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Syntheses of some fluorine-containing halomethanephosphonate and methylenebisphosphonate esters

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Abstract

The Michaelis–Becker reaction between diethyl sodiophosphite and either of the halofluoromethanes CF_2Cl_2 and CF_3Br gives tetraethyl difluoromethylenebisphosphonate. By contrast, the corresponding reaction with $CFCl_3$ gives not only diethyl dichlorofluoromethanephosphonate but also tetraethyl pyrophosphate as the major product. Diethyl dichlorofluoromethanephosphonate, readily prepared by a normal Arbusov reaction from CCl_3F, reacts with diethyl sodiophosphite to give tetraethyl fluoromethylenebisphosphonate thereby providing a simple efficient, and inexpensive synthesis of this useful material.

Introduction

The synthesis and reactions of esters of halofluoromethanephosphonic and fluoromethanephosphonic acids has commanded significant attention in recent years. Soborovski and Baina prepared esters of difluoromethanephosphonic acid (1) by the reaction of chlorodifluoromethane with dialkyl sodiophosphites [1]. In a similar way, the esters of chlorofluoromethanephosphonic (**2**) and fluoromethanephosphonic (**3**) acids have been prepared from dichlorofluoromethane [2] and bromofluoromethane [3,4*], respectively. Although iodotrifluoromethane reacts with elemental phosphorus and has thereby provided an early indirect route [5] to the synthesis of trifluoromethane-phosphonic, -phosphorous, and -phosphinous acids, photochemical activation is required [6] to bring about an Arbuzov synthesis of trifluoromethanephosphonate esters (**4**).

$(EtO)_2P(O)CFXY$

(**1**) X = H, Y = F
(**2**) X = H, Y = Cl
(**3**) X = Y = H
(**4**) X = Y = F
(**5**) X = Br, Y = F
(**6**) X = Y, = Br
(**10**) X = Cl, Y = F
(**11**) X = Y = Cl
(**14**) X = Br, Y = H

$\{(EtO)_2P(O)\}_2CXY$

(**7**) X = Y = F
(**8**) X = H, Y = F
(**9**) X = Y = H
(**12**) X = Cl, Y = F
(**13**) X = Y = F, Et = Me_2CH

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* Reference with asterisk indicates a note in the list of references.

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Burton and Flynn have described the preparation of bromodifluoromethanephosphonate (**5**) and dibromofluoromethanephosphonate (**6**) esters [7] and the former has been employed [8] in an efficient synthesis of esters of difluoromethylenebisphosphonic acid (**7**). More recently the latter esters (**6**) have been used [10] in a synthesis of tetraisopropyl fluoromethylenebisphosphonate (**8**) as an alternative to the earlier route involving the fluorination of esters of methylenebisphosphonic acid (**9**) by perchloryl fluoride [9,11] (a reagent with hazardous properties).

Our work on the use of fluoroalkylphosphonic acids as analogues of biological phosphate esters [12] has made significant use of carbanions derived from fluoromethane-, difluoromethane-, and chlorofluoromethane-phosphonic esters [2,13–15]. To this end, and in order to complete a systematic study of the second dissociation constants of fluorohalomethanephosphonic acids [16], we required viable syntheses of esters of the unknown chlorodifluoromethanephosphonic acid (**10**) and the poorly defined [17] dichlorofluoromethanephosphonic acid (**11**) in addition to needing a simplified route for the preparation of sizeable quantities of esters of chlorofluoromethanephosphonic acid (**2**). The relatively high volatility [18*] of CF_3Br and CF_2Cl_2 and the established inertness of CF_3Cl and CF_3I in a thermal Arbusov process [cf. 19] suggested that the Michaelis–Becker reactions of these Freons was worthy of investigation. We here describe the results of that study.

Results and discussion

When dichlorodifluoromethane was bubbled through a cold slurry of diethyl sodiophosphite in toluene, none of the anticipated diethyl chlorodifluoromethanephosphonate (**10**) was produced but, instead, tetraethyl difluoromethylenebisphosphonate (**7**) was obtained in 40% yield. The same phosphite anion reacted similarly with bromotrifluoromethane to give **7** in similar yield and none of the expected ester **4** was detected.

$$2(EtO)_2PONa + CF_2XY \rightarrow \underset{(\mathbf{7})}{\{(EtO)_2PO\}CF_2} + NaX + NaY$$

$(X = Y = Cl \text{ or } X = F,\ Y = Br)$.

Such a one-step synthesis of an alkylidenebisphosphonate is relatively rare [10]. The reaction between diethyl sodiophosphite and diiodomethane leads to disodium *P,P'*-diethylmethylenebisphosphonate [20] although the photochemical reaction of this anion with dibromomethane or bromochloromethane at low temperature has been reported [21] to give tetraethyl methylenebisphosphonate (**9**). The closest precedent for this reaction is the one-step reaction between dibutyl sodiophosphite and dibromodifluoromethane to give tetrabutyl difluoromethylenebisphosphonate, albeit in low yield [22]. Hutchinson has significantly improved this process through the use of the sodium salt of diisopropyl phosphite [10]. This leads to the difluoromethylenebisphosphonate ester (**13**) in yields which are comparable to those obtained in the earlier two-step procedure [9] and which involves the intermediate formation of **5**.

$$\underset{(\mathbf{5})}{(RO)_2P(O)CF_2Br} + (R'O)_2PONa \rightarrow (RO)_2P(O)CF_2Na + (R'O)_2P(O)Br \rightarrow$$

$$(RO)_2P(O)CF_2P(O)(OR')_2$$
$$(\mathbf{7})R = Et; \quad (\mathbf{13})R = Me_2CH \qquad (1)$$

The mechanism of this process clearly requires the abstraction of a bromine cation by the phosphite anion and subsequent phosphorylation of the resulting carbanion (eq. 1). In support of this view, we have shown that **11** is converted into **2** by treatment with diethyl sodiophosphite in the presence of an excess of diethyl phosphite. Such an X-philic [23] mechanism is consistent with both of the following observations:

(a) the four C-1 Freons, $CHClF_2$, $CHCl_2F$, CH_2ClF, and $CHBr_2F$ react with diethyl sodiophosphite to give, as expected, the Michaelis–Becker products **1**, **2**, **3**, and **14**, respectively;

(b) tetraethyl fluoromethylenebisphosphonate (**8**) is formed rather than the expected [17] chlorofluoromethylenebisphosphonate (**12**) from the reaction between **11** and diethyl sodiophosphite.

All these processes are centred on the intermediate existence of a bis(halogenomethanephosphonate) carbanion, $(RO)_2P(O)CX_2$, and Savignac [24] has constructed a variety of useful syntheses around this system, notably for the preparation of certain bisphosphonates.

Burton also has found evidence for the intermediacy of $(RO)_2P(O)CF_2^-$, and has suggested [25] that it can dissociate to give difluorocarbene. He has invoked that process to explain [7] the formation of mixed esters of **7** in the reaction between **5** and dibutyl sodiophosphite. Accordingly, we sought to trap difluorocarbene by carrying that reaction out in cyclohexene [26] solution but without success. However, we note that the course of the reaction responds to the change from toluene to cyclohexene solvent since the reaction of diethyl sodiophosphite with CCl_2F_2 gives not only **7** but also useful yields of the novel diethyl chlorodifluoromethanephosphonate (**10**), which we have been able to isolate and purify by distillation and chromatography.

$$(EtO)_2PONa + CCl_2F_2 \rightarrow \underset{(\mathbf{7})}{\{(EtO)_2PO\}_2CF_2} + \underset{(\mathbf{10})}{(EtO)_2P(O)CClF_2} \qquad (2)$$

It therefore seemed reasonable to attempt the preparation of chlorofluoromethylbisphosphonate esters from the corresponding reaction between diethyl sodiophosphite and trichlorofluoromethane. Contrary to expectation, the reaction provided only small yields of diethyl dichlorofluoromethanephosphonate (**11**), and the toxic tetraethyl pyrophosphate was the major product. This process is akin to that described by Todd [27] for the reaction of dialkyl phosphites with carbon tetrachloride in the presence of tertiary amines.

In order to study this process more closely, we prepared diethyl dichlorofluoromethanephosphonate (**11**) by an Arbusov reaction between triethyl phosphite and CCl_3F, which was readily accomplished using an autoclave to contain the low-boiling Freon. Diethyl ethanephosphonate was formed as a by-product which could not readily be removed by distillation but proved not to interfere with the further investigation or use of **11**.

When the ester **11** was treated with an excess of diethyl sodiophosphite, tetraethyl fluoromethylenebisphosphonate (**8**) was produced in excellent yield and there was no detectable formation of tetraethyl pyrophosphate. The sole contaminant was diethyl ethanephosphonate, which was readily removed by distillation. We also found that the treatment of **11** with diethyl sodiophosphite in the presence of an excess of diethyl phosphite gave the ester **2**. It is thus apparent that this is a double

X-philic reaction which involves initially the formation of diethyl phosphorochloridate and the anion of **2**, which then recombine to generate **11**. This bisphosphonate is then dechlorinated in a second X-philic process that gives the anion of **8** as the stable end-product of the reaction.

The contrast with the reaction involving CBr_3F is noteworthy. Clearly, much depends [10] on the increased stability of the C–Cl bond in the chloromethanephosphonate species **11** and on the difference in reactivity between diethyl phosphorochloridate and diethyl phosphorobromidate towards diethyl sodiophosphonate, which must be responsible for the non-formation of tetraethyl pyrophosphate in the present work.

$$(EtO)_2PONa + CCl_2FP(O)\underset{\mathbf{(11)}}{(OEt)_2} \rightarrow (EtO)_2POCl + (EtO)_2P(O)CClFNa \rightarrow$$

$$\underset{\mathbf{(12)}}{\{(EtO)_2PO\}_2CClF} + (EtO)_2PONa \rightarrow \{(EtO)_2PO\}CFNa + (EtO)_2POCl \qquad (3)$$

In our hands, this process has proved to be the most practical route for the efficient preparation of **8** in large quantity. It is both less expensive and less hazardous than the previously published route involving the fluorination of tetraethyl methylenebisphosphonate by perchloryl fluoride [9,11] which also suffers from the drawback of generating the difluoromethylenebisphosphonate ester as a byproduct which has to be removed by chromatography. It has a number of advantages over the related Hutchinson synthesis [10] starting from CBr_3F. First, it employs a less expensive Freon (fluorotrichloromethane is used inter alia as a dry-cleaning solvent). Secondly, it gives the tetraethyl ester **8** which we have found in previous work [2,15] to be superior to the sterically-hindered tetraisopropyl ester of **8** for use in Wadsworth–Emmons condensations. Thirdly, it avoids contamination of the desired product with tetraethyl pyrophosphate, which is stated [10] to be not easily removed from the required product. Finally, the ester **8** can be obtained in 95% purity without chromatography and used as such in Wadsworth–Emmons condensations without further purification.

Experimental

^{1}H NMR spectra were recorded on a Perkin–Elmer R24 instrument at 220 MHz with tetramethylsilane as internal standard. ^{31}P and ^{19}F NMR were recorded on a Bruker 80SY instrument at 32.4 and 75.4 MHz, respectively, with broad band decoupling and referenced to external 85% phosphoric acid and fluorotrichloromethane, respectively. The spectra were of $CDCl_3$ solutions (Table 1).

Mass spectra were determined on a Kratos MS80 machine using chemical ionisation with ammonia as reagent gas [28]. The data were processed with a Kratos DS55 data system. Analytical TLC was performed on Merck silica gel 60 F254 on 0.25 mm layered plates, and spots were revealed by use of a spray of 2% w/v $CoCl_2$ and 2% w/v NH_4SCN in ethanol.

Diethyl sodiophosphite was routinely prepared from sodium sand (23 g, 1 mol) or sodium hydride (24 g, 1 mol, thrice washed with toluene) and diethyl phosphite (138 g, 1 mol) in toluene under nitrogen.

Table 1

NMR data for phosphonate esters (in solution in $CDCl_3$)

Compound	Chemical shifts δ (ppm) and spin–spin coupling constants *J* (Hz)		
	^1H	^{31}P	^{19}F
$\{(EtO)_2PO\}_2CFH$ **(8)**	1.40(12H,t,*J*(HH)6.7); 4.32(8H,m).	11.1(d,*J*(PF)63.3)	−228.4 (dt,*J*(FH)46.0, *J*(PF)63.3)
$\{(EtO)_2PO\}_2CF_2$ (7)	1.40(12H,t,*J*(HH)8.3); 4.38(8H,m).	3.5(t,*J*(PF)86.1)	−121.9(t,*J*(PF)85.9)
$(EtO)_2P(O)CCl_2F$ **(11)**	1.43(6H,t,*J*(HH)7.2); 4.43(4H,m)	2.3(d,*J*(PF)87.9)	−73.5(d,*J*(PF)88.6)
$(EtO)_2P(O)CClF_2$ **(10)**	1.37(6H,t,*J*(HH)7.1; 4.3(4H,m)	−0.4(t,*J*(PF)101.5)	−65.7(d,*J*(PF)101.8)
$(EtO)_2P(O)CClFH$ **(2)**	1.41(6H,t,*J*(HH)7.2); 4.40(4H,m); 6.27(1H,dd,*J*(PH)9.8, *J*(FH)46.4)	7.37(d,*J*(PF)77.7)	−106.0(dd,*J*(PF)77.7, *J*(FH)46.4)

Synthesis of phosphonates

Tetraethyl difluoromethylenebisphosphonate (7). A suspension of diethyl sodiophosphite (0.43 mol) in toluene (150 ml) was stirred under nitrogen while either dry dichlorodifluoromethane or bromotrifluoromethane gas was introduced through a sintered glass bubbler. The temperature of the mixture was maintained below −15 °C with external cooling and by regulating the gas flow until the exothermic phase of the reaction was complete. The clear, syrupy, orange solution was washed with water (2 × 100 ml), dried with $MgSO_4$, and evaporated in vacuo. The residual oil was distilled to give a forerun of diethyl phosphite and diethyl ethanephosphonate (b.p. 35–50 °C/0.1 mmHg), followed by the title compound (27.5 g, 37%, b.p. 112–120 °C/0.1 mmHg). Analysis, Found: C, 33.2; H, 6.2. $C_9H_{20}F_2O_6P_2$ calc.: C, 33.3; H, 6.2%.

Diethyl chlorodifluoromethanephosphonate (10). A suspension of diethyl sodiophosphite (0.217 mol) in toluene (40 ml) was evaporated under nitrogen and the residue was suspended in cyclohexene (50 ml) and treated with dichlorodifluoromethane gas at −5 °C under nitrogen as above. After 1 h, the solution was brought to room temperature, when a vigorous reaction ensued with the formation of an orange gelatinous precipitate. The organic phase was worked up as above and distilled to give the crude product, (7.3 g, b.p. 66–70 °C/0.1 mmHg), and tetraethyl difluoromethylenebisphosphonate (10.2 g, b.p. 116–120 °C/0.1 mmHg). The title compound was further purified by redistillation and chromatography on Merck silica 60H with petroleum ether (40–60)/ethyl acetate (1/1) as eluent. Mass spectrum (NH_3/CI) $(M+H)^+$ m/z 223 (100%) and 225 (33%).

Diethyl dichlorofluoromethanephosphonate (11). A mixture of triethyl phosphite (484.5 g, 2.92 mol) and fluorotrichloromethane (687.5 g, 5 mol) was heated in a rocking autoclave for 8 h at 180 °C. The black oily product was flash-distilled to give the crude product (400 g, b.p. 35–70 °C/0.1 mmHg). ^{31}P NMR spectroscopy showed this to be a mixture of the required product (30%), diethyl ethanephosphonate (60%), and triethyl phosphite (10%). Distillation under vacuum through a column (20 × 400 mm) packed with Fenske glass helices gave a fraction (200 g, b.p. 35–60 °C), which was largely diethyl ethanephosphonate containing some 15% of

11, while the undistilled pot residue (200 g) contained the required product contaminated with some 30% of diethyl ethanephosphonate. This material was used without further purification for conversion into the bisphosponate ester **10**.

Tetraethyl fluoromethylenebisphosphonate (8). A suspension of diethyl sodiophosphite (0.38 mol) in toluene (100 ml) was stirred under nitrogen at $-12°C$ while crude diethyl dichlorofluoromethanephosphonate (0.126 mol) was added dropwise. The mixture was kept below $-8°C$ by regulating the rate of addition of **11**. The reaction was then quenched by addition of saturated sodium bicarbonate solution (150 ml) at $-4°C$ and the orange organic solution worked up as above. Distillation of the oily product gave a first fraction (40 g, b.p. 55–60°C/0.1 mmHg), shown by ^{31}P NMR to be a mixture of diethyl ethanephosphonate, triethyl phosphate, and diethyl chlorofluoromethanephosphonate (**2**). The title compound (33 g, b.p. 120–122°C/0.1 mmHg) was found to be $> 95\%$ pure by ^{31}P NMR analysis, and identical to an authentic sample [9].

Reaction of diethyl sodiophosphite with fluorotrichloromethane. A suspension of diethyl sodiophosphite (0.434 mol) in toluene (200 ml) was stirred and treated with a solution of fluorotrichloromethane (60 g, 0.434 mol) in toluene (50 ml) at $-35°C$ under nitrogen. When the mixture was warmed to $-10°C$ an exothermic reaction set in, and the temperature rose to 25°C. After the usual work up the organic product distilled to give two fractions. The first fraction, diethyl dichlorofluoromethanephosphonate (**11**) (25.2 g, b.p. 35–70°C) was further purified by chromatography on silica, with petroleum ethyl acetate (1/1) as eluent. Mass spectrum (NH_3/CI) $(M+H)^+$ m/z 239 (100%), 241 (80%), and 243 (12%). The second fraction, tetraethyl pyrophosphate (34.6 g, b.p. 90–100°C) was essentially pure. Mass spectrum (NH_3/CI) $(M+H)$ m/z 290. ^{31}P NMR δ -1.0; ^{1}H NMR δ 1.43 (12H, t, J 7.3 Hz) and 4.05 (8H, dq, J 7.3 Hz, 8 Hz, POCH).

Reaction between diethyl dichlorofluoromethanephosphonate and diethyl sodiophosphite in the presence of excess diethyl phosphite. Diethyl dichlorofluoromethanephosphonate (0.216 mol) was added slowly at $-15°C$ to a well stirred mixture of diethyl sodiophosphite (0.08 mol) and diethyl phosphite (0.12 mol) in toluene (35 ml). The temperature was held below 0°C for 1 h and the reaction then quenched by the addition of water (50 ml). The toluene solution was separated, washed with sodium bicarbonate solution, dried ($MgSO_4$), and evaporated in vacuo. The major product was identified by ^{1}H, ^{19}F, and ^{31}P NMR as diethyl chlorofluoromethanephosphonate, identical with the authentic sample of **2** prepared above.

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