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Synthetic and mechanistic aspects of halo-F-methylphosphonates

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ABSTRACT

The synthesis of a variety of new halo-F-methylphosphonates has been achieved by a Michaelis–Arbuzov type reaction between a halo-F-methane and a trialkyl phosphite. This synthesis has proved to be of wide scope and utility for the high yield preparation of a number of heretofore unknown compounds. The ^{1}H, ^{19}F, ^{13}C and ^{31}P NMR spectroscopic properties are reported in detail. The mechanism for the formation of bromodifluoromethylphosphonates has been shown to proceed through the intermediacy of difluorocarbene:CF_2. The phosphonate products have been shown to react with a wide variety of reagents. Fluoride and alkoxide ions react by attack at phosphorus with cleavage of the carbon–phosphorus bond and formation of [:CF_2] from the bromodifluoromethylphosphonates and the $CFBr_2^-$ anion from the dibromofluoromethylphosphonates. Iodide ion and tertiary phosphines react by attack at the ester carbon to give stable phosphonate salts. Hydrolysis of the phosphonate esters with 50% aqueous HCl gives the expected phosphonic acids. Trimethylsilyl bromide attacks phosphoryl oxygen to afford the bis(trimethylsilyl) esters.

1. Introduction

The synthesis and chemistry of polyfluoroalkyl phosphines and phosphoranes has been extensively reported in the chemical literature. For example, polyfluorinated phosphonium salts have been synthesized and found to be effective ylide precursors for the preparation of a variety of fluoromethylene olefins as well as precursors to halo-F-carbenes and halo-F-methyl carbanions [1]. In contrast to this chemistry, there has been relatively little work done in the investigation of fluoroalkyl phosphonates, especially the halo-F-methyl derivatives even considering the fact that phosphonic acids and their derivatives are more numerous than any of the other compounds containing the carbon–phosphorus bond [2]. We have previously reported our preliminary work on the synthesis of these halo-F-methyl phosphonates [3] and with this paper will discuss the complete details of their synthesis, the mechanism of their formation as well as the multi-centered reactivity of this interesting class of compounds.

Prior to this work there were only a few reports of any halo-F-methyl phosphonic acid derivatives. Emeleus and co-workers [4] had reported the difficult preparation of the trifluoromethyl phosphonic, phosphorous and phosphinous acids by an oxidative hydrolysis of trifluoromethylphosphine derivatives. Little further chemistry of these materials was reported at that time though the infrared spectrum of diethyl trifluoromethylphosphonate was later reported by McIvor [5] with no preparative details given. Fluoromethyl and difluoromethylphosphonates have been prepared by the reaction of a sodium dialkyphosphite with CH_2BrF or CF_2HCl respectively [6,7].

The Michaelis–Arbuzov reaction is by far the most widely employed method for the synthesis of phosphonate esters [8]. CF_3Cl and CF_3I were found to be inert to the reaction with either triethyl phosphite or sodium diethyl phosphite [9]. $CFCl_3$ was reported to react with triethyl phosphite under rigorous conditions (elevated temperature in a sealed tube) to afford the fluorodichloromethyl phosphonate although no analytical data was presented in proof of the structure [10]. The early failures or difficulty in the synthesis of these phosphonates probably discouraged further attempts at this chemistry. We now wish to expand on our earlier report on the facile Michaelis–Arbuzov reaction that the halo-F-methanes CF_2Br_2 (**1**) and $CFBr_3$ (**2**) undergo with alkyl phosphites. The halo-F-methyl phosphonate esters can be obtained in good to excellent yields in a very simple synthetic procedure and have been found to undergo a variety of reactions.

2. Results and discussion

2.1. Synthesis

When an equimolar amount of **1** is added to an ice cold solution of triethyl phosphite in the absence of a solvent, a short induction period is followed by an extremely vigorous reaction. However when the reaction is carried out in a solvent such as triethylene

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glycol dimethyl ether (triglyme, TG) or diethyl ether (EE) as a diluent the Michaelis–Arbuzov reaction occurs smoothly and readily at either room temperature or with diethyl ether, at reflux temperature and requires no special precautions, as shown in Eq. (1).

$$(EtO)_3P + CF_2Br_2(\mathbf{1}) \rightarrow (EtO)_2P(O)CF_2Br(\mathbf{4}) + EtBr \quad (1)$$

Details of the reactions and workup procedures can be found in Section 4. In addition to **1** and **2**, other halo-F-methanes including CF_2BrI and CF_2BrCl also have been found to undergo this reaction and yield phosphonates as the final products. Table 1 is a compilation of the compounds prepared and their yields as well as some solvent comparisons.

The yields of phosphonate products generally range from good to excellent. The lower yields observed in the two autoclave reactions with CF_2BrCl (Entry 17 in Table 1) and, as previously reported, $CFCl_3$ (Entry 16) can be ascribed to the significantly reduced reactivity of these two halo-F-methanes *vs.* the highly reactive **1** and **2**. Diethyl ether is the most convenient solvent for these reactions since it is easily dried and easy to separate from the product (e.g. Entry 2). The use of triglyme as solvent was found to give somewhat lower yields (see Entry 3), probably due to losses during the workup procedures. In addition, triglyme cannot typically be completely removed from the product phosphonates by distillation and is removed by brine washes prior to final purification by distillation. One important exception to note is that the reaction of trimethyl phosphite with **1** is very slow in diethyl ether while reaction in triglyme solvent is complete in 24 h (Entry 1).

On the other hand it was found that the reaction between $CFBr_3$ **2** and trialkylphosphites was most conveniently carried out neat with no additional solvent (Entries 9, 13, and 14). For these reactions, it is possible to simply mix together the phosphite and **2** at room temperature. After a short induction period, the exothermic reaction will occur with a rise in temperature to about 65 °C. After the exotherm is over the reaction is essentially complete and the product can be isolated by vacuum distillation.

As noted above the only halo-F-methane previously reported to react with triethyl phosphite was $CFCl_3$. In an attempt to duplicate this report, the reaction between $CFCl_3$ and triethyl phosphite was carried out in a 125 mL Hastelloy C autoclave at 120 °C and autogenous pressure (Entry 16). After workup and distillation of the products, it was found that in addition to the expected diethyl fluorodichloromethylphosphonate **15**, there were also three other components which were identified by NMR: $(EtO)_2P(O)H$, $(EtO)_2P(O)C_2H_5$ and $(EtO)_3P(O)$. The diethyl ethylphosphonate probably arises directly from the reaction of the co-product C_2H_5Cl with triethyl phosphite in a Michaelis–Arbuzov reaction. In a similar reaction, it was found that although CF_2BrCl did not react with triethyl phosphite at room temperature in triglyme or under the action of ultraviolet light, it did react in a similar manner to $CFCl_3$ in an autoclave (Entry 17). The only fluorinated phosphonate formed in this reaction was **4**. No $(EtO)_2P(O)CF_2Cl$ was observed.

Table 1
Halo-F-methylphosphonates. $(RO_3)P$ + halo-F-methane → $(RO)_2P(O)CFXY$[a] + RZ.[a]

Entry	No.	R	Halo-F-methane	CFXY	Solvent	Yield (%)[b]
1.	**3**	CH_3	CF_2Br_2	CF_2Br	TG	55
2.	**4**	C_2H_5	CF_2Br_2	CF_2Br	EE	95
3.	**4**	C_2H_5	CF_2Br_2	CF_2Br	TG	55
4.	**5**	n-C_3H_7	CF_2Br_2	CF_2Br	EE	55
5.	**6**	i-C_3H_7	CF_2Br_2	CF_2Br	TG	42
6.	**6**	i-C_3H_7	CF_2Br_2	CF_2Br	EE	75
7.	**7**	n-C_4H_9	CF_2Br_2	CF_2Br	EE	65
8.	**8**	i-C_4H_9	CF_2Br_2	CF_2Br	Neat	81
9.	**9**	CH_3	$CFBr_3$	$CFBr_2$	Neat	46
10.	**10**	C_2H_5	$CFBr_3$	$CFBr_2$	EE	78
11.	**10**	C_2H_5	$CFBr_3$	$CFBr_2$	TG	60
12.	**11**	i-C_3H_7	$CFBr_3$	$CFBr_2$	EE	22
13.	**12**	n-C_4H_9	$CFBr_3$	$CFBr_2$	Neat	63
14.	**13**	i-C_4H_9	$CFBr_3$	$CFBr_2$	Neat	53
15.	**14**	C_2H_5	CF_2BrI	CF_2I[c]	TG	60[c]
16.	**15**	C_2H_5	$CFCl_3$	$CFCl_2$	Neat[d]	27
17.	[e]	C_2H_5	CF_2BrCl	CF_2Br	Neat[d]	20

[a] X, Y = F, Cl, Br, I; Z = Br, Cl, I.
[b] Isolated yield based on phosphite.
[c] $(EtO)_2P(O)CF_2I$ **14** and **4** in 7/1 ratio.
[d] Reaction carried out in 125 ml Hastelloy C bomb under autogenous pressure.
[e] **4** only product formed.

In contrast to these unreactive halo-F-methanes, CF_2BrI reacted rapidly with triethyl phosphite at room temperature in triglyme (Entry 15). Two products were formed in a 7.5/1 ratio by NMR. The minor product was identified as **4** by comparison with an authentic sample. Distillation of the product, after removal of the more volatile components (found to be ethyl bromide and ethyl iodide in a 7.5/1 ratio) afforded diethyl iododifluoromethylphosphonate **14**. In diethyl ether as solvent, <1% of **4** was formed. This result will be discussed in detail in the mechanism.

In addition to the trialkyl phosphites listed in Table 1, a number of other phosphites were investigated. Triphenyl phosphite, tris-2-chloroethyl phosphite and sodium diphenyl phosphite did not react with **1** at either ambient temperature or at 80 °C to yield any phosphonate products. Somewhat surprisingly, ethyl diphenyl phosphite also did not react with **1** even at 170 °C in a pressure vessel. Apparently the substitution of a single phenyl group with an ethyl group did not give a phosphite which was appreciably more reactive than triphenyl phosphite itself. However, benzyl diethyl phosphite reacted readily with **1** to give **4** as the only product. No trace of the other possible Michaelis–Arbuzov product $(PhCH_2O)(EtO)P(O)CF_2Br$ was observed. An alternative preparation of **4** has been reported *via* the reaction of **1** with trialkyl phosphites in the absence of solvent. For safety purposes we prefer that the reaction be carried out in a solvent as diluent since the reaction can be highly exothermic [11].

As further examples of the generality of this reaction, it was found that diethyl phenyl phosphonite and ethyl diphenyl phosphinite both reacted readily with **1** giving the expected products ethyl bromodifluoromethylphenylphosphinate **16** and bromodifluoromethyldiphenylphosphine oxide **17** respectively as illustrated in Eq. (2).

$$\begin{aligned} &PhP(OEt)_2 + CF_2Br_2 \rightarrow \underset{\mathbf{16}}{PhP(O)(OEt)CF_2Br} \\ &Ph_2POEt + CF_2Br_2 \rightarrow \underset{\mathbf{17}}{Ph_2P(O)CF_2Br} \end{aligned} \quad (2)$$

A photochemical modification of the Michaelis–Arbuzov reaction to prepare halo-F-methylphosphonates which are not amenable to the reaction scheme described here has been reported previously, as shown below in Eq. (3) [12].

$$(EtO)_3P + CF_3I \xrightarrow{\text{uv light}} (EtO)_2P(O)CF_3 + EtBr \quad (3)$$

2.2. Spectroscopic properties of Halo-F-methylphosphonates

The ^1H, ^{19}F, ^{13}C and ^{31}P NMR data for the phosphonates prepared are detailed in Section 4. The ^{19}F NMR spectrum of the phosphonates exhibits in all cases a doublet due to the fluorine phosphorus coupling with $^2J_{PF}$ coupling constants in the range of 77 up to 93 Hz for the halofluoromethyl phosphonates up to 124 Hz for the previously reported $(EtO)_2P(O)CF_3$ [12]. These coupling constants display a moderate correlation with the Pauling electronegativity of the halo-F-methyl group attached to the phosphorous. The electronegativity values were calculated by summation of the electronegativities of the halo-F-methyl substituents, excluding phosphorus, using the Pauling elemental

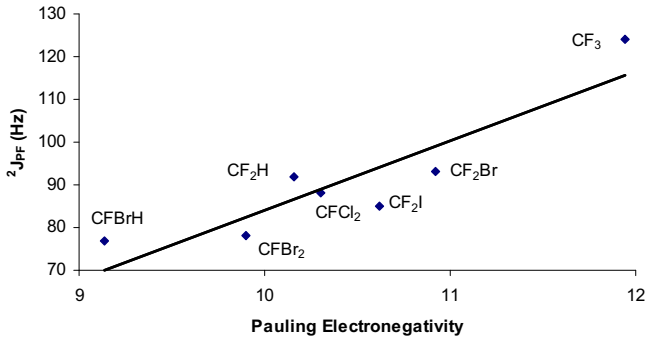


Fig. 1. $^2J_{PF}$ *vs.* Pauling electronegativity of halo-F-methyl group.

electronegativities as calculated by Allred [13]. This method was proved to be of value previously in the correlation of the ^{19}F NMR chemical shift and $^2J_{PF}$ coupling constants of a series of fluorinated quaternary phosphonium salts [14].

The ^{31}P NMR chemical shifts range from −2.6 to 7.5 and exhibit the expected multiplicity for coupling to fluorine. No correlation was observed for these chemical shifts with either the electronegativity of the halo-F-methyl group or with the variation of the substituents in the ester portion of the phosphonates (Fig. 1).

The interpretation of the ^{1}H NMR spectra is straightforward although the similarity of the $^3J_{HH}$ and $^3J_{HP}$ coupling constants led to multiplets which were not completely resolved and usually gave a multiplicity less than what would otherwise be expected. For example, in most cases, the methylene protons in the CH_3CH_2OP grouping appear to be a pentet, the methylene hydrogens in CH_2CH_2OP a quartet and so on. These couplings are described in Section 4 as "apparent" pentets, or quartets and the like and the "apparent" coupling constants given without regard to the nuclei which are coupled.

The ^{13}C NMR chemical shifts for the halo-F-methyl carbon atoms range from 84 to 120 ppm and are roughly correlated to the Pauling electronegativity of the halo-F-methyl carbon in the same manner as described above for the $^2J_{PF}$ coupling constants (Fig. 2).

No correlation was found to exist for the $^1J_{CF}$ with the alkyl substituents at phosphorus or with the Pauling electronegativity of the halo-F-methyl group. On the other hand the $^1J_{CP}$ values, while independent of the alkyl groups in the ester portion of the molecule, do correlate nicely with the Pauling electronegativities as shown in Fig. 3. The sensitivity of the $^1J_{CP}$ values to changes in the electronegativity at carbon has been previously observed and a rationale has been outlined to account for it [15,16]. The magnitude of this coupling constant is directly proportional to the degree of "s" character in the phosphorus–carbon bond and increases as the "s" character of the bond increases.

The carbons alpha and beta to oxygen in the ester portion of the phosphonates were also observed to couple to phosphorus while

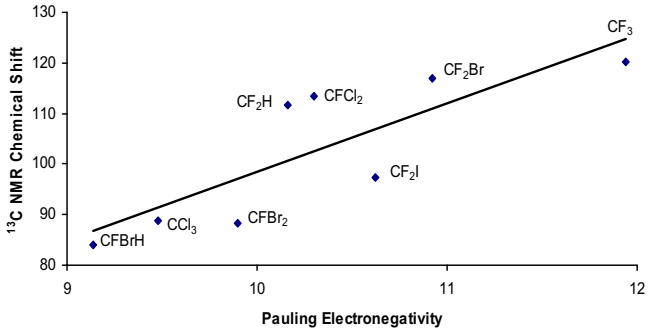


Fig. 2. ^{13}C NMR chemical shift *vs.* Pauling electronegativity of halo-F-methyl group.

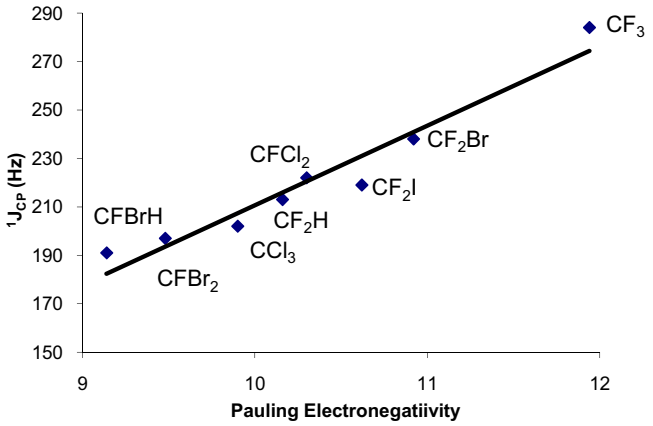
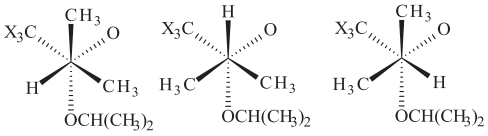
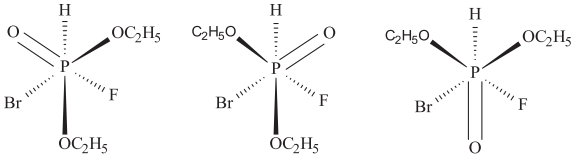


Fig. 3. $^1J_{CP}$ *vs.* Pauling electronegativity of halo-F-methyl group.

any carbons further away were always singlets. Several compounds showed more complex coupling patterns. For example, the isopropyl groups of compounds **6** and **11** show non-equivalent carbon atoms in the ^{13}C NMR spectra and thus show two doublets in the spectra instead of a simple doublet. In these cases, the phosphorus atom acts as a center for magnetic asymmetry as shown in the following projections along the C–O–P bonds (which is shown as linear for simplicity). It is obvious that the two methyl groups are non-equivalent in any rotamer. This non-equivalence was not observed at the relatively low 60 MHz resolution NMR but was easy to detect in the carbon NMR spectrum.



Diethyl bromofluoromethylphosphonate **20** whose preparation is described in Section 4 also exhibited non-equivalency of the two methylene carbons of the ester group. This compound is the only material prepared which has an asymmetric carbon contained within the molecule giving rise to this non-equivalency. A view along the phosphorus–bromofluoromethyl bond makes this non-equivalence clear.



As shown in the three rotamers, the methylene carbons are never in identical environments and hence are magnetically non-equivalent. The ethyl bromodifluoromethyl phenyl phosphinate **16** was also spectroscopically of interest. The four substitutents on phosphorus render the molecule asymmetric which should lead to non-equivalence of the CF_2 fluorines. Although this non-equivalence was slight (the ^{31}P NMR spectrum of **16** showed only a triplet), the ^{19}F NMR spectrum was an ABX pattern as would be expected for non-equivalent coupled fluorine atoms (i.e. a doublet of doublets – the outer weak lines were not observed). The observed spectrum matched the calculated spectrum very well [17].

2.3. Reactions of halo-F-methyl phosphonates

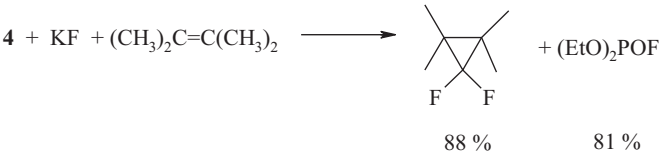
From a consideration of the general structure of a halo-F-methyl phosphonate, one can see that there are at least five

potential reactive sites within the molecule: (1) the ester carbon, (2) phosphorus, (3) phosphoryl oxygen, (4) halo-F-methyl carbon and (5) halogen. Reactions have been observed at all of these sites with the exception of **4**.

2.3.1. Reaction at phosphorus

Both fluoride anion as well as alkoxide anion were found to be effective in attack at the phosphorus atom. The driving force for these reactions is presumably the strength of the phosphorus–fluorine bond [18] (117 kcal/mol) and the phosphorus–oxygen bond (97 kcal/mol) as opposed to the phosphorus–carbon bond (63 kcal/mol).

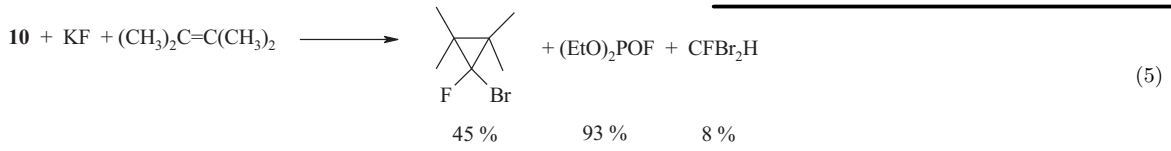
Potassium fluoride reacts with **4** to cleave the carbon–phosphorus bond and generate difluorocarbene which was readily trapped with 2,3-dimethyl-2-butene to afford the corresponding difluoromethylenecyclopropane in an 88% (^{19}F NMR) yield. When repeated on a larger scale, this cyclopropane was isolated in 63% yield as shown in Eq. (4).



(4)

The phosphorofluoridate $(EtO)_2POF$ was also observed in 81% yield but in general these materials were not isolated since this particular class of compounds is exceedingly toxic [19]. In a similar manner, 2-methyl-2-butene gave the cyclopropane in a 66% glpc yield and cyclohexene yielded 7,7-difluoronorcarane in a 30% (^{19}F NMR) yield.

The reaction of **10** with KF in the presence of 2,3-dimethyl-2-butene gave the corresponding bromofluoromethylenecyclopropane in a 45% (^{19}F NMR) yield as well as $CFBr_2H$ in an 8% (^{19}F NMR) yield, as illustrated in Eq. (5).



(5)

The reaction of **10** with KF in the presence of ethanol afforded $CFBr_2H$ (67% yield, ^{19}F NMR) and a 72% yield of the phosphorofluoridate. However the similar reaction of **4** with $KF{\cdot}2H_2O$ gave only the phosphorofluoridate with none of the anticipated CF_2BrH. These results suggest that, in the reaction of **10** with KF, the initial step is the attack by fluoride ion on phosphorus with the ejection of the $CFBr_2^-$ anion. In the case of **4**, the attack by fluoride does not generate the CF_2Br^- anion as a discreet entity, since it would be expected that this anion would be trapped by the proton source present. It is also possible that the lifetime of the CF_2Br^- anion in this system is very short and that it decomposes into bromide and difluorocarbene which then undergoes decomposition but there is no experimental evidence to support this hypothesis.

The reaction of fluoride ion with bis(trimethysilyl) bromodifluoromethylphosphonate (prepared as discussed below) was carried out to determine which site in the molecule would undergo attack by fluoride. Since the typical fluorine–silicon bond has a bond strength of about 129 kcal/mol and the typical phosphorus–fluorine bond is 117 kcal/mol, it might be expected that fluoride ion would attack silicon. When this reaction was thus carried out in the presence of 2-methyl-2-butene, the major product as characterized by ^{19}F NMR was Me_3SiF. Only a trace of the cyclopropane and phosphorofluoridate were observed indicating that fluoride ion did indeed predominately attack silicon. The structure of the product silane was further confirmed by repeating this reaction on a larger scale with isolation of the silane by glpc on Column B followed by GC–MS.

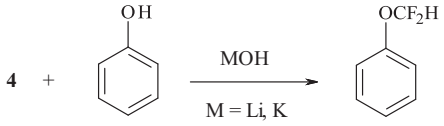
Table 2
Difluoromethyl ethers from 4 + alkoxide, $(EtO)_2P(O)CF_2Br + RONa \xrightarrow{ROH} ROCF_2H$.

R	Solvent	Product	Yield (%)[b]
CH_3	CH_3OH	CH_3OCF_2H	52
C_2H_5	C_2H_5OH	$C_2H_5OCF_2H$	56
CF_3CH_2	TG	$CF_3CH_2OCF_2H$	58
Ph	CH_3OH	CH_3OCF_2H	46
		$PhOCF_2H$	11

[a] Sodium salt formed by reaction of an excess of alcohol in the given solvent with sodium metal except for sodium phenoxide which was formed by the reaction of phenol with NaOH in methanol.
[b] ^{19}F NMR yield *vs.* $PhCF_3$ internal standard; chemical shifts of the product ethers agree well with reported values.

Alkoxide ion has also been observed to attack phosphorus in **4** with the formation of $[:CF_2]$ carbene which can be trapped in moderate yield by the alkoxide in the presence of excess alcohol to give the corresponding difluoromethyl ethers. Table 2 tabulates the ethers prepared in this reaction.

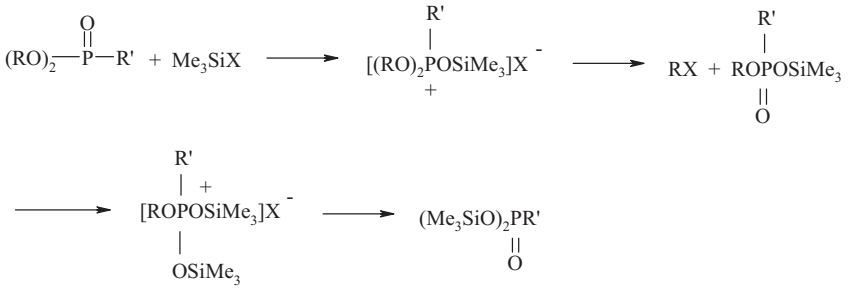
Note that the primary product from the reaction of phenoxide with **4** is difluoromethyl methyl ether rather than phenyl difluoromethyl ether. The large excess of the solvent methanol, which is an excellent trapping agent for $[:CF_2]$, served to scavenge much of the difluorocarbene generated in the reaction. The co-product in these reactions is the trialkyl phosphate. Recently Zafrani et al. have shown that the reaction of **4** with phenols and thioethers leads to good to excellent yields of the corresponding difluoromethyl ethers or thioethers. The reaction with phenol is shown below in Eq. (6) [20].



(6)

2.3.2. Reaction at oxygen

Trimethylsilyl halides are known to react with alkyl phosphonates by attack at the phosphoryl oxygen to give good yields of the bis(trimethylsilyl) esters with the alkyl halide as co-product [21,22]. In phosphonates of general structure $(RO)_2P(O)R'$, when R′ is an alkyl group and bromotrimethylsilane (Me_3SiBr) is the silylating agent, the reaction is rapid at room temperature. With a more electron withdrawing group such as trichloromethyl, the reaction proceeds slowly at room temperature and requires elevated temperatures to achieve goods yields in a reasonable time (Scheme 1).



Scheme 1. Reaction of phosphonate with trimethylsilyl halide.

Both **4** and **10** reacted with Me_3SiBr at 60 °C to give the corresponding bis(trimethylsilyl) esters which could be distilled at reduced pressure. These esters were hydrolytically unstable to solvolysis by water or methanol to give the phosphonic acids. This exchange reaction can be monitored by ^{31}P NMR which shows the growth of a signal intermediate in chemical shift between the starting material and the final bis(trimethylsilyl) phosphonate ester. After the starting material phosphonate has been completely consumed, this intermediate signal subsequently decreases as the product bis(trimethylsilyl) ester signal continues to increase and can confidently be ascribed to the intermediate alkyl trimethylsilyl ester. It was found that **10** underwent this exchange reaction at a much faster rate than **4**, giving the desired bis(trimethylsilyl) phosphonate after 2 h heating at 60 °C while **4** required the addition of a larger excess of trimethylsilyl bromide and heating to 60 °C for at least 24 h. In view of the mechanism above, this is not unexpected since the positive charge which develops in the transition state would be expected to be destabilized to a greater extent by the adjacent CF_2Br group in **4** *vs.* the $CFBr_2$ group in **10**.

The primary synthetic utility for these bis(trimethylsilyl) esters is their hydrolysis to the corresponding phosphonic acid. Solvolysis occurs rapidly and quantitatively with water or methanol. Methanol is particularly convenient since the co-product methyl trimethylsilyl ether can be easily removed from the phosphonic acid product by azeotropic distillation with the excess methanol. It was also found that simply refluxing either **4** or **10** with 50% aqueous HCl also sufficed to prepare the phosphonic acids and this method was generally used to make larger quantities of these acids.

2.3.3. Reaction at ester carbon

Iodide: Sodium iodide is a known useful reagent for the removal of alkyl groups, particularly benzyl, from phosphorus esters [23]. For phosphonates, generally monodealkylation occurs [24]. It was found that sodium iodide (or potassium iodide) in acetone reacts rapidly and quantitatively with either **4** or **10** to give the monodealkylated product as shown below in Eq. (7).

$$(EtO)_2P(O)R + NaI \xrightarrow[R=CF_2Br\ \mathbf{4};CFBr_2\ \mathbf{10}]{} Na^+O_2^-P(OEt)R + C_2H_5I \quad (7)$$

Even when an excess of sodium iodide was employed, only the monosodium salt of the phosphonate was observed. The salts prepared in this manner can be converted into the corresponding acids by passage through an ion exchange column.

Phosphines: The reaction of **4** with triphenyl phosphine in refluxing 1,2-dimethoxyethane was found to proceed relatively slowly according to the following Eq. (8).

$$Ph_3P + \mathbf{4} \rightarrow [Ph_3PEt]^+[O_2^-P(OEt)CF_2Br] \quad (8)$$

Acidifying this reaction mixture with HCl/ether caused the precipitation of a tan solid which was characterized as ethyltriphenylphosphonium chloride. The reaction between triphenyl phosphine and **3** was found to be rapid and gave a 50% isolated yield of the corresponding phosphonium salt, illustrated by Eq. (9).

$$Ph_3P + (MeO)_2P(O)CF_2Br(\mathbf{3}) \rightarrow [Ph_3PMe]^+[O_2^-P(OMe)CF_2Br] \quad (9)$$

2.3.4. Reaction at halogen

The reaction of the halo-F-methylphosphonates with phosphite anion proceeds by attack on halogen and has been previously reported [25]. For the bromodifluoromethylphosphonates, positive halogen abstraction generates the F-methylene phosphonate ylide which undergoes subsequent acylation with the phosphoryl halide produced in the first step and provided the first useful route to F-methylene bis(phosphonates). F-methylene bis(phosphonates) have subsequently been reported by Ishihara and detailed below in Eq. (10) [26].

$$(BuO)_2P(O)CF_2Br + (BuO)_2P(O)Na \rightarrow (BuO)_2P(O)CF_2^-Na^+ + (BuO)_2P(O)Br \rightarrow (BuO)_2P(O)CF_2P(O)(OBu)_2 \quad (10)$$

2.4. Mechanism of formation of halo-F-methyl phosphonates

The reaction between triethyl phosphite and **1** has been studied in depth and various details of the mechanistic aspects of this reaction have been determined. The Michaelis–Arbuzov reaction of alkyl halides with trivalent phosphorus compounds generally proceeds by an S_N2 attack of phosphorus on the halogen bearing carbon atom followed by a dealkylation step of the intermediate phosphonium salt as shown in Eq. (11).

$$(RO)_3P + R'X \rightarrow [(RO)_3PR']^+X^- \rightarrow (RO)_2P(O)R' + RX \quad (11)$$

This reaction mechanism is not observed for the reaction between triethyl phosphite and **1**. In this reaction the initial attack by phosphorus is on halogen with the concomitant formation of difluorocarbene [$:CF_2$]. The carbene is subsequently trapped by additional phosphite which is transformed through a series of steps into the final phosphonate product.

The S_N2 reaction at carbon mechanism was eliminated as a viable mechanistic pathway by analysis of the reactions of $(EtO)_3P$ with CF_2BrI and CF_2BrCl. If a simple S_N2 mechanism were operative, the reaction of $(EtO)_3P$ with CF_2BrI would be expected to yield **4** as the sole or at least major product. In a similar manner the reaction with CF_2BrCl would be expected to yield the chlorodifluoromethyl phosphonate. In both cases the better leaving group would be displaced in the formation of the intermediate phosphonium salt. The halide anion of the salt would then dealkylate the salt to give the expected phosphonate product and alkyl halide. Examples are shown below in Eqs. (12) and (13).

$$(EtO)_3P + CF_2BrI \rightarrow (EtO)_2P(O)CF_2Br + EtI \quad (12)$$

$$(EtO)_3P + CF_2BrCl \rightarrow (EtO)_2P(O)CF_2Cl + EtBr \quad (13)$$

When these reactions were carried out, however, the results were completely opposite to these expectations. The reaction of triethyl phosphite with CF_2BrI yielded the two products **4** and **14** in a 1 to 7.5 ratio. This ratio was also observed for the co-products ethyl bromide and ethyl iodide. With CF_2BrCl, the only product observed in the reaction with triethyl phosphite was **4** as detailed in Eqs. (14) and (15).

$$(EtO)_3P + CF_2BrI \rightarrow \underset{\mathbf{14}(7.5)}{(EtO)_2P(O)CF_2I} + \underset{\mathbf{4}(1)}{(EtO)_2P(O)CF_2Br} + EtI + EtBr \quad (14)$$

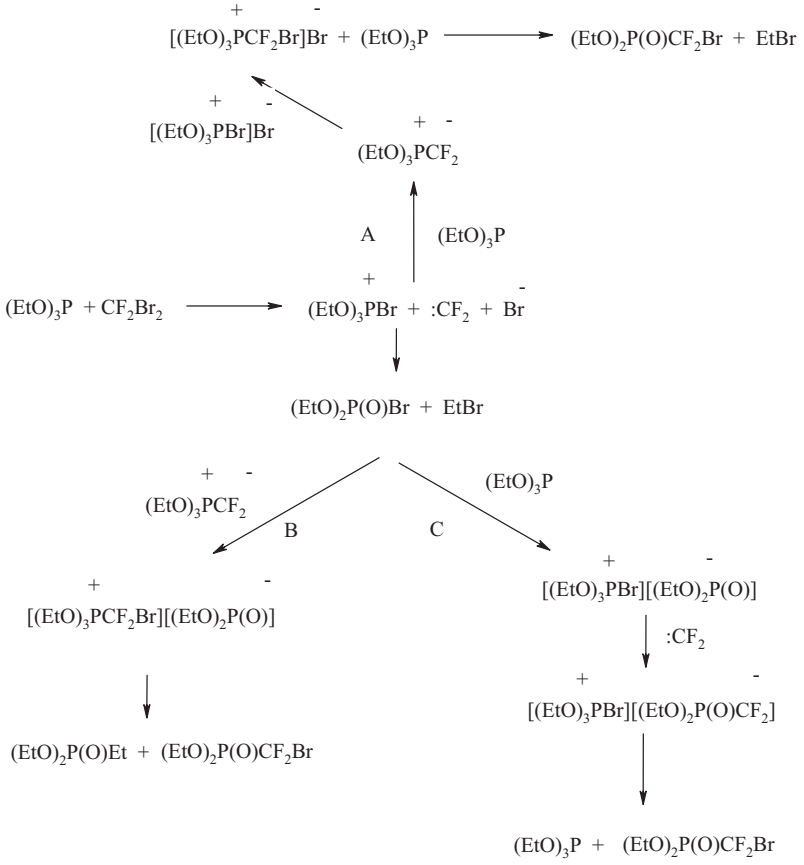
$$(EtO)_3P + CF_2BrCl \rightarrow (EtO)_2P(O)CF_2Br + EtBr \quad (15)$$

A radical pathway can be similarly eliminated since the predicted product of reaction of CF_2BrI with triethyl phosphite would again yield the opposite product mixture to that which was observed experimentally. In other words cleavage of CF_2BrI would yield the CF_2Br and I radicals. The trapping of the CF_2Br radical with phosphite and reaction of the resulting phosphoranyl radical with I radical would give the phosphonium salt $[(EtO)_3PCF_2Br]^+I^-$ which would further elaborate to a product mixture which was not observed. Furthermore when the reaction between CF_2Br_2 and triethyl phosphite was carried out in the presence of ethanol, no CF_2BrH, the expected product of the reaction of CF_2Br radical with ethanol, was observed.

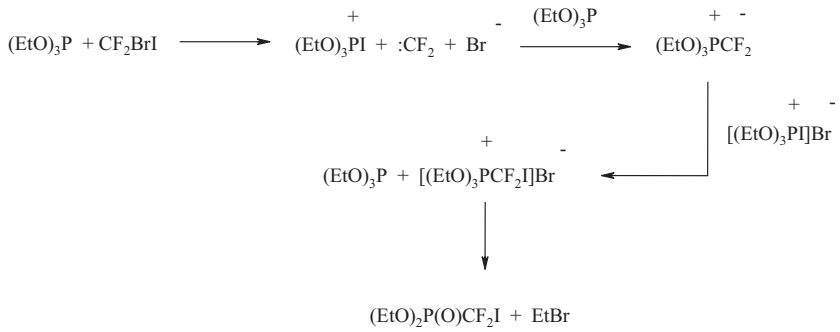
With the elimination of either an S_N2 or free radical mechanism as a viable pathway, a mechanism which involves nucleophilic attack by phosphorus on halogen remains to be considered. Nucleophilic attack by phosphorous on halogen is well-known in the literature and has been reviewed [27]. Several examples of halogen attack are also known in the reactions of tertiary phosphines with polyfluorinated methanes [28,29]. This mechanism is outlined in detail in Scheme 2.

This mechanism will now be analyzed in detail. First of all as outlined in the partial mechanism (Scheme 3) for the reaction of CF_2BrI with triethyl phosphite, the halogen which is abstracted in the first step is the halogen which is found in the final phosphonate product. A similar mechanism can be inferred for the reaction of the phosphite with CF_2BrCl. The triethyl phosphite would preferentially abstract the most polarizable halogen from each of these methanes, iodine for CF_2BrI and bromine for CF_2BrCl, leading to the observed products. For CF_2BrI this preference is not exclusive since some $(EtO)_2P(O)CF_2Br$ which arises from abstraction of positive bromine in the first step was also observed, but it was the minor product.

Paths B and C in Scheme 2 can be eliminated readily. These alternate pathways arise from consideration of another possible fate for the intermediate halophosphonium cation formed by the initial abstraction of bromine from CF_2Br_2 **1**. This cation is unstable and can decompose to diethyl phosphorobromidate and ethyl bromide as shown. In Path B, the ylide generated from more $(EtO)_3P$ and $[:CF_2]$ abstracts bromine from the cation to give the intermediate trialkoxyphosphonium/phosphonate ion pair which would then be expected to collapse to **4** and diethyl ethylphosphonate. This path can at best account for only a very small part of the reaction since no diethyl ethylphosphonate was observed as a by-product in the reaction mixture as determined by the absence of signals for this compound in H-1, P-31 and C-13 NMR. In addition this path consumes an additional mole of $(EtO)_3P$, but since yields of **4** in excess of 95% have been observed using a 1:1 stoichiometry of phosphite:**1**, this alternate path cannot be significant. If triethyl phosphite can abstract positive bromine from the phosphorobromidate, Path C arises and gives the product



Scheme 2. Mechanism of halophilic attack.



Scheme 3. Reaction of CF_2BrI with triethyl phosphite.

4 as shown in Scheme 2. Triethyl phosphite is known to react with $(EtO)_2P(O)Cl$ but the reaction only occurs at a temperature greater than 130 °C [30]. Although the bromidate would be more reactive than the chloridate it is doubtful that the reaction would proceed at room temperature. In addition another objection to both Paths B and C is that the diethyl phosphite anion which is produced in these pathways is a highly reactive species and has been found to react rapidly with the product phosphonate **4** at room temperature to afford a difluoromethylene(bis)phosphonate as shown below in Eq. (16) [25].

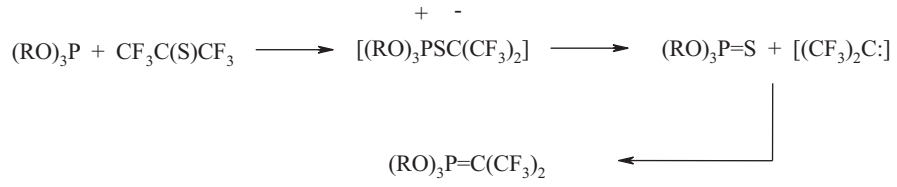
$$(EtO)_2PONa + (EtO)_2P(O)CF_2Br \rightarrow (EtO)_2P(O)CF_2P(O)(OEt)_2 \quad (16)$$

If any dialkyl phosphite were generated as an intermediate in this reaction, some (bis)phosphonate would likely have been observed by F-19 NMR analysis of the reaction mixture; however, none was detected. It is also known that dialkyl phosphonate anion does react rapidly with $(EtO)_2P(O)Cl$ to afford tetraethyl hypophosphate $(EtO)_2P(O)P(O)(OEt)_2$ in moderate yield [31]. Both of these secondary reactions would reduce the yield of the observed product **4** and hence can contribute very little to the overall mechanism.

As mentioned above, when the reaction between triethyl phosphite and **1** was carried out in the presence of ethanol in triglyme solvent, no CF_2BrH was observed. This result strongly implied that the abstraction of positive bromine from **1** produces difluorocarbene [$:CF_2$] and bromide directly without the intermediacy of the CF_2Br^- anion which if formed would be rapidly protonated by the ethanol. In Path A of Scheme 2, the difluorocarbene produced in this initial step is intercepted by another mole of the nucleophile triethyl phosphite to generate the difluoromethylene ylide intermediate which rapidly would be expected to abstract bromine from the bromophosphonium cation to generate the Michaelis–Arbuzov phosphonium salt with the regeneration of triethyl phosphite. The normal S_N2 internal attack of bromide on this salt then produces the observed phosphonate product and ethyl bromide. The overall stoichiometry of this reaction scheme is thus 1:1 phosphite/**1**. In our hands a 1:1 ratio of phosphite/**1** has led to yields in excess of 95% consistent with this mechanistic interpretation.

In an attempt to intercept the key difluorocarbene intermediate, the reaction between $(EtO)_3P$ and **1** was carried out in the presence of 2,3-dimethyl-2-butene. This NMR reaction showed an 88% yield of **4** with only a trace of the cyclopropane which suggests that the phosphite is a much better trapping agent for the carbene than the butene. A similar result was observed for the reaction of triethyl phosphite with CF_2BrI though in this case only the two expected phosphonate products were observed and none of the cyclopropane was seen.

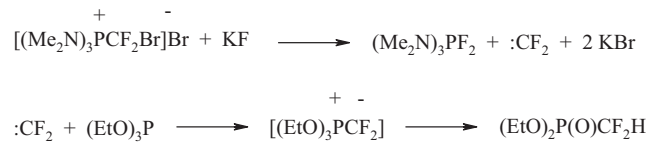
The trapping of difluorocarbene by triethyl phosphite is a crucial requirement for this mechanism. Middleton [32] has reported that hexafluorothioacetone reacts rapidly with trialkyl phosphites to afford trialkoxybis(trifluoromethyl)methylenephosphoranes in good yield. The postulated mechanism for this reaction was attack by phosphorus on sulfur to give an intermediate which collapsed to yield bis(trifluoromethyl)carbene and triethyl thiophosphate. The carbene was subsequently trapped by additional phosphite to give the isolated product as detailed in Eq. (17).



(17)

In other work, the irradiation of a mixture of trimethyl phosphite and bis(trifluoromethyl)diazirine gave an 18% yield of trimethyl bis(trifluoromethyl)methylenephosphorane [33]. It is known that the diazirine readily affords $[(CF_3)_2C:]$ carbene upon irradiation [34] and it was shown that the diazirine and trimethyl phosphite did not react in the absence of UV light [33]. The observed formation of the phosphorane is thus unequivocal evidence for the trapping of $[(CF_3)_2C:]$ by the phosphite.

Since it seemed unlikely that a better trapping agent than triethyl phosphite could be used in some other competitive reaction, a different approach to study the capture of [$:CF_2$] by triethyl phosphite was employed. A readily accessible source of difluorocarbene is $[Ph_3PCF_2Br]^+Br^-$. Under the action of KF, this phosphonium salt generates difluorocarbene at low temperature which can be readily trapped by for example 2,3-dimethyl-2-butene to give the cyclopropane [35]. In our case, under the required conditions of the reaction, it was found that triethyl phosphite reacted with this salt to give **4** in good yield in an



Scheme 4. Reaction of $[(Me_2N)_3PCF_2Br]^+Br^-$ with KF.

exchange reaction which we have previously reported Eq. (18) [36,37].

$$[Ph_3PCF_2Br]^+Br^- + (EtO)_3P \rightarrow Ph_3P + EtBr + (EtO)_2P(O)CF_2Br \quad (18)$$

Another phosphonium salt which is also a source of difluorocarbene is bromodifluoromethyl-tris-dimethylaminophosphonium bromide $[(Me_2N)_3PCF_2Br]^+Br^-$. When the reaction between this phosphonium salt, triethyl phosphite and ethanol was carried out in triglyme, no formation of the reduced phosphonium salt $[(Me_2N)_3PCF_2H]^+Br^-$,which would be formed by abstraction of positive bromide from the salt followed by protonation, was observed. Also no exchange reaction occurred between the salt and triethyl phosphite alone. The reaction between this salt, triethyl phosphite and KF was then carried out in triglyme solvent. Analysis of the reaction mixture showed the presence of $(Me_2N)_3PF_2$ (about 15% by NMR) and a low yield of the phosphonate $(EtO)_2P(O)CF_2H$ (16% NMR yield). Most of the remaining solid residue from the reaction was unreacted phosphonium salt. It thus appears that triethyl phosphite can trap difluorocarbene to yield an ylide intermediate which in this case abstracted a proton from one of the reagents (Scheme 4).

The difluoromethylene ylide in Path A of Scheme 2 is a key intermediate. This intermediate was successfully intercepted by carrying out the reaction between $(EtO)_3P$ and **1** in the presence of ethanol according to the stoichiometry shown in Eq. (19).

$$2(EtO)_3P + CF_2Br_2 + EtOH \rightarrow 2EtBr + (EtO)_2P(O)CF_2H + (EtO)_3P(O) \quad (19)$$

A control reaction between triethyl phosphite and ethanol did not yield any triethyl phosphate. The reaction between triethyl phosphite, ethanol and **1** (ratio of 1:1:1) yielded reduced difluoromethyl phosphonate and triethyl phosphate. The reduced phosphonate and triethyl phosphate were isolated by vacuum distillation as an inseparable 1:1 mixture [for a yield of 43% $(EtO)_2P(O)CF_2H$ **19** and 43% $(EtO)_3P(O)$]. These products could be readily separated by glpc and the peak assigned to triethyl phosphate was collected by the glpc capillary technique [38] and analyzed by mass spectrometry which gave a spectrum identical to that previously reported for triethyl phosphate. The reduced phosphonate was identified by comparison of its NMR spectral properties and glpc retention time with those of an authentic sample. In a similar reaction using a triethyl phosphite:ethanol:**1** ratio of 2:1:1, a 78% yield (glpc) of ethyl bromide was found along with 14% unreacted **1**. The ylide intermediate formed in Path A of Scheme 2 is protonated by ethanol to give the intermediate phosphonium salt with ethoxide as counter ion. This ethoxide anion can then attack the bromophosphonium cation with the formation of the very strong P–O bond with release of bromide. The newly formed mixture of salts can then decompose to the observed products (Scheme 5).

In summary, the key aspects of this mechanistic scheme for the reaction between $(EtO)_3P$ and **1** are as follows: (1) abstraction of positive bromine by phosphite with the concomitant formation of $[:CF_2]$; (2) interception of $[:CF_2]$ by phosphite to give an ylide intermediate; (3) abstraction of bromine from the halophosphonium cation by the ylide and (4) collapse of the resultant salt by internal S_N2 attack to give the observed products.

The mechanistic scheme for the reaction between trialkyl phosphites and $CFBr_3$ differs from that for the reaction with CF_2Br_2 although the initial step is the same. When the reaction between triethyl phosphite and $CFBr_3$ was carried out in the presence of ethanol in triglyme solvent, it was found that **10** and $CFBr_2H$ had been formed in NMR yields of 20% and 57% respectively with 10% unreacted $CFBr_3$ remaining. None of the reduced phosphonate $(EtO)_2P(O)CFBrH$ was observed. In a control reaction it was also found that **10** did not react with ethanol, as detailed in Eq. (20).

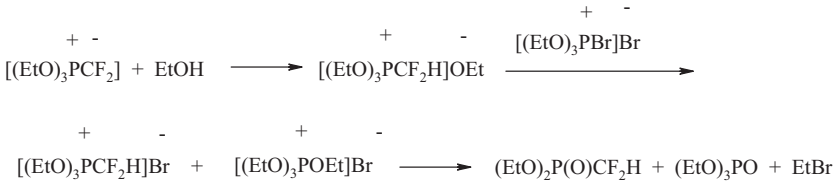
$$(EtO)_3P + CFBr_3 + EtOH \rightarrow CFBr_2H + (EtO)_2P(O)CFBr_2 \quad (20)$$

The mechanism which best fits this data is as follows in Scheme 6.

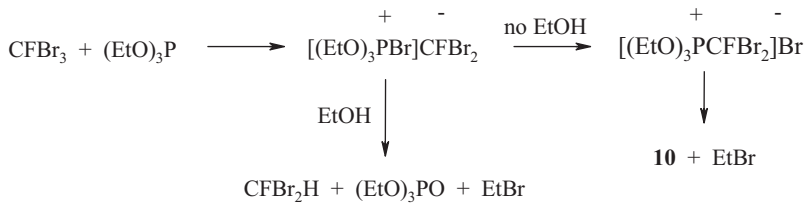
In the absence of ethanol, the initially formed phosphonium salt undergoes a recombination to a new Michaelis–Arbuzov type salt which then dealkylates to the observed products. In the presence of ethanol the $CFBr_2^-$ anion is captured to give $CFBr_2H$. Since some **10** is also formed in the presence of ethanol, one may conclude that the recombination of the initially formed salt is rapid and can compete with protonation.

More recent work that utilizes halo-F-methylphosphonates includes treatment of **10** with BuLi (1:1) at low temperature to afford by self-trapping the lithiated derivative of tetraethyl fluoromethylenediphosphonate, which can be derivatized with alkylating and halogenating agents or converted with high selectivity into (*E*)-diethyl fluorovinylphosphonates by reaction with carbonyl compounds [39]. Halo-F-methylphosphonate, **10**, has also been converted into diethyl-1-fluoromethylphosphonate *via* a halogen–metal exchange reaction between **10** and BuLi/$ClSiMe_3$ at −90 °C [40]. A one-pot conversion of trifluoroacetic esters to α-fluoro-β-trifluoromethyl-β-alkoxyvinylphosphonates has been achieved *via* a halogen–metal exchange reaction between **10** and 2 BuLi/$ClSiMe_3$ at −78 °C followed by addition of the trifluoroacetic ester [41]. The 1-lithio-1-fluoro-1-(trimethylsilyl) methylphosphonate, derived from **10**, reacts with chloroformates to give good yields of diethyl-1-fluoromethylphosphonocarboxylates. Reaction with CO_2 leads to a novel synthesis of diethyl-1-fluoromethylphosphonocarboxylic acid [42].

When **4** is treated with isopropylmagnesium chloride in THF at low temperature, $(EtO)_2P(O)CF_2MgCl$ is formed, which undergoes reaction with strong electrophiles, such as HCl, TMSCl, halogens, aldehydes and ketones. Product formation is strongly dependent on reaction conditions. 2-Hydroxyphosphonates formed from the



Scheme 5. Protonation of ylide intermediate.



Scheme 6. Reaction of $CFBr_3$ with triethyl phosphite.

reaction with aldehydes and ketones, undergo rearrangement in the presence of base (NaH, LDA) to afford 2,2-difluoroethylphosphonates without concomitant formation of 1,1-difluoroolefins [43].

3. Conclusion

The synthesis of a variety of halo-F-methylphosphonates in a Michaelis–Arbuzov type reaction has been shown to proceed in good yield to afford a number of previously unknown phosphonate esters. The mechanism of formation of **4** has been shown to proceed through the intermediacy of $[:CF_2]$ while **10** is formed *via* an intermediate $CFBr_2^-$ anion. The phosphonates have been found to undergo facile reaction with a variety of reagents at several positions in the molecule. Reagents studied include potassium fluoride, sodium alkoxides, trimethylsilyl bromide, sodium dialkyl phosphites, tertiary phosphines and sodium iodide.

4. Experimental

4.1. General experimental procedures

The ^{19}F NMR spectra were recorded on a Varian HA-100 Spectrometer operated at 94.075 MHz in the HR (non-lock) mode. The ^{19}F NMR spectra were typically obtained as 10–15% (w/v) solutions of a pure compound in $CDCl_3$ or as aliquots of reaction mixtures *vs.* an internal standard of $CFCl_3$ unless otherwise noted. Chemical shifts are reported as negative in ppm upfield of $CFCl_3$. Spectra were internally calibrated by the audio side band technique. Quantitative measurements were carried out by integration relative to an internal standard ($C_6H_5CF_3$). Routine ^1H NMR spectra were obtained as 10–15% (w/v) solutions of a pure compound in $CDCl_3$ or, occasionally, as aliquots of reaction mixtures *vs.* an internal standard of TMS on a Varian A-60 analytical NMR Spectrometer. Chemical shift values are reported in ppm downfield of TMS. ^{13}C NMR spectra were obtained as 15% (w/v) solutions in a suitable deuterated solvent (usually $CDCl_3$), which also provided the lock signal, on a Bruker HX-90E Spectrometer operated at 22.63 MHz *vs.* TMS as internal standard. In all cases, broad band proton decoupling was employed to simplify the spectra. Chemical shift values are reported in ppm downfield from TMS. ^{31}P NMR spectra were obtained as 15% (w/v) solutions of a pure compound in a suitable deuterated solvent (usually $CDCl_3$) which also provided the lock signal. The ^{31}P NMR spectra were obtained on a Bruker HX-90E Spectrometer operated at 36.435 MHz *vs.* 85% H_3PO_4 as the external standard. In most cases, broad band proton decoupling was employed to simplify the spectra. Chemical shift values, reported in ppm *vs.* external H_3PO_4, are assigned negative shifts when upfield and positive when downfield. Mass spectra were obtained on a Hitachi-Perkin Elmer RMU-6E Mass Spectrometer operated at 70 eV. Analytical GLPC were carried out on either an F & M Dual Column Gas Chromatograph Model 700, or when it was desired to collect a sample for mass spectral or C, H, N analysis on an F & M Dual Column Research Chromatograph Model 5750. Both instruments were equipped with TCD. The columns utilized in this work were as follows: Column A was a 10′ × 1/4″ column packed with 20% (w/w) Carbowax 20 M on 80-100 mesh Chromosorb P. Column B was a 10′ × 1/4″ column packed with 20% (w/w) SE-30 on 80-100 mesh Chromosorb P. Infrared spectra were obtained as thin films between NaCl plates in the case of liquid samples or as KBr pellets for solid samples on a Beckman IR-20A Infrared Spectrometer. C, H, N analyses were carried out by service personnel of this department on a Perkin Elmer 240 (automated) Elemental Analyzer. All melting points were obtained in capillaries on a Thomas-Hoover Unimelt apparatus and are uncorrected. All bp were determined during fractional distillation and are uncorrected. Potassium fluoride (J.T. Baker, anhydrous) was dried at 250 °C/0.5 mm Hg for 18 h and stored in a desiccator. Alternatively, KF was placed in an evaporating dish and heated to ~450 °C with a Bunsen burner. After breaking up of the initial crust which formed, the finely divided salt was heated for 1 h at 450 °C and transferred to a weighed container while still hot. Triglyme (triethylene glycol dimethyl ether) and other glymes were purified by distillation from a sodium benzophenone ketyl and stored in brown bottles over 4 Å molecular sieves. Diethylether was dried and stored over sodium wire in a brown bottle until used. Trichlorofluoromethane (Freon 11) and dibromodifluoromethane (Freon 12B2) were obtained commercially and used as obtained. Trifluoroethanol was obtained commercially and stored over 4 Å molecular sieves. Trimethyl, triethyl, tributyl and triisobutyl phosphites were obtained from commercial vendors, distilled from sodium metal under vacuum and stored in brown bottles over 4 Å molecular sieves. Triisopropyl, triphenyl and tris(2-chloroethyl) phosphites were obtained commercially and used as obtained. Diethylphenylphosphite was prepared from Et_3N, EtOH, and phenyldichlorophosphine in 59% yield (bp 70–73°/0.3 mm Hg). Tribromofluoromethane was prepared by the method of Birchall and Haszeldine [44] and stored in a refrigerator over copper wire. The salt $[(Me_2N)_3PCF_2Br]^+Br^-$ was prepared as previously described from this laboratory [45]. All other reagents were obtained from common commercial sources and used directly.

4.2. Preparation of halo-F-methylphosphonates in diethyl ether

4.2.1. Preparation of diethyl bromodifluoromethylphosphonate 4 in diethyl ether

A three-neck 1 l flask, fitted with a septum, stir bar, and a water condenser with a nitrogen inlet, was cooled in an ice bath. Dry ether (300 ml) and 99 g (0.6 mol) of triethylphosphite was added to the cooled flask, followed by addition (*via* syringe) of 134 g (0.64 mol) of dibromodifluoromethane **1**. The ice bath was removed and the reaction mixture refluxed for 24 h, followed by removal of the ether, excess **1** and ethyl bromide *via* rotary evaporation at reduced pressure. The remaining clear liquid was distilled under vacuum through a 6-in. Vigreaux column to give 150 g (95%) of diethyl bromodifluoromethylphosphonate (bp 99–102°/16 mm Hg). ^{19}F NMR($CDCl_3$) (ppm): $\delta = -61.9$ (d, $^2J_{PF} = 92$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = -1.2$ (t, $^2J_{PF} = 93$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 116.8$ (td, $^1J_{CF} = 330$ Hz, $^1J_{CP} = 238$ Hz),

δ = 66.3 ($^2J_{CP}$ = 7.4 Hz), δ = 16.4 (d, $^3J_{CP}$ = 5.88 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.41 (qd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 8.5 Hz), δ = 1.42 (t, $^3J_{HH}$ = 7.0 Hz). GC–MS, *m/z* (relative intensity): 268 (0.2), 266 (0.2), 137 (83), 109 (100), 93 (35), 91 (27), 81 (86), 65 (41), 29 (66): IR (P=O) 1285 cm^{-1}: Anal. Calcd. for $C_5H_{10}O_3PCF_2Br$: C, 22.47%; H, 3.75%. Found C, 22.34%; H, 3.80%.

4.2.2. Preparation of di-n-propyl bromodifluoromethylphosphonate 5 in diethyl ether

Similar to Section 4.2.1, di-n-propyl bromodifluoromethylphosphonate **5** was prepared from tri-n-propyl phosphite and **1** in 55% isolated yield (bp 79°/12 mm Hg). ^{19}F NMR($CDCl_3$) (ppm): δ = −61.4 (d, $^2J_{PF}$ = 92 Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ −0.6 (t, $^2J_{PF}$ = 93 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 116.9 (td, $^1J_{CF}$ = 329 Hz, $^1J_{CP}$ = 239 Hz), δ = 71.6 ($^2J_{CP}$ = 7.4 Hz), δ = 23.8 (d, $^3J_{CP}$ = 5.88 Hz), δ = 9.9 (s); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.23 (td, $^3J_{HH}$ = 6.6 Hz, $^3J_{HP}$ = 7.6 Hz), δ = 1.73 (apparent sextet, J = 7.0 Hz), δ = 0.97 (t, $^3J_{HH}$ = 7.0): IR (P=O) 1280 cm^{-1}: Anal. Calcd. for $C_7H_{14}O_3PCF_2Br$: C, 28.47%; H,4.75%. Found C, 28.78%; H, 4.95%.

4.2.3. Preparation of di-n-butyl bromodifluoromethylphosphonate 7 in diethyl ether

Similar to Section 4.2.1, di-n-butyl bromodifluoromethylphosphonate **7** was prepared from tri-n-butyl phosphite and **1** in 65% isolated yield (bp 107 °C/1 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): δ = −61.5 (d, $^2J_{PF}$ = 93 Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ −0.6 (t, $^2J_{PF}$ = 93 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 117.0 (td, $^1J_{CF}$ = 329 Hz, $^1J_{CP}$ = 238 Hz), δ = 69.9 ($^2J_{CP}$ = 7.4 Hz), δ = 32.5 (d, $^3J_{CP}$ = 5.89 Hz), δ = 18.6 (s), δ = 13.5 (s); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.25 (apparent quartet, J = 7.5 Hz), δ = 1.20–1.90 (multiplet), δ = 0.8–1.1 (multiplet): IR (P=O) 1283 cm^{-1}: Anal. Calcd. for $C_8H_{18}O_3PCF_2Br$: C, 33.44%; H, 5.57%. Found C, 33.64%; H, 5.93%.

4.2.4. Preparation of di-isopropyl dibromofluoromethylphosphonate 11 in diethyl ether

Similar to Section 4.2.1, di-isopropyl dibromofluoromethylphosphonate **11** was prepared from tri-isopropyl phosphite and **2** in 22% isolated yield (bp 81°/<1 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): δ = −77.2 (d, $^2J_{PF}$ = 80 Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ −0.2 (d, $^2J_{PF}$ = 78 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 89.2 (dd, $^1J_{CF}$ = 334 Hz, $^1J_{CP}$ = 204 Hz), δ = 76.1 ($^2J_{CP}$ = 7.4 Hz), δ = 24.2, 23.5 (signal appeared as two doublets due to magnetically non-equivalent geminal methyl groups, $^3J_{CP}$ = 5.9, 2.9); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.95 (apparent sextet, J = 6.5 Hz), δ = 1.44 (d, $^3J_{HH}$ = 6.0 Hz): IR (P=O) 1271 cm^{-1}.

4.3. Preparation of halo-F-methylphosphonates in triglyme

4.3.1. Preparation of 4 in triglyme

Similar to Section 4.2.1 (similar apparatus), 99 g (0.6 mol) of triethylphosphite and 134 g (0.64 mol) of **1** were stirred in triglyme (300 ml) for 24 h at RT. Flash distillation (RT, 15 mm Hg) removed most of the volatiles. The remaining solution was poured into an equal volume of ice water; the upper aqueous layer extracted with ether (2 × 100 ml) and the ether extracts combined with the lower layer. The combined layers were washed with a satd. NaCl solution (2 × 100 ml) to remove the triglyme. The remaining ether solution was dried over $CaSO_4$, the ether removed by rotary evaporation at reduced pressure and the residue distilled to give 88 g (55%) of **4** (bp 99–102°/16 mm Hg) – identical in all respects to **4** prepared in diethyl ether.

4.3.2. Preparation of dimethyl bromodifluoromethylphosphonate 3 in triglyme

Similar to Section 4.3.1, dimethylbromodifluoromethylphosphonate **3** was prepared from trimethylphosphite and **1** in 55% isolated yield (bp 85 °C/12 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): δ = −61.3 (d, $^2J_{PF}$ = 94 Hz); ^{31}P NMR ($CDCl_3$) (ppm): 1.5 (t, $^2J_{PF}$ = 94 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 116.3 (td, $^1J_{CF}$ = 329 Hz, $^1J_{CP}$ = 240 Hz), δ = 56.1 ($^2J_{CP}$ = 7.4 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.01 (d, $^3J_{HP}$ = 11 Hz). GC–MS, *m/z* (relative intensity): 159 (30), 109 (100), 93 (58), 81 (32), 79 (49), 59 (14), 47 (43), 15 (30); no molecular ion observed: IR (P=O) 1285 cm^{-1}.

4.3.3. Preparation of diisopropyl bromodifluoromethylphosphonate 6 in triglyme and diethyl ether

Similar to Section 4.3.1, diisopropyl bromodifluoromethylphosphonate was prepared from triisopropyl phosphite and **1** in 42% isolated yield (bp 98 °C/10 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): δ = −62.5 (d, $^2J_{PF}$ = 93 Hz); ^{31}P NMR ($CDCl_3$) (ppm): −2.6 (t, $^2J_{PF}$ = 93 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 117.8 (td, $^1J_{CF}$ = 329 Hz, $^1J_{CP}$ = 237 Hz), δ = 76.2 ($^2J_{CP}$ = 7.4 Hz), δ = 24.3 ($^3J_{CP}$ = 5.9 Hz), δ = 23.7 ($^4J_{CP}$ = 2.9 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.9 (unresolved sextet, J = 6.5 Hz), δ = 1.41 (d, $^4J_{HH}$ = 6 Hz). GC–MS, *m/z* (relative intensity): 123 (24), 109 (11), 83 (10), 45 (31), 43 (54), 42 (89), 41 (100), 40 (39), 39 (72); no molecular ion observed: IR (P=O) 1279 cm^{-1}: Anal. Calcd. for $C_7H_{14}O_3PCF_2Br$: C, 28.47%; H, 4.75%. Found C, 29.51%; H, 5.09%.

Similar to Section 4.2.1, diisopropyl bromodifluoromethylphosphonate was prepared from triisopropyl phosphite and **1** in 75% isolated yield using diethyl ether as the solvent with properties identical in all respects to the phosphonate prepared in triglyme.

4.3.4. Preparation of diethyl dibromofluoromethylphosphonate 10 in triglyme and diethyl ether

Similar to Section 4.3.1, diethyl dibromofluoromethylphosphonate was prepared from triethyl phosphite and **2** in 60% isolated yield ^{19}F NMR ($CDCl_3$) (ppm): δ = −76.5 (d, $^2J_{PF}$ = 77 Hz); ^{31}P NMR ($CDCl_3$) (ppm): 1.7 (t, $^2J_{PF}$ = 77 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 88.4 (dd, $^1J_{CF}$ = 334 Hz, $^1J_{CP}$ = 202 Hz), δ = 66.8 ($^2J_{CP}$ = 7.4 Hz), δ = 16.4 ($^3J_{CP}$ = 5.2 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.40 (unresolved pentet, J = 7.0 Hz), δ = 1.41 (t, $^3J_{HH}$ = 7.0 Hz). GC–MS, *m/z* (relative intensity): 193 (11), 191 (16), 138 (11), 137 (100), 110 (15), 109 (94), 93 (18), 91 (31), 81 (71), 65 (44), 59 (10), 47 (17), 45 (21), 29 (12); no molecular ion observed: IR (P=O) 1279 cm^{-1}.

Similar to Section 4.2.1, diethyl dibromofluoromethylphosphonate was prepared from triethyl phosphite and **2** in 78% isolated yield using diethyl ether as the solvent with properties identical in all respects to the phosphonate prepared in triglyme (bp 79 °C/<1 mm Hg).

4.3.5. Preparation of 14 and 4 by reaction of triethyl phosphite with CF_2BrI

Similar to Section 4.3.1, diethyl iododifluoromethylphosphonate **14** and **4** were prepared from triethyl phosphite and CF_2BrI in 60% isolated yield in a 7.5/1 ratio. The minor product was confirmed to be **4** by spiking of the NMR sample with authentic **4** prepared as described previously. Flash distillation of the crude reaction mixture at 10 mm Hg into a dry ice/isopropanol cooled trap gave a liquid which was shown to be a mixture of ethyl bromide and ethyl iodide in a 7.5/1 ratio, identified by comparison of their glpc retention times with authentic samples. The residue was vacuum distilled and the fraction at bp = 64–66 °C/0.5 mm Hg identified as pure **14**. ^{19}F NMR ($CDCl_3$) (ppm): δ = −59.3 (d, $^2J_{PF}$ = 85 Hz); ^{31}P NMR ($CDCl_3$) (ppm): −2.7 (t, $^2J_{PF}$ = 86 Hz); ^{13}C NMR ($CDCl_3$) (ppm): δ = 97.4 (td, $^1J_{CF}$ = 332 Hz, $^1J_{CP}$ = 219 Hz), δ = 66.3 ($^2J_{CP}$ = 7.4 Hz), δ = 16.4 ($^3J_{CP}$ = 5.9 Hz); ^{1}H NMR ($CDCl_3$) (ppm): δ = 4.37 (unresolved pentet, J = 7.0 Hz), δ = 1.41 (t, $^3J_{HH}$ = 7.0 Hz); GC–MS, *m/z* (relative intensity): 187 (29), 156 (26), 137 (53), 109 (100), 93 (50), 81 (89), 65 (58), 45 (51), 29 (100); molecular ion observed at 314: IR (P=O) 1282 cm^{-1}.

4.4. Preparation of halo-F-methylphosphonates "neat"

4.4.1. Preparation of dibutyl dibromofluoromethylphosphonate 12

A 25 ml one-neck round bottom flask with septum port was equipped with a magnetic stir bar and a water condensor topped by a glass tee leading to a source of dry nitrogen and a mineral oil bubbler. To the flask was added tri-n-butyl phosphite (6.25 g, 0.025 mol) and **2** (6.78 g, 0.025 mol). After an induction period of about 10 min, the flask became warm as the reaction progressed. After stirring overnight, the residue was distilled to yield 6 g (63%) of dibutyl dibromofluoromethylphosphonate (bp 117–125 °C/0.6 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -75.9$ (d, $^2J_{PF} = 78$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ 1.5 (d, $^2J_{PF} = 77$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 88.4$ (dd, $^1J_{CF} = 334$ Hz, $^1J_{CP} = 202$ Hz), $\delta = 70.4$ (d, $^2J_{CP} = 7.4$ Hz), $\delta = 32.5$ (d, $^3J_{CP} = 5.9$ Hz), $\delta = 18.6$ (s), $\delta = 13.5$ (s); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 4.34$ (apparent quartet, $J = 7.0$ Hz), $\delta = 1.20$–2.0 (multiplet), $\delta = 0.95$ (multiplet): IR (P═O) 1275 cm^{-1}: Anal. Calcd. for $C_9H_{18}O_3PCFBr_2$: C, 33.44%; H, 5.57%. Found C, 33.64%; H, 5.93%.

4.4.2. Preparation of diisobutyl dibromofluoromethylphosphonate 13 "neat"

Similar to Section 4.4.1, diisobutyl dibromofluoromethylphosphonate **13** was prepared from triisobutyl phosphite and **2** in 53% yield (bp 145 °C/1 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -75.9$ (d, $^2J_{PF} = 77$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ 2.3 (d, $^2J_{PF} = 77$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 88.2$ (dd, $^1J_{CF} = 334$ Hz, $^1J_{CP} = 203$ Hz), $\delta = 76.2$ (d, $^2J_{CP} = 8.1$ Hz), $\delta = 29.3$ (d, $^2J_{CP} = 5.9$ Hz), $\delta = 18.5$ (s); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 4.10$ (apparent triplet, $J = 6.5$ Hz), $\delta = 2.0$ (multiplet), $\delta = 1.0$ (d, $^3J_{HH} = 6.5$ Hz): IR (P═O) 1275 cm^{-1}: Anal. Calcd. for $C_8H_{18}O_3PCF_2Br$: C, 28.13%; H, 4.69%. Found C, 29.56%; H, 4.95%.

4.4.3. Preparation of diisobutyl bromodifluoromethylphosphonate 8 "neat"

Similar to Section 4.4.1, diisobutyl dibromofluoromethylphosphonate **13** was prepared from triisobutyl phosphite and **2** in 53% yield (bp 145 °C/1 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -75.9$ (d, $^2J_{PF} = 77$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): δ 2.3 (d, $^2J_{PF} = 77$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 88.2$ (dd, $^1J_{CF} = 334$ Hz, $^1J_{CP} = 203$ Hz), $\delta = 76.2$ (d, $^2J_{CP} = 8.1$ Hz), $\delta = 29.3$ (d, $^2J_{CP} = 5.9$ Hz), $\delta = 18.5$ (s); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 4.10$ (apparent triplet, $J = 6.5$ Hz), $\delta = 2.0$ (multiplet), $\delta = 1.0$ (d, $^3J_{HH} = 6.5$ Hz): IR (P═O) 1275 cm^{-1}: Anal. Calcd. for $C_8H_{18}O_3PCF_2Br$: C, 28.13%; H, 4.69%. Found C, 29.56%; H, 4.95%.

4.4.4. Preparation of dimethyl dibromofluoromethylphosphonate 9 "neat"

Similar to Section 4.4.1, dimethyl dibromofluoromethylphosphonate **9** was prepared from trimethyl phosphite and **2** in 46% yield (bp 85 °C/0.4 mm Hg). ^{19}F NMR($CDCl_3$) (ppm): $\delta = -76.4$ (d, $^2J_{PF} = 77$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 3.6$ (d, $^2J_{PF} = 77$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 87.4$ (dd, $^1J_{CF} = 334$ Hz, $^1J_{CP} = 204$ Hz), $\delta = 56.8$ (d, $^2J_{CP} = 7.4$ Hz); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 4.04$ (d, $^3J_{HP} = 11.0$ Hz): IR (P═O) 1275 cm^{-1}: Anal. Calcd. for $C_2H_6O_3PCFBr_2$: C, 12.00%; H, 2.00%. Found C, 12.14%; H, 2.21%.

4.5. Preparation of other derivatives

4.5.1. Preparation of diethyl dichlorofluoromethylphosphonate 15 by reaction of triethyl phosphite with $CFCl_3$

Triethyl phosphite (10.4 g, 0.06 mol) and $CFCl_3$ (10.3 g, 0.075 mol) were placed into a 128 ml Hastelloy C autoclave equipped with a glass liner and magnetic stir bar. The autoclave was sealed and heated to 120 °C for 10 days during which time the pressure in the autoclave remained nearly constant at 59 psig. After cooling, the autoclave was opened and the residue concentrated on a steam bath and distilled under vacuum. After distillation of the unreacted triethyl phosphite, a distillate fraction was obtained (bp = 96–99 °C/8 mm Hg) which contained **15** in approximately 30% yield. Diethyl ethylphosphonate, diethyl phosphite and triethyl phosphate were also identified as contaminants by NMR spectral data. ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -73.4$ (d, $^2J_{PF} = 88$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 2.4$ (d, $^2J_{PF} = 88$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 113.4$ (dd, $^1J_{CF} = 316$ Hz, $^1J_{CP} = 222$ Hz), $\delta = 66.6$ (d, $^2J_{CP} = 7.3$ Hz), $\delta = 16.4$ (d, $^3J_{CP} = 4.4$ Hz); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 4.40$ (apparent pentet, $J = 7.0$ Hz), $\delta = 1.42$ (t, $^3J_{HH} = 7.0$ Hz),: IR (P═O) 1277 cm^{-1}.

4.5.2. Reaction of triethyl phosphite with CF_2BrCl to give 4

Similar to Section 4.5.1, the reaction of triethyl phosphite with CF_2BrCl was carried out in a 128 ml Hastelloy C autoclave at autogenous pressure to yield **4** in 20% yield with properties identical in all respects to **4** as previously prepared.

4.5.3. Preparation of ethyl bromodifluoromethylphenylphosphinate 16

Diethyl phenylphosphonite (11.6 g, 0.059 mol) and diethyl ether (125 ml) were combined in a 250 ml round bottom flask equipped with a water condensor topped by a glass tee leading to a source of dry nitrogen and a mineral oil bubbler. After cooling the flask in an ice bath, **1** (15 g, 0.07 mol) was added. The reaction mixture was stirred overnight at ambient temperature. The ether was removed by rotary evaporation at aspirator pressure and the residue distilled to give **16** in 58% yield (bp = 109–111 °C/0.6 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): ABX pattern δ (F1) = −62.5; δ (F2) = −62.1 ($^2J_{PF1} = {}^2J_{PF2} = 82$ Hz; $^2J_{F1F2} = 180$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 20.9$ (t, $^2J_{PF} = 82$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 120.2$ (td, $^1J_{CF} = 333$ Hz, $^1J_{CP} = 150$ Hz), $\delta = 64.5$ ($^2J_{CP} = 7.4$ Hz), $\delta = 16.5$ ($^3J_{CP} = 5.9$ Hz) and for the ring carbons, $\delta = 123.5$ (d, $^1J_{CP} = 146$ Hz, α-carbon of ring), $\delta = 128.9$ (d, $^1J_{CP} = 13.2$ Hz, m-ring carbons), $\delta = 133.4$ (d, $^1J_{CP} = 10.3$ Hz, o-ring carbons), $\delta = 134$ (d, $^1J_{CP} = 2.9$ Hz, p-ring carbon); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 1.45$ (t, $^3J_{HH} = 7$ Hz), $\delta = 4.45$ (qd, $^3J_{HH} = 7$ Hz, $^3J_{HP} = 7.5$ Hz), $\delta = 7.5$–8.0 (unresolved multiplet). GC–MS, m/z (relative intensity): 169 (57), 141 (100), 77 (64), 51 (34), 47 (15), 31 (22), 29 (34); no molecular ion observed: IR (P═O) 1252 cm^{-1}: Anal. Calcd. for $C_8H_{10}O_2PCF_2Br$: C, 36.12%; H, 3.34%. Found C, 36.13%; H, 3.25%.

4.5.4. Preparation of bromodifluoromethyldiphenylphosphine oxide 17

Ethyl diphenylphosphinite (5.7 g, 0.025 mol) and diethyl ether (30 ml) were combined in a 100 ml round bottom flask equipped with a water condensor topped by a glass tee leading to a source of dry nitrogen and a mineral oil bubbler. After cooling the flask in an ice bath, **1** (7.35 g, 0.035 mol) was added. The reaction mixture was then heated at reflux for 18 h. The ether was removed by rotary evaporation at aspirator pressure to yield a clear oil which crystallized on the addition of fresh ether. The crystals were filtered and washed once with a small portion of ice cold ether to give 5.7 g (69%) **17** (mp = 66–69 °C). After recrystallization from benzene and again from Skelly B, the melting point was 68.5–69.5 °C. ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -59.2$ (d, $^2J_{PF} = 71$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 27.5$ (t, $^2J_{PF} = 71$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 123.0$ (td, $^1J_{CF} = 336$ Hz, $^1J_{CP} = 101$ Hz), $\delta = 125.5$ (d, $^1J_{CP} = 106$ Hz, α-carbon of ring), [$\delta = 129.0$ (d, $J_{CP} = 13.2$ Hz) and $\delta = 132.4$ (d, $J_{CP} = 10.3$ Hz) (o- and m-ring carbons)], $\delta = 133.8$ (d, $^4J_{CP} = 2.9$ Hz, p-ring carbon); ^{1}H NMR ($CDCl_3$) (ppm): $\delta = 7.5$–8.2 (multiplet). GC–MS, m/z (relative intensity): 201 (15), 77 (13), 39 (100); molecular ion 330, 332; intensity very low: IR (P═O) 1222 cm^{-1}:

Anal. Calcd. for $C_{12}H_{10}OPCF_2Br$: C, 47.13%; H, 3.02%. Found C, 47.18%; H, 3.02%.

4.5.5. Preparation of dibutyl difluoromethylphosphonate 18

Dibutyl difluoromethylphosphonate **18** was prepared according to the literature method by reaction of the anion of dibutyl phosphite, generated from dibutyl phosphite and sodium metal in dry Skelly B, with CF_2HCl (bp = 122–129 °C/10 mm Hg; lit. [7] bp = 124–125 °C/12 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -135.4$ (dd, $^2J_{PF} = 90$ Hz, $^2J_{HP} = 50$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 4.9$ (t, $^2J_{PF} = 91$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 111.7$ (td, $^1J_{CF} = 258$ Hz, $^1J_{CP} = 213$ Hz), $\delta = 68.2$ (d, $^2J_{CP} = 6.6$ Hz), $\delta = 32.6$ (d, $^3J_{CP} = 5.9$ Hz), $\delta = 18.6$ (s), $\delta = 13.5$ (s); ^1H NMR ($CDCl_3$) (ppm): $\delta = 5.94$ (td, $^2J_{HF} = 49.0$ Hz, $^2J_{HP} = 27.2$ Hz), $\delta = 4.22$ (apparent pentet, $J = 7.0$ Hz), $\delta = 0.8–1.8$ (multiplet): IR (P═O) 1265 cm^{-1}.

4.5.6. Preparation of diethyl difluoromethylphosphonate 19

Similar to Section 4.5.5, diethyl difluoromethylphosphonate **19** was prepared from diethyl phosphite, sodium metal and CF_2HCl in 23% yield (bp = 66–71/0.2 mm Hg).

^{19}F NMR ($CDCl_3$) (ppm): $\delta = -136.0$ (dd, $^2J_{PF} = 93$ Hz, $^2J_{HP} = 49$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 4.8$ (d, $^2J_{PF} = 91$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 111.7$ (td, $^1J_{CF} = 258$ Hz, $^1J_{CP} = 213$ Hz), $\delta = 64.6$ (d, $^2J_{CP} = 7.4$ Hz), $\delta = 16.5$ (d, $^3J_{CP} = 5.9$ Hz); ^1H NMR ($CDCl_3$) (ppm): $\delta = 5.92$ (td, $^2J_{HF} = 49.0$ Hz, $^2J_{HP} = 27.5$ Hz), $\delta = 4.32$ (apparent pentet, $J = 7.0$ Hz), $\delta = 1.39$ (t, $^3J_{HH} = 6.9$ Hz): IR (P═O) 1265 cm^{-1}: GC–MS, *m/z* (relative intensity): 173 (2), 159 (8), 138 (48), 110 (100), 92 (20), 82 (98), 66 (30), 45 (32), 29 (86); no molecular ion observed.

4.5.7. Preparation of diethyl bromofluoromethylphosphonate 20

A 50 ml flask with septum port was equipped with a magnetic stir bar and a condensor topped by a glass tee leading to a source of dry nitrogen and a mineral oil bubbler. To the flask was added diethyl phosphite (12.9 g, 0.093 mol) and sodium metal (0.6 g, 0.026 mol). The sodium metal was consumed in a vigorous reaction in <5 min. After cooling the solution in an ice bath, diethyl dibromofluoromethylphosphonate **10** was slowly added by syringe and the resulting reaction mixture stirred overnight at ambient temperature. The reaction mixture was poured into water, a lower fluorochemical layer separated and the water layer extracted twice with diethyl ether. The lower fluorochemical layer and the ether extracts were combined, washed with water and dried over anhydrous magnesium sulfate. The ether was distilled at atmospheric pressure and the residue distilled to give 1.5 g (23% yield) **20** (bp = 66–71 °C/0.2 mm Hg). ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -166.9$ (dd, $^2J_{PF} = 77$ Hz, $^2J_{HF} = 50$ Hz); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 7.5$ (d, $^2J_{PF} = 75$ Hz); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 84.1$ (dd, $^1J_{CF} = 265$ Hz, $^1J_{CP} = 191$ Hz), $\delta = 65.4$ and 64.8 (signal appears as two doublets with identical coupling constants, see discussion); ($^2J_{CP} = 7.4$ Hz), $\delta = 16.5$ ($^3J_{CP} = 5.2$ Hz); ^1H NMR ($CDCl_3$) (ppm): $\delta = 4.38$ (qd, $^3J_{HH} = 7.0$ Hz, $^3J_{HP} = 3.0$ Hz), $\delta = 1.40$ (t, $^3J_{HH} = 7.0$ Hz), $\delta = 6.51$ (dd, $^2J_{HF} = 47.5$ Hz, $^2J_{HP} = 10.4$ Hz): IR (P═O) 1255 cm^{-1}: Anal. Calcd. for $C_4H_{10}O_3PCFBrH$: C, 24.10%; H, 4.42%. Found C, 24.16%; H, 4.49%.

4.5.8. Preparation of diethyl trichloromethylphosphonate 21

Diethyl trichloromethylphosphonate **21** was prepared *via* the literature procedure [46] by reaction of carbon tetrachloride (175 ml) with triethyl phosphite (33.0 g, 0.2 mol) at reflux over 24 h. The excess carbon tetrachloride was removed by rotary evaporation at aspirator pressure and the residue distilled to yield 47.2 g (92%) product (bp = 135 °C/20 mm Hg: [46] 135–137 °C/16 mm Hg). ^{31}P NMR ($CDCl_3$) (ppm): $\delta = 5.4$ (s); ^{13}C NMR ($CDCl_3$) (ppm): $\delta = 88.8$ (d, $^1J_{CP} = 197$ Hz), $\delta = 67.0$ ($^2J_{CP} = 5.9$ Hz), $\delta = 16.4$ ($^3J_{CP} = 5.9$); ^1H NMR ($CDCl_3$) (ppm): $\delta = 4.40$ (qd, $^3J_{HH} = 7.0$ Hz, $^3J_{HP} = 8.5$ Hz), $\delta = 1.41$ (t, $^3J_{HH} = 7.0$ Hz): IR (P═O) 1275 cm^{-1}: Anal. Calcd. for $C_4H_{10}O_3PCCl_3$: C, 23.48%; H, 3.91%. Found C, 23.05%; H, 3.93%.

4.6. Reactions of halo-F-methylphosphonates

4.6.1. Reaction of 4 with KF in the presence of 2,3-dimethyl-2-butene

To a solution of **4** (9.35 g, 0.035 mol) and 2,3-dimethyl-2-butene (2.1 g, 0.025 mol) in dry triglyme (40 ml) was added anhydrous KF (2.9 g, 0.05 mol). The mixture was heated to 60 °C overnight after which time the ^{19}F NMR spectrum indicated the complete consumption of **4** with the formation of $(EtO)_2P(O)F$ [^{19}F NMR($CDCl_3$) (ppm): $\delta = -81.6$ (d, $^1J_{PF} = 981$ Hz; Lit [47]: $\delta = -81.5$); ^1H NMR ($CDCl_3$) (ppm): $\delta = 1.40$ (t, $^3J_{HH} = 7$ Hz), $\delta = 4.28$ (qd, $^3J_{HH} = 7.1$ Hz, $^2J_{HP} = 9.0$ Hz)] and of 1,1-difluorotetramethylcyclopropane. The reaction solution was then flash distilled at <1 mm Hg into a trap cooled in dry ice/isopropanol to yield 2.1 g (63%) 1,1-difluorotetramethylcyclopropane. ^{19}F NMR ($CDCl_3$) (ppm): $\delta = -148.7$ (m); ^1H NMR ($CDCl_3$) (ppm): $\delta = 1.10$ (t, $^4J_{HF} = 2.1$ Hz) [Lit. [48]: $\delta = 1.08$ (t, $^4J_{HF} = 2.0$ Hz)].

4.6.2. Small scale reaction of 4, KF and cyclohexene or 2-methyl-2-butene

To a solution of 2-methyl-2-butene (0.53 g, 0.0075 mol) and **4** (1.34 g, 0.005 mol) in triglyme (15 ml) was added anhydrous KF (0.6 g, 0.01 mol) and the reaction mixture stirred overnight. Benzotrifluoride (0.24 g, 0.0017 mol) was added as an internal glpc standard and the solution analyzed (Column A) and found to contain 1,1-difluorotrimethylcyclopropane in 66% yield by NMR [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -138.9$ and $\delta = -150.8$ (dm, $^2J_{FF} = 154$ Hz) [Lit [48]: $\delta = -139$ and $\delta = -150.8$ (dm, $^2J_{FF} = 150$ Hz)]].

In a similar manner, cyclohexene (0.62 g, 0.0075 mol) afforded a 24% NMR yield of 7,7-difluoronorcarane: [^{19}F NMR($CDCl_3$) (ppm): $\delta = -124.8$ (dt, $^2J_{FF} = 154$ Hz, $^4J_{HF} = 15$ Hz (cis F)) and $\delta = -149.8$ (d, $^2J_{FF} = 154$ Hz (trans F)) [Lit [49]: $\delta = -129.2$ (dt, $^2J_{FF} = 163$ Hz, $^4J_{HF} = 14$ Hz)]].

4.6.3. Small scale reaction of 4 with KF·2H2O

$KF{\cdot}2H_2O$ (0.94 g, 0.01 mol) was added to a solution of **4** (1.34 g, 0.005 mol) and $PhCF_3$ (0.5 g, 0.0033 mol) in triglyme (15 ml) and the mixture stirred overnight at room temperature. ^{19}F spectral analysis showed that $(EtO)_2P(O)F$ had been formed in an 83% yield. No CF_2BrH was observed.

4.6.4. Small scale reaction of 10 with anhydrous KF and ethanol

KF (0.6 g, 0.01 mol) was added to a solution of **10** (1.64 g, 0.005 mol), $PhCF_3$ (0.24 g, 0.0017 mol) and ethanol (0.46 g, 0.01 mol) in triglyme (15 ml) and the mixture stirred overnight at room temperature. ^{19}F spectral analysis showed that $CFBr_2H$ was formed in 67% yield [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -83.8$ (d, $^2J_{HF} = 49.9$ Hz) [Lit [50]: $\delta = -84.6$ (d, $^2J_{HF} = 51$ Hz)]]. Diethyl phosphorofluoridate was formed in 72% yield.

4.6.5. Small scale reaction of 10 with anhydrous KF and 2,3-dimethyl-2-butene

KF (2.6 g, 0.045 mol) was added to a solution of **10** (2.8 g, 0.0085 mol) and 2,3-dimethyl-2-butene (1.41 g, 0.017 mol) in triglyme (18 ml) and the mixture stirred overnight at room temperature. $PhCF_3$ (0.41 g, 0.0028 mol) was added and ^{19}F spectral analysis showed that the solution contained $(EtO)_2P(O)F$ (93%), $CFBr_2H$ (8%), 1-bromo-1-fluorotetramethylcyclopropane (45%) and an unknown signal at $\delta = -112.7$ (30%) which is probably a ring-opened product of the cyclopropane.

4.6.6. Reaction of 4 with sodium methoxide in methanol

Sodium metal (0.46 g, 0.02 mol) was added to anhydrous methanol (20 ml) and allowed to dissolve completely. After cooling

the solution in an ice bath, **4** (2.67 g, 0.01 mol) was added dropwise by syringe. $PhCF_3$ (0.58 g, 0.004 mol) was added and ^{19}F spectral analysis showed that the solution contained CH_3OCF_2H [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -86.6$ (d, $^2J_{HF} = 77$ Hz) [Lit [51]: $\delta = -88.2$ (d, $^2J_{HF} = 74$ Hz)]] in 52% yield.

4.6.7. Reaction of **4** *with sodium ethoxide in ethanol*

In a similar manner ethyl difluoromethyl ether was prepared in 56% NMR yield. [^{19}F NMR($CDCl_3$) (ppm): $\delta = -83.9$ (d, $^2J_{HF} = 76$ Hz) [Lit [28]: $\delta = -83.5$ (d, $^2J_{HF} = 74$ Hz)]].

4.6.8. Reaction of **4** *with sodium trifluoroethoxide in triglyme solvent*

Sodium metal (0.23 g, 0.01 mol) was added to a solution of trifluoroethanol (2.8 g, 0.028 mol) in triglyme (20 ml) and allowed to dissolve completely. Subsequently **4** (1.27 g, 0.0048 mol) was added dropwise by syringe. ^{19}F spectral analysis as above showed that the solution contained $CF_3CH_2OCF_2H$ in 58% yield [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -74.5$ (tt, $^3J_{HF} = 9.6$ Hz, $^5J_{FF} = 2.4$ Hz); $\delta = -84.6$ (dq, $^2J_{HF} = 75$ Hz, $^5J_{FF} = 2.4$ Hz) [Lit [51]: $\delta = -75.6$ (t, $^3J_{HF} = 8$ Hz); $\delta = -87.1$ (dq, $^2J_{HF} = 72$ Hz, $^5J_{FF} = 2$ Hz)]].

4.6.9. Reaction of **4** *with sodium phenoxide in methanol solvent*

Sodium hydroxide (0.4 g, 0.01 mol) and phenol (0.94 g, 0.01 mol) were added to anhydrous methanol. After complete solution had occurred, the solution was cooled in an ice bath and **4** (2.67 g, 0.01 mol) was added dropwise by syringe. $PhCF_3$ (0.58 g, 0.004 mol) was added and ^{19}F spectral analysis showed that the solution contained a mixture of CH_3OCF_2H (46%) and $PhOCF_2H$ (11%) [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -80.9$ (d, $^2J_{HF} = 75$ Hz) [Lit [51]: $^2J_{HF} = 73.9$ Hz]].

4.6.10. Reaction of **4** *with bromotrimethylsilane*

Bromotrimethylsilane (18.4 g, 0.12 mol) was added to **4** (13.6 g, 0.05 mol) and the mixture stirred under nitrogen at 60 °C for 18 h. The reaction mixture was then distilled under vacuum to afford 17 g (92% yield) $(Me_3SiO)_2P(O)CF_2Br$ (bp 82–84 °C/1.2 mm Hg). [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -63.0$ (d, $^2J_{PF} = 96$ Hz); ^1H NMR ($CDCl_3$) (ppm): $\delta = 0.38$ (s); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = -16.1$ (t, $^2J_{PF} = 96$ Hz)]. In a separate experiment it was found that a signal could be observed in the ^{31}P NMR which was intermediate between the starting material and the final silylated product at $\delta = -7.2$ ppm (t, $^2J_{PF} = 94$ Hz). This was presumably the mixed ester $EtOP(O)(CF_2Br)(OSiMe_3)$.

4.6.11. Reaction of **10** *with bromotrimethylsilane*

Bromotrimethylsilane (0.76 g, 0.005 mol) was added to **10** (0.49 g, 0.0015 mol) in a 5 mm NMR tube equipped with a wired-on septum cap and the tube heated to 60 °C for 90 min. At the end of this time the excess silane and co-product ethyl bromide were removed under vacuum. [^{19}F NMR ($CDCl_3$) (ppm): $\delta = -76.3$ (d, $^2J_{PF} = 81$ Hz); ^1H NMR ($CDCl_3$) (ppm): $\delta = 0.38$ (s); ^{31}P NMR ($CDCl_3$) (ppm): $\delta = -13.2$ (d, $^2J_{PF} = 79$ Hz)]. In a separate experiment it was found that a signal could be observed in the ^{31}P NMR which was intermediate between the starting material and the final silylated product at $\delta = -4.5$ ppm (d). This was presumably the mixed ester $EtOP(O)(CFBr_2)(OSiMe_3)$.

4.6.12. Hydrolysis reactions of $(Me_3SiO)_2P(O)CF_2Br$

$(Me_3SiO)_2P(O)CF_2Br$ was readily converted to the phosphonic acid $(HO)_2P(O)CF_2Br$ as expected by using either aqueous hydrolysis or an exchange reaction with anhydrous methanol. In the aqueous hydrolysis method, the silyl ester was treated with a large excess of water at room temperature for 24 h. The initial two phase solution became homogeneous during this time. The solution was then extracted with chloroform and the remaining aqueous layer distilled by rotary evaporation to yield the phosphonic acid as a clear, viscous oil. With the methanol solvolysis, the silyl ester was treated with a large excess of anhydrous methanol and the mixture stirred for an hour followed by an atmospheric distillation to remove the Me_3SiOMe until the distillation head reached a temperature of 64 °C. The remaining methanol was then removed by rotary evaporation.

For the larger scale syntheses of $(HO)_2P(O)CF_2Br$ and $(HO)_2P(O)CFBr_2$, it was found that hydrolysis using aqueous HCl was more efficient as described below.

4.6.13. Preparation of $(HO)_2P(O)CF_2Br$

50% aqueous hydrochloric acid (70 ml) was added to **4** (4.5 g, 0.017 mol) and the mixture heated to reflux for about 16 h. The bulk of the water was removed by rotary evaporation at reduced pressure and the residue was subsequently dried under high vacuum. [^{19}F NMR (acetone-d_6/water) (ppm): $\delta = -61.0$ (d, $^2J_{PF} = 87$ Hz); ^{31}P NMR (ppm): $\delta = -3.1$ (t, $^2J_{PF} = 89$ Hz); ^{13}C NMR (ppm): $\delta = 120.4$ (dt, $^1J_{CF} = 328$ Hz, $^1J_{CP} = 228$ Hz)].

4.6.14. Preparation of $(HO)_2P(O)CFBr_2$

50% aqueous hydrochloric acid (70 ml) was added to **10** (9.8 g, 0.03 mol) and the mixture heated to reflux for about 16 h. The bulk of the water was removed by rotary evaporation at reduced pressure and the residue was subsequently dried under high vacuum whereupon the acid crystallized to give an off-white solid which rapidly absorbed moisture from the air. ^{19}F NMR (D_2O) (ppm): $\delta = -73.7$ (d, $^2J_{PF} = 70$ Hz); ^{31}P NMR (ppm): $\delta = -2.5$ (t, $^2J_{PF} = 71$ Hz); ^{13}C NMR (acetone-d_6) (ppm): $\delta = 92.5$ (dd, $^1J_{CF} = 331$ Hz, $^1J_{CP} = 196$ Hz); Anal. Calcd. for $CH_2Br_2FO_3P.\ H_2O$: C, 4.14%; H, 1.38%. Found C, 4.08%; H, 1.45%.

4.6.15. Reaction of **4** *with sodium iodide*

Sodium iodide (7.5 g, 0.05 mol) was added to dry acetone (30 ml) and the mixture stirred until the solution was homogeneous. To this mixture was then added **4** (13.3 g, 0.05 mol) and the solution heated at reflux for 3 h. The acetone was removed by rotary evaporation to afford 12.8 g (98%) of an off-white solid identified as $Na^+\ [O_2P(OEt)CF_2Br]^-$. The melting point of the salt, following recrystallization from benzene/ethyl acetate was 227–230 °C with decomposition. [^{19}F NMR (acetone-d_6) (ppm): $\delta = -56.6$ (d, $^2J_{PF} = 76$ Hz); ^1H NMR (DMSO-d_6) (ppm): $\delta = 1.16$ (t, $^3J_{HH} = 7$ Hz), $\delta = 3.92$ (apparent pentet, $J = 7$ Hz); ^{31}P NMR (D_2O) (ppm): $\delta = -1.88$ (t, $^2J_{PF} = 82$ Hz); ^{13}C NMR (acetone-d_6) (ppm): $\delta = 124.2$ (dt, $^1J_{CF} = 334$ Hz, $^1J_{CP} = 201$ Hz), $\delta = 17.0$ (d $^3J_{CP} = 5.9$ Hz), $\delta = 63.7$ (d, $^2J_{CP} = 7.3$ Hz)]; Anal. Calcd. for $C_3H_5BrF_2NaO_3P$: C, 13.79%; H, 1.92%. Found C, 13.59%; H, 2.01%.

4.6.16. Reaction of **10** *with sodium iodide*

Sodium iodide (3.34 g, 0.022 mol) was added to dry acetone (about 30 ml) and the mixture stirred until the solution was homogeneous. To this mixture was then added **10** (7.3 g, 0.022 mol) and the solution heated at reflux for 3 h. The acetone was removed by rotary evaporation to afford 4.6 g (64%) of $Na^+\ [O_2P(OEt)CFBr_2]^-$. The salt was recrystallized from acetone/benzene (1/5). [^{19}F NMR (D_2O) (ppm): $\delta = -72.2$ (d, $^2J_{PF} = 68$ Hz); ^1H NMR (D_2O) (ppm): $\delta = 2.14$ (t, $^3J_{HH} = 7$ Hz), $\delta = 5.02$ (apparent pentet, $J = 7$ Hz); ^{31}P NMR (D_2O) (ppm): $\delta = 2.4$ (d, $^2J_{PF} = 69$ Hz); ^{13}C NMR (acetone-d_6/H_2O) (ppm): $\delta = 98.6$ (dd, $^1J_{CF} = 337$ Hz, $^1J_{CP} = 166$ Hz), $\delta = 17.1$ (d, $^3J_{CP} = 7$ Hz), $\delta = 64.6$ (d, $^2J_{CP} = 7$ Hz)]; Anal. Calcd. for $C_3H_5Br_2FNaO_3P$: C, 11.18%; H, 1.55%. Found C, 11.17%; H, 1.10%.

4.6.17. Reaction of **4** *with triphenylphosphine*

Triphenylphosphine (10.5 g, 0.04 mol) and dry dimethoxyethane (50 ml) were placed into a flask equipped with a magnetic stirrer, septum port and condensor protected from moisture with a

calcium chloride drying tube. Into this solution was syringed **4** (10.7 g, 0.04 mol) and the mixture heated to reflux for four days. After the reaction mixture was cooled to room temperature, a solution of HCl in dry diethyl ether (4.14 M, 9.7 ml, 0.04 mol) was syringed into the flask. The tan solid which precipitated was filtered, washed with ether and dried under vacuum to afford 2.5 g (20%) of a solid identified as $[Ph_3PC_2H_5]^+Cl^-$ (mp = 234–236.5 °C, Lit [52]: 234–236 °C).

*4.6.18. Reaction of **3** with triphenylphosphine*

To a solution of triphenylphosphine (15.6 g, 0.025 mol) in dry diethyl ether (25 ml) was added **3** (5.2 g, 0.025 mol) and the solution brought to reflux. The white precipitate which formed rapidly was filtered and washed with several portions of ether to afford 10 g (50%) of a solid $[Ph_3PMe]^+[O_2P(OMe)CF_2Br]^-$ which was recrystallized from benzene mp = 116–117 °C. [^{19}F NMR (ppm): $\delta = -55.7$ (d, $^2J_{PF} = 71$ Hz); ^{1}H NMR (ppm): $\delta = 3.15$ (d, $^2J_{HP} = 10$ Hz, CH_3–P), $\delta = 3.61$ (d, $^3J_{HP} = 10$ Hz, CH_3O–P), $\delta = 7.5$–8.0 (m); ^{31}P NMR (ppm): $\delta = -0.7$ (t, $^2J_{PF} = 70$ Hz), $\delta = 22$ (s); ^{13}C NMR (ppm): $\delta = 9.5$ (d, $^1J_{CP} = 58$ Hz), $\delta = 54.0$ (d, $^2J_{CP} = 7.35$ Hz), $\delta = 199.3$ (d, $^1J_{CP} = 90$ Hz), $\delta = 130.5$ (d, $^3J_{CP} = 13$ Hz), $\delta = 133.2$ (d, $^2J_{CP} = 10$ Hz), $\delta = 135.1$ (s), $\delta = 124.7$ (dt, $^1J_{CF} = 337$ Hz, $^1J_{CP} = 187$ Hz)].

4.7. Reactions in support of the reaction mechanisms

4.7.1. Reaction of $[(Me_2N)_3PCF_2Br]^+Br^-$, KF and $(EtO)_3P$

The salt $[(Me_2N)_3PCF_2Br]^+Br^-$ (5.4 g, 0.014 mol) was suspended in triglyme (30 ml) and $(EtO)_3P$ (2.4 g, 0.014 mol) syringed into the mixture. To this mixture was added anhydrous KF (0.84 g, 0.014 mol) and the mixture stirred for 18 h at room temperature. ^{19}F NMR analysis showed $\delta = -52.9$ (d, $^1J_{PF} = 707$ Hz) for the aminophosphorane $(Me_2N)_3PF_2$ and a doublet of doublets assigned to diethyl difluoromethylphosphonate **19** and confirmed by the addition of an authentic sample as prepared in Section 4.5.6. The yield of **19** was 16% using benzotrifluoride as an internal NMR standard.

*4.7.2. Reaction between $(EtO)_3P$, **1** and EtOH*

Ethanol (2.3 g, 0.05 mol), **1** (12.6 g, 0.05 mol) and triethyl phosphite (8.31 g, 0.05 mol) were combined with dimethoxyethane solvent (20 ml) in a round bottom flask equipped with a reflux condensor under dry nitrogen and the clear solution brought to reflux for about 16 h. The low boiling materials were removed by distillation at atmospheric pressure and the residue distilled under vacuum to yield 7.9 g (86%) of a 1:1 inseparable mixture of **19** and triethyl phosphate (bp = 93–99 °C/8 mm Hg). **19** was identified by comparison of its spectral data with an authentic sample. The triethyl phosphate was separated by glpc (Column B) and the peak assigned to the phosphate collected and analyzed by GC–MS [GC–MS, *m/z* (relative intensity): 182(7, M+), 155 (71), 127 (45), 125 (18), 109 (47), 99 (100), 82 (37), 81 (62), 29 (56)] which was in good agreement with the literature data [53].

In a similar reaction but using a stoichiometry of 2:1:1 for $(EtO)_3P$:**1**:EtOH, ethanol (1.15 g, 0.025 mol), **1** (6.3 g, 0.025 mol) and triethyl phosphite (8.31 g, 0.05 mol) were combined with dimethoxyethane solvent (20 ml) in a round bottom flask equipped with a reflux condensor under dry nitrogen and the clear solution brought to reflux for about 16 h. The reaction mixture was distilled at atmospheric pressure and the distillate boiling up to 84 °C collected. Salt water (25 ml) was added to the distillate and the lower layer separated and dried over anhydrous sodium sulfate. Glpc analysis of the distillate (5.0 g) showed two peaks corresponding to **1** and EtBr in a 0.97:1 ratio. Correcting for the difference in thermal conductivity, this mixture corresponded to a yield of 78% EtBr with 14% unreacted **1**.

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