toxicities of the fluoroalkenes, especially perfluoroisobutene, all experiments must be performed in an efficient 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 be removed from the bag as required using a large gas-tight syringe. Gas bags of 1 litre 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 the experiments described.

4.1. General method

A solution of benzenethiol (1.08 g, 9.82 mmol) or 2-methoxybenzenethiol (1.37 g, 9.82 mmol) in acetonitrile (25 ml) containing anhydrous potassium carbonate (1.36 g, 9.82 mmol) and a magnetic stirrer bead was placed in a 500 ml round-bottomed flask sealed with a rubber septum. Air (~300 ml) was removed from the flask using a gas-tight syringe with a large bore needle. The fluoroalkene (200 ml, 8.93 mmol) was transferred from a gas bag using a gas-tight syringe and injected into the stirred contents of the flask. After 2 h, the septum was removed and the reaction mixture analysed by TLC and GC–MS. The inorganic salts were removed by filtration, washed with acetonitrile, and the filtrate concentrated to give a liquid. Unless otherwise stated, chromatography on silica gel permitted separation of the major components.

4.2. Reaction of PFIB with benzenethiol to give (*1*)

TLC and GC–MS analysis revealed the presence of only one product. The crude product was recrystallised from hot ether and hexane to yield 1,1′-{[3,3,3-trifluoro-2-(trifluoromethyl)-prop-1-ene-1,1-diyl]bis(thio)}dibenzene **1** as a white crystalline solid (36%). Mp 62–63 °C. The spectroscopic data obtained matched those for a specimen prepared previously under different conditions [1].

4.3. Reaction of PFIB with 2-methoxybenzenethiol to give (*2a–2c*)

TLC analysis of the crude reaction mixture with hexane as eluent showed the presence of three products. The mixture was chromatograped on silica gel eluting with hexane then 1:1 hexane–acetone. The first product to elute with R_f 0.25 was 1-methoxy-2-{[1,3,3,3-tetrafluoro-2-(trifluoromethyl)propen-1-yl] thio}benzene **2a** which was isolated as a colourless liquid (26%). ^{1}H NMR: δ = 7.51 (2H, m, 4-H and 6-H), 7.02 (2H, m, 3-H and 5-H), 3.94 (3H, s, OCH_3). ^{13}C NMR: δ = 170.3 (C-S), 159.8 (2-C), 136.5 (6-C), 133.0 (4-C), 128.1 (1-C), 121.5 (CF_3, m, obscured), 121.4 (5-C), 111.6 (3-C), 102.7 (*C*-CF_3), 55.9 (OCH_3). ^{19}F NMR: δ = −63.7 (1F, m, C-F), −56.5 (3F, dq, $^4J_{FF}$ = 24 and $^3J_{FF}$ = 9 Hz, CF_3 *trans* to SAr), −55.8 (3F, dq, $^4J_{FF}$ and $^3J_{FF}$ = 9 Hz, CF_3 *cis* to SAr). IR (film): ν = 1075, 1622 (C=C), 1587, 1481, 1466, 1437, 1346, 1273, 1215, 1155, 1066, 1026, 987, 910, 862, 800, 742, 705 cm^{-1}. CI–MS (*m/z*, %): 320 (M^+, 18), 301 (M-F, 100), 281 (M-HF_2, 27), 138 (14). Calcd. for $C_{11}H_7F_7OS$: C, 41.3; H, 2.2; S, 10.0. Found: C, 41.2; H, 2.1; S, 9.8%.

The second product to elute with R_f 0.05 was 1,1′-{[3,3,3-trifluoro-2-(trifluoromethyl)prop-1-ene-1,1-diyl]bis(thio)}-bis(2-methoxybenzene) **2b** which was isolated as mobile liquid (33%). ^{1}H NMR: δ = 7.26 (2H, dd, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 2 Hz, 4-H), 6.81 (2H, dd, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 2 Hz, 6-H), 6.75 (2H, dd, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 1 Hz, 5-H), 6.73 (2H, dd, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 2 Hz, 3-H), 3.67 (6H, s, OCH_3). ^{13}C NMR: δ = 161.8 (1-C), 161.7 (C-S), 158.8 (C-2), 130.5 (C-3), 127.8 (6-H), 121.3 (q, $^1J_{CF}$ = 280 Hz, CF_3), 120.5 (C-4), 117.1 (septet, $^2J_{CF}$ = 32 Hz, *C*-CF_3), 110.7 (C-5), 55.6 (OCH_3). ^{19}F NMR: δ = −54.4 (s, CF_3). IR (film): ν = 1583, 1523 (C=C), 1479, 1464, 1433, 1308, 1277, 1252, 1227, 1027, 1149, 1068, 1041, 1026, 995, 910, 750, 735, 714 cm^{-1}. CI–MS (*m/z*, %): 441 (*M* + 1, 40), 421 (M-HF, 38), 301 (40), 246 (100), 157 (32), 139 (18), 111 (15). Calcd. for $C_{18}H_{14}F_6O_2S_2$: C, 49.1; H, 3.2; S, 14.6. Found: C, 49.1; H, 3.1; S, 14.5%.

The third product, presumed on the basis of its chemical ionisation mass spectrum to be 1,1′-{[(1*E*)-1,3,3-trifluoro-2-(trifluoromethyl)prop-1-ene-1,3-diyl]bis(thio)}bis(2-methoxybenzene) **2c**, was isolated in insufficient quantity to permit accurate characterisation. CI–MS (*m/z*, %): 440 (M^+, 4), 278 (46), 171 (100), 138 (86), 107 (8), 53 (24).

4.4. Reaction of PFP with benzenethiol to give (*E- and Z-3b*)

Analysis of the reaction mixture by GC–MS and TLC showed two products, the addition product **3a** ($R_{f\ hexane}$ 0.29) and isomers **3b** ($R_{f\ hexane}$ 0.55). Chromatography on silica gel, eluting with 16:1 hexane–acetone, gave a 6:1 mixture of {[(1*E*)-1,2,3,3,3-pentafluoroprop-1-en-1-yl]thio}benzene and {[(1*Z*)-1,2,3,3,3-pentafluoroprop-1-en-1-yl]thio}benzene **3b** (28%). ^{1}H NMR for isomeric mixture: δ = 7.51 (2H, m, 2-H and 6-H), 7.42 (3H, m, 3-H, 4-H and 5-H). ^{13}C NMR of major isomer **3b** only (CF_3CF=CF carbon resonances were of low intensity and obscured in baseline noise): δ = 133.1 (2-C and 6-C), 129.8 (4-C), 129.6 (3-C and 5-C). ^{19}F NMR for *E*-**3b**: δ = −154.9 (1F, dq, $^3J_{FF}$ = 146 and $^3J_{FF}$ = 11 Hz, C*F*CF_3), −119.4 (1F, dq, $^3J_{FF}$ = 146 and $^4J_{FF}$ = 21 Hz, CFS), −67.1 (3F, dd, $^4J_{FF}$ = 21 and $^3J_{FF}$ = 12 Hz, CF_3). ^{19}F NMR for *Z*-**3b**: δ = −135.2 (1F, dq, $^3J_{FF}$ = 11 and $^3J_{FF}$ = 3 Hz, C*F*CF_3), −99.1 (1F, dq, $^4J_{FF}$ = 11 and $^3J_{FF}$ = 3 Hz, CFS), −64.2 (3F, dd, $^3J_{FF}$ = each 11 Hz, CF_3). IR for *E*/*Z*-**3b** (film): ν = 1354 (C=C), 1213, 1147, 1024, 941, 862, 748, 719 cm^{-1}. CI–MS for *E*/*Z*-**3b** (*m/z*, %): 241 (*M* + 1, 50), 221 (M-F, 100), 201 (M-HF_2, 44). Calcd. for $C_9H_5F_5S$: C, 45.0; H, 2.1; S, 13.3. Found: C, 44.9; H, 2.0; S, 13.1%.

4.5. Reaction of PFP with 2-methoxybenzenethiol to give (*4a and 4b*)

TLC analysis of the reaction mixture with hexane as eluent showed the presence of three products. The first two were isolated by chromatography eluting first with hexane, then 20:1 hexane–acetone, followed by 6:1 hexane–acetone. The first product to elute with $R_{f\ hexane}$ 0.22 was a 6:1 mixture of 1-methoxy-2-{[(1*E*)-1,2,3,3,3-pentafluoroprop-1-en-1-yl]thio}-benzene and 1-methoxy-2-{[(1*Z*)-1,2,3,3,3-pentafluoroprop-1-en-1-yl]thio}benzene **4b** isolated as a colourless liquid (44%). ^{1}H NMR of isomeric mixture: δ = 7.42 (2H, m, $^3J_{HH}$ = 8 and

$^4J_{HH}$ = 2 Hz, 6-H), 7.41 (2H, m, 4-H), 7.02 (2H, $^3J_{HH}$ = each 8 Hz, 5-H), 6.94 (2H, m, $^3J_{HH}$ = 8 Hz, 3-H), 3.91 (6H, s, OCH_3). ^{13}C NMR of major isomer **4b** only ($CF_3CF{=}CF$ carbon resonances were of low intensity and obscured in baseline noise): δ = 158.9 (2-C), 134.1 (6-C), 132.9 (1-C), 131.4 (4-C), 121.7 (5-C), 111.8 (6-C). ^{19}F NMR for *E*-**4b**: δ = −156.1 (1F, dq, $^3J_{FF}$ = 146 and $^3J_{FF}$ = 11 Hz, CF_3CF), −120.4 (1F, dq, $^3J_{FF}$ = 146 and $^4J_{FF}$ = 21 Hz, CFS), −66.5 (3F, dd, $^4J_{FF}$ = 21 and $^3J_{FF}$ = 11 Hz, CF_3). ^{19}F NMR for *Z*-**4c**: δ = −136.6 (1F, dq, $^3J_{FF}$ = 11 and $^3J_{FF}$ = 9 Hz, CF_3CF), −100.0 (1F, dq, $^4J_{FF}$ = 11 and $^3J_{FF}$ = 9 Hz, CFS), −64.2 (3F, dd, $^3J_{FF}$ = each 11 Hz, CF_3). IR for *E*/*Z*-**4b** (film): ν = 1684, 1585, 1481, 1465, 1435, 1354 (C=C), 1296, 1279, 1252, 1211, 1146, 1066, 1026, 939, 862, 750, 719 cm^{-1}. CI–MS for *E*/*Z*-**4b** (*m*/*z*, %): 270 (M^+, 54), 251 (M-F, 100), 138 (38).

The second product to elute with $R_{f\ hexane}$ 0.11 was 1-[(1,1,2,3,3,3-hexafluoropropyl)thio]-2-methoxybenzene **4a** isolated as a colourless liquid (8%). ^{1}H NMR: δ = 7.62 (1H, dd, $^3J_{HH}$ = 8 and $^4J_{HH}$ = 2 Hz, 6-H), 7.48 (1H, m, $^3J_{HH}$ = 8 and $^4J_{HH}$ = 2 Hz, 4-H), 7.01 (2H, m, 3-H and 5-H), 4.82 (1H, m, CHF), 3.9 (3H, s, OCH_3). ^{13}C NMR: δ = 161.0 (C-2), 139.7 (C-6), 133.2 (C-4), 131.1 (C-1), 122.5 (m, CF_3), 121.3 (C-5), 119.1 (m, CF_2S), 111.8 (C-3), 85.7 (m, CHF), 56 (OCH_3). ^{19}F NMR: δ = −203.3 (1F, m, CHF), −87.9 and −82.8 (each 1F, m, CF_2S), −72.6 (3F, m, CF_3). CI–MS (*m*/*z*, %): 290 (M^+, 15), 271 (M-F, 100), 251 (M-HF_2, 12), 138 (38). Calcd. for $C_{10}H_8F_6OS$: C, 41.4; H, 2.8; S, 11.0. Found: C, 41.3; H, 2.7; S, 11.0%.

4.6. Reaction of CTFE with benzenethiol to give (*5*)

Analysis of the reaction mixture by GC–MS showed one fluorinated product. Chromatography on silica gel, eluting with hexane, gave [(2-chloro-1,1,2-trifluoroethyl)thio]benzene **5** with R_f 0.33 as a colourless liquid (58%). ^{1}H NMR: δ = 7.65 (2H, m, 2-H and 6-H), 7.48 (1H, m, 4-H), 7.41 (2H, m, 3-H and 5-H), 6.11 (1H, ddd, $^2J_{HF}$ = 48, $^3J_{HF}$ = 8 and $^3J_{HF}$ = 5 Hz, CHClF). ^{13}C NMR: δ = 137.0 (2-C and 6-C), 130.8 (4-C), 129.5 (3-C and 5-C), 124.1 (m, CF_2S), 97.1 (td, $^1J_{CF}$ = 252 and $^2J_{CF}$ = 34 Hz, CHClF). ^{19}F NMR: δ = −146.5 (1F, dt, $^2J_{HF}$ = 48 and $^3J_{FF}$ = 18 Hz, CHClF), −88.6 (1F, ddd, $^2J_{FF}$ = 221, $^3J_{FF}$ = 18 and $^3J_{HF}$ = 8 Hz, CFS), −84.1 (1F, ddd, $^2J_{FF}$ = 221, $^3J_{FF}$ = 18 and $^3J_{HF}$ = 4 Hz, CFS). CI–MS (*m*/*z*, %): 226 (M^+, 42). Calcd. for $C_8H_6ClF_3S$: C, 42.4; H, 2.7; S, 14.1. Found: C, 42.5; H, 2.6; S, 14.1%.

4.7. Reaction of CTFE with 2-methoxybenzenethiol to give (*6*)

Chromatography on silica gel, eluting with hexane, gave 1-[(2-chloro-1,1,2-trifluoroethyl)thio]-2-methoxybenzene **6** as a colourless liquid (64%). ^{1}H NMR: δ = 7.62 (1H, dd, $^3J_{HH}$ = 8 and $^4J_{HH}$ = 2 Hz, 3-H), 7.46 (1H, td, $^3J_{HH}$ = 8 and $^4J_{HH}$ = 2 Hz, 5-H), 6.99 (1H, t, $^3J_{HH}$ = 7 Hz, 6-H), 6.98 (1H, t, $^3J_{HH}$ = 7 Hz, 4-H), 6.17 (1H, ddd, $^2J_{HF}$ = 48, $^3J_{HF}$ = 8 and $^3J_{HF}$ = 8 Hz, CHClF), 3.90 (1H, s, OCH_3). ^{13}C NMR: δ = 160.9 (C-2), 139.5 (3-C), 132.9 (5-C), 123.4 (td, $^1J_{CF}$ = 283 and $^2J_{CF}$ = 27 Hz, CF_2S), 121.2 (C-6), 112.2 (C-7), 111.7 (C-4), 97.3 (dt, $^1J_{CF}$ = 253 and $^2J_{CF}$ = 38 Hz, CHClF), 56.0 (C-1). ^{19}F NMR: δ = −147.4 (dt, $^2J_{HF}$ = 48 and $^3J_{FF}$ = 18 Hz, CHClF), −90.2 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 18 and $^3J_{HF}$ = 8 Hz, CFS), −86.0 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 24 and $^3J_{HF}$ = 5 Hz, CFS). CI–MS (*m*/*z*, %): 256 (M^+, 64), 237 (M-F, 100), 138 (25). Calcd. for $C_9H_8ClF_3OS$: C, 42.1; H, 3.1; S, 12.5. Found: C, 42.0; H, 3.1; S, 12.4%.

4.8. Reaction of CTFE with 3-methoxybenzenethiol to give (*7*)

Chromatography on silica gel, eluting with hexane, gave 1-[(2-chloro-1,1,2-trifluoroethyl)thio]-3-methoxybenzene **7** as a colourless liquid (57%). ^{1}H NMR: δ = 7.32 (1H, t, $^3J_{HH}$ = 8 Hz, 5-H), 7.24 (1H, d, $^3J_{HH}$ = 8 Hz, 6-H), 7.19 (1H, m, fine coupling 2 Hz, 4-H), 7.02 (1H, ddd, $^4J_{HH}$ = 3 Hz, $^5J_{HH}$ = 3 and 1 Hz, 2-H), 6.11 (1H, ddd, $^2J_{HF}$ = 48, $^3J_{HF}$ = 8 and $^3J_{HF}$ = 8 Hz, CHClF), 3.83 (3H, s, OCH_3). ^{13}C NMR: δ = 159.9 (C-3), 130.2 (5-C), 129.0 (1-C), 124.9 (4-C), 124.0 (td, $^1J_{CF}$ = 285 and $^2J_{CF}$ = 27 Hz, CF_2S), 121.8 (C-2), 116.8 (C-6), 96.9 (dt, $^1J_{CF}$ = 252 and $^2J_{CF}$ = 38 Hz, CHClF), 55.4 (OCH_3). ^{19}F NMR: δ = −147.4 (dt, $^2J_{HF}$ = 50 and $^3J_{FF}$ = 18 Hz, CHClF), −89.6 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 18 and $^3J_{HF}$ = 8 Hz, CFS), −84.8 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 24 and $^3J_{HF}$ = 5 Hz, CFS). CI–MS (*m*/*z*, %): 256 (M^+, 66), 237 (M-F, 100), 138 (25). Calcd. for $C_9H_8ClF_3OS$: C, 42.1; H, 3.1; S, 12.5. Found: C, 42.1; H, 3.0; S, 12.5%.

4.9. Reaction of CTFE with 4-methoxybenzenethiol to give (*8*)

Chromatography on silica gel, eluting with 49:1 hexane-acetone, gave 1-[(2-chloro-1,1,2-trifluoroethyl)thio]-4-methoxybenzene **8** as a colourless liquid (68%). ^{1}H NMR: δ = 7.56 (2H, d, $^3J_{HH}$ = 9 Hz, 3-H and 5-H), 6.94 (2H, d, $^3J_{HH}$ = 8 Hz, 2-H and 6-H), 6.07 (1H, ddd, $^2J_{HF}$ = 48, $^3J_{HF}$ = 8 and $^3J_{HF}$ = 8 Hz, CHClF), 3.84 (1H, s, OCH_3). ^{13}C NMR: δ = 161.8 (4-C), 138.7 (3-C and 5-C), 123.8 (td, $^1J_{CF}$ = 284 and $^2J_{CF}$ = 27 Hz, CF_2S), 115.0 (2-C and 6-C), 114.4 (C-1), 96.9 (dt, $^1J_{CF}$ = 248 and $^2J_{CF}$ = 34 Hz, CHClF), 55.4 (OCH_3). ^{19}F NMR: δ = −147.5 (dt, $^2J_{HF}$ = 47 and $^3J_{FF}$ = 18 Hz, CHClF), −85.9 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 18 and $^3J_{HF}$ = 8 Hz, CFS), −90.8 (ddd, $^2J_{FF}$ = 222, $^3J_{FF}$ = 23 and $^3J_{HF}$ = 5 Hz, CFS). CI–MS (*m*/*z*, %): 256 (M^+, 66). Calcd. for $C_9H_8ClF_3OS$: C, 42.1; H, 3.1; S, 12.5. Found: C, 42.1; H, 3.1; S, 12.3%.

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References

[1] C.M. Timperley, J. Fluorine Chem. 94 (1999) 37–41.
[2] C.M. Timperley, J. Fluorine Chem. 125 (2004) 685–693.
[3] C.M. Timperley, J. Fluorine Chem. 125 (2004) 1265–1272.

[4] M.P. Maidment, S.K. Patel, D.G. Upshall, C.M. Timperley, J. Appl. Toxicol. 19 (1999) 113–123.
[5] A.F. Lailey, L. Hill, I.W. Lawston, D. Stanton, D.G. Upshall, Biochem. Pharmacol. 42 (1991) S47–S54.
[6] M.J. Hobbs, M. Butterworth, G.M. Cohen, D.G. Upshall, Biochem. Pharmacol. 45 (1993) 1605–1612.
[7] M.P. Maidment, D.G. Upshall, J. Appl. Toxicol. 12 (1992) 393–400.
[8] M.P. Maidment, P. Rice, D.G. Upshall, J. Appl. Toxicol. 14 (1994) 395–400.
[9] Registry of Toxic Effects of Chemical Substances (RTECS) Database.
[10] A.I. Korbakova, I.D. Makulova, Ye N. Marchenko, T.K. Nikitenko, Toxicology of Organofluorine Compounds and Industrial Hygiene in their Production, Translation of 'Toxsikologiya ftororganicheskikh soyedineniy i gigiyena truda v ikh proizvodstve', Meditsina, Moscow, 1975, 183 pp. (translated by SCITRAN, California).
[11] J.V. Dilley, V.L. Carter, E.S. Harris, Toxicol. Appl. Pharmacol. 27 (1974) 582–590.
[12] S.J. Hargus, M.E. Fitzsimmons, Y. Aniya, M.W. Anders, Biochemistry 30 (1991) 717–721.
[13] L.A. Buckley, J.W. Clayton, R.B. Nagle, A.J. Gandolfi, Fund. Appl. Toxicol. 2 (1982) 181–186.
[14] G.G. Gibson, S.E. Clarke, D. Farrar, C.R. Elcombe, in: R. Snyder (Ed.), Ethel Browning's Toxicity and Metabolism of Industrial Solvents, vol. 1, Elsevier, Oxford, 1987, pp. 362–368 (Chapter 4.3).
[15] C.M. Timperley, in: R.E. Banks (Ed.), Fluorine Chemistry at the Millenium: Fascinated by Fluorine, Elsevier, Amsterdam, 2000, pp. 499–537 (Chapter 29).
[16] S.R. Sterlin, V.M. Ismailov, V.L. Isaev, A.A. Shal', R.N. Sterlin, B.L. Dyatkin, I.L. Knunyants, Zhur. Vses. Khim. Obshch. im Mendeleeva 18 (1973) 710–713 (translated in-house at Dstl Porton Down).
[17] I.L. Knunyants, A.I. Shchekotikhin, A.V. Fokin, Russ. Chem. Bull. Int. Ed. (1953) 255–261 (Engl. Transl.).
[18] L.M. Yagupol'skii, A.M. Aleksandrov, Russ. J. Org. Chem. 38 (1968) 1453–1458 (Engl. Transl.).
[19] K.E. Rapp, R.L. Pruett, J.T. Barr, C.T. Bahner, J.D. Gibson, R.H. Lafferty, J. Am. Chem. Soc. 72 (1950) 3642–3646.
[20] R.C. Terrell, T. Ucciardi, J.F. Vitcha, J. Am. Chem. Soc. 30 (1965) 4011–4013.
[21] C. de Tollenaere, L. Ghosez, Tetrahedron 53 (1997) 17127–17138.
[22] T. Kitazume, T. Yamazaki, Experimental Methods in Organic Fluorine Chemistry, Gordon and Breach Science Publishers, Tokyo, 1998, p. 118 (Section 3.8).
[23] R. Sauvetre, J.F. Normant, Bull. Chim. Soc. Fr. 8 (1972) 3202–3205.
[24] M.J. Hobbs, N.E. Williams, S.K. Patel, D.G. Upshall, Biochem. Pharmacol. 55 (1998) 1573–1584.
[25] C.M. Timperley, S.K. Patel, R.M. Black, 1998, unpublished results.
[26] M. Koob, W. Dekant, Drug Metab. Dispos. 18 (1990) 911–916.
[27] D.R. Dohn, A.J. Quebbemann, R.F. Borch, M.W. Anders, Biochemistry 24 (1985) 5137–5143.
[28] R.G. Pearson, J. Am. Chem. Soc. 85 (1963) 3533–3539.
[29] J.W. Harris, W. Dekant, M.W. Anders, Chem. Res. Toxicol. 5 (1992) 34–41.
[30] V. Yu, A.M. Samusenko, L.M. Aleksandrov, Yagupolskii, Russ. J. Org. Chem. 11 (1975) 622–627 (Engl. Transl.).
[31] N.I. Gazieva, A.I. Shchekotikhin, V.A. Ginsburg, Russ. J. Org. Chem. 7 (1971) 1881–1882 (Engl. Transl.).
[32] A. Yu Sizov, A.N. Kovregin, A.F. Ermolov, Russian Chem. Rev. 72 (2003) 357–374.
[33] R.E. Banks, Fluorocarbons and Their Derivatives, second ed., MacDonald Technical & Scientific, London, 1970, pp. 230–237.
[34] J. Dyer, J. Lee, Trans. Faraday Soc. 62 (1966) 257–262.
[35] K.L. Williamson, Y.-F. Li, F.H. Hall, S. Swager, J. Am. Chem. Soc. 88 (1966) 5678–5680.
[36] J.A. Young, T.M. Reed, J. Org. Chem. 32 (1967) 1682–1683.