ELSEVIER

Journal of Fluorine Chemistry 104 (2000) 215–223

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Fluorinated phosphorus compounds Part 1. The synthesis and reactions of some fluoroalkyl phosphoryl compounds

Christopher M. Timperley*, Michael Bird, John F. Broderick, Ian Holden, Ian J. Morton, Matthew J. Waters

Chemical and Biological Defence Sector, Defence Evaluation and Research Agency, Porton Down, Salisbury, Wiltshire SP4 0JQ, UK

Received 16 December 1999; accepted 20 January 2000

Abstract

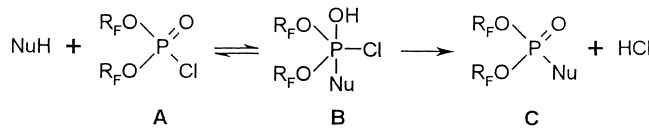
Fluoroalkyl phosphorochloridates $CF_3CH_2OP(O)Cl_2$ and $(R_FCH_2O)_2P(O)Cl$ (R_F=CF_3, C_2F_5) were prepared from phosphorus oxychloride, fluoroalcohols and triethylamine, but selective substitution was difficult. Phosphates $(R_FCH_2O)_2P(O)OR$ (R_F=CF_3, C_2F_5 and R=Me, Et, *n*-Pr, *i*-Pr) were isolated in yields of 38–84% from the reactions of the phosphorochloridates with alcohols and triethylamine. Success of the inverse reaction, *i.e.* $ROP(O)Cl_2$ and R_FCH_2OH, depended on the R group (Me, Et) and the R_F group (CF_3, C_2F_5). The phosphates did not react with bromotrimethylsilane in chloroform. Addition of amines to $CF_3CH_2OP(O)Cl_2$ or $(CF_3CH_2O)_2P(O)Cl$ gave phosphoramidates $(RR'N)_2P(O)OCH_2CF_3$ or $(CF_3CH_2O)_2P(O)NRR'$ (R and R′=H, Me, Et) in yields of 58–75%. The inverse reactions of $Me_2NP(O)Cl_2$ and $(Me_2N)_2P(O)Cl$ with trifluoroethanol were slow, but were catalysed by 4-dimethylaminopyridine. Anhydrous hydrogen chloride split one of the P–N bonds of $(Me_2N)_2P(O)OCH_2CF_3$ to give $Me_2NP(O)Cl(OCH_2CF_3)$, but was without action on $(CF_3CH_2O)_2P(O)NMe_2$.

Keywords: Alkyl bis(fluoroalkyl) phosphate; Bis(fluoroalkyl) phosphorochloridate; Fluoroalcohol; Phosphate; Phosphoramidate

1. Introduction

Although the organic chemistry of phosphorus has been studied for over a century, the possibilities offered by the introduction of fluoroalkyl groups have only just begun to be realised. Indeed, the carbon–fluorine system forms the basis of a new branch of organophosphorus chemistry, paralleling the huge and better-known field arising from carbon and hydrogen. The range of compounds capable of existence is thus enormous, particularly since mixed fluorohydrocarbon species, and their derivatives, are usually stable, and can give rise to vast numbers of isomers, all of which present new challenges. Of particular interest is the selective incorporation of fluoroalkoxy groups into pentavalent phosphorus compounds, which should enhance their phosphorylating ability.

The mechanism of phosphorylation is generally interpreted as a bimolecular displacement proceeding at the phosphorus atom (termed S_N2P) [1]. Nucleophilic attack on bis(fluoroalkyl) phosphorochloridate **A**,[1] for example, gives intermediate **B** which collapses to product **C**. The rate is accelerated by the presence of electronegative substituents in the phosphorochloridate. For example, bis(trifluoroethyl) phosphorochloridate $(CF_3CH_2O)_2P(O)Cl$ is more electrophilic than its unfluorinated counterpart $(CH_3CH_2O)_2P(O)Cl$ (a trifluoroethyl group is more electronegative than an ethyl group: the pK_a of CF_3CH_2OH is 12.4 while that of CH_3CH_2OH is 15.9 [2]).

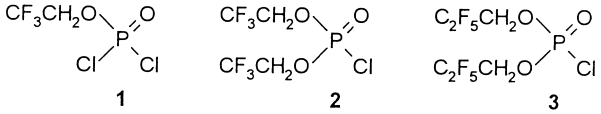


[1] Organic phosphorus compounds are named after the corresponding parent acids. Most compounds described in this paper are derivatives of phosphoric acid $(HO)_3P{=}O$. For example, the acid chloride $(R_FCH_2O)_2P(O)Cl$ is a bis(fluoroalkyl) phosphorochloridate [*i.e.* a diester of phosphorochloridic acid $(HO)_2P(O)Cl$] and the amide $(R_FCH_2O)_2P(O)NMe_2$ is a bis(fluoroalkyl) *N*,*N*–dimethylphosphoramidate [*i.e.* a diester of *N*,*N*–dimethylphosphoramidic acid $(HO)_2P(O)NMe_2$].

* Corresponding author. Tel.: +44-1980-613566; fax: +44-1980-613371.

0022-1139/00/$ – see front matter
PII: S0022-1139(00)00248-7

The rate of substitution also depends on the basicity and size of the nucleophile. While the reactions of alkyl phosphorochloridates have been widely explored, those of fluoroalkyl phosphorochloridates have remained largely uncharted. Previously, we described the synthesis of dialkyl fluoroalkyl phosphates from dialkyl phosphorochloridates and fluoroalcohols [3]. In this paper, the reactions of fluoroalkyl phosphorochloridates **1–3** with some oxygen and nitrogen nucleophiles are reported.



1 **2** **3**

This work is part of a wider study on the effects of fluoroalkyl groups on the physicochemical properties of pentavalent phosphorus compounds. The reactivities of some fluoroalkyl phosphates and phosphoramidates towards electrophiles are also discussed.

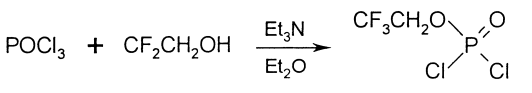
2. Results and discussion

2.1. Synthesis of fluoroalkyl phosphorochloridates

One route to alkyl phosphorodichloridates $ROP(O)Cl_2$ involves alcoholysis of phosphorus oxychloride, with removal of hydrogen chloride by passage of nitrogen through the reactants [4]. This method can be used for fluoroalkyl phosphorodichloridates $R_FOP(O)Cl_2$ only in cases where the fluoroalcohol has few fluorine atoms. One or two molar equivalents of 2-fluoroethanol (pK_a 14.4 [5]) gave $FCH_2CH_2OP(O)Cl_2$ in 34% yield [6] or $(FCH_2CH_2O)_2P(O)Cl$ in 11% yield [7]. Polyfluorinated alcohols, such as trifluoroethanol, do not react under these conditions; the acidity of CF_3CH_2OH (pK_a 12.4) approaches that of phenol (pK_a 10 [2]) and its reactivity parallels that of phenol rather than that of an unfluorinated primary alcohol. A base is required to initiate phosphorylation. Phenol [8] and trifluoroethanol [9] reacted with $POCl_3$ in the presence of pyridine to give mixtures of substitution products, regardless of the ratios of the reactants. The inductive effect of the fluoroalkoxy group is analogous to that of a phenoxy group and predominates in phosphorus compounds.

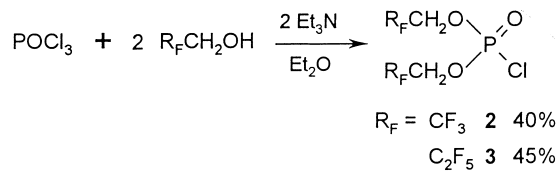
Selective mono or bis substitution of phosphorus oxychloride by fluoroalcohols might be complicated by the formation of polysubstituted by-products. It was, therefore, of interest to examine the reactions of $POCl_3$ with fluoroalcohols in the presence of triethylamine.

An equimolar ratio of phosphorus oxychloride and trifluoroethanol gave mono, bis and tris-substitution products, with dichloridate **1** predominating. The latter was isolated in 95% purity by careful fractionation of the mixture.



1 36%

The use of two molar equivalents of fluoroalcohol gave bis and tris-substitution products, fractionation furnishing monochlorides **2** and **3** in moderate yields.



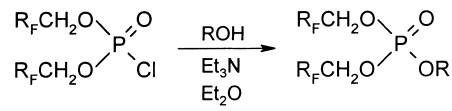
R_F = CF_3 **2** 40%

C_2F_5 **3** 45%

Unlike bis(2-fluoroethyl) phosphorochloridate $(FCH_2CH_2O)_2P(O)Cl$ which rapidly decomposes on standing [7], compounds **2** and **3** are stable when stored in the absence of moisture.

2.2. Synthesis of alkyl bis(fluoroalkyl) phosphates

The first example of an unsymmetrical phosphate bearing a fluoroalkyl group is diethyl 2-fluoroethyl phosphate $(EtO)_2P(O)OCH_2CH_2F$, prepared by Saunders *et al.* in 1945, by the addition of diethyl phosphorochloridate to 2-fluoroethanol and pyridine in ether [10]. Recently, we showed that treatment of dialkyl phosphorochloridates with fluoroalcohols gave related phosphates of structure $(RO)_2P(O)OCH_2R_F$ [3]. A logical extension to this work was to investigate ways of preparing phosphates of structure $(R_FCH_2O)_2P(O)OR$. Accordingly, it was found that treatment of chlorides **2** or **3** with alcohols in the presence of triethylamine afforded the desired phosphates **4–9** in reasonable yields (Table 1).



R_F	
CF_3	**2**
C_2F_5	**3**

R_F	R	
CF_3	Me	**4**
C_2F_5	Me	**5**
CF_3	Et	**6**
C_2F_5	Et	**7**
CF_3	*n*-Pr	**8**
CF_3	*i*-Pr	**9**

Table 1
Experimental data for alkyl bis(fluoroalkyl) phosphates $(R_FCH_2O)_2P(O)OR$[a]

Compound	R_F	R	Yield (%)	Boiling point (°C/mm Hg)
4	CF_3	Me	44	42/0.1
5	C_2F_5	Me	84	43–45/0.06
6	CF_3	Et	60[b]	37/0.01
7	C_2F_5	Et	50[b]	45–46/0.04
8	CF_3	*n*-Pr	70	45/0.015
9	CF_3	*i*-Pr	38	37/0.015

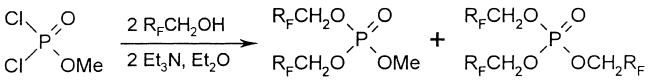
[a] Prepared by addition of an alcohol and triethylamine to the appropriate bis(fluoroalkyl) phosphorochloridate.

[b] Compounds **6** and **7** were also made by addition of the respective fluoroalcohols and triethylamine to ethyl phosphorodichloridate in yields of 52 and 35% respectively.

Table 2
Spectroscopic data for alkyl bis(fluoroalkyl) phosphates $(R_FCH_2O)_2P(O)OR$ (NMR data measured in $CDCl_3$)

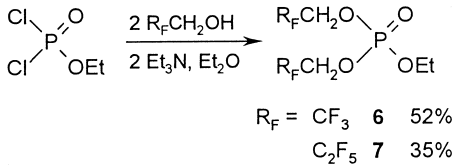
Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν(cm^{-1})	HRMS analysis
4	4.4 (4H, m, OCH_2), 3.88 (3H, d, J=11, OCH_3)	122.2 (dq, J=9, 277, CF_3), 63.9 (dq, J=4, 38, OCH_2), 55.3 (d, J=7, OCH_3)	−74.5 (6F, t, J=8, CF_3)	−2.2	1302 (P=O), 1276, 1178, 1119, 1084, 1056, 965, 877	Calc. $C_5H_7F_6O_3P$ 275.999 ($[M-H]^+$=274.991), found 274.992 (error −3.4)
5	4.48 (4H, br m, OCH_2), 3.87 (3H, d, J=11, OCH_3)	118.1 (tq, J=34, 285, CF_3), 111.3 (tq, J=8, 256, CF_2), 63 (dq, J=5, 38, OCH_2), 55.3 (d, J=7, OCH_3)	−82.9 (6F, qt, J=287, 118, 35, CF_3), −124.1 (4F, t, J=12, CF_2)	−2.4	1460, 1356, 1302 (P=O), 1205, 1159, 1112, 1065, 1032, 937, 885	Calc. $C_7H_7F_{10}O_3P$ 375.992, found 375.993 (error −2.6)
6	4.45 (4H, m, OCH_2CF_3), 4.31 (2H, dq, J=7, OCH_2), 1.38 (3H, t, J=7, CH_3)	121.5 (dq, J=9, 277, CF_3), 65.7 (m, J=7, OCH_2), 63.8 (dq, J=5, 38, OCH_2CF_3), 15.8 (m, J=6, CH_3)	−74.4 (6F, t, J=8, CF_3)	−3.4	1458, 1423, 1374, 1301 (P=O), 1275, 1178, 1117, 1086, 1041, 965, 893, 842	Calc. $C_6H_9F_6O_3P$ 290.014 ($[M-H]^+$=289.006), found 289.007 (error −0.7)
7	4.46 (4H, br m, OCH_2CF_3), 4.23 (2H, dq, J=8, 7, OCH_2), 1.39 (3H, dt, J=1, 7, CH_3)	118 (tq, J=35, 118, 287, CF_3), 111.4 (tq, J=8, 256, CF_2), 65.7 (m, J=7, OCH_2), 62.7 (dt, J=5, 29, OCH_2CF_2), 15.5 (m, J=6, CH_3)	−82.8 (6F, qt, J=287, 118, 35, CF_3), -124 (4F, t, J=12, CF_2)	−3.5	1482, 1460, 1408, 1375, 1355, 1301 (P=O), 1206, 1159, 1111, 1071, 1032, 984, 937, 888	Calc. $C_8H_9F_{10}O_3P$ 390.008 ($[M-H]^+$=389.000), found 388.999 (error 3.2)
8	4.37 (4H, m, OCH_2CF_3), 4.12 (2H, dt, J=7, 7, OCH_2), 1.76 (2H, tq, J=7, CH_2), 0.98 (3H, t, J=7, CH_3)	122.3 (dq, J=9, 277, CF_3), 71 (OCH_2), 63.8 (dq, J=5, 38, OCH_2CF_3), 23.3 (CH_2), 9.7 (CH_3)	−77.0 (6F, t, J=8, CF_3)	−3.3	1300 (P=O), 1274, 1176, 1084, 1057, 1027, 965, 891	Calc. $C_7H_{11}F_6O_3P$ 304.030 ($[M-H]^+$=303.022), found 303.021 (error 4.1)
9	5.8 (1H, dsep, J=7, OCH), 4.35 (4H, m, OCH_2CF_3), 1.4 (6H, d, J=7, CH_3)	122.4 (dq, J=9, 277, CF_3), 75.7 (m, J=6, OCH), 63.8 (dq, J=5, 33, OCH_2), 23.4 (m, J=4, CH_3)	−74.4 (6F, t, J=8, CF_3)	−4.4	1471, 1458, 1424, 1300 (P=O), 1272, 1174, 1123, 1083, 1020, 966, 891, 844	Calc. $C_7H_{11}F_6O_3P$ 304.030 ($[M-H]^+$=303.022), found 303.022 (error −1.2)

An alternative route utilises the reaction between an alkyl phosphorodichloridate and a fluoroalcohol. Treatment of methyl phosphorodichloridate with two equivalents of trifluoroethanol or pentafluoropropanol, however, gave bis phosphates **4** and **5**, in addition to tris phosphates **4a** and **5a**, and the mixtures could not be separated by distillation.



The P–OMe bonds of phosphates **4** and **5** are weakened by the electronegative trifluoroalkyl groups, which enables transesterification by the fluoroalcohols and departure of methanol. The greater nucleophilicity of trifluoroethanol compared to pentafluoropropanol may account for the greater proportion of **4a** over **5a** in the mixtures.

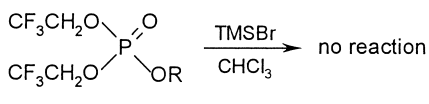
With ethyl phosphorodichloridate, unsymmetrical phosphates **6** and **7** formed exclusively. The P–OEt bond is generally stronger than the P–OMe bond, and consequently, the ethyl phosphates are not attacked by fluoroalcohols.



The structures of phosphates **4–9** were established by multinuclear NMR and infrared spectroscopy and by high resolution mass spectrometry (Table 2). The frequencies of the P=O infrared vibrations decrease as the electronegativity of the substituents attached to the phosphorus atom decreases [11]. For example: $(CF_3CH_2O)_2P(O)OEt$ **6** (1301 cm^{-1})>$(EtO)_2P(O)OCH_2CF_3$ (1271 cm^{-1})>$(EtO)_3$-P=O (1264 cm^{-1}) [3].

2.3. Reactivities of alkyl bis(trifluoroethyl) phosphates towards bromotrimethylsilane

Previously we showed that dialkyl trifluoroethyl phosphates $(RO)_2P(O)OCH_2CF_3$ reacted with bromotrimethylsilane (TMSBr) to give the silylated esters RO(TMSO)P(O)OCH_2CF_3 and $(TMSO)_2P(O)OCH_2CF_3$ (R=Me, Et) [3]. The mechanism was postulated as attack of the alkoxy oxygen atom on the silicon atom of TMSBr, followed by loss of alkyl bromide. Electronegative fluoroalkyl groups on phosphorus should decrease the nucleophilicity of the alkoxy groups in unsymmetrical phosphates, lowering their reactivity to TMSBr. It was, therefore, no surprise that phosphates **4** and **6** were not silylated even on refluxing for several hours in chloroform.

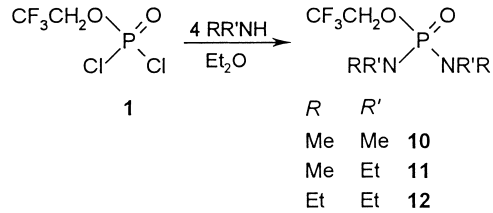


This lack of reactivity provides further evidence that the reaction of bromotrimethylsilane with fluoroalkyl phosphates is mediated through attack of the OR group rather than the P=O group (attack by the phosphoryl group occurs with unfluorinated phosphates [12]).

2.4. Synthesis of fluoroalkyl phosphoramidates

Amines are more basic than alcohols and tend to phosphorylate more readily. The synthesis of phosphorus amides from alkyl phosphorochloridates is well documented [13–15], but their preparation from fluoroalkyl phosphorochloridates is restricted to a few compounds [9,16]. In this study, the reactions of trifluoroethyl phosphorodichloridate and bis(trifluoroethyl) phosphorochloridate with various aliphatic amines were examined.

Treatment of dichloride **1** with secondary amines gave phosphorodiamidates **10–12** in yields of 58–70% (Table 3). The reaction rate depended on the size of the amine and decreased in the order Me_2NH>MeEtNH>Et_2NH.



Similarly, monochloride **2** combined with primary and secondary amines to give phosphoramidates **13–16** in yields of 66–75% (Table 3).

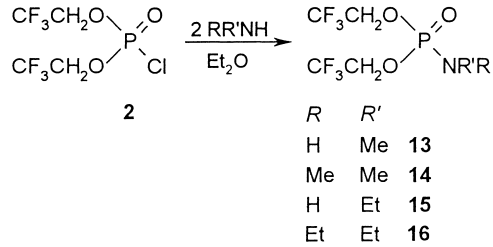


Table 3
Experimental data for the fluoroalkyl phosphoramidates[a]

Compound	R	R′	Yield (%)	Boiling point (°C/mm Hg)
Compounds of general formula $(RR'N)_2P(O)OCH_2CF_3$				
10	Me	Me	70[b]	44/0.4
11	Me	Et	63	68/1
12	Et	Et	58	82/0.06
Compounds of general formula $(CF_3CH_2O)_2P(O)NRR'$				
13	H	Me	68	84–86/1
14	Me	Me	70[b]	37/0.5
15	H	Et	66	96/0.1
16	Et	Et	75	62/1

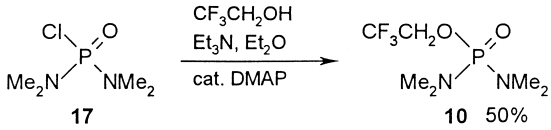
[a] Prepared by addition of amines to trifluoroethyl phosphorodichloridate.

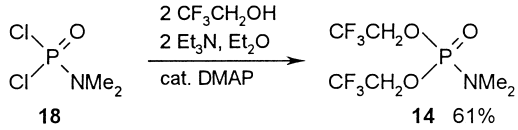
[b] Compounds **10** and **14** were also made by DMAP-catalysed addition of trifluoroethanol to the respective phosphoramidic chlorides in yields of 50 and 61%, respectively.

Table 4
Spectroscopic data for fluoroalkyl phosphoramidates (NMR data measured in $CDCl_3$)

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ, J (Hz)	^{19}F NMR δ, J (Hz)	^{31}P NMR δ	IR ν (cm^{-1})	HRMS analysis
10	4.25 (2H, dq, J=9, 6, OCH_2), 2.67 (12H, d, J=10, NCH_3)	122.7 (dq, J=11.2, 277, CF_3), 61.9 (dq, J=3, 37, OCH_2), 36.1 (NCH_3)	−74.3 (3F, t, J=8, CF_3)	19.7	1460, 1288 (P=O), 1223, 1169, 1095, 1071, 992, 964, 858	Calc. $C_6H_{14}F_3N_2O_2P$ 234.075, found 234.075 (error −3.7)
11	4.23 (2H, dq, J=9, 7, OCH_2), 3.05 (4H, dq, J=10, 6, NCH_2), 2.64 (6H, d, J=10, NCH_3), 1.13 (6H, t, J=7, CH_3)	123.3 (dq, J=11.2, 277, CF_3), 61.7 (dq, J=3, 37, OCH_2), 43.5 (NCH_2), 32.7 (NCH_3), 13.5 (CH_3)	−74.1 (3F, t, J=8, CF_3)	18.7	1655, 1458, 1419, 1383, 1346, 1288 (P=O), 1244, 1209, 1171, 1095, 1014, 962, 937, 856	Calc. $C_8H_{18}F_3N_2O_2P$ 262.106, found 262.107 (error −5.7)
12	4.25 (2H, dq, J=9, 6, OCH_2), 3.11 (8H, dq, J=7, 9, NCH_2), 1.11 (12H, t, J=7, CH_3)	123.3 (dq, J=11, 277, CF_3), 61.3 (dq, J=3, 37, OCH_2), 39.5 (NCH_2), 14 (CH_3)	−74.7 (3F, t, J=8, CF_3)	18.0	1466, 1382, 1288 (P=O), 1239, 1212, 1167, 1096, 1077, 1028, 962, 941, 832	Calc. $C_{10}H_{22}F_3N_2O_2P$ 290.137, found 290.137 (error 0.6)
13	4.32 (4H, dq, J=8, 9, OCH_2), 3.76 (1H, br, NH), 2.6 (3H, dd, J=6, 13, NCH_3)	122.5 (dq, J=10, 277, CF_3), 62.5 (dq, J=4, 38, OCH_2), 27.1 ($NHCH_3$)	−75.1 (6F, t, J=8, CF_3)	9.4	1458, 1423, 1290 (P=O), 1252, 1174, 1078, 964, 879, 795	Calc. $C_5H_8F_6NO_3P$ 275.015, found 275.013 (error 5.9)
14	4.32 (4H, dq, J=8, 9, OCH_2), 2.71 (6H, d, J=11, NCH_3)	122.7 (dq, J=10, 277, CF_3), 62.9 (dq, J=5, 38, OCH_2), 36.4 (d, J=4, NCH_3)	−74.6 (6F, t, J=8, CF_3)	9.7	1420, 1296 (P=O), 1258, 1174, 1110, 1074, 1008, 965, 877	Calc. $C_6H_{10}F_6NO_3P$ 289.030, found 289.029 (error 4.1)
15	4.32 (4H, dq, J=8, 9, OCH_2), 3.5 (1H, m, NH), 3.01 (2H, m, NCH_2), 1.17 (3H, dt, J=1, 7, CH_3)	122.7 (dq, J=10, 277, CF_3), 62.9 (dq, J=4, 38, OCH_2), 36.5 (NCH_2), 16.9 (CH_3)	−74.4 (6F, t, J=8, CF_3)	8.3	1456, 1423, 1288 (P=O), 1250, 1174, 1078, 964, 879, 812	Calc. $C_6H_{10}F_6NO_3P$ 289.030, found 289.029 (error 5.8)
16	4.29 (4H, dq, J=8, 9, OCH_2), 3.12 (4H, dq, J=7, NCH_2), 1.13 (6H, t, J=7, CH_3)	122.6 (dq, J=11, 277, CF_3), 62.6 (dq, J=3, 38, OCH_2), 39.8 (d, J=5, NCH_2), 13.8 (d, J=3, CH_3)	−74.8 (6F, t, J=8, CF_3)	9.0	1456, 1423, 1387, 1294 (P=O), 1261, 1215, 1171, 1111, 1074, 1039, 966	Calc. $C_8H_{14}F_6NO_3P$ 317.062, found 317.061 (error 1.6)

Fluoroalkyl phosphoramidates can also be synthesised from dialkylphosphoramidic chlorides, fluoroalcohols and triethylamine. Without a catalyst, the reaction is slow or does not take place at all. However, a catalytic amount of 4-dimethylaminopyridine (DMAP) facilitated the reaction of chlorides **17** and **18** with trifluoroethanol, enabling phosphoramidates **10** and **14** to be isolated in modest yields.

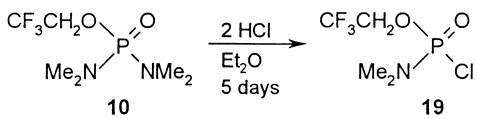




Compounds **10–16** are mobile colourless liquids (Table 3) that were fully characterised by the usual techniques (Table 4). The phosphoramidates have particularly characteristic carbon NMR spectra, the trifluoromethyl carbon appearing at around δ 120 as a doublet of quartets with coupling constants of about 10 and 280 Hz, corresponding to $^{3}J_{CP}$ and $^{1}J_{CF}$, respectively.

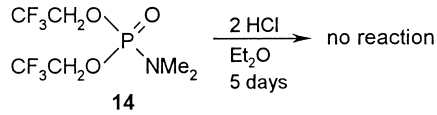
2.5. Reactivities of fluoroethyl phosphoramidates towards hydrogen chloride

Compounds of the type $(EtO)_2P(O)NR_2$ (R=H, Me, Et, Ph) react with anhydrous hydrogen chloride to form diethyl phosphorochloridate, $(EtO)_2P(O)Cl$ [17]. This process is irreversible as the detached amino group is transformed into an unreactive ammonium ion. Electronegative fluoroalkoxy groups on phosphorus lower the basicity of the amino group, decreasing its susceptibility to acid hydrolysis. An extra dimethylamino group, however, diminishes the resistance to hydrolysis. Scission of the P–N bond was possible in diamidate **10** (an exact amount of HCl was generated *in situ* from acetyl chloride and methanol), and after 5 days, a 90% conversion to monochloride **19** had occurred. However, on the small scale used, the latter could not be separated from the residual starting material by distillation.



The activating effect of an extra dimethylamino group is also seen in the contrasting behaviour of $(Me_2N)_2P(O)F$ and $Me_2NP(O)F_2$ **20** towards hydrogen chloride, the former losing both amino groups to give $Cl_2P(O)F$ [17]. Difluoride **20**, first synthesised by Schrader [18], was made by a new route that involved fluorination of *N*,*N*–dimethylphosphoramidic dichloride with triethylamine hydrofluoride; it did not react with anhydrous hydrogen chloride in ether at room temperature (see Section 4.10).

Whereas $(EtO)_2P(O)NMe_2$ gave $(EtO)_2P(O)Cl$ in 87% yield when treated with hydrogen chloride [17], the fluorinated analogue **14** remained unchanged.



This contrast in reactivity is mainly due to the electronegativity of the fluoroethyl groups. Other electron-withdrawing groups have a similar effect; the substituents on phosphorus have been placed in the sequence EtO>PhO>Cl, according to their ability to facilitate acid hydrolysis [17].

3. Conclusion

Some simple fluoroalkyl phosphorochloridates have been prepared and shown to react with alcohols (to give phosphates) and with amines (to give phosphoramidates). Inductive fluoroalkyl groups on phosphorus lower its reactivity to electrophiles. Whereas, the phosphate $(CF_3CH_2O)_2$-P(O)OEt did not react with bromotrimethylsilane, the related phosphate $(EtO)_2P(O)OCH_2CF_3$ reacted to give silylated products with retention of the fluoroalkyl group [3]. Also, the phosphoramidate $(CF_3CH_2O)_2P(O)NMe_2$ did not react with anhydrous hydrogen chloride, but the unfluorinated phosphoramidate $(EtO)_2P(O)NMe_2$ gave diethyl phosphorochloridate [17].

4. Experimental details

All reagents were of commercial quality: fluoroalcohols were purchased from Apollo Scientific Ltd (Derbyshire, UK). Anhydrous solvents were used for reactions. Triethylamine was distilled from CaH_2 and stored over CaH_2. NMR spectra were obtained on a JEOL Lambda 500 instrument (operating at 500 MHz for ^{1}H, 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 ^{1}H, 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 ^{1}H and ^{13}C, external $CFCl_3$ for ^{19}F and external $(MeO)_3P$ (δ 140 ppm) for ^{31}P spectra. Data in Tables 2 and 4 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 (Hz) and assignment. IR spectra were recorded as liquid films on a Nicolet SP210 instrument using Omnic software. Reaction mixtures were monitored by gas chromatography-mass spectrometry (GC-MS) using a Finnigan MAT GCQ instrument with chemical ionisation (CI) using methane as reagent gas. Molecular weights of pure products were confirmed with methane positive CI data. Elemental analysis was carried out on the largest stable fragment ion, using high resolution mass

spectrometry (HRMS) on a Micromass Autospec SQ Double Focusing Magnetic Sector instrument. Mode: positive ion electron impact, magnet scan *m/z* 400–100 (seconds/decade), resolution 2900. Inlet: septum (160°C), 0.2 μl introduced. Source conditions: temperature 200°C, electron energy 70 eV, and accelerating voltage 8000 V. All reaction mixtures were stirred magnetically. Spectroscopic data are recorded in Tables 2 and 4.

*4.1. General procedure for fluoroalkyl phosphorochloridates (**1–3**)*

Triethylamine (0.25 or 0.5 mol) was added dropwise to a solution of phosphorus oxychloride (0.25 mol) and fluoroalcohol (0.25 or 0.5 mol) in Et_2O (25 ml) cooled to 0–5°C. After addition, the mixture was warmed to room temperature and refluxed for 2 h. The precipitate was removed by filtration and the filtrate concentrated to a liquid. Sometimes further triethylamine hydrochloride precipitated on standing. Filtration through a short column of silica gel, removal of solvent, and fractionation under reduced pressure gave the title compounds as colourless mobile liquids.

*4.1.1. 2,2,2-Trifluoroethyl phosphorodichloridate (**1**)*

Yield 36% (bp 59–61°C/10 mm Hg, lit. bp 45.5–46°C/15 mm Hg [9]). ^{1}H NMR: δ=4.6 (2H, dq, J=7 and 7.6 Hz, OCH_2). ^{13}C NMR: δ=121.6 (dq, J=12 and 277 Hz, CF_3), 65.3 (dq, J=7 and 39 Hz, OCH_2). ^{19}F NMR: δ=−73.5 (3F, t, J=7 Hz, CF_3). ^{31}P NMR: δ=8.8. IR: ν=1454, 1421, 1302 (P=O), 1281, 1178, 1093, 1070, 962, 866, 844, 660, 598, 567, 522 cm^{-1}. HRMS: Calc. for $C_2H_2Cl_2F_3O_2P$ 215.912 ([M−HF]$^+$=195.906), found 195.906 (error −2).

*4.1.2. Bis(2,2,2-trifluoroethyl) phosphorochloridate (**2**)*

Yield 40% (bp 61–62°C/10 mm Hg, lit. bp 67–68°C/14 mm Hg [9]). ^{1}H NMR: δ=4.55 and 4.51 (4H, qdd, J=3.3, 7.6 and 15.3 Hz, OCH_2). ^{13}C NMR: δ=121.8 (dq, J=11 and 277 Hz, CF_3), 64.7 (dq, J=6 and 34 Hz, OCH_2). ^{19}F NMR: δ=−74.2 (6F, t, J=7 Hz, CF_3). ^{31}P NMR: δ=4.7. IR: ν=1456, 1423, 1377, 1301 (P=O), 1275, 1175, 1067, 963, 898, 847, 662, 587, 558, 519 cm^{-1}. HRMS: Calc. for $C_4H_4ClF_6O_3P$ 279.949 ([M-HF]$^+$=259.943), found 259.943 (error −1.9).

*4.1.3. Bis(2,2,3,3,3-pentafluoropropyl) phosphorochloridate (**3**)*

Yield 45% (bp 74–76°C/10 mm Hg). ^{1}H NMR: δ=4.61 (4H, broad m, OCH_2). ^{13}C NMR: δ=117.2 (m, CF_3), 111.3 (m, CF_2), 63.8 (m, OCH_2). ^{19}F NMR: δ=−123.5 (4F, m, CF_2) and −82.8 (6F, m, CF_3). ^{31}P NMR: δ=4.6. IR: ν=1458, 1377, 1356, 1306 (P=O), 1271, 1205, 1163, 1111, 1066, 1030, 937, 893, 843, 795, 721, 660, 623 cm^{-1}. HRMS: Calc. for $C_6H_4ClF_{10}O_3P$ 379.943 ([M−HF]$^+$=359.937), found 359.936 (error 1.7).

*4.2. Synthesis of alkyl bis(fluoroalkyl) phosphates (**4–9**)*

A solution of the alcohol (0.01 mol) and triethylamine (0.01 mol) in Et_2O (10 ml) was added dropwise by cannula to a solution of the appropriate bis(fluoroalkyl) phosphorochloridate (0.01 mol) in Et_2O (25 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and left for 12 h. Analysis by GC-MS showed that the desired product predominated. The precipitate was filtered off and the filtrate concentrated to an oil. Bulb-to-bulb distillation, or fractionation using a microdistillation apparatus, gave the title compounds as colourless mobile liquids.

4.3. Reaction of methyl phosphorodichloridate with fluoroalcohols

A solution of the fluoroalcohol (0.14 mol) and triethylamine (0.14 mol) in Et_2O (100 ml) was added dropwise to a stirred solution of methyl phosphorodichloridate (0.07 mol) in Et_2O (100 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and left for 12 h.

4.3.1. With 2,2,2-trifluoroethanol

Analysis by GC-MS showed a 2:1 mixture of desired product and tris(2,2,2-trifluoroethyl) phosphate. The precipitate was filtered off and the filtrate concentrated to a mobile oil. Distillation under reduced pressure gave a liquid (bp 37°C/0.1 mm Hg) with a ratio of bis to tris substituted phosphates **4** and **4a** similar to that of the crude product.

4.3.2. With 2,2,3,3,3-pentafluoropropanol

Analysis by GC-MS showed a 4:1 mixture of desired product and tris(2,2,3,3,3-pentafluoropropyl) phosphate. The precipitate was filtered off and the filtrate concentrated to a mobile oil. Distillation under reduced pressure gave a liquid (bp 65°C/0.2 mm Hg) with a ratio of bis to tris substituted phosphates **5** and **5a** similar to that of the crude product.

4.4. Reaction of ethyl phosphorodichloridate with fluoroalcohols

A solution of the fluoroalcohol (0.12 mol) and triethylamine (0.12 mol) in Et_2O (100 ml) was added dropwise to a solution of ethyl phosphorodichloridate (0.06 mol) in Et_2O (100 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and left for 12 h. Analysis by GC-MS showed 95% conversion to the desired product. The precipitate was filtered off and the filtrate concentrated to an oil. Fractionation under reduced pressure gave the following as colourless liquids:

Ethyl bis(2,2,2-trifluoroethyl) phosphate (**6**): bp 37°C/0.01 mm Hg (yield 52%).

Ethyl bis(2,2,3,3,3-pentafluoropropyl) phosphate (**7**): bp 45–46°C/0.04 mm Hg (yield 35%).

4.5. Attempted reaction of alkyl bis(trifluoroalkyl) phosphates with bromotrimethylsilane

Bromotrimethylsilane (1.8 mmol) was added by syringe to a solution of methyl or ethyl bis(2,2,2-fluoroethyl) phosphate **4** or **6** (1.8 mmol) in $CHCl_3$ (20 ml) under argon at room temperature. After addition, the mixture was left for 1 h. Analysis by GC-MS indicated that no reaction had taken place. Refluxing for several hours and sampling by GC-MS showed only the presence of starting phosphate.

4.6. General procedure for 2,2,2-trifluoroethyl N,N,N′,N′-tetraalkylphosphorodiamidates (*10–12*)

A solution of dialkylamine (0.16 mol) in Et_2O (10 ml) was slowly added dropwise by cannula to a solution of 2,2,2-trifluoroethyl phosphorodichloridate (0.04 mol) in Et_2O (15 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and left for 5 days. Analysis by GC-MS showed 90% conversion to the desired product. The precipitate was filtered off and the filtrate concentrated to an oil. Fractionation under reduced pressure gave the pure title compounds.

4.7. 2,2,2-Trifluoroethyl N,N,N′,N′-tetramethylphosphorodiamidate (*10*)

A solution of 2,2,2-trifluoroethanol (13 g, 0.13 mol) and triethylamine (13.1 g, 0.13 mol) in Et_2O (50 ml) was added dropwise to a solution of *N*,*N*,*N*′,*N*′–tetramethylphosphorodiamidic chloride (22.1 g, 0.13 mol) in Et_2O (50 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and then refluxed for 2 h. Analysis by GC-MS showed that no reaction had taken place. 4-Dimethylaminopyridine (0.8 g, 6.5 mmol) was added and mixture refluxed for another 26 h. Analysis by GC-MS showed that product predominated by 88%. The precipitate was filtered off and the filtrate concentrated to an oil. Fractionation under reduced pressure gave the title compound as a colourless liquid (15.2 g, 50%); bp 45°C/0.4 mm Hg.

4.8. Bis(2,2,2-trifluorethyl) N,N-dimethylphosphoramidate (*14*)

2,2,2-Trifluoroethanol (12 g, 0.12 mol) and triethylamine (12.1 g, 0.12 mol) in Et_2O (50 ml) was added dropwise to a solution of *N*,*N*–dimethylphosphoramidic dichloride (9.7 g, 0.06 mol) in Et_2O (50 ml) cooled to 0–5°C. After addition, the mixture was refluxed for 30 h. Analysis by GC-MS showed 64% desired product and 36% mono-substituted intermediate. 4-Dimethylaminopyridine (1.1 g, 9.3 mmol) was added and the mixture refluxed for a further 8 h. Analysis by GC-MS showed the mixture to comprise 96% desired product. The precipitate was filtered off and the filtrate concentrated to an oil. Fractionation under reduced pressure gave the title compound as a colourless liquid (10.9 g, 61%); bp 38°C/0.5 mmHg.

4.9. N,N–Dimethylphosphoramidic difluoride (*20*)

Triethylamine (4.04 g, 0.04 mol) was added to a solution of triethylamine trihydrofluoride (3.22 g, 0.02 mol) in ether (250 ml) in a 250 ml three-neck flask. The reaction was exothermic and triethylamine hydrofluoride precipitated as a solid. It was broken up with a glass rod to give a fine suspension upon stirring. The centre neck was fitted with a pressure equalising dropping funnel with gas bubbler. The outer necks were fitted with septa, one of which was pierced by an argon entry needle. To the funnel $Me_2NP(O)Cl_2$ (4.86 g, 0.03 mol) in Et_2O (75 ml) was added. The flask was cooled to 0°C and the phosphoramidic dichloride added dropwise with stirring over 40 min. Stirring was continued for 1 h at 0°C and a further 2 h at room temperature. The reaction mixture was left to stand under argon for 12 h. The clear liquid was decanted from the mixture through a thin layer of Celite® in a sinter funnel. Ether (80 ml) was added to the residue, which was shaken, and the liquid (and some solid) was decanted into the filter and this procedure repeated about five times until all the solid was in the funnel. The precipitate was rinsed with more Et_2O and the filtrate concentrated on a rotary evaporator (2.4 g crude product). The above procedure was repeated and the crude products combined and distilled at reduced pressure in a micro-distillation apparatus with a single receiver flask which was cooled in a dry ice–acetone slush bath. The title compound was isolated as a colourless mobile liquid (3.28 g, 42%); bp 23°C/20 mmHg (oil pump with an adjustable air bleed; lit. 28°C/10 mm Hg [18]). ^{1}H NMR: δ=2.74 (6H, dt, J=11 and 1.8 Hz, NCH_3). ^{13}C NMR: δ=32.6 (J_{CP}=5 Hz, NCH_3). ^{19}F NMR: δ=−79.7 (2F, d, J_{PF}=999 Hz, P-F). ^{31}P NMR: δ=−4.5 (t, J_{PF}=999 Hz).

4.10. Reactivities of fluorinated phosphoramidates towards hydrogen chloride

A solution of methanol (0.55 g, 0.017 mol) and acetyl chloride (1.33 g, 0.017 mol) in Et_2O (10 ml) was added dropwise by cannula to a solution of fluorinated phosphoramidate (0.009 mol) in Et_2O (25 ml) cooled to 0–5°C. After addition, the mixture was allowed to warm to room temperature and left for 5 days. An aliquot was analysed by GC-MS. With $(Me_2N)_2P(O)OCH_2CF_3$ **10**, a 90% conversion to chloride **19** had taken place. The precipitate was filtered off and the filtrate concentrated to an oil. Bulb-to-bulb distillation gave a mixture of compounds **10** and **19** in a 3:1 ratio as colourless liquid (1.6 g); bp 30°C/0.1 mm Hg. If repeated on a larger scale, a better fractionation might be possible, perhaps allowing isolation of a purer chloridate. No reaction

occurred with $(CF_3CH_2O)_2P(O)NMe_2$ **14** or $Me_2NP(O)F_2$ **20**.

Acknowledgements

Many thanks to Alison Bussey, Ella Greenaway and Steve Marriott for their excellent technical support. We also wish to thank DERA Haslar (Environmental Sciences) for funding the work.

References

[1] R.F. Hudson, Structure and Mechanism in Organophosphorus Chemistry, Academic Press, London, 1965.
[2] B.E. Smart, in: R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry — Principles and Commercial Applications, Plenum Press, London, 1994, Chapter 3, p. 57.
[3] C.M. Timperley, I.J. Morton, M.J. Waters, J.L. Yarwood, J. Fluorine Chem. 96 (1999) 95.
[4] G.M. Kosolapoff, Organophosphorus Compounds, London, Wiley, 1950, Chapter 9, p. 211.
[5] A.J. Elliott, in: M. Howe-Grant (Ed.), Fluorine Chemistry: A Comprehensive Treatment, Wiley, Chichester, 1995, p. 281.
[6] I.L. Knunyants, O.V. Kil'dasheva, E. Bykovskaya, Zh. Obshch. Khim. (Engl. transl.) 19 (1949) 93.
[7] M.I. Kabachnik, E.I. Golubeva, D.M. Paikin, M.P. Shabanova, N.M. Gamper, L.F. Efimova, Zh. Obshch. Khim. (Engl. transl.) 29 (1959) 1657.
[8] L.F. Audrieth, A.D.F. Toy, J. Am. Chem. Soc. 63 (1941) 2117.
[9] K. Sellars, J. Appl. Chem. 6 (1956) 45.
[10] B.C. Saunders, G.J. Stacey, F. Wild, I.G.E. Wilding, J. Chem. Soc. (1948) 699.
[11] J.V. Bell, J. Heisler, H. Tannenbaum, J. Goldenson, J. Am. Chem. Soc. 76 (1954) 5185.
[12] B. Borecka, J. Chojnowski, M. Cypryk, J. Michalski, J. Zielinska, J. Organomet. Chem. 171 (1979) 17.
[13] E.W. Crunden, R.F. Hudson, J. Chem. Soc. (1962) 3591.
[14] B. Loev, J.T. Massengale, J. Org. Chem. 22 (1957) 1186.
[15] D. Ramaswami, E.R. Kirch, J. Am. Chem. Soc. 75 (1953) 1763.
[16] M.V. Lenton, B. Lewis, Chem. Ind. (London) (1965) 946.
[17] Z. Skrowaczewska, P. Mastalerz, Roczniki Chemii 29 (1955) 415.
[18] G. Schrader, BIOS report 714, London, 1945.