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Fluorinated phosphorus compounds
Part 6. The synthesis of bis(fluoroalkyl) phosphites and bis(fluoroalkyl) phosphorohalidates

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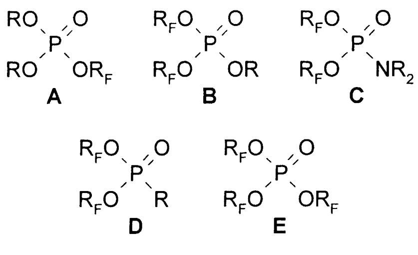
Abstract

Reaction of phosphorus trichloride with *tert*-butanol and fluoroalcohols gave bis(fluoroalkyl) phosphites $(R_FO)_2P(O)H$ in 42–89% yield, where $R_F = HCF_2CH_2$, $H(CF_2)_2CH_2$, $H(CF_2)_4CH_2$, CF_3CH_2, $C_2F_5CH_2$, $C_3F_7CH_2$, $(CF_3)_2CH$, $(FCH_2)_2CH$, $CF_3(CH_3)_2C$, $(CF_3)_2CH_3C$, $CF_3CH_2CH_2$, $C_4F_9CH_2CH_2$ and $C_6F_{13}CH_2CH_2$. Treatment of these with chlorine in dichloromethane gave the bis(fluoroalkyl) phosphorochloridates $(R_FO)_2P(O)Cl$ in 49–96% yield. The chloridate $(CF_3CH_2O)_2P(O)Cl$ was isolated in much lower yield from the interaction of thionyl chloride with bis(trifluoroethyl) phosphite. Heating the latter in dichloromethane with potassium fluoride and a catalytic amount of trifluoroacetic acid gave the corresponding fluoridate $(CF_3CH_2O)_2P(O)F$ in 84% yield. Treatment of bis(trifluoroethyl) phosphite with bromine or iodine gave the bromidate $(CF_3CH_2O)_2P(O)Br$ and iodidate $(CF_3CH_2O)_2P(O)I$ in 51 and 46% yield, respectively. The iodidate is the *first* dialkyl phosphoroiodidate to have been isolated and characterised properly—its discovery lags behind the first isolation of a dialkyl phosphorochloridate by over 130 years. The fluoroalkyl phosphoryl compounds are generally more stable than known unfluorinated counterparts. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Bis(fluoroalkyl) phosphite; Bis(trifluoroethyl) phosphorobromidate; Bis(fluoroalkyl) phosphorochloridate; Bis(trifluoroethyl) phosphorofluoridate; Bis(trifluoroethyl) phosphoroiodidate

1. Introduction

Fluoroalkyl phosphoryl compounds contain the group $R_FO–P=O$. They have structures analogous to familiar alkyl phosphoryl compounds, but in some instances, structures unparalleled in organophosphorus chemistry. The fluoroalkyl group, abbreviated to R_F, is usually derived from a fluoroalcohol. Since trifluoromethanol CF_3OH is unstable, decomposing to COF_2 and HF, the lower members are hypothetical with the exception of tris(trifluoromethyl) phosphate $(CF_3O)_3P=O$; it is also unstable and disproportionates over 3 days at 60 °C to give 3 mol of fluorophosgene COF_2 and 1 mol of phosphorus oxyfluoride POF_3 [1]. Stable phosphoryl molecules have primary or *sec*-fluoro-ester groups, e.g. $CF_3CH_2O–P$ or $(CF_3)_2CHO–P$. Few with *tert*-fluoro-ester groups have been prepared [2]. Compounds previously reported by us include dialkyl fluoroalkyl phosphates **A** [3], bis(fluoroalkyl) alkyl phosphates **B** [4], bis(fluoroalkyl) phosphoramidates **C** [4], bis(fluoroalkyl) alkylphosphonates **D** [5] and tris(fluoroalkyl) phosphates **E** [6]. Attention has focused on their biological [7] and physical properties [8] in a search for novel fire extinguishants [9].



R = alkyl group, R_F = fluoroalkyl group

So far, investigation of fluoroalkyl phosphoryl compounds of structure $(R_FO)_2P(O)X$, where X is OR, NR_2, SR, etc. has been hampered by a lack of phosphorohalidate reagents; only derivatives with $R_F = CF_3$ and C_2F_5 have been explored in any detail [4]. Here, we describe a two-stage route to bis(fluoroalkyl) phosphites **F** and

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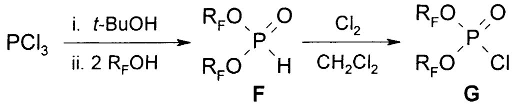
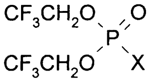
bis(fluoroalkyl) phosphorochloridates **G** starting from phosphorus trichloride.[1]



R_F = primary, secondary or tertiary fluoroalkyl group

To highlight synthetic applications of the new materials, we prepared the series of bis(trifluoroethyl) phosphorohalidates **H** which offer exciting possibilities as phosphorylation reagents.



H

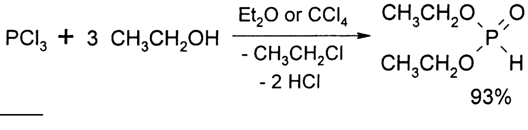
X = F, Cl, Br, I

The phosphorofluoridate is the fifth, and the phosphorobromidate the third, example of such fluoro-ester species. Bis(trifluoroethyl) phosphoroiodidate is one of only two dialkyl phosphoroiodidates—the other being $[(CF_3)_2CHO]_2P(O)I$—to have been isolated and characterised in a pure state [10]: the corresponding unfluorinated dialkyl phosphoroiodidates are stable only in solution.

2. Results and discussion

2.1. Synthesis of bis(fluoroalkyl) phosphites

Bis(fluoroalkyl) phosphites with identical fluoro-ester groups are known; routes to mixed systems, $R_FO(R'_FO)P(O)H$, have not yet been devised. Of the former, five appear in the literature and all have primary fluoro-ester groups: $(FCH_2CH_2O)_2P(O)H$ [11], $[H(CF_2)_nCH_2O]_2P(O)H$, where $n = 2, 4$ or 6 [12–14], and $(CF_3CH_2O)_2P(O)H$ [15] which is available commercially [16]. The preparation of dialkyl phosphites by alcoholysis of phosphorus trichloride has been known for a long time and studied in detail. For example, in the following scheme, the triethyl phosphite first formed is dealkylated by liberated HCl to give diethyl phosphite in high yield [17].



The analogous reaction with fluoroethanol takes place to give $(FCH_2CH_2O)_2P(O)H$ in 75% yield [18]. When the alcohol contains many fluorine atoms, as in trifluoroethanol, the tris(fluoroalkyl) phosphite is obtained [19,20]. The difference in behaviour is due to the higher basicity of the FCH_2CH_2O– oxygen atom compared to the CF_3CH_2O– oxygen atom, and the greater propensity of the former group to dealkylation:

$$PCl_3 + 3\,CF_3CH_2OH \underset{-3HCl}{\overset{\text{no solvent}}{\rightarrow}} \underset{78-80\%}{(CF_3CH_2O)_3P}$$

Routes to bis(fluoroalkyl) phosphites are shown in Fig. 1. They include acidolysis of a *tert*-phosphite. Glacial acetic acid is suitable (*route 1A*), but the by-product is the fluoroalkyl acetate. The use of phosphorous acid (*route 1B*) avoids loss of a fluoroalkyl group. Other methods start with phosphorus trichloride and involve dealkylation of the alkoxy groups by liberated HCl. The scheme involving methanol (*route 1C*) is not selective: some of the methanol reacts with the product to give around 10% mixed phosphite $H(CF_2)_nCH_2O(MeO)P(O)H$; this must be removed by careful fractionation. The *tert*-butanolysis of phosphorus trichloride (*route 1D*) produces $Cl_2P(O)H$ which can add two moles of fluoroalcohol to furnish the bis(fluoroalkyl) phosphite. This route is the most economical and gives a pure product. We investigated its wider applicability to the synthesis of a range of bis(fluoroalkyl) phosphites.

ω,α,α-Trihydroperfluoroalcohols gave phosphites (**1a**–**3a**) in acceptable yield. Curiously, phosphite **1a** and the

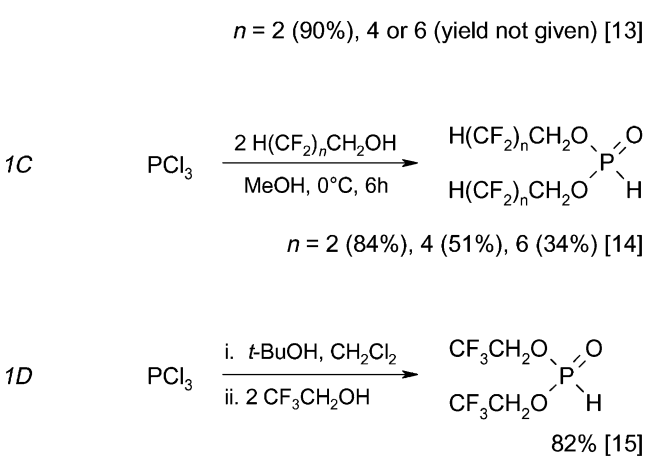


Fig. 1. Literature routes to bis(fluoroalkyl) phosphites.

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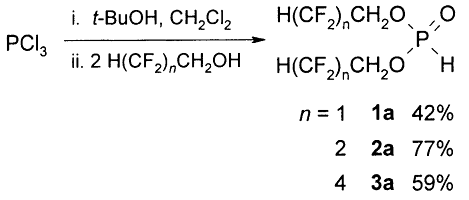
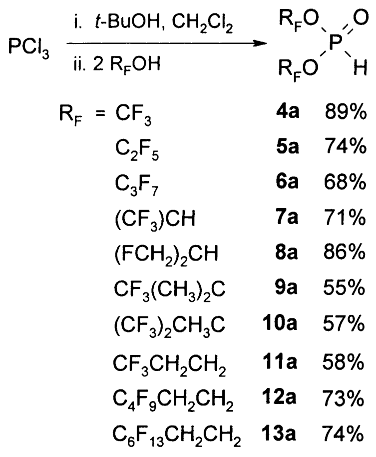
[1] Some of this work was described in a lecture entitled “The Synthesis and Properties of some Fluoroalkyl Phosphoryl Compounds”, given by one of the authors (C.M.T.) at the 16th International Symposium of Fluorine Chemistry, Durham University, UK, on 17 July 2000. In this paper, we refer to compounds of structure $(RO)_2P(O)H$ and $(R_FO)_2P(O)H$ as dialkyl phosphites and bis(fluoroalkyl) phosphites. This nomenclature, although correct, is somewhat old-fashioned; modern names are dialkyl hydrogen phosphonates or bis(fluoroalkyl) hydrogen phosphonates (or *H*-phosphonates).

corresponding phosphorochloridate **1b** (see Section 2.4) are only the second and third neutral molecules to be made that contain the $HCF_2CH_2O–P$ group. The first, tris(difluoroethyl) phosphate $(HCF_2CH_2O)_3P=O$, was prepared by Swarts in 1909 from difluoroethanol, bromine and red phosphorus [21].



Normal and branched fluoroalcohols gave phosphites **4a–13a**. Steric effects are not too important—*sec*- and *tert*-fluoroalcohols underwent double substitution without difficulty. Dominance of electronic effects over steric effects is a feature of fluoroalkyl phosphoryl chemistry and operates, for example, during the fluoroalcoholysis of alkylphosphonic dichlorides [5].



The reaction of non afluoro-*tert*-butanol $(CF_3)_3COH$ precipitated a white wax that could not be analysed due to its insolubility in organic solvents. The phosphite $[(CF_3)_3CO]_2P(O)H$ is therefore inaccessible using the chemistry described, but this is not surprising given the bulkiness and poor nucleophilicity of the fluoroalcohol. Experiments using pentafluorophenol were also unsuccessful; analysis of reaction mixtures by gas chromatography–mass spectrometry (GC–MS) showed that the intermediate $Cl_2P(O)H$ did not react, and no $(C_6F_5O)_2P(O)H$ formed.

2.2. *Physical properties of bis(fluoroalkyl) phosphites*

Bis(fluoroalkyl) phosphites (**1a–13a**) are colourless mobile liquids; compound **13a** solidified to an opaque white glass when stored in a refrigerator, but rapidly melted on warming to room temperature. Boiling points depend on the nature of the fluoro-ester groups (Table 1). Molecules with $H(CF_2)_nCH_2O$– groups have higher boiling points than those with $C_nF_{2n+1}CH_2O$– groups. The lowest boiling species have branched fluoro-ester groups. These effects have been commented on before and are general for fluoroalkyl phosphoryl species [8].

Table 1
Experimental data for bis(fluoroalkyl) phosphites $(R_FO)_2P(O)H$

Compound	R_F	Yield (%)	Boiling point (°C/mmHg)
1a	HCF_2CH_2	42	79/1
2a	$H(CF_2)_2CH_2$	77	119/0.06[a]
3a	$H(CF_2)_4CH_2$	59	104/0.1
4a	CF_3CH_2	89	62/10[b]
5a	$C_2F_5CH_2$	74	76/10
6a	$C_3F_7CH_2$	68	69/2
7a	$(CF_3)_2CH$	71	62/8
8a	$(FCH_2)_2CH$	86	116/1
9a	$CF_3(CH_3)_2C$	55	71/10
10a	$(CF_3)_2CH_3C$	57	41/10
11a	$CF_3CH_2CH_2$	58	67/0.04
12a	$C_4F_9CH_2CH_2$	73	42/5
13a	$C_6F_{13}CH_2CH_2$	74	136/0.02

[a] Previously made in 83 and 90% yield by heating $[H(CF_2)_2CH_2O]_3P$ with glacial acetic acid or phosphorous acid, respectively (literature bp 86–87 °C/1 mmHg [12] and 117–119 °C/5 mmHg [13]).

[b] Previously made in 82% yield using a similar procedure (literature bp 43–44 °C/2 mmHg) [15].

In line with their unfluorinated analogues, the bis(fluoroalkyl) phosphites show clear evidence of the P(O)H structure. A doublet is observed in the proton NMR spectrum for the phosphorus-bonded hydrogen atom; the J_{PH} coupling constant lies between 714 and 795 Hz. Phosphorus chemical shifts for **1a–13a** range between −3.6 and 7.9 ppm. In the infrared spectra, stretching vibrations for the P=O bond are strong and occur at 1288–1221 cm^{-1} (Table 2).

Unfluorinated counterparts of bis(fluoroalkyl) phosphites (**1a–13a**) are known [22], as are some chloro- or bromo-analogues. Most can be distilled under vacuum, but some cannot due to thermal instability. Pronounced effects are seen among diisopropyl phosphites having chloro- or bromo-ester groups: $[(ClCH_2)CH_3CHO]_2P(O)H$ is moderately stable to heat [23], $[(ClCH_2)_2CHO]_2P(O)H$ has a tendency to decompose on distillation [24], and $[(BrCH_2)_2CHO]_2P(O)H$ and $[(ClCH_2)(BrCH_2)CHO]_2P(O)H$ cannot be distilled [23]. In contrast, bis(difluoroisopropyl) phosphite $[(FCH_2)_2CHO]_2P(O)H$ (**8a**) distilled without decomposition. Also, di-*tert*-butyl phosphite $[(CH_3)_3CO]_2P(O)H$ decomposes with great ease on distillation [25,26], but the fluorologues[2] $[CF_3(CH_3)_2CO]_2P(O)H$ (**9a**) and $[(CF_3)_2(CH_3)CO]_2P(O)H$ (**10a**) distil without difficulty. It can be concluded that fluorinated species have enhanced thermal stability.

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[2] The term ‘fluorologue’, derived from the Greek word *logos* meaning ‘ratio or proportion’, is used here to denote a fluorinated analogue of a hydrocarbon compound. Likewise, the term ‘hydrologue’ can be suggested for a hydrocarbon analogue of a fluorocarbon compound. Using this terminology, CF_4 is a *fluorologue* of CH_4 (and CH_4 is a *hydrologue* of CF_4). Its adoption saves writing, e.g. ‘the fluorinated counterpart of’ or ‘the hydrocarbon analogue of’, which becomes cumbersome.

Table 2
Spectroscopic data for bis(fluoroalkyl) phosphites $(R_FO)_2P(O)H$ (NMR data measured in $CDCl_3$)

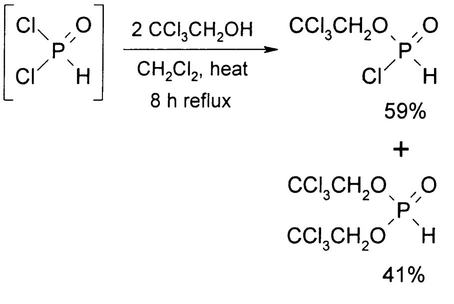
Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ	^{31}P NMR δ	IR ν (cm^{-1})	GC–MS analysis[a]
1a	6.77 (1H, d, $J = 740$, P–H), 5.98 (2H, tt, $J = 3, 55$, CF$_2$H), 4.29 (4H, ddt, $J = 4, 10, 13$, OCH$_2$)	112.4 (tt, $J = 36, 249$, CF$_2$H), 63.3 (br, OCH$_2$)	−125.9 (4F, ddt, $J = 3, 55, 13$, CF$_2$H)	7.6	1456, 1429, 1375, 1329, 1263 (P=O), 1086, 982, 838	$C_4H_7F_4O_3P$ M_w 210
2a	7.02 (1H, d, $J = 751$, P–H), 5.95 (2H, tt, $J = 5, 52$, CF$_2$H), 4.48 (4H, dt, $J = 11$, 11 plus smaller coupling, OCH$_2$)	113.8 (dtt, $J = 7, 28, 251$, CF$_2$), 109.3 (tt, $J = 36, 249$, CF$_2$H), 61.3 (br m, OCH$_2$)	−136.8 (4F, d, $J = 52$, CF$_2$H), −123.8 (4F, dt, $J = 2, 13$, CF$_2$)	7.4	1456, 1404, 1273 (P=O), 1238, 1107, 984, 870, 837	$C_6H_7F_8O_3P$ M_w 310
3a	7.06 (1H, d, $J = 757$, P–H), 6.06 (2H, tt, $J = 5, 52$, CF$_2$H), 4.57 (4H, m, OCH$_2$)	113.9 (dtt, $J = 7, 28, 251$, CF$_2$), 107.5 (tt, $J = 36, 249$, CF$_2$H), 110–109 (m, CF$_2$CF$_2$), 61.3 (br m, OCH$_2$)	−136.5 (4F, m, CF$_2$H), −129, −124.3 and −119.2 (12F, m, CF$_2$)	7.3	1458, 1404, 1269 (P=O), 1171, 1130, 987, 903, 806	$C_{10}H_7F_{16}O_3P$ M_w 510
4a	7.1 (1H, d, $J = 755$, P–H), 4.46 (4H, m, OCH$_2$)	122 (dq, $J = 6, 227$, CF$_3$), 61.7 (dt, $J = 5, 38$, OCH$_2$)	−74.8 (6F, m, CF$_3$)	7.0	1458, 1421, 1288 (P=O), 1174, 1109, 995, 962, 839	$C_4H_5F_6O_3P$ M_w 246
5a	7.05 (1H, d, $J = 758$, P–H), 4.52 (4H, complex m, OCH$_2$)	118.5 (tq, $J = 36, 287$, CF$_3$), 111.4 (dq, $J = 7, 256$, CF$_2$), 60.9 (dt, $J = 6, 29$, OCH$_2$)	−123.6 (4F, t, $J = 13$, CF$_2$), −82.7 (6F, m, CF$_3$)	7.2	1460, 1408, 1377, 1356, 1277 (P=O), 1203, 1165, 1130, 1038, 985, 935, 870	$C_6H_5F_{10}O_3P$ M_w 346
6a	7.06 (1H, d, $J = 759$, P–H), 4.58 (4H, complex m, OCH$_2$)	117.5 (tq, $J = 33, 287$, CF$_3$), 113.3 (dt, $J = 6, 34$, CF$_2$), 108.5 (ttq, $J = 5, 39, 265$, CF$_2$), 61.2 (dt, $J = 5, 27$, OCH$_2$)	−126.9 (4F, m, CF$_2$), −121 (4F, m, CF$_2$), −80.4 (6F, t, $J = 10$, CF$_3$)	7.3	1356, 1230 (P=O), 1186, 1126, 968, 926, 870	$C_8H_5F_{14}O_3P$ M_w 446
7a	7.29 (1H, d, $J = 795$, P–H), 5.22 (2H, m, OCH)	119.7 (dq, $J = 13, 283$, CF$_3$), 70 (dsep, $J = 4, 37$, OCH)	−74.2 (12F, br d, $J = 38$, CF$_3$)	7.9	1381, 1300, 1267, 1232 (P=O), 1131, 1111, 1065, 984, 904, 880	$C_6H_3F_{12}O_3P$ M_w 382
8a[b]	7.07 (1H, d, $J = 738$, P–H), 4.91 (2H, m, OCH), 4.69 and 4.59 (8H, complex m, FCH$_2$)	81.8 and 81.7 (dd, $J = 7, 173$, FCH$_2$), 73.3 (dt, $J = 6, 20$, CO)	−30.6 (2F, dt, $J = 20, 48$, FCH$_2$), −30.3 (2F, dt, $J = 20, 48$, FCH$_2$)	6.7	1462, 1412, 1365, 1261 (P=O), 1105, 1043, 964, 903, 795	$C_6H_{11}F_4O_3P$ M_w 238
9a	7.1 (1H, d, $J = 729$, P–H), 1.71 (12H, d, $J = 5$, CH$_3$)	124.6 (dq, $J = 10, 283$, CF$_3$), 82 (dq, $J = 7, 32$, CO), 22.4 (d, $J = 36$, CH$_3$)	−83.6 (6F, m, CF$_3$)	−3.6	1475, 1400, 1381, 1335, 1279, 1234 (P=O), 1169, 1132, 1036, 978, 931	$C_8H_{13}F_6O_3P$ M_w 302
10a	7.24 (1H, d, $J = 780$, P–H), 1.98 (6H, m, CH$_3$)	119.9 (dq, $J = 13, 285$, CF$_3$), 81.7 (dsep, $J = 5, 38$, CO), 15.5 (m, CH$_3$)	−77.5 (12F, m, CF$_3$)	−4.1	1464, 1400, 1309, 1223 (P=O), 1132, 1090, 976, 879, 831	$C_8H_7F_{12}O_3P$ M_w 410
11a	6.88 (1H, d, $J = 716$, P–H), 4.33 (4H, dt, $J = 6.4$ and 6.2, 6, CH$_2$), 2.55 (4H, qt, $J = 6, 4$, CH$_2$)	125 (q, $J = 277$, CF$_3$), 58.6 (dq, $J = 4, 6$, OCH$_2$), 34.9 (q, $J = 6, 30$, CH$_2$)	−64.6 (6F, m, CF$_3$)	6.3	1477, 1437, 1394, 1354, 1300, 1255 (P=O), 1159, 1136, 1078, 985, 928	$C_6H_9F_6O_3P$ M_w 274
12a	6.5 (1H, d, $J = 719$, P–H), 3.9 (4H, m, OCH$_2$), 2.0 (4H, m, CH$_2$)	120–111 (complex m, C$_4$F$_9$), 58.8 (d, $J = 22$, OCH$_2$), 32.9 (m, CH$_2$)	−125, −124, −113.7, −81 (18F, complex m, C$_4$F$_9$)	6.3	1358, 1221 (P=O), 1132, 1078, 1003, 876, 833	$C_{12}H_9F_{18}O_3P$ M_w 574
13a	6.9 (1H, d, $J = 714$, P–H), 4.39 (4H, dd, $J = 6, 13$, OCH$_2$), 2.55 (4H, m, CH$_2$)	121–107 (complex m, C$_6$F$_{13}$), 58.2 (d, $J = 5$, OCH$_2$), 32.5 (m, CH$_2$)	−126, −124, −123, −122, −113, −81 (26F, all complex m, C$_6$F$_{13}$)	6.4	1484, 1433, 1367, 1317, 1240 (P=O), 1205, 1146, 1084, 979, 810	$C_{16}H_9F_{26}O_3P$ M_w 774

[a] All mass spectra (chemical ionisation) displayed a prominent molecular ion $M + 1$ peak.

[b] The carbon, hydrogen and fluorine atoms of the side-chains are prochiral, hence, complex second-order splitting patterns.

2.3. Synthesis of other bis(2,2,2-trihaloethyl) phosphites

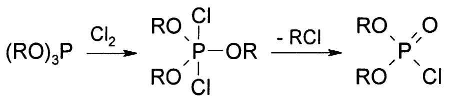
Trifluoroethanol combines with the intermediate from *tert*-butanolysis of phosphorus trichloride, but other trihaloethanols do not. Trichloroethanol furnished an undistillable mixture of mono and bis substitution products (percentages determined by GC–MS analysis).



Tribromoethanol did not react under the same conditions, or even after heating under reflux for a further 8 h in the presence of added 4-dimethylaminopyridine, often a useful phosphorylation catalyst [4]. The order of reactivity $CF_3CH_2OH > CCl_3CH_2OH > CBr_3CH_2OH$ is explained by differences in the electronegativity and size of the trihaloethoxy groups.

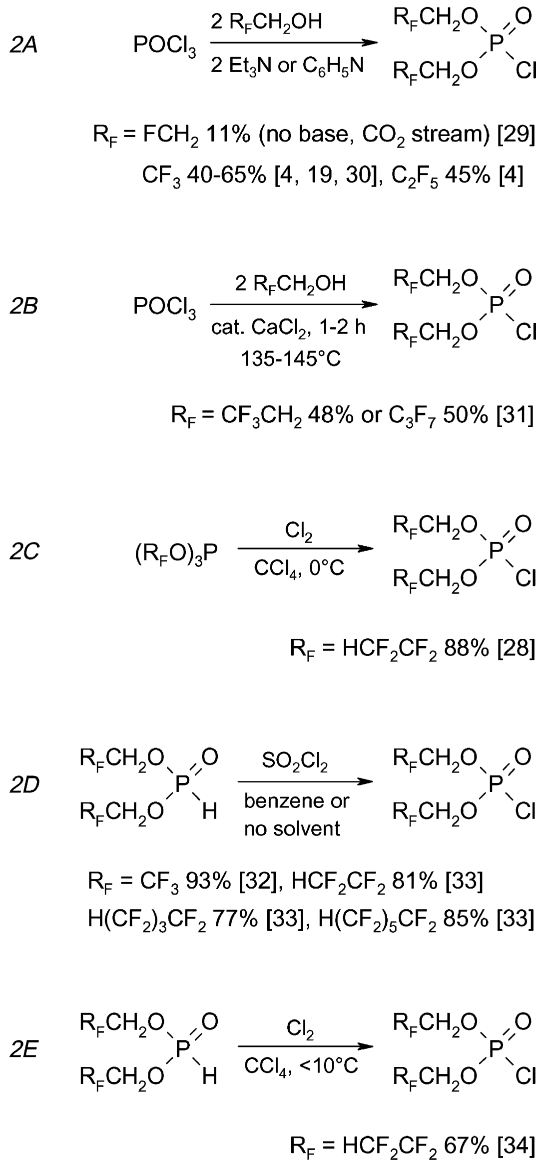
2.4. Synthesis of bis(fluoroalkyl) phosphorochloridates

Methods for the synthesis of dialkyl phosphorochloridates are not always useful for the synthesis of bis(fluoroalkyl) phosphorochloridates. For example, chlorination of trialkyl phosphites proceeds through a phosphorane that collapses to give the dialkyl phosphorochloridate in good yield [17].



Phosphoranes derived from tris(fluoroalkyl) phosphites are more stable than their hydrologues: the greater the size and electronegativity of the fluoroalkyl groups, the higher the phosphorane stability, and this can prevent the second stage of the reaction. In contrast to triisopropyl phosphite which gives the chloridate $[(CH_3)_2CHO]_2P(O)Cl$ in good yield, tris(hexafluoroisopropyl) phosphite gives the stable phosphorane $[(CF_3)_2CHO]_3PCl_2$ in 83% yield; it does not decompose even on distillation [27]. However, tri-*n*-propyl phosphite and tris(tetrafluoropropyl) phosphite give the chloridates $(CH_3CH_2CH_2O)_2P(O)Cl$ and $(HCF_2CF_2CH_2O)_2$-$P(O)Cl$ in high yield [28].

Some routes to bis(fluoroalkyl) phosphorochloridates are shown in Fig. 2. The first involves treatment of phosphorus oxychloride with a fluoroalcohol and a base, usually triethylamine or pyridine, in ether (*route 2A*). Disadvantages, especially for large scale work, lie in the large quantities of base required (removal of base hydrochloride is sometimes difficult) and the fact that a range of substitution products are produced even under conditions favouring the formation of bis(fluoroalkyl) phosphorochloridates (e.g. using an excess of phosphorus oxychloride); purification involves repeat fractionations which lower the yields. A way round using an amine base is to heat phosphorus oxychloride with a fluoroalcohol in the presence of a catalytic amount of calcium chloride (*route 2B*), but this modification also gives a range of substitution products.



$R_F = FCH_2$ 11% (no base, CO_2 stream) [29]
CF_3 40-65% [4, 19, 30], C_2F_5 45% [4]

$R_F = CF_3CH_2$ 48% or C_3F_7 50% [31]

$R_F = HCF_2CF_2$ 88% [28]

$R_F = CF_3$ 93% [32], HCF_2CF_2 81% [33]
$H(CF_2)_3CF_2$ 77% [33], $H(CF_2)_5CF_2$ 85% [33]

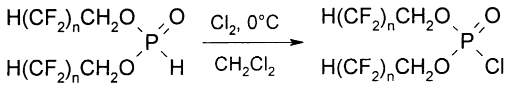
$R_F = HCF_2CF_2$ 67% [34]

Fig. 2. Literature routes to bis(fluoroalkyl) phosphorochloridates.

Although the reaction of tris(fluoroalkyl) phosphites with chlorine is satisfactory in some cases, it is costly because of the expensive methods needed for the synthesis of the fluorinated phosphite and because it results in loss of a fluoroalkyl group (*route 2C*). This difficulty is avoided by starting with the bis(fluoroalkyl) phosphite. The reaction of sulphuryl chloride with dialkyl phosphites, pioneered by

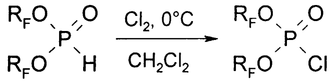
Todd and co-workers [35], has been extended to bis(fluoroalkyl) phosphites with considerable success (*route 2D*). Only one example of the reaction of chlorine with a bis(fluoroalkyl) phosphite has been reported (*route 2E*). The last two routes represent the best methods for the synthesis of bis(fluoroalkyl) phosphorochloridates as both reactions are clean and the by-products are gaseous.

We investigated the chlorination of bis(fluoroalkyl) phosphites in cold dichloromethane. Decolourisation took place the instant chlorine entered the solution; a yellow colouration indicated the end-point. Bis(ω,α,α-trihydroperfluoroalkyl) phosphites (**1a**–**3a**) gave the chloridates **1b**–**3b** in excellent yield.



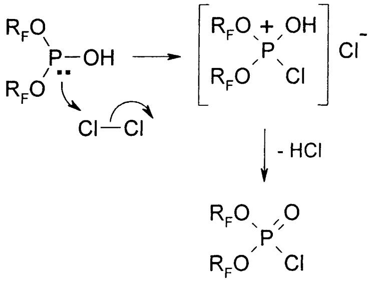
n			
1	**1a**	**1b**	91%
2	**2a**	**2b**	83%
4	**3a**	**3b**	89%

Chlorination of bis(fluoroalkyl) phosphites (**4a**–**13a**) gave the chloridates **4b**–**13b** in good yield and in a state of high purity. Replacement of dichloromethane with other chlorinated solvents, such as chloroform, did not alter the yields.



R_F =		
CF_3	**4b**	94%
C_2F_5	**5b**	84%
C_3F_7	**6b**	90%
$(CF_3)CH$	**7b**	82%
$(FCH_2)_2CH$	**8b**	79%
$CF_3(CH_3)_2C$	**9b**	88%
$(CF_3)_2CH_3C$	**10b**	62%
$CF_3CH_2CH_2$	**11b**	76%
$C_4F_9CH_2CH_2$	**12b**	49%
$C_6F_{13}CH_2CH_2$	**13b**	96%

Reactions of halogens with bis(fluoroalkyl) phosphites most likely involve nucleophilic attack by the trivalent phosphite tautomer that forms in the rate-determining step [36,37].



The tautomer $(R_FO)_2P–OH$ was not detected by NMR studies in dichloromethane or chloroform, but is assumed to be in equilibrium with the form $(R_FO)_2P(O)H$. Only a tiny amount of the 'enol' form (P–OH) is present in solutions of dialkyl phosphites [38]: the equilibrium constant for diethyl phosphite, e.g. is 10^7 in favour of the $(EtO)_2P(O)H$ form [39] and the $(EtO)_2P–OH$ form has never been detected directly by any spectroscopic technique. Thus, the phosphorus NMR spectrum for this compound, like those of the bis(fluoroalkyl) phosphites, shows only the signal from the P–H form, easily recognised by the very large $^1H–^{31}P$ coupling constant, e.g. 691 Hz for $(EtO)_2P(O)H$ [40] and 775 Hz for $(CF_3CH_2O)_2P(O)H$.

Whether the bis(fluoroethyl) phosphites $(R_FO)_2P(O)H$ contain a higher proportion of the 'enol' form compared to the corresponding dialkyl phosphites $(RO)_2P(O)H$ remains unanswered. The electronegative fluoroalkoxy groups should stabilise the P–OH form to some extent; it is known that when two (but not one) trifluoromethyl groups are present on phosphorus, as in $(CF_3)_2P–OH$, electron-attraction is so pronounced that the lone pair is unable to accept hydrogen from the OH group—in this case, no $(CF_3)_2P(O)H$ can be detected [41].

2.5. Physical properties of bis(fluoroalkyl) phosphorochloridates

Bis(fluoroalkyl) phosphorochloridates (**1b**–**12b**) are colourless mobile liquids. An exception is the long-chain compound **13b** that is a white solid (mp 27 °C). Whereas bis(fluoroethyl) phosphorochloridate $(FCH_2CH_2O)_2P(O)Cl$ rapidly decomposes on standing [29], compounds **1b**–**13b** are stable indefinitely when stored in the absence of moisture in a refrigerator. Their boiling points depend on the fluoroester groups (Table 3) and follow the same trends as the bis(fluoroalkyl) phosphites. The fluorologue $(CF_3CH_2O)_2P(O)Cl$ (**4b**) (bp 62 °C/10 mmHg) boils at a lower temperature than its hydrologue $(CH_3CH_2O)_2P(O)Cl$ (bp 94 °C/10 mmHg) [42]. The chlorinated analogue $(CCl_3CH_2O)_2P(O)Cl$ is a solid (mp 48–49 °C) [43].

Spectroscopic data for bis(fluoroalkyl) phosphorochloridates (**1b**–**13b**) appear in Table 4. Their phosphorus chemical shifts are between −7.2 and 8.9 ppm. The phosphoryl vibration appears in the range 1309–1288 cm^{-1} in the infrared spectra.

Unfluorinated counterparts of bis(fluoroalkyl) phosphorochloridates (**1b**–**13b**) are known [42,44–46] as are a few halogenated analogues. As noted in Section 2.2, the presence of fluorine atoms in the ester groups can impart high thermal stability. For example, bis(dichloroisopropyl) phosphorochloridate $[(ClCH_2)_2CHO]_2P(O)Cl$ decomposes readily during distillation [24], and di-*tert*-butyl phosphorochloridate $[(CH_3)_3CO]_2P(O)Cl$ decomposes spontaneously at room temperature after several hours [47]. The fluorologues $[(FCH_2)_2CHO]_2P(O)Cl$ and $[(CH_3)_2CF_3CO]_2P(O)Cl$ could be distilled without appreciable decomposition.

Table 3
Experimental data for bis(fluoroalkyl) phosphorochloridates $(R_FO)_2P(O)Cl$

Compound	R_F	Yield (%)	Boiling point (°C/mmHg)
1b	HCF_2CH_2	91	76/0.1
2b	$H(CF_2)_2CH_2$	83	115/0.08[a]
3b	$H(CF_2)_4CH_2$	89	100/0.1[b]
4b	CF_3CH_2	94	62/10[c]
5b	$C_2F_5CH_2$	84	71/10[d]
6b	$C_3F_7CH_2$	90	68/2[e]
7b	$(CF_3)_2CH$	82	48/10
8b	$(FCH_2)_2CH$	79	154/0.2
9b	$CF_3(CH_3)_2C$	88	80/10
10b	$(CF_3)_2CH_3C$	62	54/10
11b	$CF_3CH_2CH_2$	76	77/0.08[f]
12b	$C_4F_9CH_2CH_2$	49	141/6
13b	$C_6F_{13}CH_2CH_2$	96	Solid (mp 27 °C)[g]

[a] Previously made in 81% yield by treatment of $[H(CF_2)_2CH_2O]_2P(O)H$ with sulphuryl chloride (literature bp 101 °C/1 mmHg) [33], in 67% yield by chlorination of $[H(CF_2)_2CH_2O]_2P(O)H$ (literature bp 111–112 °C/6 mmHg) [34] and in 88% yield by chlorination of $[H(CF_2)_2CH_2O]_3P$ (literature bp 60–62 °C/0.05 mmHg) [28]; the boiling points given in the last two references do not match those we found for the pure substance.

[b] Previously made in 77% yield by treatment of $[H(CF_2)_4CH_2O]_2P(O)H$ with sulphuryl chloride (literature bp 127 °C/1 mmHg) [33].

[c] Previously made in 93% yield by treatment of $(CF_3CH_2O)_2P(O)H$ with sulphuryl chloride (literature bp 67–70 °C/14 mmHg) [32] and in yields between 40 and 65% by trifluoroethanolysis of phosphorus oxychloride in the presence of triethylamine or pyridine (literature bp 45 °C/5 mmHg [19], 67–68 °C/14 mmHg [30] and 61–62 °C/10 mmHg [4]).

[d] Previously made in 45% yield by fluoroalcoholysis of phosphorus oxychloride in the presence of triethylamine (literature bp 74–76 °C/10 mmHg) [4].

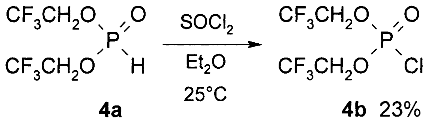
[e] Previously made in 50% yield by fluoroalcoholysis of phosphorus oxychloride in the presence of calcium chloride catalyst (bp 89–90 °C/9 mmHg) [31].

[f] Previously made in 48% yield by fluoroalcoholysis of phosphorus oxychloride in the presence of calcium chloride catalyst (literature bp 110–111 °C/9 mmHg) [31].

[g] Crude material was 98% pure by multinuclear NMR analysis after chlorination and removal of solvent—recrystallisation was not attempted and would have lowered the yield.

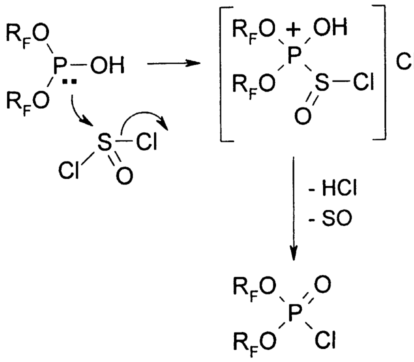
2.6. Chlorination of bis(trifluoroethyl) phosphite with thionyl chloride

The reactions of unfluorinated phosphites [48] and bis(fluoroalkyl) phosphites [32,33] with sulphuryl chloride produces the chloridates $(RO)_2P(O)Cl$ or $(R_FO)_2P(O)Cl$ in moderate to high yields. Analogous reactions with thionyl chloride are known only in the case of unfluorinated phosphites [49]. For this reason, we examined the reaction of bis(trifluoroethyl) phosphite with thionyl chloride in ether. The desired chloridate **4b** was isolated in poor yield. A yellow solid, presumed to be sulphur [49], sublimed in the distillation apparatus.



4a **4b** 23%

The mechanism most likely involves attack of the lone pair of the 'enol' phosphite form on the sulphur atom of thionyl chloride.



The unstable species $(R_FO)_2P(O)SOCl$ breaks down to give the bis(fluoroalkyl) phosphorochloridate plus sulphur monoxide. Evidence for the latter is provided by formation of sulphur during distillation: sulphur monoxide readily disproportionates to sulphur and sulphur dioxide [49]. Another possibility is disproportionation of the phosphorus intermediate:

$$2\,(R_FO)_2P(O)SOCl \xrightarrow{-S,\,-SO_2} 2\,(R_FO)_2P(O)Cl$$

Identical mechanistic arguments were proposed by Poshkus and Herweh [49] who studied the reaction of trialkyl phosphites with thionyl chloride.

2.7. Synthesis of bis(trifluoroethyl) phosphorofluoridate

Among the first dialkyl phosphorofluoridates, described by Lange and von Krüeger [50], was the diethyl derivative $(CH_3CH_2O)_2P(O)F$ (bp 63 °C/12 mmHg). It was isolated in poor yield by heating the di-silver salt of phosphorofluoridic acid $(AgO)_2P(O)F$ with two molar equivalents of ethyl iodide. More efficient routes to this and related compounds were developed during the 1940s by Saunders in the UK and by Schrader in Germany [51]. Both research groups found that dialkyl phosphorofluoridates could be prepared much more easily, and in high yield, by alcoholysis of phosphoryl dichlorofluoride $Cl_2P(O)F$, or by heating the corresponding phosphorochloridates $(RO)_2P(O)Cl$ with an alkali metal fluoride (e.g. NaF or KF) in an inert solvent (e.g. benzene or acetonitrile).

This discovery prompted the synthesis of the first dialkyl phosphorofluoridates with fluoro-ester groups, all derived formally from the parent compound $(CH_3CH_2O)_2P(O)F$. The work of Saunders led to fluoridate **14** [52,53] and that of Schrader to fluoridates **15** and **16** [54]. The most recent bis(fluoroalkyl) phosphorofluoridate (**17**), reported by Fokin et al. [55], was isolated from a 1:1 mixture of phosphorus pentoxide and tetrafluoropropanol

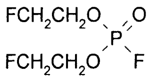
Table 4
Spectroscopic data for bis(fluoroalkyl) phosphorochloridates $(R_FO)_2P(O)Cl$ (NMR data measured in $CDCl_3$)

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})	GC–MS analysis[a]
1b	6.01 (2H, tt, $J = 4, 54$, CF_2H), 4.36 (4H, complex m, OCH_2)	111.8 (dt, $J = 10, 42$, CF_2H), 66.3 (dt, $J = 6, 30$, OCH_2)	−126.1 (4F, dt, $J = 13, 53$, CF_2H)	4.6	1456, 1429, 1375, 1302 (P=O), 1086, 962, 903, 827	$C_4H_6ClF_4O_3P$ M_w 244
2b	5.94 (2H, tt, $J = 6, 53$, CF_2H), 4.55 (4H, complex m, OCH_2)	113.1 (dtt, $J = 10, 29, 251$, CF_2), 108.9 (tt, $J = 37, 251$, CF_2H), 64.1 (dt, $J = 5, 30$, OCH_2)	−136.6 (4F, d, $J = 53$, CF_2H), −123.5 (4F, dt, $J = 3, 12$, CF_2)	4.5	1458, 1404, 1300 (P=O), 1259, 1238, 1213, 1109, 1063, 951, 895	$C_6H_6ClF_8O_3P$ M_w 344
3b	6.06 (4H, tt, $J = 6, 52$, HCF_2), 4.64 (2H, m, OCH_2)	113 (dtt, $J = 6, 31, 251$, CF_2), 107.8 (tt, $J = 37, 249$, CF_2H), 110–109 (m, CF_2CF_2), 64.2 (dt, $J = 28$, OCH_2)	−138 (4F, m, CF_2H), −130, −126.5 and −119.8 (12F, m, CF_2)	4.7	1458, 1404, 1298 (P=O), 1173, 1132, 1078, 1011, 989, 958, 904, 808	$C_{10}H_6ClF_{16}O_3P$ M_w 544
4b	4.55 and 4.51 (4H, qdd, $J = 3.3, 7.6, 15.3$, OCH_2)	121.8 (dq, $J = 11, 277$, CF_3), 64.7 (dq, $J = 6, 34$, OCH_2)	−74.2 (6F, t, $J = 7$, CF_3)	4.7	1456, 1421, 1304 (P=O), 1279, 1178, 1078, 964, 897, 847	$C_4H_4ClF_6O_3P$ M_w 280
5b	4.61 (4H, broad m, OCH2)	117.2 (m, CF_3), 111.3 (m, CF_2), 63.8 (m, OCH_2)	−123.5 (4F, m, CF_2) −82.8 (6F, m, CF_3)	4.6	1458, 1409, 1306 (P=O), 1271, 1205, 1163, 1111, 1030, 957, 935, 893	$C_6H_4ClF_{10}O_3P$ M_w 380
6b	4.64 (4H, complex m, OCH_2)	117.5 (tq, $J = 33, 288$, CF_3), 113.1 (ttd, $J = 11, 31, 258$, CF_2), 108.6 (tqd, $J = 5, 40, 264$, CF_2), 64.2 (dt, $J = 5, 28$, OCH_2)	−126.7 (4F, m, CF_2), −120.5 (4F, m, CF_2), −80.2 (6F, t, $J = 10$, CF_3)	4.8	1356, 1302 (P=O), 1232, 1186, 1132, 1078, 1014, 970, 933	$C_8H_4ClF_{14}O_3P$ M_w 480
7b	5.32 (2H, dsept, $J = 3.7, 5.2$, OCH)	119.7 (dq, $J = 5, 281$, CF_3) and 119.6 (dq, $J = 5, 283$, CF_3), 72.6 (dsep, $J = 4.3, 36.6$, OCH)	−73.6 (6F, m, CF_3) and −73.2 (6F, br d, $J = 38$, CF_3)	8.9	1379, 1298 (P=O), 1267, 1234, 1205, 1113, 1018, 930, 904, 883	$C_6H_2ClF_{12}O_3P$ M_w 416
8b[b]	4.95 (2H, m, OCH), 4.60 and 4.75 (8H, m complex, FCH_2)	81.8 and 81.7 (dd, $J = 7, 173$, FCH_2), 73.3 (dt, $J = 6, 20$, CO)	−31 (2F, dt, $J = 18, 46$, FCH_2), −31.6 (2F, dt, $J = 18, 48$, FCH_2)	4.2	1460, 1414, 1365, 1288 (P=O), 1093, 1047, 1001, 904	$C_6H_{10}ClF_4O_3P$ M_w 272
9b	1.77 (12H, d, $J = 5$, CH_3)	124 (dq, $J = 14, 283$, CF_3), 84.7 (dq, $J = 6, 32$, CO), 21.6 (d, $J = 36$, CH_3)	−83.6 (6F, m, CF_3)	−7.2	1477, 1402, 1381, 1335, 1298 (P=O), 1236, 1171, 1128, 1024, 931	$C_8H_{12}ClF_6O_3P$ M_w 336
10b	2.07 (6H, m, CH_3)	121 (qm, $J = 287$, ∼8, CF_3), 82.9 (dsep, $J = 6, 33$, CO), 14.3 (m, CH_3)	−98.7 (6F, q, $J = 8$ CF_3), −98.3 (6F, q, $J = 8$, CF_3)	−7.7	1462, 1400, 1309 (P=O), 1228, 1167, 1134, 1093, 1012, 879, 835	$C_8H_6ClF_{12}O_3P$ M_w 444
11b	4.42 (4H, m, OCH_2), 2.61 (4H, m, CH_2)	125 (q, $J = 277$, CF_3), 62.1 (m, OCH_2), 34.3 (dq, $J = 30$, CH_2)	−64.6 (6F, CF_3)	2.7	1437, 1394, 1354, 1300 (P=O), 1257, 1163, 1136, 1070, 1026, 937	$C_6H_8ClF_6O_3P$ M_w 308
12b	4.5 (4H, m, OCH_2), 2.6 (4H, m, CH_2)	120–105 (complex m, C_4F_9), 61.5 (dt, $J = 5, 6$, OCH_2), 31.7 (dt, $J = 8, 21$, CH_2)	−125.7, −124.1, −113.4, −80.7 (18F, complex m, C_4F_9)	3.0	1365, 1302 (P=O), 1223, 1134, 1051, 1014, 877, 835	$C_{12}H_8ClF_{18}O_3P$ M_w 608
13b	4.41 (4H, m, OCH_2), 2.52 (4H, m, CH_2)	121 to 108 (complex m, C_6F_{13}), 61.9 (d, $J = 6.2$, OCH_2), 31.9 (dt, 8.3, 20.7, CH_2)	−125.8, −123.1, −122.4, −121, −113, −80.9 (26F, complex m, C_6F_{13})	2.3	1483, 1430, 1343, 1299 (P=O), 1240, 1205, 1146, 1078, 843, 810	$C_{16}H_8ClF_{26}O_3P$$M_w$ 808

[a] All mass spectra (chemical ionisation) displayed a prominent molecular ion $M + 1$ peak.

[b] The carbon, hydrogen and fluorine atoms of the side-chains are prochiral, hence, complex second-order splitting patterns.

that had been heated at 170–180 °C for 2–3 h.



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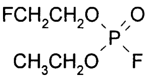
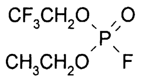


15

bp 126°C / 13 mmHg 80°C / 14 mmHg



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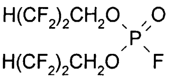
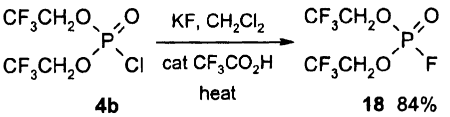


17

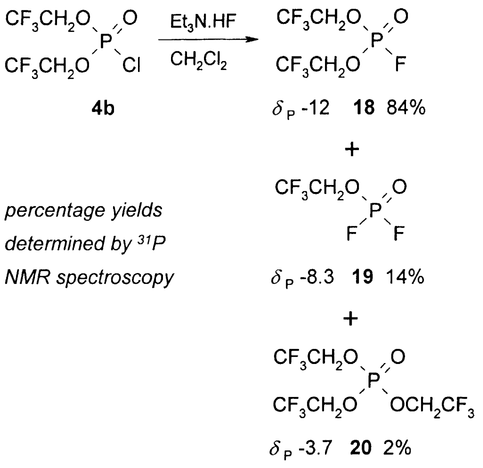
bp 56°C / 13 mmHg 61°C / 1 mmHg

We sought to prepare bis(trifluoroethyl) phosphorofluoridate $(CF_3CH_2O)_2P(O)F$, but heating chloridate **4b** with NaF or KF in dichloromethane did not result in fluorination. As fluoro-ester groups are stable to acids, an acid catalyst could be used. Conversion of chloridate **4b** to fluoridate **18** was effected using potassium fluoride and a catalytic amount of trifluoroacetic acid. Bis(trifluoroethyl) phosphorofluoridate (**18**) is a colourless mobile liquid (bp 61 °C/40 mmHg).



The mechanism of catalysis presumably involves displacement of HF from potassium fluoride by trifluoroacetic acid. The HF then converts the chloridate into fluoridate, with released HCl reacting with potassium fluoride to liberate more hydrogen fluoride.

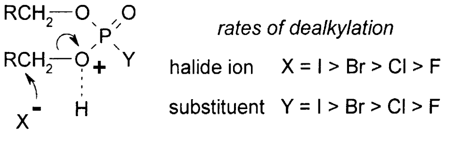
Another reagent for introducing the P–F bond is triethylamine hydrofluoride (made by dilution of commercial triethylamine trihydrofluoride with triethylamine). It converts amidochloridates to amidofluoridates, e.g. $Me_2NP(O)Cl_2$ to $Me_2NP(O)F_2$ in 42% yield [4]. Its potential for fluorination of other phosphorus halides is presently unknown, but requires exploration. We examined its effect on bis(trifluoroethyl) phosphorochloridate (**4b**). The three products that formed could not be separated by fractional distillation: bis(trifluoroethyl) phosphorofluoridate (**18**), trifluoroethyl phosphorodifluoridate (**19**) and tris(trifluoroethyl) phosphate (**20**).



Difluoridate **19** gave a characteristic triplet in its phosphorus NMR spectrum (δ_P −8.3, J_{PF} 1000 Hz). It is only the second fluoroalkyl phosphorodifluoridate to have been identified; the first was $H(CF_2)_2CH_2OP(O)F_2$ by Fokin et al. [55]. The identity of phosphate **20** was confirmed by comparison of its spectroscopic data with that of a pure specimen prepared previously in our laboratories [6]. How are compounds **19** and **20** produced? The best explanation is that some fluoridate **18** reacts with fluoride ion, with loss of a trifluoroethoxy group, thus giving difluoridate **19**. The liberated trifluoroethanol presumably reacts with fluoridate **18** to give the fluoroalkyl phosphate **20**.

2.8. Synthesis of bis(trifluoroethyl) phosphorobromidate

Few dialkyl phosphorobromidates are known. Reasons for this are two-fold. First, dialkyl phosphorochloridates are easily accessible and combine with nucleophiles under mild conditions; the corresponding bromidates furnish the same products, but the bromidates are more difficult to obtain pure. Second, chlorination of dialkyl phosphites gives the chloridate plus hydrogen chloride. The reaction with bromine liberates hydrogen bromide, a better dealkylating agent than hydrogen chloride. Thus, bromination of phosphites is often accompanied by side-reactions, the produced HBr reacting with the phosphorobromidate to give the bromo acids HO(RO)P(O)Br and/or $(HO)_2P(O)Br$ with loss of alkyl bromide [56]. Dealkylation occurs by an S_N2 process where the bromide ion, a soft base, attacks the α-carbon of the ester group, a soft acid (for an account of the concept of hard and soft acids and bases applied to multi-centre reactions, refer to [57]).



The first method to suppress dealkylation of the product is to use a dialkyl phosphite with hindered ester groups: Gerrard et al. [58] isolated $(\textit{tert}\text{-}BuCH_2O)_2P(O)Br$ from treatment of the dialkyl phosphite with bromine in the absence of solvent. The second method is to use a dialkyl phosphite with electronegative ester groups. Their lower basicity prevents protonation, and renders the α-carbon atom a harder acid, and hence, the ester groups are less susceptible to attack by the soft halide ion. Fluoroester groups resist dealkylation more than ester groups: heavily fluorinated ester groups are less vulnerable than lightly fluorinated ones. We recognised the potential of bis(fluoroalkyl) phosphites as precursors to a range of hitherto inaccessible fluoroalkyl phosphorobromidates, many of which are expected to have unstable hydrologues. Treatment of bis(trifluoroethyl) phosphite (**4a**) with bromine in benzene or dichloromethane gave

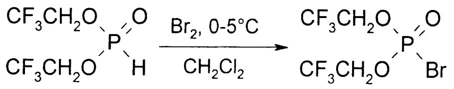
Table 5
Spectroscopic data for bis(trifluoroethyl) phosphorohalidates $(CF_3CH_2O)_2P(O)X$ (NMR data measured in $CDCl_3$)

Compound	X	^1H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ	^{31}P NMR δ	IR ν (cm^{-1})	GC–MS analysis
18	F	4.53 (4H, dt, $J = 10, 8$, OCH_2)	123 (dq, $J = 9, 278$, CF_3), 63.7 (dq, $J = 3, 39$, OCH_2)	−78.4 (1F, d, $J_{P–F} = 1002$, P–F), −74.7 (6F, br s, CF_3)	−12 (d, $J_{P–F} = 1002$)	1458, 1425, 1333, 1306 (P=O), 1282, 1182, 1086, 966, 922, 843	$C_4H_4F_7O_3P$ 265 ($M + 1$, 95) 245 ($M - F$, 48)
4b[a]	Cl	4.55 and 4.51 (4H, qdd, $J = 3, 8, 15$, OCH_2)	121.8 (dq, $J = 11, 277$, CF_3), 64.7 (dq, $J = 6, 34$, OCH_2)	−74.2 (6F, t, $J = 7$, CF_3)	4.7	1456, 1421, 1304 (P=O), 1279, 1178, 1078, 964, 897, 847	$C_4H_4ClF_6O_3P$ 281 ($M + 1$, 100) 261 ($M - F$, 12) 245 ($M - Cl$, 8)
21	Br	4.52 (4H, m, $J = 2, 8$, OCH_2)	121.7 (dq, $J = 11, 278$, CF_3), 64.6 (dq, $J = 6, 34$, OCH_2)	−73.9 (6F, t, $J = 7$, CF_3)	−8.6	1454, 1421, 1302 (P=O), 1275, 1178, 1070, 964, 910, 849, 737	$C_4H_4BrF_6O_3P$ 325 (M^+, 100) 305 ($M - F$, 32) 245 ($M - Br$, 28)
22[b]	I	4.45 (4H, m, OCH_2)	121.4 (dq, $J = 13, 278$, CF_3), 69.4 (dq, $J = 5, 37$, OCH_2)	−74.1 (6F, t, $J = 7$, CF_3)	−47.7	1454, 1421, 1296 (P=O), 1174, 1070, 962, 883, 849	$C_4H_4F_6IO_3P$ 373 ($M + 1$, 100) 353 ($M - F$, 18) 245 ($M - I$, 36)

[a] High resolution mass spectral data for this chloridate appears elsewhere [4].

[b] High resolution mass spectral data for this iodidate appears elsewhere [10].

the phosphorobromidate **21** as a colourless mobile liquid (bp 38 °C/0.8 mmHg).



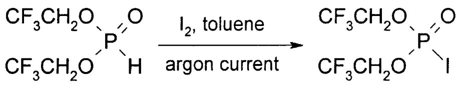
4a **21** 51%

Bromidate **21** is apparently formed when the phosphorane $(CF_3CH_2O)_3PBr_2$, from bromination of tris(trifluoroethyl) phosphite, decomposes at temperatures above −40 °C [59]; however, until now it has not been isolated or characterised properly. When pure, it is stable at room temperature, but best stored in a refrigerator, where it keeps for long periods of time without degradation. This contrasts with the unfluorinated analogue $(CH_3CH_2O)_2P(O)Br$ (bp 75 °C/ 1.5 mmHg) which decomposes readily, giving ethyl bromide and a polymeric, bromine-free residue after 72 h at 17 °C or 20 min at 100 °C [60]. Interestingly, the trichloroethyl analogue $(CCl_3CH_2O)_2P(O)Br$, prepared by heating the phosphorane $(CCl_3CH_2O)_3PBr_2$ at 130 °C, is a solid compound (mp 51–53 °C) [43].

Compound **21** is only the third bis(fluoroalkyl) phosphorobromidate to have been characterised. The other two compounds $[H(CF_2)_2CH_2O]_2P(O)Br$ and $[H(CF_2)_4CH_2O]_2$-$P(O)Br$, were isolated in 74 and 76% yield from reaction of the tris(fluoroalkyl) phosphites with bromine in carbon tetrachloride [28]. Bis(α,α,ω-trihydroperfluorobutyl) phosphorobromidate $[H(CF_2)_2CH_2O]_2P(O)Br$ was also isolated after treating the corresponding bis(fluoroalkyl) phosphite with bromine in dichloromethane at −20°C (yield not quoted) [61] and by treatment of the tris(fluoroalkyl) phosphite with cyanogen bromide (spectroscopic support not provided) [62]. The homologue $[H(CF_2)_4CH_2O]_2$-$P(O)Br$ also formed in 38% yield on oxidation of the dibromidate $H(CF_2)_4CH_2OPBr_2$ by dimethyl sulfoxide; however, it could not be separated from the two other products: $H(CF_2)_4CH_2OP(O)Br_2$ and $[H(CF_2)_4CH_2O]_3$-$P{=}O$ [63].

2.9. Synthesis of bis(trifluoroethyl) phosphoroiodidate

No dialkyl phosphoroiodidates of structure $(RO)_2P(O)I$ have been isolated out of solution. Treatment of triethyl phosphite $(EtO)_3P$ with iodine in ether, or chloroethane, gives diethyl phosphoroiodidate $(EtO)_2P(O)I$ which is thermally unstable and decomposes during work-up [64–66]. Diethyl phosphite $(EtO)_2P(O)H$, initially stated to remain unchanged by the action of iodine [64], was later said to give a mixture of dealkylation products due to ester cleavage by liberated hydrogen iodide [56]. In contrast, we found exposure of bis(trifluoroethyl) phosphite (**4a**) to a solution of iodine in toluene, with argon blowing through the mixture, gave phosphoroiodidate **22** which survived purification by vacuum distillation (bp 40 °C/ 0.02 mmHg).



4b **22** 46%

Compound **22** is the first of two dialkyl phosphoroiodidates ever to have been isolated and characterised (see [10] for further details). Its discovery, which lags behind the first isolation of a dialkyl phosphorochloridate by over 130 years, opens up new frontiers in organic phosphorus and iodine chemistry. The method of performing the reaction is described in the note referred to and need not be repeated in Section 4.

2.10. Physical properties of bis(2,2,2-trifluoroethyl) phosphorohalidates

The bis(trifluoroethyl) phosphorohalidates are liquids. Their spectroscopic data appear in Table 5. The phosphorus chemical shifts, measured in deuteriochloroform, are characteristic of each class of compound, but as with all phosphorus NMR data, difficult to rationalise theoretically. The greater shielding observed for $(CF_3CH_2O)_2P(O)F$ (δ_P −12 ppm) compared to the corresponding chloridate $(CF_3CH_2O)_2P(O)Cl$ (δ_P +4.7 ppm) may be attributed to the former having increased positive charge on phosphorus. This in turn causes increased back-bonding from the phosphoryl oxygen. Literature phosphorus shifts for diethyl phosphorohalidates $(CH_3CH_2O)_2P(O)Br$ and $(CH_3CH_2O)_2$-$P(O)I$ in chloroethane are −9.7 and −41 ppm, respectively [65]. The corresponding values for bis(trifluoroethyl) phosphorohalidates in deuteriochloroform are −8.6 and −47.7 ppm. The strong shielding observed for the phosphoroiodidate probably results from expansion of the P–O bond angles due to the large size of the iodine atom.

The frequency of the phosphoryl vibration ($\nu_{P=O}$) rises as the electronegativity of the substituents on phosphorus increases. For the bis(trifluoroethyl) phosphorohalidates, $\nu_{P=O}$ decreases as expected: P–F ($1306\,cm^{-1}$) > P–Cl ($1304\,cm^{-1}$) > P–Br ($1302\,cm^{-1}$) > P–I ($1296\,cm^{-1}$). The literature value for diethyl phosphoroiodidate is $1270\,cm^{-1}$ [66], considerably lower than that for bis(trifluoroethyl) phosphoroiodidate. The chemical ionisation mass spectra of bis(trifluoroethyl) phosphorohalidates comprised a main $M+1$ peak of high intensity and $M-F$ and $M-$ halogen peaks of much lower intensity.

3. Conclusion

We have described facile routes to bis(fluoroalkyl) phosphites and bis(fluoroalkyl) phosphorochloridates that have enabled the synthesis of pure materials. The methods in Section 4 were reproduced successfully by several chemists in our laboratories and we intend to submit some for publication in "Organic Syntheses". Their discovery will have a marked effect on the course of fluoroalkyl phosphoryl chemistry as it is now possible to prepare a range of bis(fluoroalkyl) phosphorohalidates from readily accessible starting materials. By the reactions of amines, alcohols and thiols on the bis(fluoroalkyl) phosphorochloridates in the presence of triethylamine, the corresponding amidates $(R_FO)_2P(O)NR_2$, phosphates $(R_FO)_2P(O)OR$ and thiolates $(R_FO)_2P(O)SR$ are produced, and we hope shortly to publish details of their preparation and general properties.

Finally, the use of the new bis(fluoroalkyl) phosphites and phosphorohalidates as reagents for the synthesis of polynucleotides by the phosphotriester approach is an area that merits investigation. The use of $P–OCH_2CCl_3$ species as protected phosphoric or phosphonic acids in nucleotide synthesis is recognised [67–72]. However, the application of $P–OR_F$ species to the preparation of nucleotides is in its infancy; only two references could be found and these describe $(CF_3CH_2O)_2P(O)H$ as the phosphorylation reagent [15,73]. The new bis(fluoroalkyl) phosphites could also be used, in principle, to obtain phosphonic-based oligonucleotides: the Michaelis–Becker reaction of sodium bis(trifluoroethyl) phosphite $(CF_3CH_2O)_2P–ONa$ with α-haloesters $XCHRCO_2R'$, e.g. gave the corresponding phosphonates $(CF_3CH_2O)_2P(O)CHRCO_2R'$ albeit in low yield [74]. The synthesis and properties of oligonucleotides containing fluoroalkoxy-substituted phosphoryl and phosphonyl units are awaited with much interest.

4. Experimental details

All reagents were of commercial quality: fluoroalcohols were obtained from Apollo Scientific Ltd. (UK). Anhydrous solvents were used for reactions. 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 GC–MS using a Finnigan MAT GCQ instrument with chemical ionisation (CI) using methane as reagent gas. Molecular weights of pure products were confirmed with methane positive CI data. They gave satisfactory microanalyses: C ± 0.13, H ± 0.11, O ± 0.12.

*4.1. General procedure for bis(fluoroalkyl) phosphites (**1a–13a**)*

A solution of anhydrous *tert*-butanol (1 mol) in dichloromethane (100 ml) was added dropwise over a period of 45 min to a stirred solution of phosphorus trichloride (1 mol) in dichloromethane (200 ml) cooled at 0–5 °C. The mixture was stirred at this temperature for a further hour. The fluoroalcohol (2 mol)[3] in dichloromethane (100 ml) was added dropwise over a period of 30 min to the cooled solution. The mixture was left at room temperature for 12 h. It was heated under reflux for 3 h to drive out any dissolved hydrogen chloride. The solvent was removed. Distillation of the residue under reduced pressure gave a forerun of unreacted alcohol and a main fraction of the bis(fluoroalkyl) phosphite (**1a**–**13a**) as a colourless liquid. Experimental and spectroscopic data appear in Tables 1 and 2.

*4.2. General procedure for bis(fluoroalkyl) phosphorochloridates (**1b–13b**)*

Chlorine gas was bubbled into a solution of bis(fluoroalkyl) phosphite (0.2 mol) in dichloromethane or chloroform (50 ml) until a yellow colour persisted in the reaction mixture. The solvent was removed. Distillation of the residue gave the bis(fluoroalkyl) phosphorochloridate (**1b**–**12b**) as a colourless liquid. Bis(*1H*,*1H*,*2H*,*2H*-perfluoro-1-octyl) phosphite (**13b**) was not distilled; removal of solvent gave pure material as a white solid. Experimental and spectroscopic data appear in Tables 3 and 4.

4.3. Reaction of bis(2,2,2-trifluoroethyl) phosphite with thionyl chloride

A solution of thionyl chloride (11.8 g, 0.1 mol) in ether (50 ml) was added dropwise to a solution of bis(2,2,2-trifluoroethyl) phosphite (24.6 g, 0.1 mol) in ether (50 ml) at room temperature. The reaction was mildly exothermic. Analysis by GC–MS showed that the expected product, bis(2,2,2-trifluoroethyl) phosphorochloridate, predominated. The solvent was removed and the residue fractionated under reduced pressure to give chloridate **4b** as a colourless liquid (6.5 g, 23%) at bp 61–62 °C/10 mmHg. A cloudy brown residue remained in the distillation flask and a yellow sublimate, presumably sulphur, adhered to the fractionating column.

*4.4. Synthesis of bis(2,2,2-trifluoroethyl) phosphorofluoridate (**18**)*

Finely-divided KF (1.7 g, 28.7 mmol) was added to a stirred solution of bis(2,2,2-trifluoroethyl) phosphorochloridate

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[3] *1H,1H,2H,2H*-perfluoro-1-octanol is insoluble in dichloromethane: the two-phase mixture was added and became homogeneous as the phosphite formed.

(4 g, 14.4 mmol) in dichloromethane (40 ml). The resultant suspension was heated under reflux for 2 h, then assayed by GC–MS analysis; only a trace of product was present. Trifluoroacetic acid (0.15 ml, 2 mmol) was added by syringe and the mixture heated under reflux for a further 2 h. A heavy white precipitate of KCl formed. Analysis of the reaction mixture by GC–MS showed excellent conversion to the desired product. The solids were removed by filtration and the filtrate concentrated. Fractionation of the residue under reduced pressure gave the title compound as a volatile colourless liquid (3.2 g, 84%) at bp 61 °C/40 mmHg.

4.5. Reaction of bis(2,2,2-trifluoroethyl) phosphorochloridate with triethylamine hydrofluoride

A solution of triethylamine (1.34 ml, 9.6 mmol) and triethylamine trishydrofluoride (0.78 ml, 4.8 mmol) in dichloromethane (20 ml) was added dropwise to a stirred solution of bis(2,2,2-trifluoroethyl) phosphorochloridate (4.03 g, 14.4 mmol) in dichloromethane (30 ml). An exothermic reaction ensued. The mixture was left for 12 h. Colourless needles of triethylamine hydrochloride had formed. The mixture was filtered and the filtrate concentrated to an oily white residue. Addition of ether (10 ml) and passage of the resultant suspension through a short plug of silica gave a clear solution. Removal of solvent and bulb-to-bulb distillation yielded a mixture comprising bis(trifluoroethyl) phosphorofluoridate (**18**) (84%), trifluoroethyl phosphorodifluoridate (**19**) (14%) and tris(trifluoroethyl) phosphate (**20**) (2%); percentages of components were determined by phosphorus NMR analysis.

*4.6. Bis(2,2,2-trifluoroethyl) phosphorobromidate (**21**)*

A solution of bromine (3.2 g, 0.02 mol) in dichloromethane (20 ml) was added dropwise to a solution of bis(2,2,2-trifluoroethyl) phosphite (4.9 g, 0.02 mol) in dichloromethane (30 ml) at 0–5 °C with stirring. After addition, the solution was warmed to room temperature and left for 14 h; the yellow colour of the bromine had faded. The dichloromethane was removed. Fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (3.3 g, 51%) at bp 38 °C/0.8 mmHg.

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