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Fluorinated phosphorus compounds Part 8. The reactions of bis(fluoroalkyl) phosphorochloridates with sulfur nucleophiles

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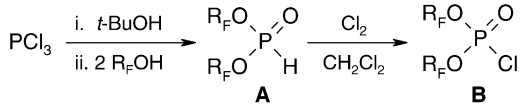
Abstract

The reactivity of bis(fluoroalkyl) phosphorochloridates to nucleophiles is summarised. Previous data and the results described here indicate that reactivities decrease in the order: amines > alcohols > thiols. The synthesis of $CF_3CH_2OP(O)(SEt)_2$ in 30% yield was accomplished by treating $CF_3CH_2OP(O)Cl_2$ with two molar equivalents of EtSH and Et_3N in ether. The chloridates $(CF_3CH_2O)_2P(O)Cl$ and $(C_2F_5CH_2O)_2$-P(O)Cl did not react with MeSH in ether at −78 °C or when heated with $Pb(SMe)_2$ in benzene. Ethanethiol and propanethiol reacted with fluorinated chloridates in the presence of triethylamine to give thiolates $(R_FO)_2P(O)SR$ in 13–41% yield where R_F was CF_3CH_2, $C_2F_5CH_2$, $C_3F_7CH_2$ or $(CF_3)_2CH$ and R was Et or *n*-Pr. Similarly, reaction of phosphorobromidates $(R_FCH_2O)_2P(O)Br$, made by brominating the corresponding bis(fluoroalkyl) *H*-phosphonates, with benzenethiol gave derivatives $(R_FCH_2O)_2P(O)SPh$ in 43 and 46% yield where R_F was CF_3 and C_2F_5, respectively. Treatment of the chloridothiolate Cl(EtO)P(O)SMe, prepared in two steps from triethyl phosphite, with fluoroalcohols and triethylamine in ether gave species $R_FO(EtO)P(O)SMe$ in 62–74% yield where R_F was CF_3CH_2, $C_2F_5CH_2$, $C_3F_7CH_2$ or $(CF_3)_2CH$. The reactions of bis(trifluoroethyl) phosphorochloridate with 2-mercaptoethanol, 3-mercaptopropanol and ethane-1,2-dithiol gave several unexpected products whose structures were tentatively assigned.

Keywords: *O*-Alkyl *O*-fluoroalkyl *S*-alkyl phosphorothiolate; Bis(fluoroalkyl) phosphorobromidate; Bis(fluoroalkyl) phosphorochloridate; *O*,*O*-bis(fluoroalkyl) *S*-alkyl phosphorothiolate; *O*-Fluoroalkyl *S*,*S*-dialkyl phosphorothiolate

1. Introduction

In Part 6, phosphorus trichloride was shown to react with *tert*-butanol and two molar equivalents of a fluoroalcohol to give bis(fluoroalkyl) *H*-phosphonates **A** which underwent chlorination to yield the phosphorochloridates **B** [1]. These compounds are colourless liquids or low-melting solids that can be stored in a refrigerator for many months without degradation. The route permitted the preparation of significant quantities of the pure chloridates for the first time.



R_F = primary, secondary or tertiary fluoroalkyl group

New research opportunities emerged once it was realised that the chemistry of the fluorinated phosphorochloridates might parallel, and in places diverge from, that of conventional phosphorochloridates. Polyfluoro-alkoxy groups are larger than alkoxy groups and more electronegative: the phosphorus atom of bis(fluoroalkyl) phosphorochloridates $(R_FO)_2P(O)Cl$ is more hindered and more electrophilic than that of dialkyl phosphorochloridates $(RO)_2P(O)Cl$ [2]. Both classes of chloridate undergo reactions typical of electrophiles, the chlorine atom being displaced easily by a range of nucleophiles. This process is termed phosphorylation [3].

The mechanism of phosphorylation has been studied extensively and is generally interpreted as a bimolecular substitution reaction proceeding at the phosphorus atom (S_N2P process) [4]. Nucleophilic attack on the dialkyl phosphorochloridate **C** produces the trigonal bipyramidal intermediate **D**. The nucleophile adopts an apical position

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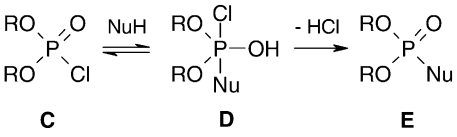
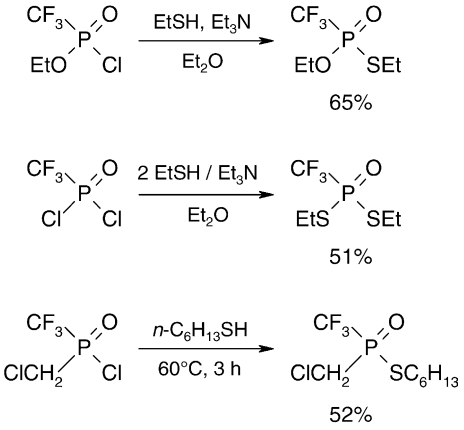
and the leaving group departs from an apical position [5], yielding the tetrahedral product **E**.



The rate of substitution depends on the size and electronegativity of the alkoxy groups in the phosphorochloridate. Small or electronegative alkoxy groups increase the rate, large or electropositive groups slow it down. Less is known about the comparative reactivities of nucleophiles, although enough data are available to draw some conclusions [6,7]. The best picture is gleaned from the behaviour of diisopropyl phosphorochloridate to nucleophiles: the reactivities of anions decrease in the order $F^- > EtO^- > PhO^- > PhS^-$ [8], *n*-butylamine reacts three times faster than water (*N*- to *O*-phosphorylation ratio 14:1) [9] and ethanolamine reacts mainly at the amino group (*N*- to *O*-phosphorylation ratio 23:1) [10]. The reactivity order does not change if the chloridate has electronegative substituents: an equimolar mixture of diphenyl phosphorochloridate, *n*-butanol and *n*-butylamine in the presence of triethylamine resulted in exclusive *N*-phosphorylation [11]. Phosphoryl dichlorofluoride $Cl_2P(O)F$ gave the diesters $(RO)_2P(O)F$ in 45–93% yield on treatment with excess ethanol, 2-fluoroethanol, *n*- or *i*-propanol, cyclohexanol or 2-methylcyclohexanol [12]. Phenol, a weaker nucleophile, did not react unless *N*,*N*-dimethylaniline was employed as base [12]. No reaction occurred with ethanethiol, but substitution did take place in the presence of *N*,*N*-dimethylaniline to give $(EtS)_2P(O)F$ [12].

It can be concluded that, regardless of the electronic character of the alkoxy group/s, the phosphorus atom of phosphorochloridates behaves as a hard acid.[1] It reacts preferentially with hard bases (nucleophiles in which the donor atom is of high electronegativity, low polarisability and difficult to oxidise, i.e. F^-, RNH_2, R_2NH, RO^-), rather than with soft bases (nucleophiles in which the donor atom is of low electronegativity, high polarisability and easy to oxidise, i.e. R^-, RS^-, CN^-).

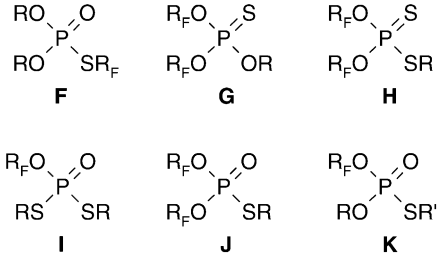
For bimolecular nucleophilic substitution reactions, basicity data are often available and can be used as a guide to nucleophilicity provided like is being compared with like. Thus, if the attacking atom is the same, then the two should run reasonably parallel, and the stronger the base the more powerful the nucleophile (e.g. $EtO^- > PhO^-$). For a given phosphorochloridate, a general rule is that the reactivity of nucleophiles decreases in the order: fluoride ion > primary and secondary amines > aromatic amines > aliphatic alcohols > aromatic alcohols > aliphatic thiols > aromatic thiols.



Scheme 1.

Previous papers in this series have confirmed that bis-(fluoroalkyl) phosphorochloridates obey this rule. The most complete set of data is obtained from knowledge of the reactions of $(CF_3CH_2O)_2P(O)Cl$. Displacement of the chlorine atom by hard nucleophiles such as fluoride [1], azide [2], primary and secondary amines [2,15], methoxyamine [2], fluoroalkylamines [16], alcohols and fluoroalcohols [15,17] has been demonstrated. Displacement by soft nucleophiles, with the exception of a few Grignard reagents [18], has not yet been explored. The reactions of sulfur nucleophiles with fluorinated phosphorus chloridates have been neglected and only two phosphonates [19] and a phosphinate [20] appear to have been made this way (Scheme 1).

The possibilities presented by the introduction of fluorine into phosphorus–sulfur compounds are vast. Some generic classes of compound are shown. Only one compound of class **F** is known: $(EtO)_2P(O)SCH_2CH_2F$ from alkylation of $(EtO)_2P(O)SNa$ with $BrCH_2CH_2F$ in hot ethanol [21]. Two compounds of class **G** are known: $(FCH_2CH_2O)_2P(S)OC_6H_4NO_2$-*p*, from treatment of the chloridothioate with *para*-nitrophenol and triethylamine in ether, and $(FCH_2CH_2O)_2P(S)OEt$ from heating the mixed phosphite with sulfur [21]. Ten compounds belonging to class **H** are known. They comprise the acids $[H(CF_2)_nCH_2O]_2P(S)SH$ where *n* is 2 and 4, made by fluoroalcoholysis of phosphorus pentasulfide [22,23], and eight derivatives $(HCF_2CF_2CH_2O)_2P(S)SR$, made by treating the sodium or potassium salt of the thioacid with various alkyl halides [24,25].



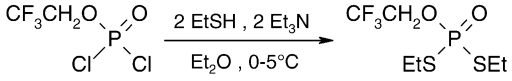
[1] For discussion of the concept of hard or soft acids and bases refer to the classic paper by Pearson [13]. A useful review of its application to multicentre reactions, with reference to phosphorus chemistry, has also been published [14].

Molecules belonging to class **I** have not been made yet. Those of class **J** that are known have the structure $(HCF_2CF_2CH_2O)_2P(O)SR$ where R is methyl, ethyl, propyl, butyl, *sec*-butyl, pentyl or benzyl [26]. Three members of class **K** have been reported: $FCH_2CH_2O(EtO)P(O)SEt$ [21] and isomers $HCF_2CF_2CH_2O(MeO)P(O)SEt$ and $HCF_2CF_2CH_2O(EtO)P(O)SMe$, but it is unclear whether the last two were obtained pure [27,28]. In this paper, we describe the reactions of thiol nucleophiles with a selection of phosphorochloridates to give some new compounds belonging to classes **I**–**K**.[2]

2. Results and discussion

2.1. Synthesis of the first dithiolate of structure *I*

Few phosphoryl compounds containing one trifluoroethoxy group are known. All are derived from trifluoroethyl phosphorodichloridate. They include the phosphoramidates $CF_3CH_2OP(O)R_2$ where R equals NMe_2, NMeEt, NEt_2 [15], NHC_6H_5 and $NHC_6H_4CH_3$-*p* [29], and the phosphates $CF_3CH_2OP(O)(OR_F)_2$ where R_F equals $CH_2CF_2CF_2H$, $CH_2C_2F_5$, $CH_2C_3F_7$ [17] and C_6H_4F-*m* [29]. We made the first sulfur analogue by treatment of trifluoroethyl phosphorochloridate **1** in ether with two molar equivalents of ethanethiol and triethylamine (the reaction was much slower than that of primary amines such as ethylamine [15] in agreement with the general rules of reactivity discussed in the previous section). Dithiolate **2** was isolated in 85% purity by bulb-to-bulb distillation under reduced pressure. The distillate was further purified by chromatography over silica gel and obtained as an analytically pure colourless liquid. The isolated yield was low as a consequence of the additional purification step.



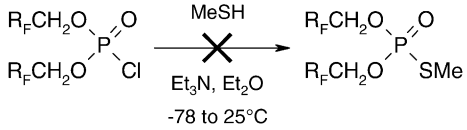
1 **2** 30%

The phosphorus chemical shift of compound **2** appears at 59.2 ppm, downfield of that for the perprotio analogue $(EtS)_2P(O)OEt$ which appears at 53.5 ppm [30].

[2] The nomenclature of phosphorus–sulfur compounds can be confusing and the names used throughout the text were chosen for clarity. The materials described in this paper are derivatives of dithiophosphoric acid $HOP(O)(SH)_2$ or thiophosphoric acid $(HO)_2P(O)SH$. The structures of these acids is complicated by tautomeric equilibria between the O=P–SH and HO–P=S forms. The position of the sulfur atoms is only defined precisely when all the hydrogen atoms are replaced by alkyl groups, and even then, under certain conditions, thiono (P=S) to thiolo (P–S) rearrangement can occur. Compounds with one sulfur atom are classed as phosphorothionates if they have a P=S bond or as phosphorothiolates if they have a P–S bond. Using these rules, names for each class of compound are as follows: **F**, *O*,*O*-dialkyl *S*-(fluoroalkyl) phosphorothiolates; **G**, *O*,*O*-bis(fluoroalkyl) *O*-alkyl phosphorothionates; **H**, *O*,*O*-bis(fluoroalkyl) *S*-alkyl phosphorodithioates; **I**, *O*-(fluoroalkyl) *S*,*S*-dialkyl phosphorodithiolates; **J**, *O*,*O*-bis(fluoroalkyl) *S*-alkyl phosphorothiolates; **K**, *O*-alkyl *O*-(fluoroalkyl) *S*-alkyl phosphorothiolates.

2.2. Attempted syntheses of thiolates of structure *J*

Bis(trifluoroethyl) phosphorochloridate and bis(pentafluoropropyl) phosphorochloridate did not react with methanethiol in ether in the presence of triethylamine. No precipitate was observed and the chloridates were recovered unchanged.



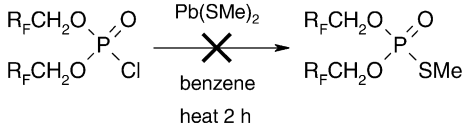
$R_F = CF_3$ or C_2F_5

With methanol instead of methanethiol, reaction occurred instantly and methyl esters were isolated in good yield (these experiments will be reported in a subsequent paper). Here, thiols are much less reactive than alcohols, but exact comparison between the two types of nucleophile is difficult. Ambiguity arises from the fact that thiols are more acidic (the pK_a for MeSH is 10.3 [31] while that of MeOH is 15.1 [32]). Consequently, the thiolate ion RS^- is always more likely to be present than the alkoxide ion RO^-, and thiolate ions are more nucleophilic than unionised thiols.

A disadvantage of methanethiol, besides its stench, is its low volatility (bp 6 °C). To circumvent this, it was converted into its lead salt. Some lead thiolates were reported in 1971 by Shaw and Woods [33] but the methanethiolate was missing. A good method for preparing it is given in Section 4.3. Methanethiol was bubbled into a solution of lead (II) acetate in aqueous ethanol. The thiolate precipitated as a yellow solid (Eq. (1)).

$$Pb(OAc)_2 + 2\,MeSH \xrightarrow[EtOH]{H_2O} Pb(SMe)_2 + 2\,AcOH \quad (1)$$

Lead alkylthiolates transfer alkylthio groups to sulfuryl chloride [34], carboxylic acid chlorides [35], chlorotrialkylsilanes [36–38], phosphorus trichloride or tribromide [39], phosphorus oxychloride $POCl_3$ or phosphorus thiochloride $PSCl_3$. Treatment of the latter with 1.5 molar equivalents of lead alkylthiolate in boiling benzene produced $(RS)_3P{=}O$ or $(RS)_3P{=}S$ with some conversion of the lead reagent to the dialkyl disulfide [40]. Experiments with dialkyl phosphorochloridates have not been conducted. No change occurred when diethyl phosphorochloridate, bis(trifluoroethyl) phosphorochloridate or bis(pentafluoropropyl) phosphorochloridate were heated under reflux with a suspension of lead methanethiolate in benzene.



$R_F = CH_3$, CF_3 , C_2F_5

The reason for their inertness is unclear. The lead salt was not inactive as some reacted with methylphosphonic

dichloride $MeP(O)Cl_2$ to give the disubstituted product $MeP(O)(SMe)_2$. The latter was made for studies of the fragmentation of phosphorus compounds in an ion trap mass spectrometer [41] and details will appear elsewhere.

An inability to obtain compounds $(R_FO)_2P(O)SMe$ from methanethiol or its lead salt is surprising as homologues were made from higher alkanethiols (see Section 2.3). Approaches worth studying, but outside the scope of this paper, include treatment of the dichloridate $Cl_2P(O)SMe$ [42] with fluoroalcohols in the presence of tertiary amine, a process that works well for alcohols [43], and alkylation of thioacids; $[H(CF_2)_2CH_2O]_2P(O)SMe$ and derivatives have been made by treating the sodium or potassium salts of the thioacid $[H(CF_2)_2CH_2O]_2P(O)SH$ with alkyl iodides [24,25].

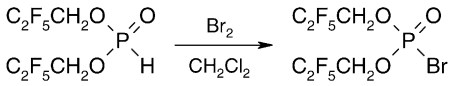
2.3. Successful syntheses of aliphatic thiolates of structure *J*

Ethanethiol and propanethiol reacted with bis(fluoroalkyl) phosphorochloridates in ether in the presence of triethylamine to afford phosphorothiolates **3a–d** and **4a–d** as colourless liquids.[3] They were purified by bulb-to-bulb distillation. Yields and boiling points for the phosphorothiolates appear in Table 1.

Spectroscopic data for thiolates **3a–d** and **4a–d** appear in Table 2. They have phosphorus chemical shifts around 30–35 ppm, a region diagnostic for dialkyl phosphorothiolates [26,51,52]. The shift for $(CF_3CH_2O)_2P(O)SEt$ **3a** appears at 30.7 ppm, downfield of that for its perprotio analouge $(CH_3CH_2O)_2P(O)SEt$ which appears at 26.4 ppm [30]. In the infrared spectra, the phosphoryl stretch for unfluorinated dialkyl phosphorothiolates appears between 1270 and 1245 cm^{-1}. The fluorinated compounds gave strong C–F stretching bands between 1300 and 1000 cm^{-1} which prevented assignment of the P=O frequencies.

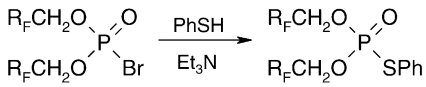
2.4. Syntheses of aromatic thiolates of structure *J*

In Part 6, we described the synthesis of bis(trifluoroethyl) phosphorobromidate from the corresponding phosphite and bromine [1]. We extended this methodology and obtained bis(pentafluoropropyl) phosphorobromidate **5** as a colourless liquid (bp 88 °C/1 mmHg).



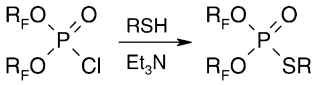
5 87%

The chemistry of bis(fluoroalkyl) phosphorobromidates has not been charted and fluoroalkyl phosphorothiolates with arylthio groups are unknown. Treatment of the phosphorobromidates with benzenethiol in ether in the presence of triethylamine gave compounds **6a–b**. The former **6a**, a solid (mp 35–36 °C), was isolated by flash chromatography.[4] The latter **6b**, a liquid (bp 96 °C/1 mmHg), was purified by bulb-to-bulb distillation. They have phosphorus chemical shifts around 25 ppm; a singlet appears at 25.3 ppm for compound **6a**, more downfield than that for the perprotio analogue $(EtO)_2P(O)SPh$ which appears at 22 ppm [30,54]. Their synthesis illustrates the potential of bis(fluoroalkyl) phosphorobromidates as phosphorylating agents.



R_F = CF_3 **6a** 43%
C_2F_5 **6b** 46%

Table 1
Experimental data for phosphorothiolates of structure $(R_FO)_2P(O)SR$



3a-d , **4a-d**

Compound	R_F	R	Yield (%)	bp (°C/mmHg)[a]
3a	CF_3CH_2	Et	19	44/0.05[b]
3b	$C_2F_5CH_2$	Et	13	43/0.03
3c	$C_3F_7CH_2$	Et	41	53/0.02
3d	$(CF_3)_2CH$	Et	28	35/0.03
4a	CF_3CH_2	*n*-Pr	19	50/0.04[c]
4b	$C_2F_5CH_2$	*n*-Pr	21	53/0.03
4c	$C_3F_7CH_2$	*n*-Pr	37	43/0.02
4d	$(CF_3)_2CH$	*n*-Pr	21	38/0.03

[a] Approximate oven temperature for bulb-to-bulb distillations.
[b] Unfluorinated analogue $(EtO)_2P(O)SEt$ is a liquid with bp 80 °C/0.5 mmHg [45].
[c] Unfluorinated analogue $(EtO)_2P(O)SPr$ is a liquid with bp 70 °C/0.3 mmHg [46].

[3] Unfluorinated analogues are generally prepared differently. The perprotio analogue of **3a**, $(EtO)_2P(O)SEt$, also a distillable liquid, can be prepared in 56% yield by treating an ethanolic solution of diethyl sodium phosphite $(EtO)_2PONa$ with sulfur then ethyl bromide [44]. It has also been made in 74 and 71% yield by reacting the same salt with diethyl disulfide or ethyl phenyl disulfide in tetrahydrofuran [45], in 77% yield by reacting triethyl phosphite with diethyl disulfide [46] and in 70% yield by isomerising the thionate $(EtO)_3P=S$ at 180–185 °C for 23 h [47]. A particularly convenient route involves the Arbusov reaction between triethyl phosphite and ethyl thiocyanate, which proceeds smoothly on warming, and gives the product in 90–91% yield and the easily-removed by-product, ethyl cyanide [48,49]. Ethyl sulfenyl chloride can be used instead of ethyl thiocyanate, but less effectively (76% yield) [50]. Many unfluorinated compounds of formula $(RO)_2P(O)SR'$ can be obtained by such methods. Their application to the synthesis of fluoroalkyl-substituted phosphorothiolates warrants examination.

[4] The perprotio analogue of **6a**, $(EtO)_2P(O)SPh$, is a liquid. It has been made in 50, 70 and 92% yield by the Arbusov reaction of triethyl phosphite with phenyl 2,4-dinitrophenyl disulfide in xylene, diphenyl disulfide in benzene, and pentachlorophenyl phenyl disulfide in ether [46]. It was also obtained in 67% yield by treating diethyl sodium phosphite $(EtO)_2PONa$ in benzene with diphenyl disulfide [53]. Purification entailed chromatography on Florisil [46] or distillation (bp 95 °C/1 mmHg) [53].

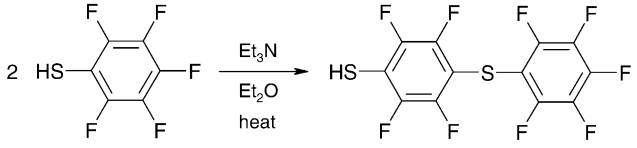
Table 2
Spectroscopic data for bis(fluoroalkyl) *S*-alkyl phosphorothiolates $(R_FO)_2P(O)SR$ **3a–d** and **4a–d** (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ	^{31}P NMR δ	IR ν (cm^{-1})	Elemental analysis (%)
3a	4.45 (4H, m, OCH_2), 2.95 (2H, dq, $J = 15$ and 7, SCH_2), 1.42 (3H, t, $J = 7$, CH_3)	122.3 (dq, $J = 11$ and 277, CF_3), 62.3 (dq, $J = 38$ and 6, OCH_2), 25.5 (d, $J = 4$, SCH_2), 15.9 (d, $J = 7$, CH_3)	−74.6 (6F, t, $J = 6$, CF_3)	30.7[a]	1456, 1419, 1296, 1174, 1063, 964, 874, 659	Calc. for $C_6H_9F_6O_3PS$ (M_w 306): C 23.5, H 2.9, F 37.3. Found: C 24.1, H 3.1, F 37.5
3b	4.49 (4H, m, OCH_2), 2.95 (2H, dq, $J = 15$ and 7, SCH_2), 1.42 (3H, t, $J = 7$, CH_3)	125–108 (complex m, CF_2 and CF_3), 62.2 (dt, $J = 29$ and 6, OCH_2), 26 (d, $J = 5$, SCH_2), 15.9 (d, $J = 6$, CH_3)	−123.7 (4F, m, CF_2), −82.5 (6F, m, $J = 287$, 118 and 35, CF_3)	30.7	1458, 1354, 1280, 1203, 1157, 1111, 1055, 1024, 935, 872, 721, 620	Calc. for $C_8H_9F_{10}O_3PS$ (M_w 406): C 23.6, H 2.2, F 46.8. Found: C 23.8, H 2.1, F 47.1
3c	5.19 (4H, m, OCH_2), 3.03 (2H, dq, $J = 15$ and 7, SCH_2), 1.42 (3H, t, $J = 7$, CH_3)	125–115 (complex m, C_3F_7), 71.5 (m, OCH_2), 25.7 (d, $J = 5$, SCH_2), 15.9 (d, $J = 8$, CH_3)	−126.5 (4F, m, CF_2), −120.4 (4F, m, CF_2), −79.9 (6F, m, CF_3)	35.3	1457, 1356, 1228, 1184, 1130, 1066, 1014, 966, 926, 868, 760, 729	Calc. for $C_{10}H_9F_{14}O_3PS$ (M_w 506): C 23.7, H 1.8, F 52.6. Found: C 23.5, H 1.6, F 52.8
3d	5.15 (2H, dsep, $J = 6$ each, CH), 3.02 (2H, dt, $J = 17$ and 7, SCH_2), 1.42 (3H, t, $J = 7$, CH_3)	117 (dq, $J = 7$ and 277, CF_3), 71.2 (dsep, $J = 6$ and 28, OCH), 26.3 (d, $J = 5$, SCH_2), 16.5 (d, $J = 8$, CH_3)	−72.7 (3F, br t, CF_3), −73.1 (3F, br s, CF_3)	35.3	Not obtained[b]	Not obtained[b]
4a	4.41 (4H, m, OCH_2), 2.91 (2H, dt, $J = 15$, 7, SCH_2), 1.74 (2H, sextet, $J = 7$, CH_2), 1.05 (3H, t, $J = 7$, CH_3)	123.4 (dq, $J = 11$ and 277, CF_3), 63.9 (dq, $J = 38$ and 6, OCH_2), 33.3 (d, $J = 4$, SCH_2), 23.8 (d, $J = 6$, CH_2), 13.7 (s, CH_3)	−74.0 (6F, t, $J = 9$, CF_3)	31.1[a]	1458, 1419, 1294, 1259, 1173, 1095, 1061, 962, 874, 659	Calc. for $C_7H_{11}F_6O_3PS$ (M_w 320): C 26.3, H 3.4, F 35.6. Found: C 26.4, H 3.7, F 35.2
4b	4.5 (4H, m, OCH_2), 2.93 (2H, dt, $J = 15$ and 7, SCH_2), 1.71 (2H, sextet, $J = 7$, CH_2), 1.06 (3H, t, $J = 7$, CH_3)	122–108 (complex m, C_2F_5), 62.5 (dt, $J = 29$ and 5, OCH_2), 33.5 (d, $J = 4$, SCH_2), 24.1 (d, $J = 6$, CH_2), 12.5 (s, CH_3)	−123.4 (4F, m, CF_2), −82.5 (6F, m, CF_3)	31.3	1459, 1269, 1203, 1157, 1111, 1026, 935, 870, 721, 621	Calc. for $C_9H_{11}F_{10}O_3PS$ (M_w 420): C 25.7, H 2.6, F 45.2. Found: 25.9, H 2.8, F 45.5
4c	4.53 (4H, m, OCH_2), 2.93 (2H, dt, $J = 14$ and 7, SCH_2), 1.75 (2H, sextet, $J = 7$, CH_2), 1.04 (3H, t, $J = 7$, CH_3)	124–110 (m, C_3F_7), 63.8 (m, OCH_2), 33.2 (d, $J = 4$, SCH_2), 24.1 (d, $J = 7$, CH_2), 12.6 (s, CH_3)	−126.7 (4F, m, CF_2), −120.0 (4F, m, CF_2), −80.1 (6F, m, CF_3)	31.1	1460, 1356, 1228, 1184, 1130, 1066, 1014, 966, 926, 868	Calc. For $C_{11}H_{11}F_{14}O_3PS$ (M_w 520): C 25.4, H 2.1, F 51.2. Found: C 25.6, H 2.4, F 51.3
4d	5.17 (2H, dsep, $J = 6$ each, CH), 2.96 (2H, dt, $J = 16$ and 7, SCH_2), 1.77 (2H, sextet, $J = 7$, CH_2), 1.04 (3H, t, $J = 7$, CH_3)	120 (dq, $J = 7$ and 277, CF_3), 72 (dsep, $J = 6$ and 28, OCH), 33.3 (d, $J = 4$, SCH_2), 23.6 (d, $J = 7$, CH_2), 12.7 (s, CH_3)	−72.7 (3F, br t, CF_3), −73.1 (3F, br s, CF_3)	35.7	Not obtained[b]	Not obtained[b]

[a] The phosphorus chemical shifts of compounds **3a** and **4a**, namely $(CF_3CH_2O)_2P(O)SEt$ and $(CF_3CH_2O)_2P(O)SPr$, appear downfield of those of their perprotio analogues $(EtO)_2P(O)SEt$ and $(EtO)_2P(O)SPr$ which feature at 26.4 and 26.5 ppm, respectively [30].

[b] Compound only 90% pure by ^{31}P NMR analysis.

Experiments to investigate the interaction of bis(fluoroalkyl) phosphorohalidates with pentafluorobenzenethiol did not proceed as expected: derivatives of structure $(R_FCH_2O)_2P(O)SC_6F_5$ could not be isolated. Bis(trifluoroethyl) phosphorobromidate and equimolar amounts of pentafluorobenzenethiol and triethylamine produced only traces of triethylamine hydrobromide on mixing. After heating under reflux for 48 h, the situation did not improve and gas chromatography–mass spectrometry (GC–MS) analysis showed the mixture to comprise unreacted bromidate and thiol, and an unknown of *m/z* 380. This latter was not isolated, but was presumed to be sulfide **8** from substitution of one molecule of pentafluorobenzenethiol by another.



8

It is reasonable to assume *para* orientation in light of data for attack of nucleophiles on substituted pentafluorobenzenes [55,56] despite deficient knowledge of the directional effect of the SH group. Neither pentafluorobenzenethiol nor sulfide **8** reacted with the bromidate under the conditions studied, contrasting with benzenethiol that reacted at the phosphorus atom. The difference is mainly electronic in origin and attributable to the greater basicity of benzenethiol and in the case of pentafluorobenzenethiol, its ability to self-condense under basic conditions [57,58].

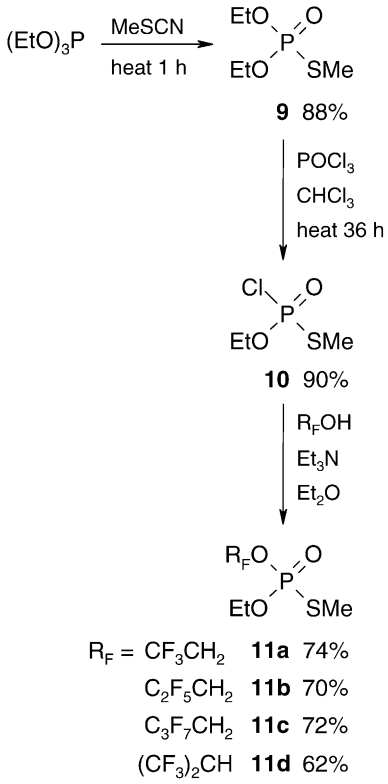
2.5. Synthesis of thiolates of structure *K*

The synthesis of compounds of general formula $(R_FO)ROP(O)SR'$ was accomplished in three steps. The strategy involved introducing the alkylthio group first and incorporating the fluoroester group last. Arbusov reaction of triethyl phosphite with methyl thiocyanate yielded phosphorothiolate **9** that was transformed into chloridothiolate **10** by heating with phosphorus oxychloride. The chloridothiolate, on treatment with fluoroalcohols and triethylamine, gave compounds **11a–d** (Scheme 2). They were purified by chromatography or short-path distillation and were obtained as colourless liquids.

Spectroscopic data for compounds **11a–d** appear in Table 3. They contain a chiral phosphorus atom. No attempt was made to resolve the racemic mixtures.

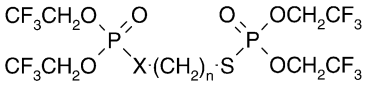
2.6. Reactions of bis(trifluoroethyl) phosphorochloridate with bis-nucleophiles

The behaviour of bis(trifluoroethyl) phosphorochloridate towards bis-nucleophiles containing one or more thiol



Scheme 2.

groups was examined. Two molar equivalents of chloridate were treated with a molar equivalent of 2-mercaptoethanol, 3-mercaptopropanol or ethane-1,2-dithiol in ether, in the presence of two molar equivalents of triethylamine and a catalytic quantity of 4-dimethylaminopyridine. The anticipated bis-substitution products **12** did not form.



12

X = O n = 2 and 3
X = S n = 2

1,2-Mercaptoethanol and 1,3-mercaptopropanol gave three tentative products—phosphoric acid **13**, phosphate **14** and pyrophosphate **15**—as indicated by GC–MS analysis (Table 4). Ethane-1,2-dithiol gave three products: phosphate **14** and two pyrophosphates differing in the bridging atom (oxygen **15** or sulfur **16**). The percentage of each was calculated by integration of its peak relative to the other components and is approximate: some volatile products may have escaped detection. We failed to separate the product mixtures by chromatography or distillation. The mechanism of reaction is obscure and merits further investigation.

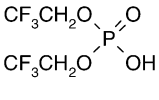
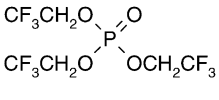
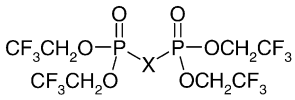
Table 3
Spectroscopic data for *O*-ethyl *O*-fluoroalkyl *S*-methyl phosphorothiolates $R_FO(EtO)P(O)SMe$ **11a–d** (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	Elemental analysis (%)
11a	4.43 (2H, m, OCH_2CF_3), 4.23 (2H, m, OCH_2), 2.31 (3H, d, $J = 16$, SCH_3), 1.41 (3H, t, $J = 7$, CH_3)	122.8 (dq, $J = 11$ and 277, CF_3), 64.6 (d, $J = 6$, OCH_2), 62.7 (dq, $J = 38$ and 4, OCH_2CF_3), 15.9 (d, $J = 7$, SCH_3), 12.2 (d, $J = 4$, CH_3)	−74.6 (3F, t, $J = 10$, CF_3)	29.0[a]	1421, 1394, 1290, 1257, 1173, 1090, 1024, 964, 860, 841, 777, 660, 611, 582	Calc. for $C_5H_{10}F_3O_3PS$ (M_w 238): C 25.2, H 4.2, F 23.9. Found: C 25.2, H 4.4, F 24.2
11b	4.48 (2H, m, $OCH_2C_2F_5$), 4.25 (2H, m, OCH_2), 2.33 (3H, d, $J = 16$, SCH_3), 1.39 (3H, t, $J = 7$, CH_3)	118.5 (tq, $J = 287$ and 34, CF_3), 111.8 (dq, $J = 10$ and 256, CF_2), 64.7 (d, $J = 6$, OCH_2), 61.7 (dt, $J = 29$ and 4, $OCH_2C_2F_5$), 15.7 (d, $J = 7$, SCH_3), 12.1 (d, $J = 4$, CH_3)	−123.5 (2F, m, CF_2), −82.5 (3F, m, CF_3)	29.1	1446, 1394, 1354, 1265, 1203, 1155, 1111, 1078, 1020, 970, 852, 773, 719, 657, 621	Calc. For $C_6H_{10}F_5O_3PS$ (M_w 288): C 25.0, H 3.5, F 33.0. Found: C 25.1, H 3.4, F 32.7
11c	4.53 (2H, m, $OCH_2C_3F_7$), 4.26 (2H, m, OCH_2), 2.32 (3H, d, $J = 16$, SCH_3), 1.41 (3H, t, $J = 7$, CH_3)	120–105 (complex m, C_3F_7), 64.7 (d, $J = 6$, OCH_2), 61.9 (dt, $J = 28$ and 4, $OCH_2C_3F_7$), 15.9 (d, $J = 6$, SCH_3), 12.1 (d, $J = 5$, CH_3)	−126.5 (2F, m, CF_2), −120.5 (2F, m, CF_2), −80.0 (3F, m, CF_3)	29.3	1444, 1394, 1356, 1327, 1230, 1184, 1132, 1090, 1030, 1014, 966, 924, 852, 759, 727, 611, 584	Calc. For $C_7H_{10}F_7O_3PS$ (M_w 338): C 24.9, H 3.0, F 39.3. Found: C 25.1, H 2.7, F 39.1
11d	5.23 (1H, dsep, $J = 6$ each, OCH), 4.28 (2H, dq, $J = 7$, OCH_2), 2.36 (3H, d, $J = 17$, SCH_3), 1.42 (3H, t, $J = 7$, CH_3)	120.6 (dq, $J = 7$ and 280, CF_3), 70.4 (dsep, $J = 6$ and 35, OCH), 65.5 (d, $J = 7$, OCH), 15.7 (d, $J = 7$, SCH_3), 12.1 (d, $J = 5$, CH_3)	−73.5 (3F, 'q', $J = 8$, CF_3) and −73.6 (3F, 'q', $J = 8$, CF_3)[b]	31.3	1383, 1296, 1234, 1201, 1113, 1026, 972, 901, 877, 775, 734, 688, 602	Calc. For $C_6H_9F_6O_3PS$ (M_w 306): C 23.5, H 2.9, F 37.3. Found: C 23.8, H 3.2, F 37.3

[a] The phosphorus chemical shift of compound **11a**, $CF_3CH_2O(EtO)P(O)SMe$, is only slightly downfield of that of the perprotio analogue $(EtO)_2P(O)SMe$ which appears at 28.6 ppm [30]. One fluoroethoxy group hardly affects the position of the shift, yet two fluoroethoxy groups have a more profound influence (refer to Table 2, footnote a).

[b] Compound **11d**, $(CF_3)_2CHO(EtO)P(O)SMe$, contains two magnetically non-equivalent CF_3 groups due to the chiral phosphorus centre: the trifluoromethyl resonances appear as slightly overlapping quartets.

Table 4
Tentative products of reactions of some bis-nucleophiles with bis-(2,2,2-trifluoroethyl) phosphorochloridate

Nucleophile	Possible products			
				
			X = O	X = S
	13	**14**	**15**	**16**
$HOCH_2CH_2SH$ (%)	17	8	75	–
$HOCH_2(CH_2)_2SH$ (%)	20	10	70	–
$HSCH_2CH_2SH$ (%)	–	24	38	38

3. Conclusion

Thiols react less efficiently with bis(fluoroalkyl) phosphorochloridates than alcohols or amines. Although it is possible to prepare compounds of structure $R_FOP(O)(SR)_2$ and $(R_FO)_2P(O)SR$ in modest quantities from phosphorohalidates, better routes need to be developed. Reactions of chloridates already containing the RS–P(O) grouping are more efficient; fluoroalcoholysis of MeS(EtO)P(O)Cl gave derivatives $MeS(EtO)P(O)OR_F$ in 62–74% yield. Reactions of bis-nucleophiles containing thiol groups with bis(trifluoroethyl) phosphorochloridate gave complex mixtures. The chemistry of fluoroalkyl phosphoryl compounds containing sulfur groups should mature once high-yielding synthetic routes become available.

4. Experimental details

2,2,2-Trifluoroethyl phosphorodichloridate [15], bis-(fluoroalkyl) phosphorochloridates, bis(2,2,2-trifluoroethyl) phosphorobromidate and bis(2,2,3,3,3-pentafluoropropyl) *H*-phosphonate [1] were obtained in high purity using previously reported methods. All reagents were of commercial quality: alkanethiols and lead (II) acetate trihydrate were purchased from Aldrich (Gillingham, UK) and fluoroalcohols from Apollo Scientific Ltd. (Derbyshire, UK). They were used as received. Anhydrous solvents were used in all experiments. Thin layer chromatography (TLC) plates, MK6F silica gel 60 Å (2.5 cm × 7.5 cm, layer thickness 250 μg), were obtained from Whatman (Maidstone, UK). Spots were visualised with iodine vapour. Silica gel for flash chromatography was from BDH Laboratory Supplies (Poole, UK). NMR spectra were obtained on a JEOL Lambda 500 instrument (operating at 500 MHz for ^1H, 125 MHz for ^{13}C, 470 MHz for ^{19}F, and 202 MHz for ^{31}P spectra) or a JEOL Lambda 300 instrument (operating at 300 MHz for ^1H, 75 MHz for ^{13}C, 282 MHz for ^{19}F, and 121.5 MHz for ^{31}P spectra) as solutions in $CDCl_3$, with internal reference $SiMe_4$ for ^1H and ^{13}C, external $CFCl_3$ for ^{19}F and external $(MeO)_3P$ (δ 140 ppm) for ^{31}P spectra. Data are recorded as follows: chemical shifts in ppm from reference on the δ scale, integration, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet and sep: septet; br: broad), coupling constant (*J*/Hz) and assignment. IR spectra were recorded as liquid films on a Nicolet SP210 instrument using Omnic software. Reaction mixtures were monitored by gas chromatography–mass spectrometry (GC–MS) using a Finnigan MAT GCQ instrument with chemical ionisation (CI) using methane as reagent gas. Molecular masses of pure products were confirmed with methane positive CI data (70 eV). All compounds containing sulfur appeared as one spot by TLC and were >98% pure by multinuclear NMR and GC–MS analyses, unless stated otherwise.

*4.1. Synthesis of S,S-diethyl O-(2,2,2-trifluoroethyl) phosphorothiolate (**2**)*

A solution of ethanethiol (1.49 g, 24 mmol) and triethylamine (3.34 ml, 24 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of 2,2,2-trifluoroethyl phosphorochloridate (2.6 g, 12 mmol) in ether (30 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature. After 14 h, an aliquot was withdrawn for analysis by GC–MS. The reaction was 90% complete. The precipitate was filtered off and the filtrate concentrated. Bulb-to-bulb distillation of the residue (oven temperature 45 °C at 0.015 mmHg) gave a liquid that was 85% pure by phosphorus NMR spectroscopy. The liquid was subsequently chromatographed on silica gel, eluting with 12:1 hexane–acetone, to give the title compound as a colourless liquid (0.97 g, 30%). R_f 0.48. ^1H NMR: $\delta = 4.4$ (2H, m, OCH_2), 2.97 (4H, dq, $J = 15$ and 7 Hz, SCH_2), 1.42 (6H, t, $J = 7$ Hz, CH_3). ^{13}C NMR: $\delta = 122.6$ (dq, $J = 11$ and 277 Hz, CF_3), 62.4 (dq, $J = 38$ and 7 Hz, OCH_2), 26.7 (d, $J = 4$ Hz, SCH_2), 15.4 (d, $J = 6$ Hz, CH_3). ^{19}F NMR: $\delta = -74.2$ (3F, t, $J = 8$ Hz, CF_3). ^{31}P NMR: $\delta = 59.2$. IR (film): $\nu = 1452$, 1417, 1379, 1284, 1230 (P=O), 1171, 1068, 962, 850, 657, 602 cm^{-1}. HRMS: calculated $C_6H_{12}F_3O_2PS_2$ 268.248 ($[M\text{-HF}]^+ = 248.242$), found 248.211 (error 0.8).

4.2. Attempted reaction of bis(fluoroalkyl) phosphorochloridates with methanethiol

A round-bottomed flask was equipped with a T-adaptor and a dry ice condenser whose outlet was fitted with a guard tube containing anhydrous calcium chloride. The flask was charged with a solution of bis(fluoroalkyl) phosphorochloridate (4 mmol) and triethylamine (4 mmol) in ether (20 ml). The flask and the condenser were cooled to −78 °C (dry ice/acetone) and methanethiol was passed through the T-adaptor. Liquefied methanethiol was allowed to condense into the reaction mixture until it was clear that excess had been added. The gas flow was stopped and the flask warmed to room temperature (the condenser containing dry ice remained at −78 °C). Once the flask reached room temperature, the dry ice in the cold finger was allowed to evaporate. The reaction mixture was left to stand for 12 h. No precipitate formed and analysis by GC-MS indicated that no reaction had taken place. Removal of solvent gave the starting chloridates.

4.3. Preparation of lead methanethiolate

Lead (II) acetate trihydrate (22.8 g, 60 mmol) was suspended in ethanol (200 ml) maintained at 50 °C. Deionised water (ca. 25 ml) was added and the suspension stirred until the solid dissolved. Methanethiol was bubbled through the solution until a yellow precipitate formed. This was filtered off, washed with ethanol, and dried under high vacuum (17.4 g, 96%); mp 128 °C (dec.).

4.4. Attempted reactions of phosphorochloridates with lead methanethiolate

Lead methanethiolate (1.08 g, 3.6 mmol) was added in one portion to a solution of phosphorochloridate (7.1 mmol) in benzene (50 ml) at room temperature. The reaction mixture was heated under reflux for 2 h. The yellow thiolate salt discoloured and went slightly grey. Experiments were carried out with bis(trifluoroethyl) phosphorochloridate, bis(pentafluoropropyl) phosphorochloridate and diethyl phosphorochloridate. No reaction occurred as shown by TLC, GC–MS and multinuclear NMR analyses.

4.5. General procedure or O,O-bis(fluoroalkyl) S-alkyl phosphorothiolates (**3a–d**) and (**4a–d**)

A solution of ethanethiol or propanethiol (4 mmol) and triethylamine (0.56 ml, 4 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of bis(fluoroalkyl) phosphorochloridate (4 mmol) in ether (25 ml) at 0–5 °C. After addition, the mixture was warmed to room temperature and left for 14 h before a portion was analysed by GC–MS. When product predominated, the precipitate was removed using silicone-treated filter paper. The filtrate was concentrated to give a liquid that was purified by bulb-to-bulb distillation under reduced pressure. Boiling points appear in Table 1 and spectroscopic data in Table 2.

4.6. Preparation of bis(pentafluoropropyl) phosphorobromidate (**5**)

A solution of bromine (4.62 g, 28.9 mmol) in dichloromethane (20 ml) was added dropwise to a stirred solution of bis(2,2,3,3,3-pentafluoropropyl) *H*-phosphonate (10 g, 28.9 mmol) in dichloromethane (30 ml) at 0–5 °C. The added bromine decolourised rapidly. After addition the mixture was allowed to warm to room temperature and left for 12 h. The solvent was removed. Distillation of the residue under reduced pressure gave the title compound as a colourless liquid (10.71 g, 87%); bp 88 °C/1 mmHg and 46 °C/0.1 mmHg. ^{1}H NMR: $\delta = 4.56$ (4H, m, OCH_2). ^{13}C NMR: $\delta = 116$ (tq, $J = 34$ and 286 Hz, CF_3), 109.4 (dq, $J = 8$ and 256 Hz, CF_2), 63.7 (dt, $J = 6$ and 29 Hz, OCH_2). ^{19}F NMR: $\delta = -123.9$ (4F, m, CF_2), −83.2 (6F, m, CF_3). ^{31}P NMR: $\delta = -8.9$. IR (film): $\nu = 1377$, 1356, 1304 (P=O), 1269, 1205, 1163, 1126, 1111, 1031, 935, 889 cm^{-1}. HRMS: calculated $C_6H_4BrF_{10}O_3P$ 424.953 ($[M\text{-HF}]^+ = 404.947$), found 404.932 (error 1.2).

4.7. Preparation of O,O-bis(trifluoroethyl) S-phenyl phosphorothiolate (**6a**)

A solution of benzenethiol (0.68 g, 6.18 mmol) and triethylamine (0.86 ml, 6.18 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of bis-(2,2,2-trifluoroethyl) phosphorobromidate (2 g, 6.18 mmol) in ether (40 ml) at 0–5 °C. An instant precipitate of triethylamine hydrobromide formed. After addition the mixture was allowed to warm to room temperature and was left for 2 h. The precipitate was removed by filtration. Concentration of the filtrate gave a semi-solid residue. Chromatography on silica gel, eluting with 4:1 hexane–acetone, gave the title compound as a white solid (0.95 g, 43%); mp 35–36 °C. ^{1}H NMR: $\delta = 7.61-7.42$ (5H, m, phenyl), 4.37 (4H, m, OCH_2). ^{13}C NMR: $\delta = 151.17$ (d, $J = 8$ Hz, phenyl *ipso* C), 135.5 (d, $J = 5$ Hz, phenyl *ortho* C), 130.3 (d, $J = 3$ Hz, phenyl *meta* C), 129.9 (d, $J = 3$ Hz, phenyl *para* C), 121.2 (dq, $J = 11$ and 277 Hz, CF_3), 63.5 (dq, $J = 38$ and 6 Hz, OCH_2). ^{19}F NMR: $\delta = -74.6$ (6F, t, $J = 8$ Hz, CF_3). ^{31}P NMR $\delta = 25.3$. IR (KBr disc): $\nu = 2252$, 1581, 1475, 1454, 1442, 1417, 1296, 1259, 1174, 1095, 1063, 962, 910, 877, 845, 818, 746, 737 cm^{-1}. HRMS calculated $C_{10}H_9F_6O_3PS$ 354.201 ($[M\text{-HF}]^+ = 334.195$), found 334.201 (error 1.8).

4.8. Preparation of O,O-bis(pentafluoropropyl) S-phenyl phosphorothiolate (**6b**)

A solution of benzenethiol (0.51 g, 4.64 mmol) and triethylamine (0.65 g, 4.64 mmol) in ether (10 ml) was added

dropwise by cannula to a stirred solution of bis(2,2,3,3,3-pentafluoropropyl) phosphorobromidate (1.97 g, 4.64 mmol) in ether (40 ml) at 0–5 °C. An instant precipitate of triethylamine hydrobromide formed. After addition the mixture was allowed to warm to room temperature and was left for 24 h. The precipitate was removed by filtration. Concentration of the filtrate gave a liquid that was distilled under reduced pressure using a Kugelrohr apparatus. The title compound was obtained as a colourless liquid (0.98 g, 46%); bp 96 °C/1 mmHg. ^{1}H NMR: $\delta = 7.62-7.35$ (5H, m, phenyl), 4.44 (4H, m, OCH_2). ^{13}C NMR: $\delta = 151.1$ (d, $J = 8$ Hz, phenyl *ipso* C), 135.5 (d, $J = 5$ Hz, phenyl *ortho* C), 130.3 (d, $J = 3$ Hz, phenyl *meta* C), 129.9 (d, $J = 3$ Hz, phenyl *para* C), 118.1 (tq, $J = 34$ and 285 Hz, CF_3), 111.3 (tq, $J = 9$ and 256 Hz, CF_2), 62.7 (dq, $J = 29$ and 6 Hz, OCH_2). ^{19}F NMR: $\delta = -123.6$ (4F, m, CF_2), -82.6 (6F, m, CF_3). ^{31}P NMR: $\delta = 25.5$. IR (KBr disc): $\nu = 2254$, 1442, 1354, 1267, 1209, 1159, 1124, 1065, 1026, 908, 876, 837, 735 cm^{-1}. HRMS calculated $C_{12}H_9F_{10}O_3PS$ 454.215 ([*M*-HF]$^+$ = 434.209), found 434.202 (error 0.3).

4.9. Preparation of *O,O*-diethyl *S*-methyl phosphorothiolate (**9**)

Triethyl phosphite (166 g, 1 mol) and methyl thiocyanate (73 g, 1 mol) were heated under reflux for 1 h. Analysis by TLC and GC–MS showed excellent conversion to the product. Distillation under reduced pressure gave the title compound as a colourless liquid (162 g, 88%); bp 90 °C/0.6 mmHg. Purity 95% (determined by phosphorus NMR and GC–MS analyses). ^{1}H NMR: $\delta = 4.18$ (4H, m, OCH_2), 2.28 (3H, d, $J = 15$ Hz, SCH_3), 1.39 (6H, t, $J = 7$ Hz, CH_3). ^{13}C NMR: $\delta = 63.4$ (d, $J = 6$ Hz, OCH_2), 15.9 (d, $J = 7$ Hz, SCH_3), 12.2 (d, $J = 5$ Hz, CH_3). ^{31}P NMR: $\delta = 27.4$. IR (film): $\nu = 2983$, 2918, 2848, 1392, 1253 (P=O), 1163, 1097, 1018, 972, 793 cm^{-1}.

4.10. Preparation of *O*-ethyl *S*-methyl phosphorochloridothiolate (**10**)

A solution of phosphorus oxychloride (29.2 g, 0.19 mol) in chloroform (30 ml) was added in one portion to a solution of *O,O*-diethyl *S*-methyl phosphorothiolate (35 g, 0.19 mol) in chloroform (30 ml). The mixture was heated under reflux and monitored by GC–MS. After 36 h, the reaction would not progress further. Removal of the solvent and fractionation of the residue under reduced pressure gave the pure title compound (29.8 g, 90%); bp 104 °C/12 mmHg. ^{1}H NMR: $\delta = 4.35$ (2H, m, OCH_2), 2.5 (3H, d, $J = 19$ Hz, SCH_3), 1.44 (3H, t, $J = 7$ Hz, CH_3). ^{13}C NMR: $\delta = 66.0$ (d, $J = 9$ Hz, OCH_2), 15.7 (d, $J = 8$ Hz, SCH_3), 13.5 (d, $J = 5$ Hz, CH_3). ^{31}P NMR: $\delta = 36.0$. IR (film): $\nu = 2985$, 2937, 1475, 1433, 1392, 1323, 1263 (P=O), 1159, 1097, 1016, 966, 773, 692 cm^{-1}. CIMS *m/z* (rel. int.): 175 [*M*+1]$^+$ (45).

Table 5
Experimental data for phosphorothiolates of structure (R_FO)EtOP(O)SMe

Compound	Chromatography solvent[a]	Retention factor	bp (°C/mmHg)
11a	3:1 hexane–acetone	0.35	–
11b	3:1 hexane–acetone	0.46	–
11c	6:1 hexane–acetone	0.42	–
11d	–	–	35/0.02[b]

[a] Chromatography plates developed with iodine vapour.
[b] Approximate oven temperature for bulb-to-bulb distillation.

4.11. General method for *O*-ethyl *O*-(fluoroalkyl) *S*-methyl phosphorothiolates (**11a–d**)

A solution of fluoroalcohol (15 mmol) and triethylamine (2.09 ml, 15 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of *O*-ethyl *S*-methyl phosphorochloridothiolate (2.61 g, 15 mmol) in ether (15 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature. Within 1 h, a thick precipitate of triethylamine hydrochloride formed. The precipitate was filtered off, the filter cake washed with ether (2× 10 ml) and the combined washings concentrated. Chromatography of the residue on silica gel, eluting with solvent systems listed in Table 5, gave the title compounds as colourless liquids.

4.12. Reactions of bis(2,2,2-trifluoroethyl) phosphorochloridate with bis-nucleophiles

A solution of 2-mercaptoethanol, 3-mercaptoethanol or ethane-1,2-dithiol (4 mmol) and triethylamine (1.12 ml, 8 mmol) in ether (25 ml) was added dropwise by cannula to a stirred solution of bis(2,2,2-trifluoroethyl) phosphorochloridate (2.24 g, 8 mmol) in ether (25 ml) at 0–5 °C. After addition, a catalytic amount of 4-dimethylaminopyridine was added and the mixture was allowed to warm to room temperature. After 12 h, an aliquot of the reaction mixture was analysed by GC–MS. The products are discussed in Section 2.6. Attempts to separate them by fractionation under reduced pressure or by chromatography on silica gel failed.

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