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Fluorinated phosphorus compounds Part 7. The reactions of bis(fluoroalkyl) phosphorochloridates with nitrogen nucleophiles

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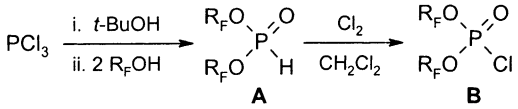
Abstract

Forty bis(fluoroalkyl) phosphoramidates $(R_FO)_2P(O)R$ were prepared in 10–91% yield by treating phosphorochloridates $(R_FO)_2P(O)Cl$ where R_F was HCF_2CH_2, $HCF_2CF_2CH_2$, $HCF_2CF_2CF_2CF_2CH_2$, CF_3CH_2, $C_2F_5CH_2$, $C_3F_7CH_2$, $(CF_3)_2CH$, $(FCH_2)_2CH$ and $(CH_3)_2CF_3C$ with nucleophiles HR, where R was NH_2, NHMe, NMe_2, NHEt and NEt_2 in diethyl ether at 0–5 °C. The bulky chloridate $[(CH_3)_2CF_3CO]_2P(O)Cl$ reacted with ammonia, methylamine, dimethylamine and ethylamine, but not with diethylamine—even on heating in the presence of 4-dimethylaminopyridine—due to steric hindrance at phosphorus. Fluorinated phosphoramidates have lower basicity and nucleophilicity than their unfluorinated counterparts: $(EtO)_2P(O)NH_2$ is more easily hydrolysed by HCl than $(CF_3CH_2O)_2P(O)NH_2$ and whereas, $(EtO)_2P(O)NH_2$ is known to react with oxalyl chloride and thionyl chloride to give $(EtO)_2P(O)NCO$ and $(EtO)_2P(O)NSO$ respectively, $(CF_3CH_2O)_2P(O)NH_2$ reacted only with oxalyl chloride to give $(CF_3CH_2O)_2P(O)NCO$ in 10% yield. Two other new fluorinated species, $(CF_3CH_2O)_2P(O)NHOMe$ and $(CF_3CH_2O)_2P(O)N_3$, were prepared by nucleophilic substitution of bis(trifluoroethyl) phosphorochloridate with methoxyamine and azide ion. Published by Elsevier Science B.V.

Keywords: Bis(fluoroalkyl) phosphoramidate; Bis(fluoroalkyl) phosphorochloridate; Bis(trifluoroethyl) *N*-alkoxyphosphoramidate; Bis(trifluoroethyl) phosphorazidate; Bis(trifluoroethyl) phosphoroisocyanidate

1. Introduction

The previous paper in this series described the synthesis of some bis(fluoroalkyl) phosphites **A** that were converted into the corresponding chloridates **B** [1]. The discovery of this route opens up a new field of research as many of the reactions of dialkyl phosphorochloridates might be realised with bis(fluoroalkyl) phosphorochloridates.[1]



R_F = primary, secondary or tertiary fluoroalkyl group

To understand the differences between unfluorinated and fluorinated systems, two main factors must be understood: the steric and electronic effects of replacing a proton with a fluorine atom. A fluorine atom is larger (atomic van der Waals' radii, $F = 1.35$ and $H = 1.2$ Å) and much more electronegative (on Pauling's scale, $F = 4.0$ and $H = 2.1$) [2–5]. Replacement of protons with fluorine atoms alters steric and electronic parameters, and this is well illustrated in the case of fluoroalkyl phosphorus compounds. For example, although it is useful to compare $(CH_3CH_2O)_2P(O)Cl$ with $(CF_3CH_2O)_2P(O)Cl$, they have very different characters; the latter has a more electrophilic and hindered phosphorus atom (what extent these opposing effects influence the reactivities of the fluorinated phosphorohalidates to nucleophiles is unknown). Comparison of the van

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[1] Organic phosphorus compounds are named after the corresponding parent acids. The substances described in this paper are derivatives of phosphoric acid $(HO)_3P{=}O$. Compounds of structure $(R_FO)_2P(O)Cl$ are bis(fluoroalkyl) phosphorochloridates. Their amino derivatives are phosphoramidates $(R_FO)_2P(O)NH_2$, *N*-alkylphosphoramidates $(R_FO)_2P(O)NHR$ and *N*,*N*-dialkylphosphoramidates $(R_FO)_2P(O)NR_2$. Compounds of structure $(R_FO)_2P(O)NCO$ are phosphoroisocyanidates, those of structure $(R_FO)_2P(O)NHOR$ are *N*-alkoxyphosphoramidates, while those of structure $(R_FO)_2P(O)N_3$ are phosphorazidates.

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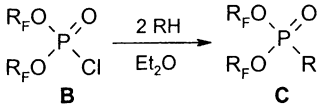
der Waals volumes of CH_3 (13.7 $cm^3\,mol^{-1}$) and CF_3 (21.3 $cm^3\,mol^{-1}$) suggests the CF_3 group approximates to an isopropyl group in size [2–5]. When comparing $(CH_3CH_2O)_2P(O)Cl$ with $(CF_3CH_2O)_2P(O)Cl$, it is helpful to picture the latter as having the dimensions of $[i\text{-}PrCH_2O]_2P(O)Cl$, but with a phosphorus atom of reversed polarity.[2] Such analogy cannot be extended to many other perfluoroalkyl groups as steric parameters have not yet been reported. A simple way to probe such effects is to examine reactions between a range of homologous electrophiles and nucleophiles.

Here, we describe the interactions of bis(fluoroalkyl) phosphorochloridates **B** with ammonia, and primary and secondary amines with one to four carbon atoms, and some properties of the products **C**. This work extends our earlier studies on the synthesis of fluoroalkyl-substituted phosphoramidates [7].



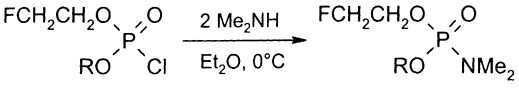
B **C**

R_F = HCF_2CH_2, $HCF_2CF_2CH_2$, $HCF_2CF_2CF_2CF_2CH_2$, CF_3CH_2, $C_2F_5CH_2$, $C_3F_7CH_2$, $(CF_3)_2CH$, $(FCH_2)_2CH$, $(CH_3)_2CF_3C$

R = NH_2, NHMe, NMe_2, NHEt, NEt_2

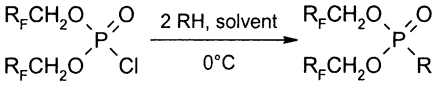
One of the aims was to find the point at which steric hindrance prevented product formation. Another was to demonstrate the powerful phosphorylation action of bis(fluoroalkyl) phosphorochloridates; subsequent papers will describe the phosphorylation of other nucleophiles such as thiols and alcohols.

The synthesis of fluoroalkyl phosphoramidates has advanced little since Lenton and Lewis prepared $HCF_2CF_2CH_2OP(O)(NH_2)_2$ in 1965 [8]. Like the analogues $CF_3CH_2OP(O)R_2$ where R is NMe_2, NMeEt or NEt_2 [7], it was made by treating trifluoroethyl phosphorodichloridate with four molar equivalents of nitrogen nucleophile. Phosphoramidates containing a 2-fluoroethyl group, reported by Kabachnik et al. [9], were made in the same way:



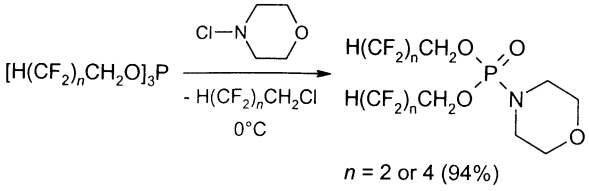
R = Me 85%, Et 93%, *i*-Pr 91%, *i*-Bu 94%

Phosphoramidates containing two fluoroalkyl groups were derived from the bis(fluoroalkyl) phosphorochloridate [7,10,11]:



R_F	R	Ref.
CF_3	NH_2, NHPh (yields not stated)	[10]
	NHMe 68%, NHEt 66%	[7]
	NMe_2 70%, NEt_2 75%	[7]
$H(CF_2)_2$	NHPh 67%, *N*-morpholino 90%	[11]
$H(CF_2)_4$	*N*-morpholino 93%	[11]

Other approaches have been studied less. The reverse reaction of *N*,*N*,*N*′,*N*′-tetra-alkylphosphoramidic chlorides $(R_2N)_2P(O)Cl$ with fluoroalcohols, is much slower because of the poorly electrophilic and hindered phosphorus atom of the amidic chloride and the low nucleophilicity of the fluoroalcohol. Even with 4-dimethylaminopyridine catalyst, phosphorylation is slow [7]. The Arbusov reaction of tris(fluoroalkyl) phosphites with *N*-chloramines, illustrated below [11], is of low utility due to the poor availability of both reagents.



n = 2 or 4 (94%)

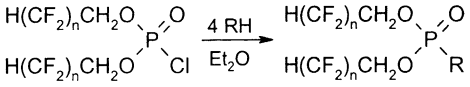
Nothing is known about the chemistry of bis(fluoroalkyl) phosphoramidates, besides the inertness of $(CF_3CH_2O)_2P(O)NMe_2$ to acid hydrolysis [7]. We now describe the preparation of a homologous series of such molecules, and examine the behaviour of $(CF_3CH_2O)_2P(O)NH_2$ to certain electrophiles (HCl, oxalyl chloride and thionyl chloride). The chemical and physical properties of the new phosphoramidates are compared with conventional analogues that do not contain fluorine. Also described are the first examples of two new classes of bis(fluoroalkyl) phosphoryl species, the *N*-alkoxyphosphoramidate $(CF_3CH_2O)_2P(O)NHOMe$ and the phosphorazidate $(CF_3CH_2O)_2P(O)N_3$.

2. Results and discussion

2.1. Phosphoramidates of structure $[H(CF_2)_nCH_2O]_2P(O)NR_2$

Only three compounds obeying this formula appear in the literature: $[H(CF_2)_2CH_2O]_2P(O)NHPh$ and $[H(CF_2)_n\text{-}CH_2O]_2P(O)N(CH_2)_2O$ where *n* is 2 or 4 [11]. We found that treatment of bis(α,α,ω-trihydroperfluoroalkyl) phosphorochloridates with ammonia and amines gave phosphoramidates **1a–e**, **2a–e** and **3a–e**. Reaction was instantaneous.

[2] Acid dissociation constants measured in ethanol for $(CH_3CH_2O)_2P(O)OH$ and $(CF_3CH_2O)_2P(O)OH$ are 6.8 and 4.1 respectively [6]. These data show the increase in acidity caused by replacement of the electron-donating ethyl group with the electron-withdrawing trifluoroethyl group.



n = 1	R =	NH_2	**1a**	35%
		NHMe	**1b**	47%
		NMe_2	**1c**	70%
		NHEt	**1d**	55%
		NEt_2	**1e**	62%
n = 2	R =	NH_2	**2a**	66%
		NHMe	**2b**	68%
		NMe_2	**2c**	70%
		NHEt	**2d**	30%
		NEt_2	**2e**	60%
n = 4	R =	NH_2	**3a**	46%
		NHMe	**3b**	32%
		NMe_2	**3c**	32%
		NHEt	**3d**	40%
		NEt_2	**3e**	54%

Phosphoryl compounds containing the difluoroethyl group are rare. The first, tris(difluoroethyl) phosphate $(HCF_2CH_2O)_3P{=}O$, was made in 1909 by Swarts from difluoroethanol, bromine and red phosphorus [12]. To the best of our knowledge, over 90 years elapsed before the next species were isolated: $(HCF_2CH_2O)_2P(O)H$ and $(HCF_2CH_2O)_2P(O)Cl$ [1]. Phosphoramidates **1a–e** extend this small family.

Physical data for the phosphoramidates appear in Tables 1 and 2. Their phosphorus chemical shifts in deuterated chloroform are between 7.9 and 10.4 ppm. Characteristic vibrations in the infrared spectra for the phosphoryl group (P=O) and the phosphoramido group (P–N) appear at 1236–1265 and 945–976 cm^{-1} respectively.

Table 1
Experimental data for phosphoramidates $[H(CF_2)_nCH_2O]_2P(O)R$

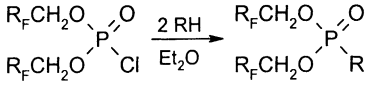
Compound	R	Bp (°C/mmHg)[a]	Mp (°C)
n = 1	Bis(difluoroethyl) phosphoramidates		
1a	NH_2	80/0.015	–
1b	NHMe	71/0.015	–
1c	NMe_2	58/0.02	–
1d	NHEt	65/0.015	–
1e	NEt_2	62/0.02	–
n = 2	Bis(tetrafluoropropyl) phosphoramidates		
2a	NH_2	88/0.015	36
2b	NHMe	83/0.01	40
2c	NMe_2	62/0.015	–
2d	NHEt	75/0.01	–
2e	NEt_2	69/0.015	–
n = 4	Bis(octafluoropentyl) phosphoramidates		
3a	NH_2	83/0.015	–
3b	NHMe	75/0.015	–
3c	NMe_2	65/0.01	–
3d	NHEt	84/0.02	–
3e	NEt_2	68/0.01	–

[a] Approximate oven temperatures for bulb-to-bulb distillations are quoted.

2.2. Phosphoramidates of structure $(R_FCH_2O)_2P(O)NR_2$

Replacing the ω-proton of fluoroalcohols of structure $H(CF_2)_nCH_2OH$ with a ω-fluorine atom produces fluoroalcohols of structure $F(CF_2)_nCH_2OH$. Both classes of fluoroalcohols have similar acidities. The acid dissociation constant, for example, of difluoroethanol is 12 while that of trifluoroethanol is 12.4 [13]. In phosphoryl compounds, the introduction of fluoro-ester groups increases the acid strength without changing the general rules known for fluoroalcohols or fluorocarboxylic acids [6]. The dissociation constants measured in absolute ethanol for the two phosphoric acids $[H(CF_2)_2CH_2O]_2P(O)OH$ and $[F(CF_2)_3CH_2O]_2P(O)OH$ are 4.15 and 4.18, respectively [6]. The pair of chloridates, $[H(CF_2)_2CH_2O]_2P(O)Cl$ and $[C_2F_5CH_2O]_2P(O)Cl$ will contain phosphorus atoms of comparable electrophilicity (due to similar inductive effects) and steric accessibility (as the ends of the fluoro-ester groups are sufficiently distant from phosphorus). They should therefore react with nucleophiles in the same way.

Bis(trifluoroethyl) phosphorochloridate underwent facile ammonolysis and gave the phosphoramidate **4** in excellent yield. Derivatives containing the methylamino, dimethylamino, ethylamino and diethylamino groups are described in Part 1 [7]. Bis(pentafluoropropyl) and bis(heptafluorobutyl) phosphorochloridates gave compounds **5a–e** and **6a–e** respectively.



$R_F = CF_3$	R =	NH_2	**4**	91%
$R_F = C_2F_5$	R =	NH_2	**5a**	76%
		NHMe	**5b**	68%
		NMe_2	**5c**	74%
		NHEt	**5d**	81%
		NEt_2	**5e**	74%
$R_F = C_3F_7$	R =	NH_2	**6a**	70%
		NHMe	**6b**	11%
		NMe_2	**6c**	54%
		NHEt	**6d**	40%
		NEt_2	**6e**	70%

Physical data for the phosphoramidates appear in Tables 3 and 4. Their phosphorus chemical shifts in deuterated chloroform are between 7.7 and 9.5 ppm. The infrared spectra are complex due to many overlapping bands from the P–N bond. It was not possible to assign the peaks unambiguously.

Table 2
Spectroscopic data for bis(fluoroalkyl) phosphoramidates $[H(CF_2)_nCH_2O]_2P(O)R$ **1a–e**, **2a–e** and **3a–e** (NMR data measured in $CDCl_3$)

Compound[a]	^{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 (%)
1a (M_w 225)	6.0 (2H, tt, J = 4, 55, CF_2H), 4.2 (4H, ddt, J = 4, 8, 14, OCH_2), 3.7 (2H, d, J = 6, NH_2)	112.8 (dt, J = 9, 242, CF_2H), 64.2 (dt, J = 4, 29, OCH_2)	−126.4 (4F, dt, J = 14, 14, CF_2H)	9.9	1568, 1456, 1429, 1373, 1329, 1248 (P=O), 1146, 1086, 945 (P–N), 903, 856	Calcd. for $C_4H_8F_4NO_3P$: C, 21.3; H, 3.6; F, 33.8; N, 6.2. Found: C, 21.1; H, 3.7; F, 33.7; N, 6.1.
1b (M_w 239)	5.94 (2H, tt, J = 4, 55, CF_2H), 4.16 (4H, ddt, J = 4, 9, 15, OCH_2), 3.32 (1H, m, NH), 2.62 (3H, dd, J = 6, 13, NCH_3)	113.6 (dt, J = 8, 242, CF_2H), 64.4 (dt, J = 5, 31, OCH_2), 25.9 (s, $NHCH_3$)	−125.7 (4F, dt, J = 14, 14, CF_2H)	10.0	1641, 1456, 1429, 1375, 1327, 1244 (P=O), 1146, 1082, 953 (P–N), 906	Calcd. for $C_5H_{10}F_4NO_3P$: C, 25.1; H, 4.2; F, 31.8; N, 5.9. Found: C, 25; H, 4.1; F, 31.7; N, 5.9.
1c (M_w 253)	5.94 (2H, tt, J = 4, 55, CF_2H), 4.14 (4H, m, OCH_2), 2.74 (6H, d, J = 10, NCH_3)	111.9 (dt, J = 8, 241, CF_2H), 64.0 (dt, J = 5, 30, OCH_2), 35.5 (d, J = 3, NCH_3)	−125.7 (4F, dt, J = 13, 25, CF_2H)	10.4	1458, 1427, 1317, 1250 (P=O), 1144, 1078, 1047, 1005, 949 (P–N), 903, 839	Calcd. for $C_6H_{12}F_4NO_3P$: C, 28.5; H, 4.7; F, 30; N, 5.5. Found: C, 28.4; H, 4.6; F, 29.9; N, 5.4.
1d (M_w 253)	5.95 (2H, tt, J = 4, 55, CF_2H), 4.23 (4H, m, OCH_2), 3.25 (1H, m, NH) 2.99 (2H, m, NCH_2), 1.17 (3H, dt, J = 1, 7, CH_3)	111.2 (dt, J = 8, 241, CF_2H), 63.4 (dt, J = 4, 30, OCH_2), 36.9 (s, NCH_2), 17.3 (d, J = 6, CH_3)	−125.9 (4F, dt, J = 13, 26, CF_2H)	8.9	1456, 1429, 1373, 1327, 1244 (P=O), 1144, 1078, 976 (P–N), 947, 904, 872	Calcd. for $C_6H_{12}F_4NO_3P$: C, 28.5; H, 4.7; F, 30; N, 5.5. Found: C, 28.5; H, 4.6; F, 30.1; N, 5.4.
1e (M_w 281)	5.96 (2H, tt, J = 4, 55, CF_2H), 4.14 (4H, m, OCH_2), 3.13 (4H, dt, J = 7, 12, NCH_2), 1.11 (6H, t, J = 7, CH_3)	112.6 (dt, J = 9, 242, CF_2H), 63.8 (dt, J = 4, 30, OCH_2), 39.3 (d, J = 4, NCH_2), 13.2 (s, CH_3)	−126.8 (4F, dt, J = 13, 26, CF_2H)	9.8	1633, 1456, 1427, 1385, 1327, 1252 (P=O), 1213, 1144, 1080, 1038, 962 (P–N), 945, 903, 839	Calcd. for $C_8H_{16}F_4NO_3P$: C, 34.2; H, 5.7; F, 27; N, 5. Found: C, 34.1; H, 5.5; F, 26.8; N, 4.9.
2a (M_w 325)	5.94 (2H, tt, J = 4, 53, CF_2H), 4.4 (4H, dt, J = 11, 12, OCH_2), 3.48 (2H, m, NH_2)	113.8 (dtt, J = 7, 34, 256, CF_2), 109.3 (tt, J = 36, 250, CF_2H), 62.1 (dt, J = 5, 30, OCH_2)	−137.5 (4F, d, J = 53, CF_2H), −124.6 (4F, dt, J = 5, 13, CF_2)	8.8	1566, 1460, 1402, 1348, 1238 (P=O), 1213, 1105, 1068, 989, 951 (P–N)	Calcd. for $C_6H_8F_8NO_3P$: C, 22.2; H, 2.5; F, 46.8; N, 4.3. Found C, 22.2; H, 2.5; F, 46.6; N, 4.1.
2b (M_w 339)	5.92 (2H, tt, J = 4, 53, CF_2H), 4.36 (4H, dt, J = 11, 12, OCH_2), 3.06 (1H, m, NH), 2.65 (3H, dd, J = 6, 13, CH_3)	114.9 (m, CF_2), 109 (tt, J = 36, 250, CF_2H), 62.2 (dt, J = 5, 30, OCH_2), 27.5 ($NHCH_3$)	−136.9 (4F, d, J = 53, CF_2H), −123.9 (4F, dt, J = 8, 16, CF_2)	9.0	1460, 1402, 1356, 1257, 1236 (P=O), 1211, 1109, 1066, 951 (P–N), 937, 874, 833	Calcd. for $C_7H_{10}F_8NO_3P$: C, 24.8; H, 2.9; F, 44.8; N, 4.1. Found: C, 24.8; H, 3; F, 43.9; N, 4.1.
2c (M_w 353)	5.94 (2H, tt, J = 4, 53, CF_2H), 4.3 (4H, dt, J = 11, 12, OCH_2), 2.71 (6H, d, J = 10, NCH_3)	114 (tt, J = 9, 250, CF_2), 109.1 (tt, J = 36, 250, CF_2H), 62.2 (dt, J = 5, 30, OCH_2), 36.4 (d, J = 4, NCH_3)	−136.9 (4F, dt, J = 17, 53, CF_2H), −123.9 (4F, dt, J = 9, 18, CF_2)	9.6	1489, 1460, 1414, 1319, 1259, 1236 (P=O), 1211, 1190, 1107, 1061, 1007, 951 (P–N), 937	Calcd. for $C_8H_{12}F_8NO_3P$: C, 27.2; H, 3.4; F, 43.1; N, 4. Found: C, 27.2; H, 3.3; F, 43.1; N, 3.8.
2d (M_w 353)	5.91 (2H, tt, J = 4, 53, CF_2H), 4.3 (4H, dt, J = 11, 13, OCH_2), 3.34 (1H, m, NH), 2.99 (2H, m, NCH_2), 1.16 (3H, dt, J = 1, 7, CH_3)	114.1 (tt, J = 10, 250, CF_2), 108.9 (tt, J = 36, 250, CF_2H), 62.1 (dt, J = 4, 26, OCH_2), 36.4 (m, NCH_2), 16.8 (d, J = 6, CH_3)	−136.9 (4F, dt, J = 17, 55, CF_2H), −124.2 (4F, dt, J = 9, 18, CF_2)	8.1	1458, 1441, 1356, 1286, 1236 (P=O), 1213, 1109, 1066, 968, 951 (P–N), 937, 877, 835	Calcd. for $C_8H_{12}F_8NO_3P$: C, 27.2; H, 3.4; F, 43.1; N, 4. Found: C, 27; H, 3.3; F, 43.2; N, 3.9.
2e (M_w 381)	5.91 (2H, tt, J = 4, 53, CF_2H), 4.32 (4H, dt, J = 12, 14, OCH_2), 3.11 (4H, q, J = 7, NCH_2), 1.13 (6H, t, J = 7, CH_3)	114.1 (tt, J = 10, 250, CF_2), 109 (tt, J = 36, 250, CF_2H), 62.1 (dt, J = 5, 28, OCH_2), 39.8 (m, NCH_2), 1.39 (d, J = 7, CH_3)	−137 (4F, d, J = 53, CF_2H), −124 (4F, dt, J = 9, 24, CF_2)	9.1	1460, 1387, 1267, 1236 (P=O), 1211, 1176, 1107, 1061, 1039, 964 (P–N), 937, 870, 833	Calcd. for $C_{10}H_{16}F_8NO_3P$: C, 31.5; H, 4.2; F, 39.9; N, 3.7. Found: C, 31.4; H, 4.2; F, 39.8; N, 3.6.
3a (M_w 525)	6.06 (2H, tt, J = 5, 52, CF_2H), 4.47 (4H, m, OCH_2), 3.48 (2H, m, NH_2)	108–116 (dtt, J = 5, 29, 248, CF_2), 107.1 (tt, J = 36, 249, CF_2H), 62.1 (m, OCH_2)	−136.5 (4F, m, CF_2H), −129.6, −124.9 and −120.6 (12F, m, CF_2)	8.8	1564, 1460, 1404, 1261 (P=O), 1173, 1132, 1086, 989, 964 (P–N), 906, 877, 808	Calcd. for $C_{10}H_8F_{16}NO_3P$: C, 22.9; H, 1.5; F, 57.9; N, 2.7. Found: C, 22.8; H, 1.4; F, 57.9; N, 2.8.
3b (M_w 539)	6.05 (2H, tt, J = 5, 52, CF_2H), 4.44 (4H, dt, J = 7, 13, OCH_2), 3.29 (1H, m, NH), 2.65 (3H, dd, J = 6, 13, NCH_3)	108–116 (dtt, J = 8, 28, 248, CF_2), 107.4 (tt, J = 36, 249, CF_2H), 62 (m, OCH_2), 26.9 (s, NCH_3)	−136.4 (4F, m, CF_2H), −129.1, −124.4 and −120 (12F, m, CF_2)	9.0	1460, 1402, 1362, 1255 (P=O), 1173, 1132, 1012, 991, 960 (P–N), 904, 808	Calcd. for $C_{11}H_{10}F_{16}NO_3P$: C, 24.5; H, 1.9; F, 56.4; N, 2.6. Found: C, 24.5; H, 2.1; F, 56.2; N, 2.5.
3c (M_w 553)	6.05 (2H, tt, J = 6, 52, CF_2H), 4.41 (4H, m, OCH_2), 2.73 (6H, d, J = 11, NCH_3)	108–116 (dtt, J = 6, 28, 249, CF_2), 107.6 (tt, J = 31, 254, CF_2H), 62.2 (t, J = 28, OCH_2), 36.3 (d, J = 4, NCH_3)	−136.6 (4F, m, CF_2H), −128.9, −123.9 and −119.8 (12F, m, CF_2)	9.5	1489, 1460, 1404, 1319, 1265 (P=O), 1174, 1132, 1074, 1009, 960 (P–N), 906, 872, 808	Calcd. for $C_{12}H_{12}F_{16}NO_3P$: C, 26; H, 2.2; F, 55; N, 2.5. Found: C, 25.8; H, 2.1; F, 54.7; N, 2.4.
3d (M_w 553)	6.08 (2H, tt, J = 5, 52, CF_2H), 4.44 (4H, dt, J = 7, 13, OCH_2), 3.21 (1H, s, NH), 3.0 (2H, m, NCH_2), 1.16 (3H, dt, J = 1, 7, CH_3)	108–116 (dtt, J = 6, 29, 245, CF_2), 109.6 (tt, J = 30, 246, CF_2H), 62.2 (t, J = 28, OCH_2), 5.7 (s, NCH_2), −13.9 (d, J = 6, CH_3)	−136.9 (4F, m, CF_2H), −129.8, −124.8 and −120.6 (12F, m, CF_2)	7.9	1460, 1441, 1406, 1288, 1252 (P=O), 1174, 1132, 1082, 966 (P–N), 910, 876, 808	Calcd. for $C_{12}H_{12}F_{16}NO_3P$: C, 26; H, 2.2; F, 55; N, 2.5. Found: C, 25.8; H, 2.2; F, 55.1; N, 2.3.
3e (M_w 581)	6.04 (2H, tt, J = 5, 52, CF_2H), 4.4 (4H, m, OCH_2), 3.03 (4H, q, J = 7, NCH_2), 1.12 (6H, t, J = 7, CH_3)	113.8 (dtt, J = 7, 32, 248, CF_2), 107.6 (tt, J = 32, 254, CF_2H), 108–110 (m, CF_2CF_2), 61.9 (m, OCH_2), 39.6 (d, J = 5, NCH_2), 1.32 (m, CH_3)	−136.4 (4F, d, J = 52, CF_2H), −129.2, −124.2 and −119.8 (12F, m, CF_2)	9.0	1460, 1387, 1271 (P=O), 1213, 1174, 1132, 1072, 1041, 991, 964 (P–N), 908, 868, 808	Calcd. for $C_{14}H_{16}F_{16}NO_3P$: 28.9; H, 2.8; F, 52.3; N, 2.4. Found: C, 28.9; H, 2.8; F, 52.1; N, 2.4.

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

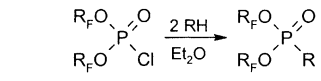
Table 3
Experimental data for phosphoramidates $[R_FCH_2O]_2P(O)R$

Compound	R	Bp (°C/mmHg)[a]	Mp (°C)
$R_F = CF_3$	Bis(trifluoroethyl) phosphoramidate		
4	NH_2	–	42–43
$R_F = C_2F_5$	Bis(pentafluoropropyl) phosphoramidates		
5a	NH_2	76/0.02	35
5b	NHMe	56/0.015	37
5c	NMe_2	36/0.015	–
5d	NHEt	58/0.1	30
5e	NEt_2	39/0.06	–
$R_F = C_3F_7$	Bis(heptafluorobutyl) phosphoramidates		
6a	NH_2	–	62
6b	NHMe	66/0.02	–
6c	NMe_2	46/0.03	–
6d	NHEt	63/0.02	–
6e	NEt_2	50/0.03	–

[a] Approximate oven-temperatures for bulb-to-bulb distillations are quoted.

2.3. Phosphoramidates of structure $(R_FO)_2P(O)NR_2$

Pronounced stereoelectronic effects are observed for bis(fluoroalkyl) phosphorochloridates containing secondary and tertiary fluoro-ester groups. The electrophilicities of the three chloridates considered in this section should decrease in the order $[(CF_3)_2CHO]_2P(O)Cl > [(CH_3)_2CF_3CO]_2P(O)Cl \sim [(FCH_2)_2CHO]_2P(O)Cl$, mirroring pK_a values for the fluoroalcohols: values for hexafluoroisopropanol and 2-(trifluoromethyl)-2-propyl are 9.3 and 11.6 respectively [14]. These chloridates contain a phosphorus atom hindered by the secondary fluoro-ester groups. Although $(CF_3)_2CH$ and $(CH_3)_2CF_3C$ are larger than $(FCH_2)_2CH$—van der Waals volumes for CF_3, FCH_2 and CH_3 are 21.3, 16 and 13.7 $cm^3\ mol^{-1}$ [2,3]—ranking the first two groups in size is difficult. The accessibility of the phosphorus atoms of the two isopropyl chloridates will be $[(FCH_2)_2CHO]_2P(O)Cl > [(CF_3)_2CHO]_2P(O)Cl$, the reverse of their electrophilicity order. Despite such antagonistic effects, both chloridates combined with nitrogen nucleophiles to give phosphoramidates **7a–e** and **8a–e**.



$R_F = (CF_3)_2CH$	R =	NH_2	**7a**	79%
		NHMe	**7b**	84%
		NMe_2	**7c**	38%
		NHEt	**7d**	29%
		NEt_2	**7e**	58%
$R_F = (FCH_2)_2CH$	R =	NH_2	**8a**	23%
		NHMe	**8b**	20%
		NMe_2	**8c**	63%
		NHEt	**8d**	54%
		NEt_2	**8e**	39%
$R_F = (CH_3)_2CF_3C$	R =	NH_2	**9a**	10%
		NHMe	**9b**	86%
		NMe_2	**9c**	63%
		NHEt	**9d**	77%

Bis[2-(trifluoromethyl)-2-propyl] phosphorochloridate $[(CH_3)_2CF_3CO]_2P(O)Cl$, the only chloridate examined with a tertiary group, combined with ammonia, methylamine, dimethylamine and ethylamine, giving phosphoramidates **9a–d**. It did not react with diethylamine even after 14 h of heating under reflux in the presence of 4-dimethylaminopyridine, often a useful phosphorylation catalyst [7]. Its inertness cannot be ascribed to electronic effects as $(CF_3CH_2O)_2P(O)Cl$ reacted readily with diethylamine; the pK_a of CF_3CH_2OH is 12.4 compared to that of $(CH_3)_2CF_3COH$ which is 11.6 [14]. It must therefore be a purely steric phenomenon. Although the hexafluoroisopropyl group is more electronegative than the 2-(trifluoromethyl)-2-propyl group, the latter is probably larger in size.

Bis(trifluoroethyl) phosphoramidates **7a–e**, **8a–e** and **9a–d** are the first to have been prepared that contain secondary and tertiary fluoro-ester groups. Physical data appear in Tables 5 and 6. Their phosphorus chemical shifts in deuterated chloroform are between −0.3 and 9.7 ppm.

2.4. Some physical properties of bis(fluoroalkyl) phosphoramidates

Previously it was shown that the boiling points (bps) of fluoroalkyl phosphoryl compounds depend on the location of the fluoroalkyl groups [15]. Fluoroalkyl molecules often boil at lower temperatures than their unfluorinated counterparts despite their higher molecular weights (M_ws), but sometimes boil at higher temperatures due to hydrogen-fluorine bonding. This unpredictability is shared by the bis(fluoroalkyl) phosphoramidates whose bps and melting points (mps) follow no simple trend. Whereas, phosphoramidates **4**, **5a** and **7a** melt at lower temperatures than their

Table 5
Experimental data for phosphoramidates $(R_FO)_2P(O)R$

Compound	R	Bp (°C/mmHg)[a]	Mp (°C)
$R_F = (CF_3)_2CH$	Bis(hexafluoroisopropyl) phosphoramidates		
7a	NH_2	85/1	32–33
7b	NHMe	–	84
7c	NMe_2	30/0.02	–
7d	NHEt	66/0.015	50
7e	NEt_2	45/0.015	–
$R_F = (FCH_2)_2CH$	Bis(difluoroisopropyl) phosphoramidates		
8a	NH_2	90/0.015	–
8b	NHMe	92/0.03	34
8c	NMe_2	69/0.02	–
8d	NHEt	85/0.015	–
8e	NEt_2	72/0.015	–
$R_F = (CH_3)_2CF_3C$	Bis(trifluoro-*t*-butyl) phosphoramidates		
9a	NH_2	–	148
9b	NHMe	–	79
9c	NMe_2	38/0.015	–
9d	NHEt	–	58

[a] Approximate oven temperatures for bulb-to-bulb distillations are quoted.

Table 4
Spectroscopic data for bis(fluoroalkyl) phosphoramidates $(R_FCH_2O)_2P(O)R$ **4**, **5a–e** and **6a–e** (NMR data measured in $CDCl_3$)

Compound[a]	^{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 (%)
4 (M_w 261)	4.34 (4H, qdd, J = 3, 8, 15, OCH_2), 3.65 (2H, d, J = 5, NH_2)	122.4 (dq, J = 10, 277, CF_3), 62.4 (dq, J = 4, 38, OCH_2)	−84.6 (6F, m, CF_3)	9.2	1568, 1458, 1423, 1290, 1254, 1174, 1113, 1078, 964, 879	Calcd. for $C_4H_6F_6NO_3P$: C, 18.4; H, 2.3; F, 43.7; N, 5.4. Found: C, 18.4; H, 2.1; F, 43.5; N, 5.2.
5a (M_w 361)	4.38 (4H, m, OCH_2), 3.52 (2H, m, NH_2)	116.4 (tq, J = 36, 289, CF_3), 113 (dq, J = 8, 256, CF_2), 62.4 (dt, J = 4, 29, OCH_2)	−124.3 (4F, m, CF_2), −83.2 (6F, m, CF_3)	8.7	1564, 1460, 1377, 1356, 1201, 1165, 1111, 1072, 1030, 956, 935, 877	Calcd. for $C_6H_6F_{10}NO_3P$: C, 19.9; H, 1.7; F, 52.6; N, 3.9. Found: C, 20; H, 1.5; F, 52.7; N, 3.8.
5b (M_w 375)	4.42 (4H, dt, J = 7, 12, OCH_2), 3.01 (1H, m, NH), 2.65 (3H, dd, J = 6, 12, NCH_3)	117.2 (tq, J = 35, 288, CF_3), 112.4 (dq, J = 8, 259, CF_2), 61.8(dt, J = 4, 29, OCH_2), 27.4 (s, CH_3)	−123.6 (4F, m, CF_2), −82.5 (6F, m, CF_3)	8.7	1377, 1356, 1263, 1203, 1157, 1111, 1070, 1028, 958, 903, 872, 808	Calcd. for $C_7H_8F_{10}NO_3P$: C, 22.4; H, 2.1; F, 50.7; N, 3.7. Found: C, 22.2; H, 2.1; F, 50.7; N, 3.5.
5c (M_w 389)	4.42 (4H, dt, J = 7, 13, OCH_2), 2.81 (6H, d, J = 11, NCH_3)	118.6 (tq, J = 34, 287, CF_3), 112 (dq, J = 9, 256, CF_2), 62 (dt, J = 5, 29, OCH_2), 36.3 (d, J = 3, NCH_3)	−123.7 (4F, m, CF_2), −82.6 (6F, m, CF_3)	9.4	1489, 1460, 1408, 1375, 1356, 1321, 1273, 1205, 1155, 1111, 1066, 1028, 1009, 937, 874	Calcd. For $C_8H_{10}F_{10}NO_3P$: C, 24.7; H, 2.6; F, 48.8; N, 3.6. Found: C, 24.6; H, 2.6; F, 48.6; N, 3.4.
5d (M_w 389)	4.42 (4H, dt, J = 7, 13, OCH_2), 3.2 (1H, m, NH), 3.0 (2H, dd, J = 7, 11, NCH_2), 1.19 (3H, dd, J = 1, 7, CH_3)	116.9 (m, CF_3), 112.2 (m, CF_2), 63.1 (dt, J = 4, 29, OCH_2), 36.7 (d, J = 2, NCH_2), 17.7 (d, J = 7, CH_3)	−124.3 (4F, m, CF_2), −83.2 (6F, m, CF_3)	7.7	1564, 1457, 1343, 1203, 1157, 1120, 1072, 1028, 960, 874	Calcd. for $C_8H_{10}F_{10}NO_3P$: C, 24.7; H, 2.6; F, 48.8; N, 3.6. Found: C, 24.6; H, 2.4; F, 48.7; N, 3.6.
5e (M_w 417)	4.38 (4H, dt, J = 7, 13, OCH_2), 3.14 (4H, dq, J = 7, 12, NCH_2), 1.11 (6H, d, J = 7, CH_3)	116.5 (tq, J = 36, 287, CF_3), 111.8 (dq, J = 7, 256, CF_2), 62.1 (dt, J = 4, 5, OCH_2), 38.7 (d, J = 4, NCH_2), 13.9 (d, J = 2, CH_3)	−124.2 (4F, m, CF_2), −83.2 (6F, m, CF_3)	8.7	1568, 1428, 1378, 1340, 1207, 1163, 1028, 957, 906, 690, 526, 401	Calcd. for $C_{10}H_{14}F_{10}NO_3P$: C, 28.8; H, 3.6; F, 45.6; N, 3.4. Found: C, 28.9; H, 3.6; F, 45.4; N, 3.1.
6a (M_w 461)	4.47 (4H, m, OCH_2), 3.52 (2H, d, J = 6, NH_2)	107–120 (complex m, C_3F_7), 62.1 (dt, J = 4, 28, OCH_2)	−126.7 (4F, m, CF_2), −120.8 (4F, m, CF_2), −80.1 (6F, t, J = 11, CF_3)	8.9	1560, 1458, 1408, 1356, 1228, 1184, 1126, 1082, 1016, 966, 926, 876	Calcd. for $C_8H_6F_{14}NO_3P$: C, 20.8; H, 1.3; F, 57.7; N, 3. Found: C, 20.6; H, 1.2; F, 57.4; N, 2.7.
6b (M_w 475)	4.46 (4H, m, OCH_2), 3.22 (1H, m, NH), 2.65 (3H, dd, J = 6, 13, CH_3)	108–121 (complex m, C_3F_7), 62.4 (dt, J = 4, 29, OCH_2), 27.6 (m, CH_3)	−126.7 (4F, m, CF_2), −120.7 (4F, m, CF_2), −80.0 (6F, t, J = 11, CF_3)	8.9	1431, 1356, 1300, 1230, 1186, 1128, 1082, 1016, 966, 928, 872	Calcd. for $C_9H_8F_{14}NO_3P$: C, 22.7; H, 1.7; F, 56; N, 2.9. Found: C, 22.7; H, 1.6; F, 55.6; N, 2.8.
6c (M_w 489)	4.41 (4H, m, OCH_2), 2.72 (6H, d, J = 11, CH_3)	108–121 (complex m, C_3F_7), 61.6 (dd, J = 4, 28, OCH_2), 36.3 (d, J = 4, CH_3)	−126.7 (4F, m, CF_2), −120.7 (4F, m, CF_2), −80.1 (6F, t, J = 13, CF_3)	9.5	1489, 1460, 1408, 1348, 1321, 1228, 1186, 1130, 1074, 1007, 966, 926	Calcd. for $C_{10}H_{10}F_{14}NO_3P$: C, 24.5; H, 2; F, 54.4; N, 2.9. Found: C, 24.6; H, 1.9; F, 54.3; N, 2.7.
6d (M_w 489)	4.46 (4H, m, OCH_2), 3.33 (1H, m, NH), 3.01 (2H, dd, J = 7, 11, CH_2), 1.18 (3H, dt, J = 1, 7, CH_3)	108–121 (complex m, C_3F_7), 62.3 (dd, J = 3, 28, OCH_2), 36.3 (m, CH_2), 16.9 (d, J = 7, CH_3)	−126.7 (4F, m, CF_2), −120.7 (4F, m, CF_2), −80.1 (6F, t, J = 13, CF_3)	8.0	1460, 1442, 1356, 1230, 1186, 1128, 1082, 1016, 968, 928, 874	Calcd. for $C_{10}H_{10}F_{14}NO_3P$: C, 24.5; H, 2; F, 54.4; N, 2.9. Found: C, 24.6; H, 2.1; F, 54.4; N, 2.9.
6e (M_w 517)	4.37 (4H, m, OCH_2), 3.11 (4H, dq, J = 7, 13, CH_2), 1.14 (6H, t, J = 7, CH_3)	108–120 (complex m, C_3F_7), 61.9 (dd, J = 4, 28, OCH_2), 39.8 (d, J = 5, CH_2), 14.2 (d, J = 7, CH_3)	−126.7 (4F, m, CF_2), −120.6 (4F, m, CF_2), −80 (6F, m, CF_3)	8.9	1458, 1387, 1350, 1228, 1184, 1130, 1074, 1039, 1016, 966, 926, 868	Calcd. for $C_{12}H_{14}F_{14}NO_3P$: C, 27.9; H, 2.7; F, 51.5; N, 2.7. Found: C, 27.8; H, 2.6; F, 51.2; N, 2.6.

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

Table 6
Spectroscopic data for bis(fluoroalkyl) phosphoramidates $(R_FO)_2P(O)R$ (NMR data measured in $CDCl_3$)

Compound[a]	^{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 (%)
7a (M_w 397)	5.08 (2H, m, OCH), 3.94 (2H, d, J = 8, NH_2)	120.1 (dq, J = 5, 288, CF_3), 71.2 (dsep, J = 4, 35, OCH)	−73.9 (12F, br d, J = 59, CF_3)	9.7	1558, 1458, 1383, 1236, 1207, 1111, 937, 901, 877, 833	Calcd. for $C_6H_4F_{12}NO_3P$: C, 18.1; H, 1; F, 57.4; N, 3.5. Found: C, 17.9; H, 0.9; F, 57.3; N, 3.4.
7b (M_w 411)	5.2 (2H, m, OCH), 2.68 (3H, d, J = 13, CH_3), 2.58 (1H, m, NH)	121.5 (dq, J = 4, 281, CF_3), 70.3 (dsep, J = 4, 35, OCH), 27.1 (m, CH_3)	−73.3 (12F, br d, J = 38, CF_3)	9.5	1439, 1383, 1358, 1298, 1275, 1205, 1188, 1107, 904, 874	Calcd. for $C_7H_6F_{12}NO_3P$: C, 20.4; H, 1.5; F, 55.5; N, 3.4. Found: C, 20.1; H, 1.3; F, 55.4; N, 3.3.
7c (M_w 425)	5.0 (2H, m, OCH), 2.76 (6H, d, J = 11, CH_3)	120.7 (dq, J = 9, 274, CF_3), 71.4 (dsep, J = 4, 31, OCH), 37 (m, CH_3)	−73.2 (12F, br d, J = 37, CF_3)	9.4	1489, 1460, 1371, 1329, 1300, 1265, 1234, 1201, 1130, 1113, 1090, 1009, 899	Calcd. for $C_8H_8F_{12}NO_3P$: C, 22.6; H, 1.9; F, 53.6; N, 3.3. Found: C, 22.5; H, 1.9; F, 53.3; N, 3.1.
7d (M_w 425)	5.2 (2H, m, OCH), 3.02 (2H, m, CH_2), 2.63 (1H, m, NH), 1.17 (3H, dd, J = 1, 7, CH_3)	122.2 (ddq, J = 4, 282, 290, CF_3), 70.5 (m, OCH), 36.1 (m, CH_2), 17.5 (d, J = 7, CH_3)	−73.2 (12F, br d, J = 39, CF_3)	9.2	1441, 1381, 1294, 1194, 1111, 985, 877	Calcd. for $C_8H_8F_{12}NO_3P$: C, 22.6; H, 1.9; F, 53.6; N, 3.3. Found: C, 22.5; H, 1.9; F, 53.3; N, 3.1.
7e (M_w 453)	5.03 (2H, m, OCH), 3.17 (4H, dq, J = 7, 13, CH_2), 1.18 (6H, t, J = 7, CH_3)	120.2 (dq, J = 4, 277, CF_3), 71.5 (dd, J = 4, 36, OCH), 39.8 (d, J = 4, CH_2), 13.7 (d, J = 2, CH_3)	−73.1 (12F, br d, J = 118, CF_3)	9.0	1469, 1371, 1267, 1201, 1113, 1090, 1039, 968	Calcd. for $C_{10}H_{12}F_{12}NO_3P$: C, 26.5; H, 2.6; F, 50.3; N, 3.1. Found: C, 26.5; H, 2.5; F, 50; N, 2.8.
8a (M_w 253)	4.72 (2H, complex m, OCH), 4.61 (8H, m, FCH_2), 3.34 (2H, m, NH_2)	81.9 and 80.4 (dd, J = 9, 183, FCH_2), 73.9 (dt, J = 6, 21, CO)	−30.9 (2F, dt, J = 17, 46, FCH_2), −30.9 (2F, dt, J = 19, 46, FCH_2)	8.7	1564, 1460, 1412, 1385, 1244, 1103, 1039, 991, 901	Calcd. for $C_6H_{12}F_4NO_3P$: C, 28.5; H, 4.7; F, 30; N, 5.5. Found: C, 28.5; H, 4.7; F, 29.7; N, 5.3.
8b (M_w 267)	4.65 (2H, complex m, OCH), 4.52 (8H, m, FCH_2), 2.78 (1H, m, NH), 2.58 (3H, d, J = 13, NCH_3)	81.9 and 80.4 (dd, J = 9, 183, FCH_2), 73.4 (dt, J = 5, 21, CO), 27.4 (m, $NHCH_3$)	−30.9 (2F, dt, J = 17, 46, FCH_2), −30.9 (2F, dt, J = 18, 46, FCH_2)	8.8	1462, 1427, 1414, 1242, 1103, 1041, 987, 891, 802	Calcd. for $C_7H_{14}F_4NO_3P$: C, 31.5; H, 5.2; F, 28.5; N, 5.2. Found: C, 31; H, 5; F, 28.2; N, 5.1.
8c (M_w 281)	4.7 (2H, complex m, OCH), 4.56 (8H, m, FCH_2), 2.70 (6H, d, J = 11, CH_3)	82.2 and 79.9 (dd, J = 12, 188, FCH_2), 73.1 (dt, J = 6, 21, CO), 36.1 (d, J = 4, CH_3)	−48.2 (2F, dt, J = 17, 46, FCH_2), −46.9 (2F, dt, J = 18, 46, FCH_2)	9.2	1460, 1412, 1315, 1252, 1190, 1105, 1043, 1001, 903, 876, 804	Calcd. for $C_8H_{16}F_4NO_3P$: C, 34.2; H, 5.7; F, 27; N, 5. Found: 34.2; H, 5.6; F, 26.6; N, 4.8.
8d (M_w 281)	4.71 (2H, complex m, OCH), 4.55 (8H, m, FCH_2), 3.47 (2H, q, J = 7, NCH_2), 3.02 (1H, m, NH), 1.18 (3H, t, J = 7, CH_3)	82.0 and 79.9 (dd, J = 10, 177, FCH_2), 73.1 (dt, J = 6, 21, CO), 36.2 (s, CH_2), 16.6 (d, J = 7, CH_3)	−48.1 (2F, dt, J = 19, 46, FCH_2), −46.9 (2F, dt, J = 21, 48, FCH_2)	7.8	1639, 1460, 1439, 1383, 1360, 1242, 1107, 1043, 987, 903, 879, 802	Calcd. for $C_8H_{16}F_4NO_3P$: C, 34.2; H, 5.7; F, 27; N, 5. Found: C, 34.1; H, 5.5; F, 26.6; N, 4.8.
8e (M_w 309)	4.71 (2H, complex m, OCH), 4.56 (8H, m, FCH_2), 3.12 (4H, dt, J = 7, 12, NCH_2), 1.12 (6H, t, J = 7, CH_3)	82.1 and 79.9 (dd, J = 10, 177, FCH_2), 72.9 (dt, J = 6, 21, CO), 39.4 (d, J = 4, CH_2), 13.5 (d, J = 2, CH_3)	−48.3 (2F, dt, J = 16, 46, FCH_2), −46.9 (2F, dt, J = 19, 45, FCH_2)	8.8	1466, 1385, 1300, 1255, 1213, 1176, 1105, 1039, 970, 901, 874	Calcd. for $C_{10}H_{20}F_4NO_3P$: C, 38.8; H, 6.5; F, 24.6; N, 4.5. Found: C, 38.7; H, 6.5; F, 24.5; N, 4.3.
9a (M_w 317)	3.1 (2H, s, NH_2), 1.7 (12H, d, J = 16, CH_3)	125.5 (dq, J = 10, 289, CF_3), 80.4 (dq, J = 5, 31, CO), 20.9 (m, CH_3)	−83.2 (6F, m, CF_3)	−0.9	1568, 1475, 1398, 1335, 1246, 1165, 1130, 1003, 931, 908, 810	Calcd. for $C_8H_{14}F_6NO_3P$: C, 30.3; H, 4.4; F, 36; N, 4.4. Found: C, 30.1; H, 4.4; F, 35.5; N, 4.2.
9b (M_w 331)	2.94 (1H, s, NH), 2.5 (3H, dd, J = 6, 13, CH_3), 1.58 (12H, d, J = 6, CH_3)	124.9 (dq, J = 13, 283, CF_3), 80.5 (dq, J = 6, 30, CO), 27.1 (d, J = 2, CH_3), 21.3 (m, CH_3)	−83.9 (6F, m, CF_3)	−0.7	1478, 1460, 1425, 1397, 1378, 1333, 1249, 1231, 1164, 1143, 1108, 1035, 1002, 932, 911	Calcd. for $C_9H_{16}F_6NO_3P$: C, 32.6; H, 4.8; F, 34.4; N, 4.2. Found: C, 32.5; H, 4.6; F, 34.2; N, 4.1.
9c (M_w 345)	2.64 (6H, d, J = 11, NCH_3), 1.64 (12H, d, J = 7, CH_3)	122.2 (dq, J = 13, 278, CF_3), 77.4 (dq, J = 6, 31, CO), 32.9 (m, CH_3), 18.4 (d, J = 51, NCH_3)	−83.3 (6F, m, CF_3)	−0.3	1475, 1398, 1335, 1267, 1167, 1130, 997, 928, 804	Calcd. for $C_{10}H_{18}F_6NO_3P$: C, 34.8; H, 5.2; F, 33; N, 4.1. Found: C, 34.8; H, 5.1; F, 33.1; N, 4.
9d (M_w 345)	2.94 (4H, dq, J = 7, 11, NCH_2), 1.68 (12H, d, J = 11, CH_3), 1.13 (6H, dt, J = 1, 7, CH_3)	124.9 (dq, J = 13, 286, CF_3), 80.8 (dq, J = 5, 31, CO), 36.6 (m, NCH_2), 21.4 (d, J = 29, CH_3), 16.4 (d, J = 7, CH_3)	−83.3 (6F, m, CF_3)	−1.7	1604, 1458, 1425, 1396, 1377, 1333, 1284, 1244, 1163, 1142, 1001, 964, 926, 858	Calcd. for $C_{10}H_{18}F_6NO_3P$: C, 34.8; H, 5.2; F, 33; N, 4.1. Found: C, 34.5; H, 5.1; F, 32.9; N, 3.9.

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

Table 7
Mp data for dialkyl phosphoramidates of structure $(RO)_2P(O)NH_2$

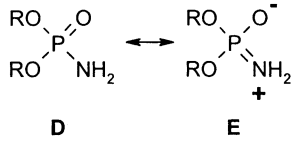
Group	Compound	R	Mp (°C)	References
Ethyl	**4**	CF_3CH_2	42–43	–
		CH_3CH_2	50–51	[16]
Propyl	**5a**	$C_2F_5CH_2$	35	–
		$C_2H_5CH_2$	39–42	[17]
Isopropyl	**7a**	$(CF_3)_2CH$	32–33	–
		$(CH_3)_2CH$	56–57	[16]
t-Butyl	**9a**	$(CH_3)_2CF_3CO$	148	–
		$(CH_3)_2CH_3CO$	122–125	[18]

unfluorinated counterparts, phosphoramidate **9a** melts at a higher temperature than its counterpart (Table 7). Factors affecting the mps of fluorinated phosphoramidates are the size of the fluoro-ester groups, which affect packing in the solid state, and hydrogen-fluorine bonding (intermolecular associations between C–F. . .H–C or C–F. . .H–N are only vaguely understood).

The relationship between bp and amido groups is clear, the bp decreasing in the order $–NH_2 > NHR > NR_2$ due to intermolecular hydrogen bonding, as noted before [15].

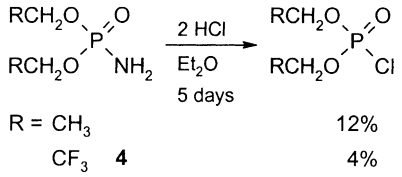
2.5. Acid hydrolysis studies

In phosphoramidates, overlap of the p-π electrons of nitrogen with the vacant *d* orbitals of phosphorus produces complex bonding. Electron-donating alkyl substituents such as ethyl groups favour resonance hybrid **D**. Electron-withdrawing alkyl substituents such as trifluoroethyl groups favour resonance hybrid **E**; here increased back-bonding from the lone pair on nitrogen reduces its basicity, explaining the easier acid hydrolysis of $(CH_3CH_2O)_2P(O)NMe_2$ compared to $(CF_3CH_2O)_2P(O)NMe_2$ [7].



D **E**

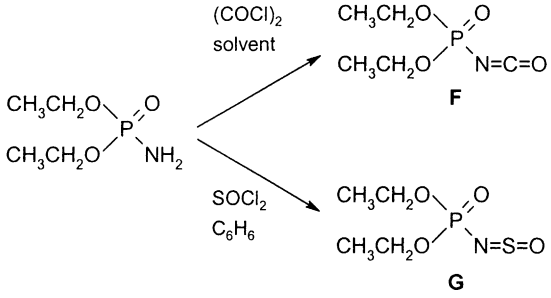
Phosphoramidates $(RO)_2P(O)NR_2$ sometimes react with an excess of anhydrous hydrogen chloride to form dialkyl phosphorochloridates $(RO)_2P(O)Cl$ [19]. The mechanism initially involves protonation of the amino function. Attack by chloride ion on the phosphorus atom then liberates ammonia which is intercepted by extra hydrogen chloride. Ammonium chloride precipitates from the reaction mixture and ensures that the process is irreversible. Earlier we showed that $(EtO)_2P(O)NMe_2$ underwent 87% conversion to $(EtO)_2P(O)Cl$ in 5 days at room temperature when treated with two molar equivalents of HCl in ether; $(CF_3CH_2O)_2P(O)NMe_2$ under identical conditions remained intact [7]. The contrast in reactivity is due to electronic differences between the two phosphoramidates. It was of interest to examine the effect of replacing the dimethylamino group with the less electron-donating amino group (this should retard hydrolysis). Treatment of diethyl phosphoramidate and bis(trifluoroethyl) phosphoramidate **4** with two molar equivalents of HCl gave, after 5 days at room temperature, low conversion to the phosphorochloridates.



It follows from these experiments and previous ones [7] that the reaction of phosphoramidates with hydrogen chloride depends greatly on the groups on the phosphorus and nitrogen atoms. The substituents on phosphorus may be placed in the following sequence $CH_3CH_2O > CF_3CH_2O$, while those on nitrogen may be placed in the order Me > H, according to their ability to facilitate hydrolysis. As a general rule, electron-withdrawing groups on either phosphorus or nitrogen reduce the basicity of the nitrogen atom and suppress acidolysis.

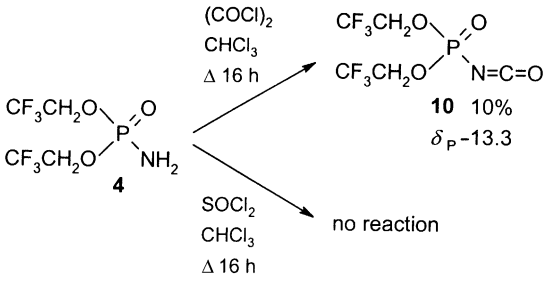
2.6. The behaviour of bis(trifluoroethyl) phosphoramidate to selected electrophiles

Dialkyl phosphoramidates react with oxalyl chloride in the presence of base, e.g. pyridine or triethylamine, to give phosphoroisocyanidates **F** [20,21]. They also react with thionyl chloride to give phosphoro(thionylamidates) **G** [22].



Compared to their unfluorinated analogues, bis(fluoroalkyl) phosphoramidates contain a much less nucleophilic amino group for reasons already discussed. We decided to check if the amino group was sufficiently nucleophilic to combine with oxalyl or thionyl chloride. Prolonged heating of amidate **4** with oxalyl chloride in chloroform gave bis(trifluoroethyl) phosphoroisocyanidate **10**. It was isolated

in low yield as a colourless liquid (bp 34 °C/0.02 mmHg). The infrared spectrum exhibited bands at 2293 cm^{-1} for stretching of the NCO group, at 1423–1500 cm^{-1} for its symmetrical vibration, and at 574 cm^{-1} for its deformation [23]. The C=O stretch appeared at 1712 cm^{-1}.

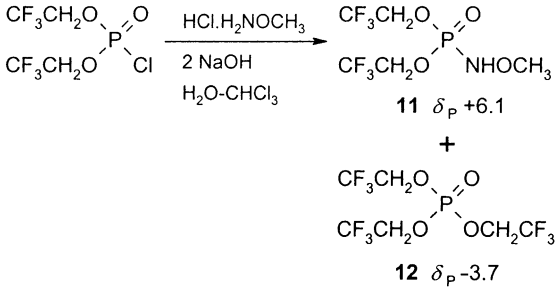


The analogous reaction with thionyl chloride did not occur, further confirming the deactivating effect of fluoroester groups on nucleophilic sites attached to phosphorus.

2.7. Reaction of bis(trifluoroethyl) phosphorochloridate with methoxyamine in a two-phase system

While exploring the chemistry of bis(fluoroalkyl) phosphorochloridates, it became evident they phosphorylate amines more readily than alcohols or thiols. This is in accord with the known behaviour of dialkyl phosphorochloridates towards nucleophiles where the selectivity of phosphorylation decreases in the order $RNH_2 > ROH > RSH$. With primary amines, *N*-phosphorylation can take place exclusively in the presence of a primary alcohol [24,25]. It might be possible for organic solutions of dialkyl phosphorochloridates to react with aqueous solutions of nitrogen nucleophiles, and this would be of great utility. However, this process is not used much as dialkyl phosphorochloridates are reasonably water-soluble and often easily hydrolysed to phosphoric acids $(RO)_2P(O)OH$ and/or pyrophosphates $(RO)_2P(O)OP(O)(OR)_2$. The latter can be appreciably toxic and their accidental formation is best avoided.

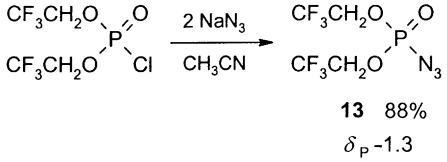
The use of bis(fluoroalkyl) phosphorochloridates may be more interesting for two reasons. Polyfluorinated ester groups shield such molecules from attack by water, and if hydrolysis does occur, only the acids $(R_FO)_2P(O)OH$ will form [6]; pyrophosphates of structure $(R_FO)_2P(O)$-$P(O)(OR_F)_2$ are not yet known and are unlikely to be stable to moisture. Such reasoning led us to examine a model two-phase system. Treatment of aqueous *O*-methylhydroxylamine with bis(trifluoroethyl) phosphorochloridate in chloroform produced a 9:1 mixture of phosphorylated product **11** and tris(trifluoroethyl) phosphate **12**; the identity of the latter, whose formation is difficult to rationalise, was confirmed by comparison of its analytical data with those of an authentic specimen [26]. The mixture could not be purified by distillation as both products co-distilled.



The *N*-methoxyphosphoramidate is an unusual phosphorus compound and the first such fluorinated species. The unfluorinated equivalents are little known. Two reports claim that diethyl *N*-methoxyphosphoramidate [27] and diphenyl *N*-methoxyphosphoramidate [28] can be prepared by Todd–Atherton reaction of the corresponding phosphite with *O*-methylhydroxylamine. A phase-transfer modification, using methylhydroxylamine hydrochloride, has also been used to obtain $(CH_3CH_2O)P(O)NHOCH_3$ in 78% yield [29]. This, like the fluoro-analogue **11**, is a colourless liquid that is stable at room temperature.

2.8. Reaction of bis(trifluoroethyl) phosphorochloridate with sodium azide

The first phosphorus acid azides were described in 1954 by Schrader [30] and Hartley and Pound [31]. Unlike other organic azides, they are often relatively stable [32]. Diethyl phosphorazidate $(CH_3CH_2O)_2P(O)N_3$, a distillable liquid made by heating a solution of diethyl phosphorochloridate with sodium azide in acetone, was reported in 1967 by Scott et al. [33]. We found that reaction of bis(trifluoroethyl) phosphorochloridate with sodium azide in acetonitrile was complete after 3 h at room temperature. The phosphorazidate **13**, the first example of such a species, was isolated after filtration and removal of solvent as a mobile colourless liquid. It was 97% pure by NMR and gas chromatography–mass spectrometry (GC–MS) analyses. Distillation was not attempted for fear of explosion.



The infrared spectrum of azidate **13** showed a strong azide stretch at 2182 cm^{-1}. The usual range for unfluorinated phosphoryl azides is 2138–2195 cm^{-1} [32]. The azide stretch for diethyl phosphorazidate appears at 2140 cm^{-1} [33]. The large difference of 42 cm^{-1} between the stretches of the fluoro and hydrocarbon analogues is due the much greater electronegativity of the $(CF_3CH_2O)_2P(O)$-fragment. In the chemical ionisation mass spectrum of compound **13**, a major ion $[(CF_3CH_2O)_2PO]^+$ is observed at *m*/*z* 245, arising from loss of the azide group.

3. Conclusion

Bis(fluoroalkyl) phosphorochloridates are highly reactive towards ammonia and primary and secondary aliphatic amines. A range of new bis(fluoroalkyl) phosphoramidates have been obtained whose properties remain largely unexplored. Their nitrogen basicity and nucleophilicity is lower than that of unfluorinated phosphoramidates. The chlorine atom of bis(fluoroalkyl) phosphorochloridates is displaced by *O*-alkylhydroxylamines in a water-chloroform system and this approach may prove useful for substitutions where the nitrogen nucleophile is best handled as a salt. The chemistry of the produced bis(fluoroalkyl) *N*-alkoxyphosphoramidates $(R_FO)_2P(O)NHOR$ awaits exploration. They should undergo some reactions characteristic of unfluorinated analogues, e.g. conversion to *N*-alkoxy-*N*-chlorophosphoramidates $(RO)_2P(O)N(Cl)OR$ by chlorination [29]. The chlorine atom of bis(fluoroalkyl) phosphorochloridates is also replaced by azide ion. Nothing is known about the chemistry of the produced phosphorazidates $(R_FO)_2P(O)N_3$. By analogy with their unfluorinated counterparts [32], they should be capable of a range of useful transformations. These might include addition of trivalent phosphorus reagents (the Staudinger reaction), nucleophilic substitutions where the azide behaves as a pseudohalogen, photolysis to generate the nitrene, and reactions with unsaturated compounds (1,3-dipolar cycloadditions). Research along these lines will surely lead to some interesting and novel phosphorus chemistry.

4. Experimental details

Bis(fluoroalkyl) phosphorochloridates were obtained in high purity using previously reported chemistry [1]. Diethyl phosphoramidate was purchased from Aldrich (Gillingham, UK). All reagents were of commerical quality and were used without extra purification. 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. M_ws of pure products were confirmed with methane +ve CI data (70 eV).

Caution: although no safety problems were encountered during work with methoxyamine hydrochloride or sodium azide, precautions against possible explosions should be implemented when handling the solids, their solutions, and the phosphorus derivatives. A plastic spatula was used when handling sodium azide. The phosphorus compounds may have anticholinesterase activity and should be manipulated with care.

4.1. Reactions with ammonia

This general procedure is illustrated for the synthesis of bis(2,2,2-trifluoroethyl) phosphoramidate **4**. 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(2,2,2-trifluoroethyl) phosphorochloridate (10 g, 35.7 mmol) in ether (50 ml). The flask and the condenser were cooled to −78 °C (dry ice-acetone) and ammonia gas was passed through the T-adaptor and allowed to condense into the solution. An instant precipitate of ammonium chloride was observed. Liquefied ammonia was allowed to drop into the reaction mixture until it was clear that more than two molar equivalents had been added. The ammonia supply was turned off and the flask allowed to warm 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 2 h. The precipitate was filtered off and the filtrate concentrated to yield bis(2,2,2-trifluoroethyl) phosphoramidate **4** as a white crystalline solid (8.5 g, 91%); mp 42–43 °C. Multinuclear NMR analysis indicated 99% purity. In other cases, concentration of the filtrate gave a liquid that was purified by bulb-to-bulb distillation under reduced pressure.

4.2. Reactions with methylamine and ethylamine

These were conducted as described in the previous section but on a smaller scale: bis(fluoroalkyl) phosphorochloridate (5 mmol) in ether (20 ml). After filtration, concentration of the filtrate gave solid or liquid products. The solids were found to be very pure and did not require recrystallisation (this would have only lowered the yields). Liquids were purified by bulb-to-bulb distillation under reduced pressure.

4.3. Reactions with dimethylamine and diethylamine

An excess of chilled dimethylamine was pipetted into a stirred solution of the appropriate bis(fluoroalkyl) phosphorochloridate (5 mmol) in ether (50 ml) at 0–5 °C. After addition, the mixture was kept at this temperature for a further 30 min, then allowed to warm to room temperature; excess dimethylamine evaporated. After 2 h, the precipitated amine hydrochloride salt was removed by filtration. Concentration of the filtrate and bulb-to-bulb distillation of the

residue under reduced pressure gave bis(fluoroalkyl) *N*,*N*-dimethylphosphoramidates as colourless liquids. Similarly, the addition of two molar equivalents of diethylamine (10 mmol) in ether (10 ml) to the phosphorochloridate (5 mmol) in ether (50 ml), and work-up as described above, gave bis(fluoroalkyl) *N*,*N*-diethylphosphoramidates as colourless liquids or white solids. The chloridate $[(CH_3)_2CF_3CO]_2P(O)Cl$ did not react with diethylamine in ether even when heated under reflux for 14 h in the presence of a small amount of 4-dimethylaminopyridine.

4.4. Reactivities of diethyl phosphoramidate and bis(2,2,2-trifluoroethyl) phosphoramidate to hydrogen chloride

A solution of methanol (0.32 g, 10 mmol) and acetyl chloride (0.79 g, 10 mmol) in ether (10 ml) was added drop-wise by cannula to a stirred solution of the phosphoramidate (5 mmol) in ether (25 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature and left to stand. Some ammonium chloride precipitated; its amount increased slowly over time. The reaction was monitored by GC–MS after 2 h and after 5 days. No product was observed after 2 h, but 12% $(CH_3CH_2O)_2P(O)Cl$ and 4% $(CF_3CH_2O)_2P(O)Cl$ had formed after 5 days. The only other materials detected were the unchanged phosphoramidates.

4.5. Synthesis of bis(2,2,2-trifluoroethyl) phosphoroisocyanidate (**10**)

Oxalyl chloride (0.76 g, 6 mmol) in chloroform (25 ml) was added drop-wise to a stirred solution of bis(2,2,2-trifluoroethyl) phosphoramidate (1.68 g, 6 mmol) in chloroform (30 ml) at 0–5 °C. After addition, the mixture was allowed to warm to room temperature and left to stand for 14 h. The mixture was heated under reflux for a further 14 h and the progress of the reaction monitored by GC–MS. After this time, it was evident that the reaction would not progress beyond 76% completion. The solvent was removed. Distillation of the residue in a Kugelrohr apparatus gave the title compound as a moisture-sensitive colourless liquid (0.17 g, 10%). Bp 34 °C/0.02 mmHg. ^{1}H NMR: $\delta = 4.46$ (4H, qdd, $J = 2$, 8 and 15 Hz, OCH_2). ^{13}C NMR: $\delta = 125.1$ (very weak m, NCO), 122.4 (dq, $J = 9$ and 277 Hz, CF_3), 64.2 (dq, $J = 4$ and 39 Hz, OCH_2). ^{19}F NMR: $\delta = -74.9$ (6F, m, CF_3). ^{31}P NMR: $\delta = -13.3$. IR (film): $\nu = 3122, 2293, 1712$ (C=O), 1500, 1423, 1294 (P=O), 1255, 1174, 1093, 964, 928, 844, 654, 574 cm^{-1}. CIMS *m*/*z* (rel. int.): 288 $[M + 1]^+$ (100), 268 $[M - F]^+$ (22). Calcd. for $C_5H_4F_6NO_4P$: C, 20.9; H, 1.4; F, 39.7; N, 4.9. Found: C, 20.9; H, 1.4; F, 39.8; N, 4.9%.

An analogous procedure using thionyl chloride in place of oxalyl chloride was unsuccessful; no conversion to the desired phosphoro(thionylamidate) was detected by GC–MS even after heating the reaction mixture under reflux for 16 h.

4.6. Synthesis of bis(2,2,2-trifluoroethyl) N-methoxyphosphoramidate (**11**)

A solution of bis(2,2,2-trifluoroethyl) phosphorochloridate (2 g, 7.14 mmol) in $CHCl_3$ (10 ml) was added in one portion to a solution of *O*-methylhydroxylamine hydrochoride (0.66 g, 7.85 mmol) and sodium hydroxide (0.63 g, 15.71 mmol) in H_2O (10 ml). The two-phase mixture was stirred vigorously for 3 h. The organic layer was separated, washed with water (2 × 20 ml), dried over Na_2SO_4, filtered and the filtrate concentrated. Bulb-to-bulb distillation of the residue gave a mobile colourless liquid (1.3 g). Multinuclear NMR and mass spectral analyses showed it to be a 1:9 mixture of tris(trifluoroethyl) phosphate $(CF_3CH_2O)_3P{=}O$ and the title compound. The latter has the following spectroscopic data: ^{1}H NMR: $\delta = 7.4$ (1H, br s, NH), 4.4 (4H, complex m, OCH_2), 3.7 (3H, s, OCH_3). ^{13}C NMR: $\delta = 122.7$ (dq, $J = 10$ and 277 Hz, CF_3), 65.2 (d, $J = 5$, OCH_3), 63.5 (dq, $J = 4$ and 38 Hz, OCH_2). ^{19}F NMR: $\delta = -74.5$ (6F, t, $J = 9$ Hz, CF_3). ^{31}P NMR: $\delta = 6.1$. CIMS *m*/*z* (rel. int.): 292 $[M + 1]^+$ (100), 272 $[M - F]^+$ (18).

4.7. Synthesis of bis(2,2,2-trifluoroethyl) phosphorazidate (**13**)

Finely-divided sodium azide (0.93 g, 14.28 mmol) was added in one portion to a stirred solution of bis(2,2,2-trifluoroethyl) phosphorochloridate (2 g, 7.14 mmol) in acetonitrile (30 ml). The suspension was stirred briskly for 3 h. The solids were removed by filtration and the filtrate concentrated to a liquid that still contained a small amount of solid. Further precipitation of solid was induced by the addition of diethyl ether (5 ml). Passage of the resulting solution through a Pasteur pipette containing a small plug of glass wool, and removal of solvent and drying under high vacuum, gave the title compound as a mobile colourless oil (1.8 g, 88%). It was shown to be 97% pure by multinuclear NMR and mass spectral analyses. ^{1}H NMR: $\delta = 4.5$ (4H, qdd, $J = 2.1$, 7.6 and 15.3 Hz, OCH_2). ^{13}C NMR: $\delta = 121.6$ (dq, $J = 9$ and 277 Hz, CF_3), 64.1 (dq, $J = 5$ and 39 Hz, OCH_2). ^{19}F NMR: $\delta = -74.4$ (6F, br m, CF_3). ^{31}P NMR: $\delta = -1.3$. IR (film): $\nu = 2182$ (N_3), 1457, 1422, 1285 (P=O), 1175, 1102, 1075, 964, 898, 842, 764, 660, 600, 559 cm^{-1}. CIMS *m*/*z* (rel. int.): 288 $[M + 1]^+$ (100), 268 $[M - F]^+$ (20), 245 $[M - N_3]^+$ (10). Calcd. for $C_4H_4F_6N_3O_3P$: C, 16.7; H, 1.4; F, 39.7; N, 14.6. Found: C, 16.6; H, 1.2; F, 39.7; N, 14.6%.

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