Trihalogenomethylsulphenylation of Tetraisopropyl Methylenebisphosphonates

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Trihalogenomethylthiomethylenebisphosphonates, $[(Pr^iO)_2PO]_2CRSCCl_nF_{3-n}$ (n = 0–2; R = H,Me), are formed by the reaction of salts of tetraisopropyl methylenebisphosphonates, $[(Pr^iO)_2PO]_2CRM$ (M = Li,Na; R = H,Me), with trihalogenomethanesulphenyl chlorides, $CCl_nF_{3-n}SCl$ (n = 0—2). The ester products are transesterified with bromotrimethylsilane and hydrolysed with aqueous methanolic sodium hydroxide to give the corresponding tetrasodium salts of the bisphosphonic acids. The sulphenylation reactions are complex and are facilitated by the use of Lewis acids. Sulphenylations using chlorodifluoro-and dichloro-methanesulphenyl chlorides afford unexpected additional products arising from chlorine replacement by fluorine.

The reaction of the methylenebisphosphonate carbanion (**1**), $[(RO)_2PO]_2CH^-M^+$ (M = Li, Na, K; R = alkyl), with alkyl halides gives[1–4] the appropriate derivatives, $[(RO)_2PO]_2CHR'$ (R,R' = alkyl). The carbanion (**1**) can also be acylated[5–7] and halogenated with chlorine,[1,8] bromine,[1,8] or iodine.[1] While fluorination cannot be achieved using elemental fluorine, which results in replacement of all possible hydrogens by fluorine,[9,10] the use of perchloryl fluoride, $FClO_3$, as the fluorinating agent[11] leads to the formation of the monofluoro and difluoro derivatives of the methylenebisphosphonates.[12,13] Such halogenated methylenebisphosphonic acids can be considered as isosteric and/or isopolar analogues of pyrophosphoric acid and have found useful application in compounds of biological interest.[14,15]

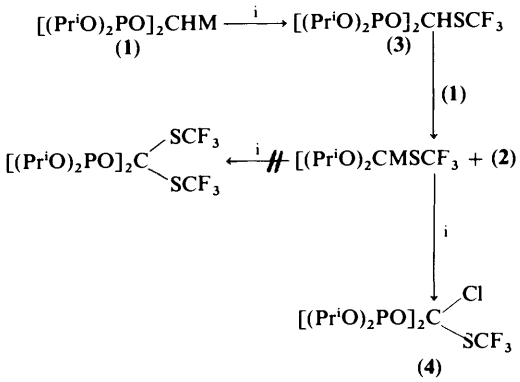
It has been established that, in many respects, the trihalogenomethylsulphenyl chlorides are comparable in behaviour to the halogens,[16] *e.g.* in the electronegativity of the CF_3S group-estimated[17] at 2.90. This relationship has led us to explore the reactions between the trihalogenomethanesulphenyl chlorides and metallated methylenebisphosphonate esters in order to generate isopolar but non-isosteric[14] analogues of pyrophosphoric acid.

Results and Discussion

The species $CCl_nF_{3-n}SCl$ (n = 0—2) initially react with methylenebisphosphonates (**2**) in the form of their anions (**1**) to give the expected α-substituted derivatives (**3**), (**5**), and (**9**). We have routinely used the tetraisopropyl bisphosphonate ester as this is most conveniently converted into the anion (**1**) by means of butyl-lithium, sodium hydride, or sodium as base. A variety of additional products are generated whose nature and range depends on the sulphenyl chloride used. The simplest case is the reaction of (**1**) with trifluoromethanesulphenyl chloride. The tetraisopropyl esters of trifluoromethylthiomethylenebisphosphonate (**3**) and of 1-chloro-1-trifluoromethylthiomethylenebisphosphonate (**4**) are the exclusive products while some 15% of the parent ester (**2**) is recovered, notwithstanding the use of a two-fold excess of sulphenyl chloride [equation (1)]. This result typifies the principal reactions for all the sulphenyl chlorides used.

$$\underset{(1)\ (M = Li,Na)}{[(Pr^iO)_2PO]_2CHM} + CF_3SCl \longrightarrow \underset{(3)}{[(Pr^iO)_2]_2CHSCF_3} + \underset{(4)}{[(Pr^iO)_2PO]_2CClSCF_3} + \underset{(2)}{[(Pr^iO)_2PO]_2CH_2} \quad (1)$$

Neither changes in the base (BuLi, NaH, or Na) employed to generate the carbanion (**1**) from the ester (**2**), nor variations in the temperature, duration or solvent used for the reaction significantly affected this situation. The conversion of (**3**) into (**4**) is a chlorination process which results from the fact that the introduction of the strongly electron-withdrawing SCF_3 group into (**3**) makes the remaining proton more acidic than that in (**2**). Thus, proton transfer from (**3**) to (**1**) generates $[(Pr^iO)_2PO]_2C(SCF_3)M$ which reacts further with CF_3SCl to form (**4**). It is noteworthy that the formation of (**3**) and (**4**) show high regioselectivity with *neither* bis-sulphenylation *nor* bis-chlorination of (**2**) being observed. Moreover, treatment of the anion of (**3**) with CF_3SCl gives only the chlorinated product (**4**) (Scheme 1). The reasons for attributing this regioselectivity to steric factors rather than to frontier orbital effects are discussed in the sequel.



Scheme 1. *Reagent:* i, CF_3SCl. M = Li or Na

It is well-known that the Friedel-Crafts reactions of trihalogenomethanesulphenyl chlorides with arenes are much facilitated by Lewis acids.[18,19] The beneficial effect has been attributed to the formation of an intermediate, *e.g.* $CCl_nF_{3-n}S^+ AlCl_4^-$, which leads to improved sulphenylation and diminished chlorination.[20] We therefore examined the use of such reagents in the reactions of trihalogenomethanesulphenyl chlorides with the carbanions of bisphosphonates.

Boron trifluoride–diethyl ether caused a small improvement in sulphenylation, though subsequent chlorination to give (**4**) remained a major component of the reaction. However, the use of aluminium trichloride resulted in a fourfold enhancement of the ratio of sulphenylation to chlorination (Table 1). This effect was equally important in reactions involving other sulphenyl chlorides and proved to be essential for the formation of sulphenylation products in viable amounts.

The uncatalysed reaction between (1) and chlorodifluoromethanesulphenyl chloride gives low yields of the sulphenylation product and chlorination is the principal reaction, leading to the formation of (7). In the presence of aluminium trichloride the major product is tetraisopropyl chlorodifluoromethylthiomethylenebisphosphonate (5). This material is further chlorinated to give the disubstitution product (6). Two minor products are also formed (Scheme 2). The first, tetraisopropyl chloromethylenebisphosphonate (3), could arise by replacement of chlorine by fluorine either in the product (5) or in an intermediate species in the reaction mixture. We shall return to discuss this problem in the sequel.

The aluminium trichloride-promoted reaction of (1) with dichlorofluoromethanesulphenyl chloride follows a similar pattern but affords an even wider variety of products. Direct chlorination is now the major process and leads first to the monochloromethylenebisphosphonate (7) and then to the dichloromethylenebisphosphonate (8), which is the major product (Scheme 3). Direct sulphenylation to give the dichlorofluoromethylthiomethylenebisphosphonate (9) is now much reduced (compared to the trifluoromethyl- and chlorodifluoromethane-sulphenyl chloride reactions). Finally, single and double replacement of chlorine by fluorine results in the formation of (5) and (3) respectively (Scheme 3).

Two features of these reactions call for further examination, namely the exchange of chlorine by fluorine and the competition between sulphenylation and chlorination.

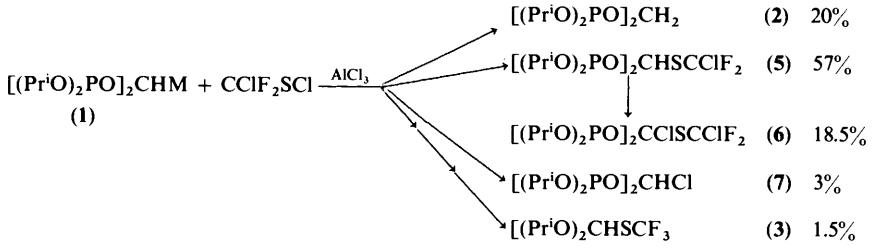
The sulphenyl chlorides $CClF_2SCl$ and CCl_2FSCl used were analytically pure. Thus the formation of (3) as a minor product from the reactions of both of these chlorides with (1) must result either from fluorination of (9) to generate (5), then of (5) to give (3) *or* from the formation of CF_3SCl *in situ*. This latter possibility was tested by examining the products of reaction of (1) with pure CCl_3SCl in the presence of an excess of dry lithium fluoride under standard reaction conditions. The reaction mixture was monitored by ^{19}F n.m.r. which clearly showed the formation of monofluoro- difluoro-, and trifluoro-products, (9), (5), and (3) respectively, in small (*ca.* 1%) quantities. *Per contra*, when (1) was first treated with CCl_3SCl under standard conditions, then excess sulphenyl chloride removed by evaporation and lithium fluoride added, no traces of these fluorination products were detectable even after prolonged incubation.

We therefore concluded that the exchange process involved fluoride ions operating on a by-product prior to sulphenylation

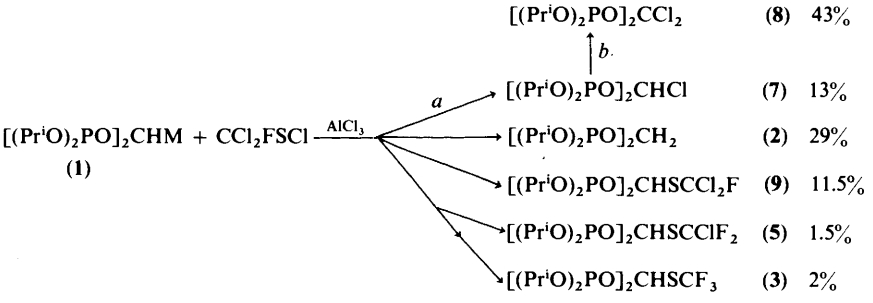
Table 1. Products of the reaction of CF_3SCl with $[(Pr^iO)_2PO]_2CHM$

Base	Lewis Acid	Products/yield* (%) (2)	(3)	(4)
NaH or Na	—	15	35	50
BuLi	—	14	43	43
BuLi	$BF_3{\cdot}OEt_2$	9	51	40
BuLi	$AlCl_3$	10	74	16

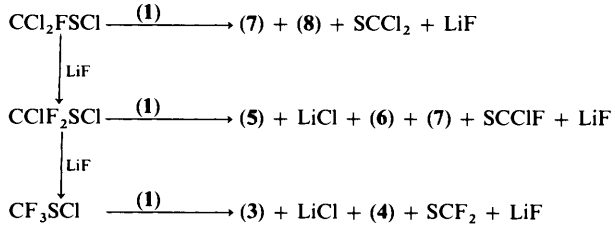
* Yields based on products separated by flash chromatography



Scheme 2.



Scheme 3.



Scheme 4.

Table 2. N.m.r. data for $[(Pr^iO)_2PO]_2C(R)SCCl_nF_{3-n}$ and corresponding sodium salts

Product	^{19}F/p.p.m.	^{31}P/p.p.m.	^1H/p.p.m.	$^3J_{H\beta H\gamma}$	$^4J_{PF}$	$^4J_{FH\alpha}$	$^2J_{PH\alpha}$	$^3J_{PH\beta}$
$[(Pr^iO)_2PO]_2CHSCF_3$ (3)	−42.4 m	13.1 m	3.33, tq, H^α 4.87, m, H^β 1.37, 1.35 d, H^γ	6.1	3.6	2.5	22.3	8.0
$[(Pr^iO)_2PO]_2CClSCF_3$ (4)	−35.9 t	7.9 m	4.88, m, H^β 1.37, 1.35 d, H^γ	6.1	3.7	—	—	8.1
$[(Pr^iO)_2PO]_2CHSCClF_2$ (5)	−28.2 m	13.0 m	3.34. tt, H^α 4.88, m, H^β 1.37, 1.35 d, H^γ	6.2	3.6	2.7	22.2	8.1
$[(Pr^iO)_2PO]_2CHSCCl_2F$ (9)	−17.6 m	12.8 m	3.33, td, H^α 4.88, m, H^β 1.36, 1.34, d, H^γ	6.1	3.5	2.7	22.2	8.1
$[(Pr^iO)_2PO]_2CClSCClF_2$ (6)	−23.9 t	7.7 m	4.87 m, H^β 1.36, 1.34, d, H^γ	6.1	3.6	—	—	8.0
$[(Pr^iO)_2PO]_2CMeSCF_3$ (12)	−33.7 m	16.2 m	2.20, tq, $H^{\alpha'}$ 4.87, m, H^β 1.36, 1.34, d, H^γ	6.1	3.7	1.4*	16.0	8.1
$[(NaO)_2PO]_2CHSCF_3$ (13a)	−40.9 m	12.9 dq	—	—	3.6	2.5	22.3	—
$[(NaO)_2PO]_2CHSCClF_2$ (13b)	−27.1 m	12.8 dq	—	—	3.6	2.7	22.2	—
$[(NaO)_2PO]_2CClSCF_3$ (13c)	−35.8 t	7.6 q	—	—	3.7	—	—	—
$[(NaO)_2PO]_2CMeSCF_3$ (13d)	−32.9 t	16.2 qq	—	—	3.7	1.4*	16.0	—

* $^5J_{PH\alpha'}$

Hydrogen nuclei designated as $CH_3{}^\gamma$–$CH_2{}^\beta$–O–P–C(H$^\alpha$($CH_3{}^{\alpha'}$))–P(SCX_3)

Table 3. Physical data for esters $[(Pr^iO)_2PO]_2CRSCX_3$

Compound	m.s. (%)[a]	$\nu_{max.}$ (cm^{-1})	$n_D{}^{20}$	R_F[b]
(3)	445 (5.4) ($M + H^+$), 403 (3.9), 361 (2.0). 345 (0.2), 319 (0.5)	1 260s (P=O) 1 025vs, 990vs (C–F) 753s (CF_3 and C–S)	1.4288	0.29
(4)	479 (1.7) ($M + H^+$), 445 (2.0), 437 (0.9), 403 (1.1), 395 (0.2), 378 (0.2)	1 265s (P=O) 1 020vs, 990vs (C–F) 755s (CF_3 and C–S)	1.4431	0.47
(5)	461 (3.9) ($M + H^+$), 419 (1.9), 377 (0.8), 345 (1.6), 335 (0.4)	1 260s (P=O) 1 020vs 995vs (C–F) 750 (CF_2 and C–S)	1.4450	0.28
(6)	495 (4.3) ($M + H^+$), 460 (1.0), 453 (2.7), 411 (1.3), 378 (0.4), 369 (0.2)	1 262s (P=O) 1 015vs, 988vs, (C–F) 750s, (CF_2 and C–S)	1.4513	0.45
(9)	477 (5.6) ($M + H^+$), 435 (3.3), 393 (1.9), 351 (0.7), 345 (0.6), 309 (0.2)	1 255s (P=O) 1 013vs, 985vs (C–F) 750s (C–S)	1.4546	0.27
(12)	459 (13.1) ($M + H^+$), 417 (8.5), 375 (4.3), 359 (1.1), 336 (0.8), 294 (0.3)	1 258s (P=O) 1 020vs, 990vs (C–F) 754s (CF_3 and C–S)	1.4357	0.21

[a] Ions shown only for ^{35}Cl. [b] Solvent: ethyl acetate–light petroleum (b.p. 60/80 °C) (1:1 v/v) on silica.

of (1). The key to this process (Scheme 4) is the fact that the chlorination reactions leading to the formation of (4), (6), (7), and (8) can produce lithium fluoride along with a thio(fluoro)phosgene. As the concentration of lithium fluoride increased, it successively fluorinated the sulphenyl chloride precursor to generate first $CClF_2SCl$ and then $CClF_2SCl$, both reactions for which there is adequate precedent.[21,22] Once formed, these reagents then reacted with (1) to generate (5) and (3) respectively.

The second feature concerns the growing preference for the chlorination of (1) by sulphenyl chlorides in the series $CF_3SCl < CClF_2SCl \ll CCl_2FSCl$ (Table 1, Schemes 1—3). The present study strongly suggests that steric factors are primarily responsible. It is evident that the last of these sulphenyl chlorides acts predominantly as a chlorinating agent (Scheme 3, *a* and *b*). The pertinent difference between chlorodifluoro- and dichlorofluoro-methanesulphenyl chlorides is the diminished steric accessibility of sulphur in the latter to

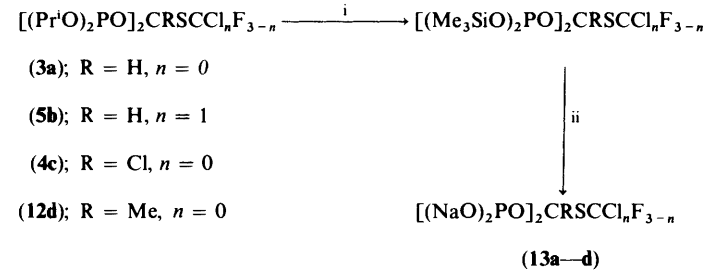
nucleophilic attack by the carbanion (**1**). This analysis is supported by two additional experimental observations. On the one hand, further substitution of (**3**), which is a major part of the product-forming reactions of (**1**) with CF_3SCl, occurs exclusively by chlorination to give (**4**) (Scheme 1); we have never detected bis-sulphenylation products from the reaction of trihalomethanesulphenyl chlorides with (**1**)* On the other hand, the reaction of tetraisopropyl ethylidene-1,1-bisphosphonate as its lithio derivative (**10**), with CF_3SCl gives chlorination (**11**) and sulphenylation (**12**) products in a 2:1 ratio (equation 2).

$$[(Pr^iO)_2PO]_2\,CLiMe + CF_3SCl \xrightarrow{AlCl_3} [(Pr^iO)_2PO]_2CClMe$$
(**10**) (**11**) 40%

$$+ [(Pr^iO)_2PO]_2CMeSCF_3 \ldots \quad (2)$$
(**12**) 23%

We concluded that the trihalomethanesulphenyl chlorides are ambident electrophiles whose sulphenylating activity is subject to steric hindrance leading to nucleophilic attack at chlorine by bulky nucleophiles.

The products of each of the above reactions can readily be purified by flash chromatography affording the product esters as oils. These have been fully characterised by n.m.r., i.r., and mass spectrometry (Table 2). Some of the more readily available products were transesterified by bromotrimethylsilane to give the tetrakistrimethylsilyl esters in quantitative yield. These esters were hydrolysed without purification using aqueous methanolic sodium hydroxide solution to give the tetrasodium salts of the corresponding free acids (**13a—d**) (Scheme 5).



Scheme 5. *Reagents:* i. Me_3SiBr; ii, MeOH–water–NaOH.

These sodium salts are water-soluble species which are stable in water under ambient conditions and neutral pH (Table 3). Their potential as analogues of pyrophosphoric acid is under further examination.

Experimental

Tetraisopropyl methylenebisphosphonate was obtained from Lancaster Synthesis Ltd. Bromotrimethylsilane, sodium, sodium hydride (60% dispersion in mineral oil), sodium hydroxide, and n-butyl-lithium (1.6M in n-hexane) were purchased from Aldrich Chemicals. Sodium hydride was washed free from mineral oil using dry ether. Silica gel 60 (230—400 mesh ASTM) was obtained from Merck, Darmstadt. Tetraisopropyl ethylidene-1,1-bisphosphonate was prepared as described by Quimby[1] and the trihalogenomethanesulphenyl chlorides were made by the methods of Tullock[21] and of Kühle.[22] 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 (FT) instrument in the deuterium-locked mode on $CDCl_3$ solutions for esters and on aqueous (20% D_2O) solution for sodium salts. ^1H N.m.r. spectra were recorded using a Perkin-Elmer R34 (220 MHz CW) machine with $SiMe_4$ as internal standard. I.r. spectra were determined on liquid films with a Perkin-Elmer 45F instrument and mass spectra were measured on a Kratos MS80 machine using ammonia chemical ionisation with data analysis provided by a Nova 4X accessory. Ether refers to diethyl ether.

General Preparation of $[(Pr^iO)]_2C(R)SCCl_nF_{3-n}$.—Tetraisopropyl methylenebisphosphonate (0.01 mol, 3.4 g) was dissolved in dry ether (15 ml) under nitrogen. Butyl-lithium (0.01 mol in hexane) was slowly added *via* syringe under nitrogen at a temperature below 25 °C. In reactions employing sodium or sodium hydride, the ester was added to the base dispersed in ether (20 ml). A slightly cloudy solution of the sodium salt (**1**) resulted which was filtered under positive pressure of nitrogen into a dropping funnel and thence added dropwise to a solution of the sulphenyl chloride (0.02 mol) in dry ether (20 ml), with prior addition of aluminium trichloride (0.01 mol) as appropriate. After 4 h, water (10 ml) was added and the organic layer separated. The aqueous layer was extracted with ether (20 ml) and the combined ether layers dried ($MgSO_4$). Volatiles were removed under reduced pressure and the yellow residues purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1 v/v). The recovered tetraisopropyl methylenebisphosphonate (**2**) can be reused after distillation.

Products (**11**) and (**12**) were prepared similarly from tetraisopropyl ethylidene-1,1-bisphosphonate (0.01 mol). Yields and physical data for the newly formed compounds are recorded in Tables 1—3, and Schemes 2 and 3. The chlorinated products, tetraisopropyl chloromethylenebisphosphonate[1] (**7**), dichloromethylenebisphosphonate[1] (**8**), and 1-chloroethylidene-1-1-bisphosphonate[1] (**11**) were characterised by ^{31}P n.m.r. and mass spectroscopy only.

Reactions of (**1**) *with Trichloromethanesulphenyl Chloride and Lithium Fluoride.*—Tetraisopropyl methylenebisphosphonate (0.01 mol) in dry ether (15 ml) was treated as above with butyl-lithium (0.01 mol in hexane) and then with trichloromethanesulphenyl chloride (0.02 mol) in the presence of an excess of dry lithium fluoride (0.06 mol). The reaction was monitored continuously by ^{19}F n.m.r. for the formation of (**3**), (**5**), and (**9**), characterised by the appearance of weak multiplets at −42.4, −28.2, and −17.6 p.p.m. respectively. Their intensity was gauged at *ca.* 1% yield by comparison with solutions of authentic samples.

* However, the reaction between (**1**) and trifluoromethyldisulphane, $(CF_3S)_2$, gave a product which showed traces of tetraisopropyl 1,1-bistrifluoromethylthiomethylenebisphosphonate, $[(Pr^iO)_2PO]_2C(SCF_3)_2$, (*m/z* 545, $M + H^+$) admixed with (**3**) as the major product.

A similar reaction with 4 h incubation of the reagents and removal of volatiles under reduced pressure prior to the addition of lithium fluoride in dry ether did not lead to the appearance of any of the above n.m.r. signals.

Hydrolysis of the Esters (**3**)—(**4**) *and* (**12**) *to give the Tetrasodium Salts* (**13a**—**d**).—Bromotrimethylsilane (22 mmol) was added slowly *via* syringe through a septum cap under nitrogen to a solution of the tetraisopropyl ester (5 mmol). After 8 h, volatiles were removed under reduced pressure and an aqueous methanolic solution of sodium hydroxide (20 mmol) was added in portions. After 15 min volatiles were removed under reduced pressure to leave the sodium salts of the appropriate methylenebisphosphonates (**13a**—**d**) in an analytically pure state and in quantitative yield. Spectroscopic data are recorded in Table 2.

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