The Synthesis of *O,O*-Bistrimethylsilyl *S*-Trihalogenomethyl Phosphorothioates

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O,O-Bistrimethylsilyl *S*-trihalogenomethyl phosphorothioates are formed quantitatively in the pure state from the reaction between bistrimethylsilyl phosphite and trihalogenomethylsulphenyl chlorides, $CCl_{3-n}F_nSCl$ (n = 1—3) in dry benzene or toluene. The corresponding di-isopropyl *S*-trihalogenomethyl phosphorothioates $(Pr^iO)_2P(O)SCCl_{3-n}F_n$ are likewise obtained from di-isopropyl phosphite with significant advantage in yield and purity over other methods. Bromotrimethylsilane smoothly converts these isopropyl esters into the corresponding trimethylsilyl esters to give an alternative synthesis of the title compounds. Chemical ionisation mass spectrometry of these esters provides valuable structural information and, for the isopropyl esters, generates a family of ammonia-containing ions. The bis-silyl esters hydrolyse rapidly and spontaneously in water under acidic, neutral, and mildly basic conditions although the expected *S*-trihalogenomethyl phosphorothioates decompose too rapidly to permit their characterisation.

S-Perhalogenomethyl esters of phosphorothioic acids, $(RO)_2P(O)SCX_3$ (R = alkyl or aryl; X = F,Cl), have been known for several years [1-3] and their industrial potential has been explored.[1-2] However, the relative instability of these substances has hitherto created technical difficulties for their preparation in a pure state; their lability is promoted by trace impurities,[4] by traces of moisture,[4] and especially by pyrolysis during purification by distillation.[1,4] This instability is even more marked in the case of the acid chlorides, *e.g.* trifluoromethyl thiophosphorodichloridate, $CF_3SP(O)Cl_2$.[4]

Previous preparations of these compounds have employed one of two routes. Firstly, the Arbusov reaction[5] between a trialkyl or alkyl diaryl phosphite and a trihalogenomethylsulphenyl chloride has been applied[1-3] to the formation of methyl, ethyl, and phenyl esters of the desired species [equation (1)].

$$(RO)_3P + CCl_{3-n}F_nSCl \rightarrow (RO)_2P(O)SCCl_{3-n}F_n + RCl + (RO)_2P(O)Cl + CCl_{3-n}F_nSR \quad (1)$$

R = Me, Et, Ph; *n* = 0—3.

Similar results have been obtained from a Michaelis-Becker[6] reaction between a dialkyl (or diaryl) phosphite, or its sodium derivative, and the sulphenyl chlorides[1,2] [equation (2)].

$$(RO)_2P(O)M + CCl_{3-n}F_nSCl \rightarrow (RO)_2P(O)SCCl_{3-n}F_n + MCl \quad (2)$$

M = H,Na; R = Me, Et, Pr^i, Ph; *n* = 0—2.

In both cases, the elevated temperatures required either to achieve reaction or for purification of the products by distillation lead to significant and unwanted by-product formation. In particular, the formation of phosphorofluoridate material in such preparations makes the products unsuitable for biological evaluation.

More recently, Haas has provided two alternative routes to the esters under investigation. Reaction of bistrifluoromethyl disulphide with diethyl phosphite gives good yields of *O,O*-diethyl *S*-trifluoromethyl phosphorothioate of moderate purity[7] while the alcoholysis of trifluoromethyl thiophosphorodichloridate provides a range of alkyl and aryl esters of *S*-trifluoromethyl thiophosphoric acid.[4]

As part of a study of the biological properties of compounds containing the P–S–C–F entity, we have investigated the potential of trimethylsilyl esters of phosphorus acids containing this functionality as precursors of the corresponding halogenomethyl thiophosphates. We describe here a simple and direct method for their preparation in a pure state and in quantitative yield. Full spectroscopic data are given for a series of esters, and preliminary toxicity data are provided.

Results and Discussion

In an initial survey, a range of experiments was carried out to evaluate the syntheses described above. In all cases, the product mixtures were analysed by ^{19}F and ^{31}P n.m.r. spectroscopy. This showed the formation of the products hitherto described[1,2,6] and also the presence of a variety of impurities and/or excess reagents. High vacuum distillation of these product mixtures removed much of the unwanted material but invariably led to the contamination of the desired compounds by pyrolysis by-products. The general pattern of thermolytic breakdown corresponds to loss of a thiocarbonyl dihalide, SCX_2, with concomitant formation of a dialkyl phosphoryl fluoride or chloride. Thus, trifluoromethyl and trichloromethyl species give phosphorofluoridate and phosphorochloridate by-products respectively, readily identified[8,9] by ^{19}F and ^{31}P n.m.r. spectroscopy [equation (3); X = F,Cl]. For mixed chlorofluoro species, the phosphorochloridate impurity predominated.

$$(RO)_2P(O)SCX_3 \longrightarrow (RO)_2P(O)X + SCX_2 \quad (3)$$

Because of the well-known anticholinesterase activity of many dialkyl phosphorofluoridates,[10,11] we sought to develop a method for the preparation of trihalogenomethylthiophosphate diesters devoid of these toxic by-products. Our attention turned to the use of trimethylsilyl esters of phosphorus oxyacid precursors both because of their general reactivity and because of their facile solvolysis, which has been of special benefit in the synthesis of labile phosphonic acids.[12]

We have found that the optimum conditions involve the treatment of bistrimethylsilyl phosphite with 2 equiv. of the trihalogenomethylsulphenyl chloride in dry benzene or toluene at room temperature. After evaporation of solvent and excess of sulphenyl chloride under reduced pressure, the desired products (**1a—c**) are obtained quantitatively and with no impurities that can be detected by ^{19}F or ^{31}P n.m.r. spectroscopy [equation (4)].

In order to obtain the additional mass spectrometric information that can be derived from alkyl phosphate esters (see

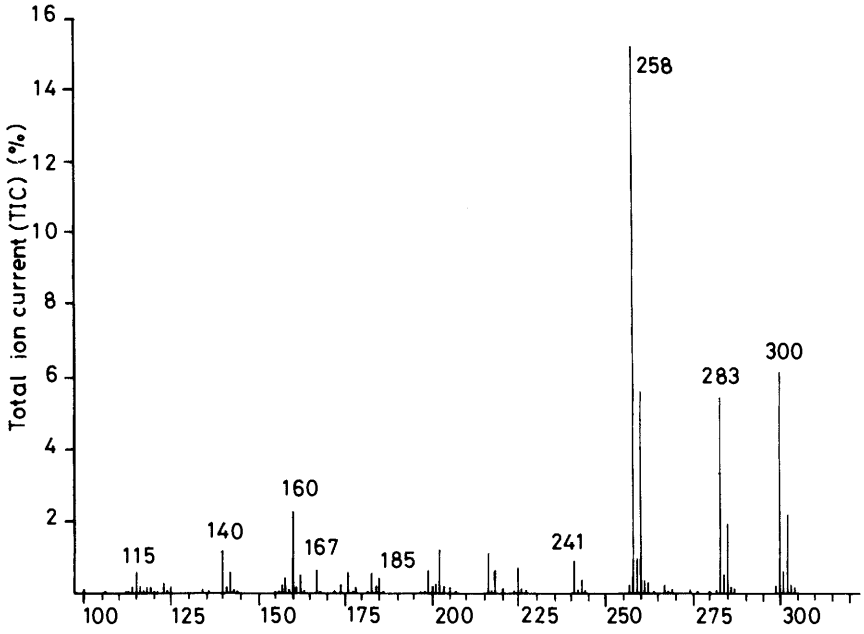

Figure. Ammonia chemical ionisation (CI) mass spectrum for *O,O*-di-isopropyl *S*-chlorodifluoromethyl thiophosphate (**2b**)

$$(Me_3SiO)_2PHO + Cl_{3-n}F_nCSCl \xrightarrow[24\ h]{20\ °C} (Me_3SiO)_2P(O)SCCl_{3-n}F_n + HCl \quad (4)$$

(**1**)

a; $n = 3$
b; $n = 2$
c; $n = 1$

later) and because of the greater ease of availability of alkyl rather than trimethylsilyl phosphites, we carried out the same reactions using di-isopropyl phosphite [equation (5)]. In all three cases we obtained the corresponding di-isopropyl esters (**2a**—**c**) quantitatively and pure, as gauged by ^{19}F and ^{31}P n.m.r. analysis.

$$(Pr^iO)_2PHO + 2Cl_{3-n}F_nCSCl \longrightarrow (Pr^iO)_2P(O)SCCl_{3-n}F_n + HCl \quad (5)$$

(**2**)

a; $n = 3$
b; $n = 2$
c; $n = 1$

These di-isopropyl esters (**2a**—**c**) were treated with 2.25 equiv. of bromotrimethylsilane in dry chloroform under nitrogen and evaporated after 24 h to afford the pure silyl esters (**1a**—**c**). These silyl esters (**1a**—**c**) cannot be distilled without severe decomposition. The pattern of pyrolysis is essentially the same as that observed (see above) for the dialkyl esters: $(Me_3SiO)_2P(O)F$ is formed from (**1a**) and $(Me_3SiO)_2P(O)Cl$ is generated from esters (**1b**—**c**).

The silyl esters (**1a**—**c**) are viscous, pale yellow oils which are extremely sensitive to moisture. However, they are stable if kept under an inert atmosphere at 0 °C for several weeks.

The bistrimethylsilyl esters (**1**) were dissolved in water or methanol and the course of the reaction followed by n.m.r. spectroscopy. For all three esters (**1a**—**c**) the ^{31}P n.m.r. spectrum showed the immediate replacement of the signal at δ 5—6 by a single line at δ 0—0.5, characteristic of phosphoric acid. For the trifluoromethyl thioester (**1a**) the ^{19}F signal at −35 p.p.m. vanishes and is replaced by a singlet at +31.6 p.p.m., characteristic of CF_3SH, which slowly disappears. Similar results were obtained when the solvolysis was performed in the presence of a base, *e.g.* NaOH.

Mass spectrometric analysis of both the bistrimethylsilyl esters (**1a**—**c**) and the di-isopropyl esters (**2a**—**c**) using the electron impact (EI) ionisation mode gave rather poor results. This problem is well-recognised for esters of phosphorus oxyacids where facile fragmentation often leads to more than 99% of the total ion current (TIC) being carried by fragment ions of relatively small mass and giving little structural information.[13,14] By contrast, the use of chemical ionisation (CI), with ammonia as the reagent gas, as recommended by Cload and Hutchinson,[15] has proved to be a major advance in the application of mass spectrometry to phosphate and phosphonate esters. It proved unusually well-suited to the present investigation.

All six esters gave good cation spectra in the CI mode. The pattern of ions for the pairs of halogen homologues simplified the analysis of the fragment ions and revealed quite different behaviour for the two series of esters (Table 1).

The trimethylsilyl esters (**1a**—**c**) gave weak, protonated molecular ions (1% TIC)* with somewhat stronger intensities for ions resulting from the loss of SCX_2 and of SCX_3, the latter being associated with proton capture. Peaks resulting from the loss of a trimethylsilyl(oxy) fragment were not seen. While very weak ions (TIC *ca.* 0.01%) were observed for addition of HF to the protonated molecular ion ($M + 21$), there were no ions resulting from the capture of the reagent gas, ammonia. Some general fragmentation processes provided peaks for $(Me_3SiO)_3PH^+$ and $(Me_3SiO)_3POH^+$ in all three spectra.

The isopropyl esters (**2a**—**c**) gave very different results showing three major characteristics. First, a large part of the TIC is carried by ions of relatively high molecular mass. Secondly, the loss of either or both of the ester groups is a typical feature of the spectra. Thirdly, the parent ions and their fragments all show capture of the ammonia and these nitrogen-containing species carry most of the ion current (Table 1). This

* For simplicity, *m/z* data are presented for ^{35}Cl species only but TIC data is given for (^{35}Cl + ^{37}Cl) isotopes together (cf. Figure).

Table 1. Principal cations[a] and (%TIC)[b] carried in CI mass spectra of esters $(RO)_2P(O)SCX_3$ [$P^+ = (M + \overset{+}{H})$]

Compd.	$(P + HF)^+$	P^+	$(P - SCF_2)^+$	$(P - SCF_3 + H)^+$	$(P - SCClF)^+$	$(P - SCClF_2 + H)^+$	$(P - SCl_2)^+$	$(P - SCl_2F + H)^+$
(1a)	347(0.01)	327(0.3)	245(3.7)	227(1.6)				
(1b)	363(0.01)	343(1.1)	261(0.4)		245(0.9)	227(1.2)		
(1c)	379(0.02)	359(0.4)			261(2.9		245(1.1)	227(3.8)
	$(P + NH_3)^+$	P^+	$(P + NH_3 - C_3H_6)^+$	$(P - C_3H_6)^+$	$(P + NH_3 - C_6H_{12})^+$	$(P - C_6H_{12})^+$	$(P + NH_3 - SCF_2)^+$	$(P - SCF_2^+$
(2a)	284(19.8)	267(5.9)	242(8.5)	225(0.7)	200(1.0)	183(0.6)	202(17.4)	184(4.4)
(2b)	300(8.5)	283(7.4)	258(21.2)	241(1.2)	216(1.5)	199(1.0)	218(1.1)	
(2c)	316(11.0)	299(4.0)	274(8.0)	257(0.3)	232(0.4)	215(0.1)		
	$(P - SCF_3 + H)^+$	$(P + NH_3 - SCClF)^+$	$(P - SCClF)^+$	$(P - SCF_2Cl + H)^+$	$(P + NH_3 - SCCl_2)^+$	$(P - SCCl_2)^+$	$(P - SCCl_2F + H)^+$	
(2a)	167(6.5)							
(2b)		202(1.2)	185(0.4)	167(0.1)				
(2c)		218(1.1)	201(0.3)		202(1.3)	184(1.2)	167(1.2)	

[a] Ions for ^{35}Cl only. [b] TIC Corrected for (^{35}Cl + ^{37}Cl).

Table 2. Spectroscopic data for bistrimethylsilyl esters $(Me_3SiO)_2P(O)SCX_3$ and di-isopropyl esters, $(Pr^iO)_2P(O)SX_3$.

Compd.	^{19}F (p.p.m.)	$^3J_{PF}$	^{31}P (p.p.m.)	^1H (p.p.m.)	ν/cm^{-1}
$(Me_3SiO)_2P(O)SCF_3$	−34.58(d)	9.9 Hz	5.23(q)	0.36(s)	2 985m, 1 265s (PO), 1 060, 1 050vs, 1025vs (CF)
(1a)					762s (CF_3 and CS)
$(Me_3SiO)_2P(O)SCClF_2$	−20.48(d)	7.3 Hz	5.51(t)	0.35(s)	2 980m, 1 263s (PO), 1 070vs, 1 055vs, 1 025vs (CF)
(1b)					765 (CF_2 and CS)
$(Me_3SiO)_2P(O)SCCl_2F$	−17.85(d)	5.8 Hz	5.70(d)	0.35(s)	2 985m, 1 264s (PO), 1 065vs, 1 055vs, 1 010vs (CF)
(1c)					760s (CF and CS)
$(Pr^iO)_2P(O)SCF_3$	−34.66(d)	7.8 Hz	10.22(q)	4.88(m)	2 995m, 2 940m, 2 880w, 1 280s (PO),
				1.40(dd)	1 020vs, 1 005vx, 995vs (CF)
(2a)	(−33.2(d)[4])	8.0 (Hz)[4]	7.1(q)[4]	$^3J_{HH}$6.7 Hz	760s (CF_3 and CS)
$(Pr^iO)_2P(O)SCClF_2$	−20.19(d)	6.4 Hz	10.49(t)	4.88(m),	2 990m, 2 942m, 2 882w, 1 278s (PO)
				1.39(dd)	1 030vs, 1 010vs, 985vs (CF)
(2b)				$^3J_{HH}$6.7 Hz	765s (CF_2 and CS)
$(Pr^iO)_2P(O)SCCl_2F$	−17.98(d)	4.9 Hz	10.57(d)	4.88(m)	2 990m, 2 942m, 2 882w, 1 278s, (PO)
				1.40(dd)	1 050vs, 1 025vs, 990vs (CF)
(2c)				$^3J_{HH}$6.7 Hz	762s (CF and CS)

Table 3. Toxicity of di-isopropyl esters of *S*-trihalogenomethyl thiophosphates

Compd.	Toxicity LD_{50}/mg kg^{-1} i/v Mouse[a]	p/c Rat
$(Pr^iO)_2P(O)SCF_3$ (**2a**)	8.4	>100
$(Pr^iO)_2P(O)SCClF_2$ (**2b**)	7.7	>100
$(Pr^iO)_2P(O)SCCl_2F$ (**2c**)	24	15—25
$(Pr^iO)_2P(O)F$[d] (DPPF)	3.4	3.8[b] (0.5[c])

[a] PEG300 used as a solvent. [b] p/c Mouse. [c] p/c Rabbit. [d] B. V. Ramachandran, *Biochem. Pharmacol.*, 1966, **15**, 169; B. A. Kilby and M. Kilby, *Br. J. Pharmacol.*, 1947, **2**, 234.

phenomenon of ammonia capture, noted as a minor feature of the CI spectrum for diethylphosphonoacetic acid,[15] is in our experience a common feature of the ammonia CI mass spectra of esters of phosphorus oxyacids bearing electron-withdrawing substituents on phosphorus,[16] in this case the SCX_3 group. An example of this behaviour is provided by the CI spectrum for diethyl phosphorochloridate which shows only two sets of peaks above 60 MU: the protonated molecular ion (*m/z* 173, 175) carries 28% of the TIC and its ammonia adduct (*m/z* 190, 192) carries 12.5%. General features of the spectra are illustrated for *O,O*-di-isopropyl *S*-chlorodifluoromethyl thiophosphate (**2b**) (Figure). That this behaviour is not manifest for the corresponding bistrimethylsilyl esters must, for the present, be attributed to a combination of steric and electronic effects.

The phosphorus and fluorine n.m.r. spectra[17] of the esters, like their i.r. spectra,[18,19] showed expected features and fully confirm the structures assigned (Table 2). They were particularly valuable in confirming the presence (or absence) of small quantities of di-isopropyl phosphorofluoridate,[17,18] DPPF, (^{31}P δ −4.5 $^1J_{FP}$ 963 Hz) which were readily identified in crude preparations of the esters (**2a**—**c**), prepared by published methods.[1-3]

The toxicity of the di-isopropyl esters was evaluated by intravenous (i.v.) delivery to mice, and skin application (p/c) to the clipped skin of rats. The results (Table 3) show that in contrast to the very high anticholinesterase activity of di-isopropyl phosphorofluoridate,[10,11] the esters (**2a**—**c**) proved to be but weakly toxic in injection and rather less so when applied topically. In particular, the low skin toxicity of (**2a**) and (**2b**) is proof of the absence of DPPF from these preparations.

Experimental

Di-isopropyl phosphite and bromotrimethylsilane were obtained from Aldrich chemicals and were distilled prior to use. Bistrimethylsilyl phosphite[20] and the trihalogenomethylsulphenyl chlorides[21,22] were prepared by literature methods. N.m.r. spectra were recorded for ^{19}F relative to $CFCl_3$ and for ^{31}P relative to 85% phosphoric acid using a Bruker WP80SY instrument in the deuterium locked mode on $CDCl_3$ solutions. I.r. spectra were determined on liquid films and mass spectra were recorded on a Kratos MS80 machine with data analysis using a Nova 4X accessory.

O,O-*Bistrimethylsilyl* S-*Trihalogenomethyl Phosphorothioates*, $(Me_3SiO)_2P(O)SCX_3$.—The appropriate sulphenyl chloride,[21,22] (0.02 mol) in dry toluene (20 ml) was stirred in a two-necked flask under dry nitrogen while bistrimethylsilyl phosphite[20] (2.2 g, 0.01 mol) in dry toluene (15 ml) was added dropwise with the temperature maintained at 20 °C. The solution was constantly flushed with toluene-saturated nitrogen to remove HCl gas. After being stirred overnight, the solution was evaporated under reduced pressure at 20 °C to leave the *product* (**1a**—**c**) as a viscous, slightly yellow oil. Spectroscopic data were recorded as described (Tables 1 and 2).

O,O-*Di-isopropyl* S-*Trihalogenomethyl Phosphorothioates*, $(Pr^iO)_2P(O)SCX_3$.—The appropriate sulphenyl chloride (6 mmol) in dry benzene (25 ml) was stirred in a two-necked flask under dry nitrogen while di-isopropyl phosphite (0.5 g, 3 mmol) in dry benzene (20 ml) was added dropwise. Hydrogen chloride evolution started immediately and the gas was removed by flushing the solution with nitrogen. The solution was stirred for 24 h then evaporated under reduced pressure at 20 °C to leave the product as a colourless oil. Spectroscopic data were recorded as described (Tables 1 and 2).

Transesterification of Di-isopropyl Esters with Bromotrimethylsilane.—The di-isopropyl ester, $(Pr^iO)_2P(O)SCX_3$, (**2a**—**c**) (8 mmol) in dry chloroform (10 ml) was stirred with bromotrimethylsilane (18 mmol) added slowly through a 'septum' cap with a syringe under nitrogen. After 20 h the mixture was evaporated under reduced pressure to give the *product* (**1a**—**c**), identical with that prepared above.

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References

1 U. S. P. 2811543 (1955), Eastman Kodak Co; H. W. Coover and J. B. Dickey (*Chem. Abstr.*, 1958, **52**, P4922c).
2 Farbenfabriken Bayer AG; H. Malz, H. Kuchenthal, W. Behrenz, E. Klauke, and E. Kühle, Belg. P. 632757 (*Chem. Abstr.*, 1964, **61**, P9402).
3 Y. O. El Nigumi and H. J. Emeléus, *J. Inorg. Nucl. Chem.*, 1970, **32**, 3213.
4 A. Hass and W. Kortmann, *Z. Anorg. Allg. Chem.*, 1983, **501**, 79.
5 A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687.
6 A. Michaelis and T. Becker, *Berichte*, 1897, **30**, 1003.
7 A. Hass and A. Łopusinski, *Chem. Ber.*, 1981, **114**, 3176.
8 V. V. Sheluchenko, M. A. Landau, S. S. Dubov, A. A. Neimysheva, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR*, 1967, **177**, 1379.
9 R. R. Dean and W. McFarlane, *J. Chem. Soc., Chem. Commun.*, 1967, 840.
10 E. D. Adrian, W. Geldberg, and B. A. Kirby, *Nature (London)*, 1946, **158**, 625.
11 J. F. Mackworth and E. C. Webb, *J. Biochem.*, 1948, **42**, 91.
12 G. M. Blackburn and D. Ingleson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1150.
13 R. G. Gillis and J. L. Occolowitz, 'The Mass Spectrometry of Phosphorus Compounds,' ed. M. Halman, Interscience, New York, 1972.
14 S. Meyerson, E. S. Kuhn, F. Ramirez, J. F. Marecek, and H. Okazaki, *J. Am. Chem. Soc.*, 1980, **102**, 2398.
15 P. A. Cload and D. W. Hutchinson, *Org. Mass Spectrom.*, 1983, **18**, 57.
16 M. J. Parratt and T. W. Maciej, unpublished results.
17 W. Gombler, *Z. Naturforsch. Teil* B., 1981, **36**, 535.
18 J. K. Wilmshurst, *J. Chem. Phys.*, 1957, **26**, 426.
19 J. V. Bell, J. Heisler, H. Tannenbaum, and J. Goldensen, *J. Am. Chem. Soc.*, 1954, **76**, 5185.
20 M. G. Voronkov, V. A. Kolesova, and V. N. Zgonnik, *Izv. Akad. Nauk SSSR*, 1957, 1363 (*Chem. Abstr.*, 1958, **52**, 7128e).
21 C. W. Tullock and D. D. Coffman, *J. Org. Chem.*, 1960, **25**, 2016.
22 E. Kühle, E. Klauke, and F. Grewe, *Angew. Chem.*, 1964, **76**, 807.

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