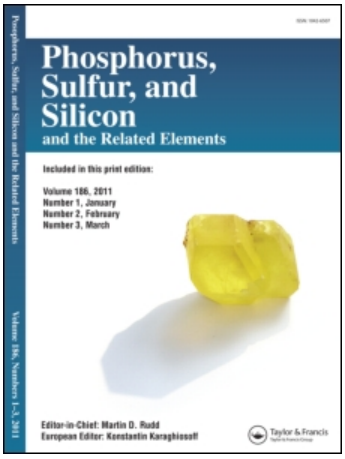

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Anomalous Reaction of Ethyl Bromofluoro- and Difluoro-Acetates with Dialkylphosphonites

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The Michaelis–Arbuzov reaction of ethyl α-bromo-α-fluoro- and α,α-difluoro-acetates with dialkyl phenylphosphonites leads to the formation of unusual products including a fluorophosphinate. The reaction of ethyl bromofluoracetate with diisopropyl- and dimethyl-phenylphosphonites furnishes a complex mixture of eight and five compounds respectively. Five different compounds are obtained when ethyl bromodifluoroacetate is reacted with diisopropyl phenylphosphonite. Dimethyl phenylphosphonite yields three compounds when heated with bromochloromethane. The probable mechanism of formation of the compounds and their mass spectral characterization using GC-MS, tandem MS-MS and DART™ techniques are presented in this paper.

Keywords α-fluoro- and difluoro-esters; DART mass spectrometry; dialkylphosphonites; free radical Arbuzov reaction; GC-MS; MS-MS; Michaelis–Arbuzov reaction

INTRODUCTION

The Michaelis–Arbuzov reaction is regarded as one of the most important reactions employed in the synthesis of organophosphorus compounds containing the phosphoryl (P=O) bond.[1a–1f] Though organic halides are generally employed in this reaction, alkyl and aryl radicals have been shown to react with trivalent phosphorus esters to furnish the expected products.[2] Thus, photolysis of triethylphosphite has been found to generate O- and P-centered as well as ethyl radicals.[3] The phenyl radical has been stated to be more electrophilic than alkyl radicals.[4a] In fact, the following order of electronegativity has been described: t-butoxy > phenyl > methyl > cyclohexyl.[4b] In view of the above,

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the rapid, irreversible reaction of the *in situ* generated phenyl radicals with trialkyl phosphites to yield phenyl dialkylphosphonates, does not seem to be surprising.[4c]

Fluorine-containing organic halides have been stated to furnish unexpected Arbuzov products. Thus, the reaction of pentafluoroethyl ethyl pentanone with trimethyl phosphite yielded methoxy-perfluoro-2-pentene and dimethyl fluorophosphononate,[5a] while perfluoropropenyl ketone gave trialkyl (perfluoroethenylcarbonyl)fluorophosphonate. Perfluoropropene has been reported to give perfluoropropenyl phosphinofluoridate.[5b–5c] The proposed mechanism involves the abstraction of the α-fluorine by phosphorus. It should be stated here that tris-silyloxyphosphites also undergo the normal Arbuzov reaction with perfluoroalkenes and fluoroalkyl halides respectively.[6]

Since the Arbuzov reaction of diialkylphosphonites is the primary process for the preparation of unsymmetrical phosphoryl derivatives, the reaction of diisopropyl phenylphosphonite with ethyl bromofluoro- and bromo difluoro-acetates has been examined and found to furnish unexpected products. The Arbuzov reaction of the substrate with bromofluoromethane at ambient temperature appears to be very sluggish. This communication describes the identification of the various compounds thus formed using GC-MS, high resolution tandem MS-MS and DART^{TM}-mass spectrometric techniques and the probable mechanism of their formation.

RESULTS AND DISCUSSION

The facile formation of phosphonium salts from the reaction of trialkyl and triarylphosphines with bromofluoro acetic acid esters and their subsequent use in the Wittig reaction have been reported.[7] [(Carbethoxy)fluoromethyl] diethylphosphonate has been obtained from the Michaelis–Becker reaction of diethyl sodiophosphonate with ethyl bromo-fluoroacetate.[8a] The Arbuzov reaction of fluorine containing organic halides has been reported to yield unexpected fluorinated phosphorus products. Thus, the reaction of α, β-dichloro-ω-iodofluoroalkenes with triethylphosphite has been shown to yield products corresponding to dechlorination, as well as α-(phosphoryl-ω-iodo,α, α-perfluoroalkene.[8b] The same substrate when reacted with perfluroisobutylene at -70°C gave diethyl-(perfluoroisobutenyl)flurophosphonate via the migration of fluorine from carbon to phosphorus.[8c] This unusual reaction of fluorinated reactants has been attributed to the enhancement of the activity of the terminal fluorine by the double bond and the increased affinity between fluorine and phosphorus. The reaction of perfluorovinyl iodide with tris-isopropylphosphite gave

1,2-difluoro-1-iodo-diisopropylphosphnate (cis and trans).[8d] However, with two equivalents of the phosphinate, trans difluoroethylene bisphosphoic acid tetra-isopropyl ester was obtained along with the previously mentioned compounds. Triethylphosphite has been observed to react with ethyl bromofluoroacetate at 145°C to give the expected [(carbethoxy)-fluoromethyl] diisopropyl-phosphonate.[8e] The influence of the bond strength and steric and configurational constraints and considerations on the stability of the phosphoranyl radicals has been examined in the free radical catalyzed reactions.[7a] The size of the alkoxy group attached to the P-atom appears to control the rate of the Arbuzov reaction.[9b]

Since virtually no report on the Vibrational Circular Dichroism (VCD) studies of the phosphoryl group (P=O) has appeared, it was considered interesting to examine the VCD of substituted chiral P=O group containing compounds and to examine the overall effect of the substituents on the absorption frequencies of the P=O group. The P=O linkage is very stable and strong and its dissociation energy has been reported to be between 120∼140 kcal/mol.[10] The infrared stretching frequencies of $F_3P{=}O$ and $CH_3P{=}O$ have been reported to be 1418 cm^{-1} and 1170 cm^{-1}, respectively.[10a] This clearly demonstrates that the substituents do exert considerable influence on the P=O absorption frequencies.

As stated earlier, the compounds containing phosphoryl group (P=O) are usually obtained via the classical Michaelis–Arbuzov reaction catalyzed by alkyl halides[1] and also through the oxidation of the respective precursors.[2] In continuation of our interest in developing methodology to permit the synthesis of optically active and/ or pro-chiral phosphorus compounds, the reaction of dialkyl phenyl phosphonites with activated halides such as (bromo)(chloro)methane and ethyl α-bromo-α-fluoro- and α-bromo-α, α-difluoroacetates has been examined and found to furnish unexpected products.

A mixture containing stoichiometric amounts of diisopropyl phenylphosphonite (**1**) and ethyl α-bromo-α-fluoroacetate (**2**) was heated with stirring under nitrogen at 85–90°C for 4 h. The GC-MS analysis of the reaction product permitted the characterization of the following compounds: (1) ethyl α-bromo-α-fluoroacetate (**2**); (2) fluoro isopropyl phenylphosphinate (**3**); (3) Hydrogen isopropyl phenylphosphinate (**4**), (4) diisopropyl phenylphosphonate (**5**); (5) (carbethoxy) isopropyl phenyl-phosphinate (**6**); (6) (carbethoxyfluoromethyl) isopropyl phenylphosphinate (**7**); (8) diphenyl carbethoxyphosphinate (**8**); (9) diisopropyl phenyl [(carbethoxyfluoromethyl) pyrophosphate (**9**) and (10) isomer of **9**, namely diisopropyl phenyl [(carbethoxyfluoromethyl) pyrophosphate (**10**).

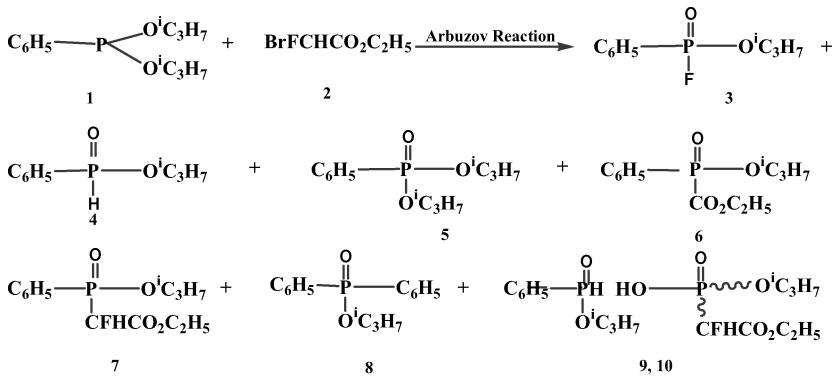

FIGURE 1 Structures of compounds cited in Table I.

Figure 1 lists all the components formed during the free radical catalyzed Michaelis-Arbuzov reaction of diidopropyl phenylphosphonite (**1**) with ethyl bromofluoroacetate (**2**). The major product of the reaction is [(carbethoxy)(fluromethyl)] isopropyl phenylphosiphinate (**7**, 46.8%) and the relative proportions of the remaining compounds are given in the experimental part. The diastereomers have been shown with wavy lines. Compound **4** can also arise from **7** via the loss of [:$CFCO_2C_2H_5$] entity from the intermediate **7** (Figure 2). The formation of the phosphonates from the phosphonites via oxidation of the latter is apparent.

Compounds **4** and **5** must have been formed either during the course of the reaction or on the hot chromatographic column from their precursor molecules. This inference stands supported by precedents.[11] Impurities present in the starting material have been reported to lead the Arbuzov products even in the absence of organic halides.[11a–b] The reaction has also been found to occur without any catalysts around 240°C.[11c] Phosphinites [R_2POR] have been reported to undergo isomerization to phosphine oxides even in the absence of the catalysts.[11d] The formation of the fluoroisopropylphenylphosphinate (**3**) is quite reminiscent of the formation of the P—F bond containing products from methylphosphite.[5a] In compound **2**, the fluorine is certainly activated by the presence of the neighboring Br and $CO_2C_2H_5$ groups. When the fluorine gets abstracted from **2** via the free radical process, it leaves behind a radical intermediate **11**, which loses the CHBr moiety to give a carbethoxy radical. A similar fate can be envisaged for the radical intermediate **12** from the homolytic fission of **2** by splitting off **Br**. Carbethoxy isopropyl phenylphosphinate (**6**) arises from the free radical reaction of the substrate (**1**) with carbethoxy radical to form intermediate **13**, followed by the free radical catalyzed Arbuzov reaction. Compound

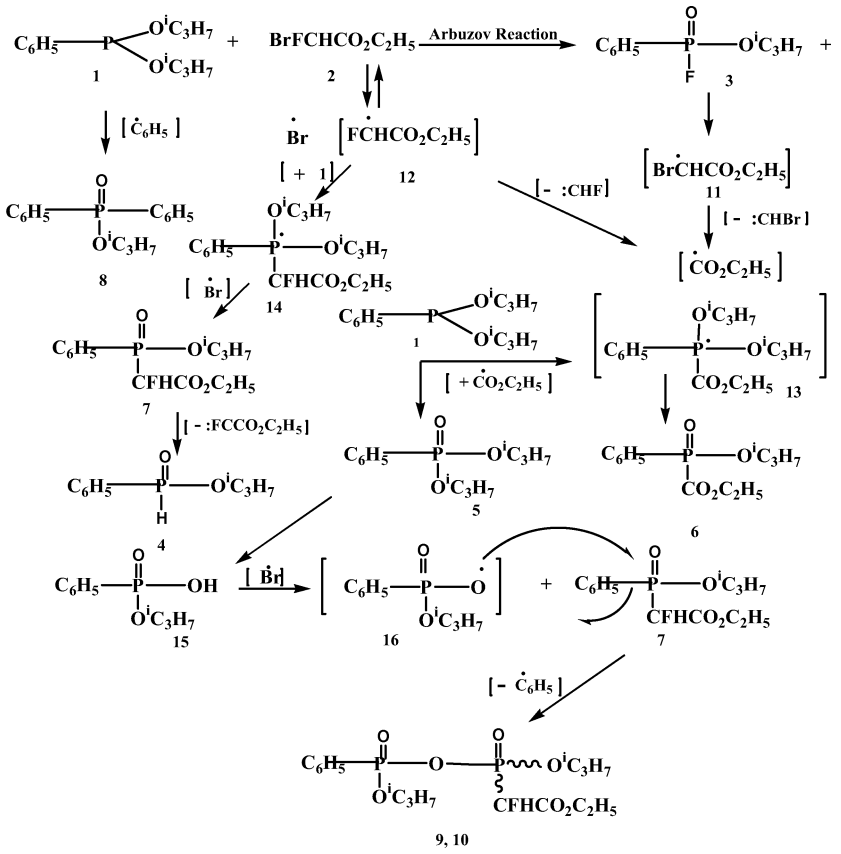

FIGURE 2 Probable mechanism of formation of compounds cited in Fig. 1.

7, is the expected reaction product of the Arbuzov reaction. Compounds **1** and **12** react to form radical intermediate **14**, which subsequently undergoes rearrangement to yield **7** in the presence of $Br^{\cdot}$ (cf. Figure 2).

The characterization of compound **8**, namely (diphenyl) isopropylphosphinate, required additional confirmation, although its molecular weight and GC-MS breakdown pattern did indicate the structure assigned to it. Additional supportive evidence was obtained from DART mass spectrometry and tandem MS-MS (cf. Table II). The former permitted the trapping of the ion corresponding to this compound and then examining its breakdown behavior in detail.

It is interesting to note that the proposed cleavage of the phenyl group attached to phosphorus derives support from two precedents. Firstly,

TABLE I Mass Spectral Fragmentation of Compounds 1 Through 10 (Fig. 1)

1. **Diisopropyl phneylphosphonite (1)**: M+ = 226, r.t = 7. 35 min.); 21 1 (M-CH_3); 184 (M -C_3H_6); 167 (M-OC_3H_7); 142 [$C_6H_5P(O)H(OH)$; 100%]; 125 (142-OH); 107 ($HP(O)OC_3H_7$); 96 ($HP(O)OCH_3$); 78 (C_6H_6); 65 (HP(O)OH); 51 (C_4H_3) and 43 C_3H_7).
2. **Ethyl α-bromo-α-fluoroacetate (2)***: M^+ = 184, 139 (C_2HBrFO or M-CH_3-CO); 120 (C_2HBrCO); 111 [M-$CO_2C_2H_5$), 100%]; 105 (M-Br); 93 (141-CHO-F); 79 (Br); 73 ($CO_2C_2H_5$); 60 (C_2HFO); 49 (CH_2FO) and 41 (C_2HO).
3. **Fluoro-isopropylphenylphosphinate (3)**: M^+ = 202, 187 (M-CH_3); 161[M-C_3H_5), 100%]; 143 (M-OC_3H_7); 94 ($C_2H_7O_2P$); 77 (C_6H_5); 51 (C_4H_3) and 41(C_3H_5).
4. **Hydrogen isopropyl phneylphosphinate (4)**: M^+ =184, 183 (M-H); 169 (M-CH_3); 143 [M -(C_3H_5), 100%]; 125 (M-OC_3H_7); 78 (C_6H_6); 65 (HP(O)OH); 51 (C_4H_3) and 43 C_3H_7).
5. **Diisopropyl phneylphosphonate (5)**: M^+ = 242; 201 [M-(C_3H_5); 183 (M-OC_3H_7); 159 [201 -(C_3H_6), 100%]; 141 [159-H_2O or $C_6H_5P(O)OH$]; 94 ($C_2H_7O_2P$); 77 (C_6H_5); 65 (HP(O)OH); 63 ($P0_2$);51(C_4H_3)and41(C_3H_5).
6. **Carbethoxy isopropyl phneylphosphinate (6)**: M^+ = 256; 255 (M-H); 214 (M-C_3H_6) ; 183 (M-$CO_2C_2H_5$); 169 (183-CH_2); 159 ($C_6H_8PO_3$); 141 [$C_6H_6PO_2$ or 159-H_2O), 100%]; 124 (141 -OH); 77 (C_6H_5); 65 (HP(O)OH); 51 (C_4H_3) and41(C_3H_5).
7. **(Carbethoxy-fluoromethyl) isopropyl phenylphosphinate (7)**: M^+ = 288, 287 (M-H); 273 (M-CH_3); 259 (M-C_2H_5); 246 (M-C_3H_6) ; 229 (M-OC_3H_7); 217 (246-C_2H_5); 201 (217-O); 183 (M-$CHFCO_2C_2H_5$); 169 (183-CH_2); 159 ($C_6H_8PO_3$); 141 [$C_6H_6PO_2$), 100%]; 125 (141-O); 109 ($C_2H_3O_2P$); 91 (C_7H_7 or $C_2H_4O_2P$); 77 (C_6H_5); 65 (H_2PO_2); 51 (C_4H_3) and 41(C_3H_5).
8. **Diphenyl isopropylphosphinate (8)**: M^+ = 260; 245 (M-CH_3); 219 [M-C_3H_5), 100%]; 201 (M-OC_3H_7); 183 (M-C_6H_5); 141 [$C_6H_5P(O)OH$ or 219-C_6H_6]; 125 [$C_6H_5P(O)H$]; 105 (183-C_6H_5 -H); 94 ($C_2H_70_2P$); 77 (C_6H_5); 51 (C_4H_3) and 41(C_3H_5).
9. **1, 2-Diisopropyl-l-phenyl-2-[(carbethoxy(fluoromethyl)]pyrophosphate (9)**: M^+ = 396; 381 (M-CH_3); 355 (M-C_3H_5); 339 (355-O); 312 (355-C_3H_7); 295 (312-OH); 277 (M-C_6H_5-C_3H_6); 249 (277-C_2H_4 or CO); 235 (312-C_6H_5); 221 (235-CH_2); 205 (221-O); 159 (C_6H_8PO ; 141 [$C_6H_6P0_2$), 100%]; 125 [$C_6H_5P(O)H$]; 107 [$P(O)HOC_3H_7$]; 77 (C_6H_5); 63 (PO_2) and41(C_3H_5).
10. **1, 2-Diisopropyl-l-phenyl-2-[(carbethoxy(fluoromethyl)]pyrophosphate (10)**: M^+ = 396. Isomer of 9 and its' mass spectral fragmentation is very similar to 9 except four minor peaks, appearing at m/e= 234, 248, 313 and 354 in the mass spectrum of 10 appear at m/e = 235, 249, 312 and 355 of 9.

*All Br and Cl containing compounds showed their corresponding isotope peaks.

TABLE II MS-MS Fragmentation of Compounds 8 and 9

1. **Diphenyl isopropylphosphinate (8)**: M^+ = 261 (M+H); 243 (M-CH_4 .H); 218 [M-C_3H_5, 100%]; 201 (M-OC_3H_7); 182 (M-C_6H_5); 141 [218-CgHj]; 77 (C_6H_5) and 52 (C_4H_4 or $P(O)CH_3$).
2. **1, 2-Disopropyl-l-phenyl-2-(carbethoxyfluoromethyl) pyrophosphate (9)**: M^+ = 397 (M+H); 355 (M-C_3H_5); 313 (355-C3H_6, 100%); 294 (312-H_2O); 283 (355-C $O_2C_2H_5$). 264 (283-F); 235 (312-C6H_5); 205 (235-OCH_2); 159 ($C_6H_8PO_3$); 141 [$C_6H_5P(O)OH$]; 125 [$C_6H_5P(O)H$]; 91 ($C_2H_4O_2P$). 79 (C_6H_7) and 65 (PH_2O_2).

the reaction of n-bromopropane with triphenylphosphine has been reported to give diphenyl n-propylphosphine oxide via the oxidation of the hydroxyl group attached to phosphorus.[12a] Secondly, the reduction of triphenyl-phosphinealkylidene (the Wittig reagent) with $LiAlH_4$ proceeds with the reduction of the double bond, followed by the fission of the bond between the phenyl group and the phosphorus atom.[12b–12d]

We must rationalize the formation of the two diastereomers, **9** and **10**. Compound **5** can lose the propylene entity to form isopropyl phenylphosphinic acid **15**, the hydrogen of which then gets abstracted by Br·-radical to yield the phospphoranyl radical intermediate (**16**), which in turn attacks **7**. The concomitant fission of the P-C_6H_5 bond leads to the diastereomers, **9** and **10** (cf. Figure 2). The presence of the phosphoranyl radical similar to **16** has been previously invoked.[13] The assignment of the structure to the isomers squarely rests on the presence of the ions corresponding to the loss of the two isopropyl entities, phenyl fragment, and $CHFCO_2C_2H_5$ moiety from the parent molecule. Figure 2 describes the probable mechanism of the formation of the compounds cited in Figure 1 and Tables I and IA give the mass spectral fragmentation of the compounds cited in Figure 1.

The reaction of diisopropyl phenylphosphonite (**1**) with ethyl α-bromo-α, α -difluoroacetate (**17**) was carried in an analogous manner except that compound **2** was replaced with **17** (Figure 3). The routine processing of the reaction product, followed by the GC-analysis indicated the presence of 6 components. The GC-MS analysis and a careful analysis of the mass spectral fragmentation patterns permitted the identification of the following compounds: (1) ethyl α-bromo-α, α-fluoroacetate (**17**); (1) (fluoro) isopropyl phenylphosphinate (**3**); (3) hydrogen isopropyl phenylphosphinate (**4**); (4) ethyl isopropyl phenylphosphonate (**18**); (5) diisopropyl phenyl-phosphonate (**5**); and (6) (carbethoxy) isopropyl

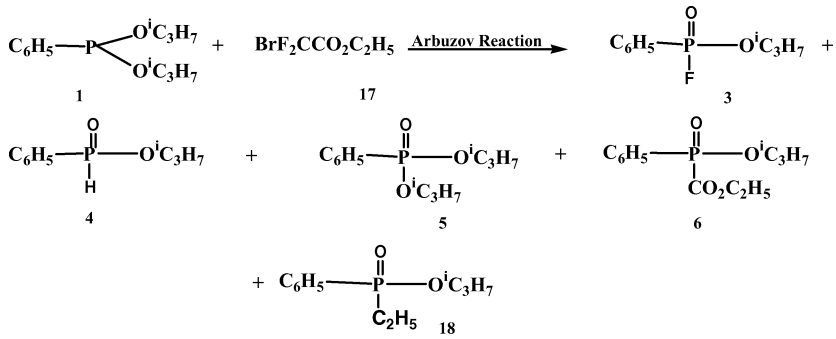

FIGURE 3 Structures of compounds cited in Table II.

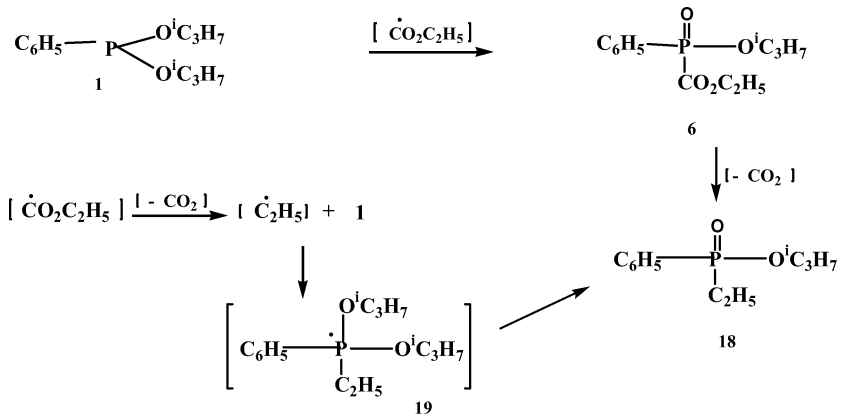

FIGURE 4 Genesis of ethyl isopropyloxy phenylphosphinate (18).

phenylphosphinate (**6**). The origin of all but one compound, namely **18**, arising from this reaction has been previously rationalized.

It can be surmised that the source of the ethyl moiety is the carbethoxy radical (cf. Figure 4). This carbethoxy intermediate can lose CO_2 and generate the C_2H_5-radical, which then goes on to react with **1** and to form the radical intermediate **19**, which finally furnishes compound **18** (cf. Figure 4). Or compound **6** itself undergoes metathesis losing CO_2 and yielding **18**. Interestingly compounds **3**, **4**, **5**, and **6** are also formed during the Arbuzov reaction of diisopropyl phenylphosphinate (**1**) with ethyl bromofluroacetate (**2**), as well as with ethyl bromodifluoroacetate (**17**). The expected product from the reaction of **1** with **17**, [(carbethoxy)(difluoromethyl)] isopropylphenylphosphinate was not detected at all.

The reaction of dimethyl phenylphosphonite (**20**) with ethyl α-bromo-α-fluoroacetate (**2**) was carried in an analogous manner. The usual processing of the reaction product furnished a mixture containing five compounds. The GC-MS analysis enabled the identification of the following compounds; (1) ethyl α-bromo-α-fluoroacetate (**2**) dimethyl phenylphosphonite (**20**)); (3) dimethyl phenylphosphonate (**21**); (4) [(carbethoxy)(fluoromethyl)] methyl phenylphosphinate (**22**); and (5) a stereoisomer of **22**, namely [(carbethoxy)-(fluoromethyl)] methyl phenylphosphinate (**23**). The mass spectral fragmentation of these compounds is described in Table III. Compound **21** certainly arises from the oxidation of the substrate (**20**) under the reaction conditions. What is interesting is the presence of the isomers, **22** and **23** (Figure 5). Their formation can be ascribed to the steric bulk of the alkoxy group attached to the phosphorus atom. The formation of the diastereomers

TABLE III Mass Spectral Fragmentation of Compounds Cited in Figs. 3, 5, and 6

1. **Ethyl-α-bromo, α-fluoroacetate (2)**: See Table 1.
2. **Ethyl isopropyl phenylphosphinate (18)**: $M^+ = 228$, 215 (M-CH_3); 199 (M-C_2H_5); 187 (M -C_3H_5, 99%); 169 (M-OC_3H_7); 159 (187-C_2H_4, 95%); 141 ((C_6H_5)P(O)(OH), 100%); 94 [$PH_2(0)(OC_2H_5)$]; 77 (C_6H_5) and 43 (C_3H_7).
3. **Dimethyl phenylphosphonite (20)**: $M^+ = 170$, 169 (M-H, 79%); 155 (M-CH_3, 100%); 140 (M-OCH_2); 125 [$C_6H_5P(O)H$]; 109 [$P(O)(OCH_3)_2$]; 91 (C_7H_7); 77 (C_6H_5); 63 (PO_2) and 51 (C_4H_3).
4. **Dimethyl phenylphosphonate (21)**: $M^+ = 186$ (78%); 185 (M-H, 100%); 171 (M-CH_3); 156 (M-OCH_2); 155 (M-OCH_3); 141 (155-CH_2); 124 (141-OH); 91 (C_7H_7); 77 (C_6H_5); 63 (PO_2) and 51 (C_4H_3).
5. **[(Carbethoxy)(fluoromethyl)] methyl phenylphosphinate (22)**: $M^+ = 260$; 231 (M-C_2H_5); 215 (M-OC_2H_5); 173 [$C_6H_5P(O)F(OCH_2)$] 155 (M-$CHFCO_2C_2H_5$, 100%); 141 [$C_6H_5P(0)(OH)$]; 125 [$C_6H_5P(O)H$]; 109 [$P(O)(OCH_3)_2$]; 91 (C_7H_7); 77 (C_6H_5); 63 (PO_2), 51 (C_4H_3) and 43 (C_2H_3O or C_2F).
6. **[(Carbethoxy)(fluoromethyl)] methyl phenylphosphinate (23)**: $M^+ = 260$; stereomer of **22**. The mass spectral fragmentation of **23** is identical with that of compound 22.
7. **(Chloromethyl) methyl phenylphosphinate (25)**: $M^+ = 204$; 169 (M-Cl); 155 (M-CH_2C1, 100%); 139 (169-OCH_2); 125 [$C_6H_5P(O)H$]; 77 (C_6H_5); 65 (PH_2O_2) and 51 (C_4H_3).
8. **Hydrogen methyl phenylphosphinate (26)**: $M^+ = 156$; 155 (M-H, 100%); 141 M-CH_3); 126 (M-OCH_2); 91 (C_7H_7); 79 (M-C_6H_5); 65 (PH_2O_2) and 51 (C_4H_3).

22 and **23** is directly attributable to the classical Michaelis-Arbuzov reaction. This inference stands supported by a precedence.[9b]

The reaction of dimethyl phenylphosphonite (**20**) with bromochloromethane (**24**) is very sluggish at best at ambient temperature. Even after several days, only trace amounts of **25** was detected by GC-MS. This type of compounds are routinely formed during the course of the said reaction.[1f]

In view of the low boiling point of (bromo)(chloro)methane (**24**), the reaction of dimethyl phenylphosphonite (**20**) with (bromo)

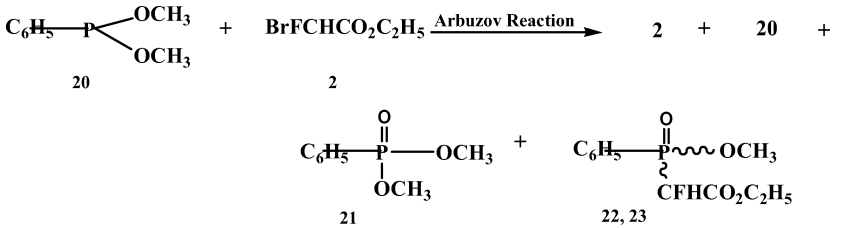

FIGURE 5 Structures of compounds cited in Table II.

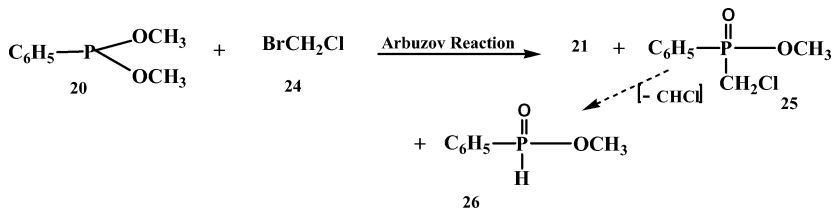

FIGURE 6 Structures of compounds cited in Table II.

(chloro)methane (**24)** was carried out by stirring a mixture containing stoichiometric amounts dimethyl phenylphosphonite (**20**) and (bromo)(chloro)methane (**24**) under nitrogen for 2 days at 40°C with a reflux condenser attached to the reaction flask. After the volatile organics were removed under house vacuum, the residue on gas-chromatographic analysis indicated the presence of four components. The GC-MS analysis of the reaction product permitted the characterization of the following compounds (cf. Figure 6): (1) (chloromethyl) methyl phenylphosphinate (**25**); (2) dimethyl phenylphosphonite (**20**); (3) dimethyl phenylphosphonate (**21**) and (4) hydrogen methyl phenylphosphinate (**26**). The formation of **26** from **25** is explained in Figure 6 (cf. broken line). Compound **25** is the expected product of the Arbuzov reaction of dimethyl phenylphosphonite (**20**) with bromochloromethane (**24**). Hydrogen phenylphospinate (**26**) arises from the splitting off of the carbene (:CHCl) from **25**.

In summary, the observed formation of anomalous products appears to be a consequence of the use of dialkylphosphonites instead of trialkylphosphites and to the steric bulk of the alkoxy group attached to the phosphorus atom. The isopropoxy moiety being bulkier than the methoxy group hinders the attack by the bulky free radicals on the phosphorus atom. It is because of the problems associated with the direct synthesis of α-fluorophosphonates, alternate methods for introducing fluorine into the α-position have been developed.[14]

EXPERIMENTAL

EI mass spectra were obtained using a model 5973i GC/MSD (Agilent Technologies, Wilmington, DE) equipped with a 30 m $\times$ 0.25 mm HP-5ms capillary column (0.25 μm film). The carrier gas was helium at 1.1 mL/min (constant flow), injection temperature was 250°C, transfer line temperature was 280°C, electron energy was 70 eV, and the oven was programmed from 60°C to 280°C at 15°C/min

with a 10 min hold at 280°C. The mass range was scanned from 45–500 daltons at 1.66 scans/sec. Injection was in the split (50:1) mode.

CI mass spectra were obtained using a model TSQ-7000 GC/MS/MS (ThermoFisher, San Jose, CA) equipped with a 30 m × 0.25 mm HP-5ms capillary column (0.25 μm film). The carrier gas was helium at 1 mL/min, injection temperature was 250°C, transfer line temperature was 250°C, electron energy was 200 eV, and the oven was programmed from 60°C to 270°C at 15°C/min with a 14 min hold at 270°C. Methane (UHP grade) was used as the CI reagent gas at 3500 mT. The mass range was scanned from 60–500 daltons at 0.7 s/scan. Injection was in the split (50:1) mode.

DART™ Tass Spectral Technique

The sample was also analyzed by DART™ (Direct Analysis in Real Time) using a JEOL AccuTOF mass spectrometer. Approximately 100 nanograms of sample were applied to a glass rod and introduced to the DART™ ion source. Mass spectra were generated over the mass range of 100 to 450 Da. Formulae were confirmed by exact mass measurement to an accuracy of 0.001 Da.

Electrospray Ionization Tandem Mass Spectrometry

The sample was also analyzed by Electrospray Ionization tandem mass spectrometry using a Finigan TSQuantum triple quadrupole mass spectrometer operated in positive ion mode. The sample was introduced using Flow Injection Analysis, a 50% aqueous methanol solution was continuously infused into the ESI source at 100 ul/min, and 5 ul injections of a solution of the sample in acetone were made with a Finnigan Surveyor autosampler into the solvent stream. ESI mass spectra were obtained over the mass range 50−600 Da., using Q1 operated at slightly better than unit resolution with a scan time of 1s. Product Ion mass spectra were obtained by selecting the parent ion in Q1 using slightly better than unit resolution, and fragmenting the ions in Q2 using Argon as the collision gas and an energy of 15eV, and mass analyzing the fragment ions with Q3 operated at slightly better than unit resolution and scanning from 50 Da. to just above the mass of the parent ion, with a scan time of 1 s.

Reaction of Diisopropyl phenylphosphonite (1) with Ethyl α-Bromo-α -Fluoroacetate (2)

A mixture containing stoichiometric amounts of diisopropyl phenylphosphonite (**1**) and ethyl α-bromo-α-fluoroacetate (**2**) was heated with stirring under nitrogen at 85−90°C for 4 h. The reaction mixture was cooled to room temperature; the volatile organics were removed under house vacuum and the residue on gas-chromatographic analysis showed it to contain seven components. The GC-MS analysis of the reaction product permitted the characterization of the following compounds: (1) ethyl α-bromo-α-fluoroacetate (**2**, $M^+ = 184$, r.t. = 2.59 min, 4.7%); (2) fluoro isopropyl phenylphosphinate (**3**, $M^+ = 202$, r.t. = 6.84 min, 2.1%); (3) Hydrogen isopropyl phenylphosphinate (**4**, $M^+ = 184$, r.t. = 7.92 min, 3.9%); (4) diisopropyl phenylphosphonate (**5**, $M^+ = 242$, r.t. = 8.61 min, 28.7%); (5) (carbethoxy) isopropyl phenylphosphinate (**6**, $M^+ = 256$, r.t. = 10.30 min, 7.6%);(6) [(carbethoxy)(fluoromethyl)] isopropyl phenyl-phosphinate (**7**, $M^+ = 288$, r.t. = 11.00 min, 46.8%); (8) diphenyl isopropyl-phosphinate (**8**, $M^+ = 260$, r.t. = 11.91 min, 0.5%); (9) diisopropyl phenyl (carbethoxyfluoromethyl) pyrophosphate (**9**, $M^+ = 396$, r.t. = 15.66 min, 2.3%) and (10) isomer of **9**, namely diisopropyl phenyl (carbethoxyfluoromethyl) pyrophosphate (**10**, $M^+ = 396$, r.t. = 15.72 min, 3.3%). The mass spectral fragmentation of compounds cited above is given in Table I.

Reaction of Diisopropyl Phenylphosphonite (1) with Eethyl α-Bromo-α, α -Difluoroacetate (17)

The reaction of diisopropyl phenylphosphonite (**1**) with ethyl α-bromo-α, α-fluoroacetate (**17**) was carried our in an analogous manner except that compound **2** was replaced with **17**. The routine processing of the reaction product, followed by the GC-analysis indicated the presence of 6 components. The GC-MS analysis and the mass spectral fragmentation patterns enabled the identification of the following compounds: (1) ethyl α-bromo-α, α -fluoroacetate (**17**, $M^+ = 202$, r. t. = 2.58 min, 5.5%); (1) (fluoro) isopropyl phenylphosphinate (**3**, $M^+ = 202$, r. t. = 8.49 min, 18.8%); (3) hydrogen isopropyl phenylphosphinate (**4**, $M^+ = 184$, r. t. = 9.57 min, 11.1%); (4) ethyl isopropyl phenylphosphonate (**18**, $M^+ = 228$, r. t. = 10.15 min, 1.8%); (5) diisopropyl phenylphosphonate (**5**, $M^+ = 242$, r. t. = 10.27 min, 44.8%); and (6) (carbethoxy) isopropyl phenylphosphinate (**6**, $M^+ = 256$, r. t. = 11.95 min, 18.1%) (Figure 3).

Reaction of Dimethyl phenylphosphonite (20) with Ethyl α-Bromo-α-Fluoroacetate (2)

This reaction was carried in an analogous manner except that diisopropyl phenylphosphonite (**1**) was replaced by dimethyl phenylphosphonite (**20**) (Figure 5). The usual processing of the reaction product furnished a mixture containing five compounds. The GC-MS analysis enabled the identification of the following compounds; (1) ethyl α-bromo-α-fluoroacetate (**2**, $M^+ = 184$, r.t. = 2.59 min, 11.2%);(2) dimethyl phenylphosphonite (**20**, $M^+ = 170$, r.t. = 7.38 min, 63.0%)); (3) dimethyl phenylphosphonate (**21**, $M^+ = 186$, r.t. = 7.47 min, 12.1%)); (4) [(carbethoxy)(fluoromethyl)] methyl phenylphosphinate (**22**, $M^+ = 260$, r.t. = 10.53 min, 6.0%); and (5) a stereoisomer of **22**, namely [(carbethoxy)(fluoromethyl) methyl phenylphosphinate (**23**, $M^+ = 260$, r.t. = 10.6 min, 7.9%). The mass spectral breakdown of the above compounds is described in Table II.

Reaction of Dimethyl phenylphosphonite (20) with (Bromo)(Chloro)-Methane (24)

In view of the low boiling point of (bromo)(chloro)methane (**24**), a mixture containing stochiometric amounts dimethyl phenyl-phosphonite (**20**) and (bromo)(chloro)methane (**24**) was stirred under nitrogen for several days at ambient temperature. After the volatile organics, were removed under house vacuum and the residue on gas-chromatographic analysis indicated the presence of four components. The GC-MS analysis of the reaction product permitted the characterization of the following compounds: (1) hydrogen methyl phenylphosphinate (**26**, $M^+ = 156$, r.t. = 7.06 min, 3.2%); (2) dimethyl phenylphosphonite (**20**, $M^+ = 170$, r.t. = 7.45 min, 82.6%); (3) dimethyl phenylphosphonate (**21**, $M^+ = 186$, r.t. = 7.53 min, 13.9%) and (4) (chloromethyl) methyl phenylphosphinate (**25**, $M^+ = 204$, r.t. = 9.17 min, 0.4%) (Figure 6).

REFERENCES AND NOTES

[1] (a) E. Breuer, In The Chemistry of Organophosphorus Compounds, , E. R. Hartley, Ed. (Wiley and Sons, New York, 1996), No. 4, Ch. 7; (b) G. M. Blackburn, *Chem. Ind.* (London), 134 (1981); (c) A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, **81,** 415 (1981); (d) R. Engel, Ed., *Synthesis of Carbon-Phosphorus Bonds* (CRC Press, Boca Raton FL, 1988); (e) R. Engel, Ed., *Handbook of Organophosphorus Chemistry*, (Marcel Dekker, New York, 1992), p. 279; (f) L. D. Quinm, *A Guide to Organophosphorus Chemistry* (Wiley-Interscience, New York, 2000).

[2] (a) R. K. Sharma and N. Kharasch, *Angew. Chem. Int. Ed.*, **7,** 36 (1968); (b) R. S. Davidson, *Tetrahedron*, **25,** 3383 (1969); (c) J. Kochi and P. J. Krusic, *J. Am. Chem.*

Soc., **91,** 3944 (1969); (d) J. B. Plumb, R. Obrycki, and C. E. Griffin, *J. Org. Chem.*, **33,** 632 (1968) and refs. cited therein).

[3] R. B. Lacount and C. E. Griffin, *Tetrahedron Lett.*, 3071 (1965).

[4] (a) A. F. Gaines and F. M. Page, *Trans. Faraday Soc.*, **62,** 3086 (1966) and refs. cited therein; (b) Krishnaji and S. Chandra, *Chem. Abstr.*, **69,** 46136b (1968); (c) J.-J. L. Fu, and W. G. Bentrude, *J. Am. Chem. Soc.*, **94,** 1717 (1972).

[5] (a) D. H. Wiley and H. E. Simmons, *J. Org. Chem.*, **29,** 1876 (1964); (b) S. Z. Ivin, V. K. Promonenkov and B. A Fokin, *Chem. Abstr*., **71,** 1485 (1969); (c) I. L. Knunyants, R. N. Sterlin, V. V. Tyuleneva and L. N. Pinkina, *Chem. Abstr.,* **59,** 8784 (1963).

[6] (a) H. Wessolowski, G. L. Gard, and G. V. Roschenthaler, *J. Fluorine Chem.*, **80,** 149 (1996); (b) D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, **10,** 329 (1977).

[7] (a) A. Thenappan and D. J. Burton, *J. Org. Chem.*, **55,** 2311 (1990); (b) H. Machleidt and R. Wessendorf, *Ann. Chem.*, **674,** 1 (1964); H. -J. Tsai, A. Thenappan, and D. J. Burton, *Phosphorus, Sulfur, and Silicon*, **105,** 205 (1995); (d) E. Elkik and M. Imbreaux, *Synthesis*, 861 (1989); (e) J. Kvicala, R. Vlaskova, J. Plocar, P. Paleta, and A. Pelter, *Coll. Czech. Chem. Comm.*,**66,** 77 (2000); (f) G. Etemad-Moghadam and J. Seyden-Penne, *Bull. Soc. Chim.* (France) 448 (1985).

[8] (a) A. V. Folkin, V. I. Zimin, Y. N. Studnev and A. I. Raplein, *Chem. Abstr.*, **74,** 124736 (1971); (b) I. L. Knunynats, and E. Y. Pervova, *Chem. Abstr.*, **62,** 2791c (1965); (c) I. L. Knunynats, V. V. Tyuleneva, E. Y. Pervova, and R. N. Sterlin, *Chem. Abstr.*, **62** 2791d (1965); (d)R. Dittrich and G. Hegele, *Phosphorus and Sulfur*, **10,** 127 (1981); (e) E. Elkik and I. Imbeaux, *Synthesis*, 861 (1989).

[9] (a) J. -J. L. Fu, W. G. Bentrude, and C. E. Griffin, *J. Am. Chem. Soc.*, **94,** 1710 (1972); (b) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

[10] (a) F. R. Hartley, Ed*., The Chemistry of Organophosphorus Compounds* , (Wiley and Sons, New York, 1990), Vol. 2; (b) W. Kutzelnigg, *Angew. Chem. Int. Ed.*, **23,** 272 (1984); (c) D. G. Gilheany, *Chem. Rev.*, **94,** 1339 (1994).

[11] (a) A. E. Arbuzov, *Chem. Abstr.*, **64,** 6680 (19660; (b) G. Kamai and R. K. Ismagilov, *Chem. Abstr.*, **60,** 77340 (1968); (c) A. N. Pudovik and V. K. Krupnov, *Chem. Abstr.*,**69,** 77340 (1965); (d) A. E. Arbuzov and K. V. Nikomorov, *Chem. Abstr.*, **43,** 3801i (1949).

[12] (a) H. D. Buss and S. Warren*, J. Chem. Soc., Perkin Trans.*, **1,** 2307 (1985); (b) M. Sanders and G. Buschman, *Tetrahedron Lett.*, 8 (1959), (c) S. T. D. Gough and S. Tripett, *J. Chem. Soc.*, 4263 (1961); (d) V. D. Makhaev and A. P. Borisov, *J. Gen. Chem., USSR* (English), **54,** 2279 (1984).

[13] J. Fossey, D. Lefort, and J. Sorba, *Free Radicals in Organic Chemistry* (Wiley, New York, 1995).

[14] (a) Z.-Q. Xu and D. D. DesMarteau, *J. Chem. Soc., Perkin Trans.*, **1,** 313 (1992); (b) P. Savignac and B. Iorga, *Modern Phosphonate Chemistry* (CRC Press, New York, 2003).