Novel Dialkyl (β-Halotetrafluoroethyl)phosphonates: Facile Synthesis *via* Thermally and Photochemically Induced Radical Reactions. A Unique Photochemical Transformation of $BrCF_2CF_2I$

H. K. Nair and D. J. Burton*

Department of Chemistry, University of Iowa
Iowa City, Iowa 52242

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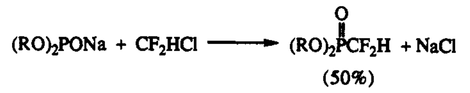
Phosphonates are an important class of compounds by virtue of their similarity to phosphates, and the preparation and biochemical investigation of a number of new phosphonates have been reported.[1] However, reports on the fluorinated analogues of these compounds are scarce although it is well established that incorporation of fluorine into biologically significant compounds imparts enhanced activity and stability compared to the nonfluorinated counterparts.[2] This dearth of fluorinated analogues is due to the lack of useful synthetic procedures, since conventional methods of synthesis of phosphonates cannot usually be applied to fluorinated cases.

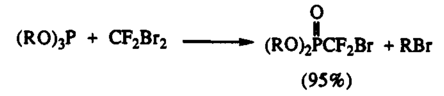
On the basis of both electronic and steric considerations, it had been proposed by Blackburn and co-workers[3] that replacement of a bridging oxygen in a pyrophosphate or the methylene group in a methane diphosphonate by a difluoromethylene group is isosteric and isopolar and the fluorinated analogue should exhibit chemical and physical properties similar to those of the corresponding phosphonates. In fact, fluorinated phosphonates were found to be excellent mimics of phosphate esters; for example, Danzin and co-workers have demonstrated the superiority of difluorophosphonate, 9-(5,5-difluoro-5-phosphonopentyl)guanine as a purine nucleoside phosphorylase inhibitor.[4] Therefore, there is considerable current interest in the preparation of the fluorinated phosphonates and exploration of their potential for biological activity.[5] In addition to their potential as phosphate mimics, fluorinated phosphonates have also been investigated as fuel cell electrolytes[6] as well as chelating agents.[7] A recent spate of efforts in this area has resulted in the syntheses of new fluorinated acids $(HO)_2P(O)CF_2P(O)(OH)_2$,[8] $(HO)_2P(O)(CF_2)_nP(O)(OH)_2$ (n = 2, 3, and 4),[9] $(HO)_2P(O)CF_2CO_2H$,[10] $(HO)_2P(O)CF_2SO_3H$,[11] and $(HO)_2P(O)CF{=}CFP(O)(OH)_2$.[12]

The preparation of α,α-difluorinated phosphonates, $(RO)_2P(O)CF_2H$ and $(RO)_2P(O)CF_2Br$ (R = Et, i-C_3H_7), has been reported[13] (eqs 1 and 2). Although these reactions appear to be S_N2 type displacements, they proceed *via* formation and subsequent trapping of difluorocarbene.[14] Consequently, these transformations are specific for difluoromethyl analogues and cannot be extended to the preparation of (β-halotetrafluoroethyl)phosphonates. Currently, to our knowledge, there exists no method for the preparation of phosphonates $(RO)_2P(O)CF_2CF_2X$ (R = alkyl; X = Cl, Br, I), and our continued quest in this area prompted us to explore different synthetic routes for these compounds. Herein, we report the synthesis of new phosphonates, $(RO)_2P(O)CF_2CF_2X$, in good yields from commercially available starting materials, and a unique photochemical reaction of $BrCF_2CF_2I$.



$$(RO)_2PONa + CF_2HCl \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}CF_2H + NaCl \quad (1)$$

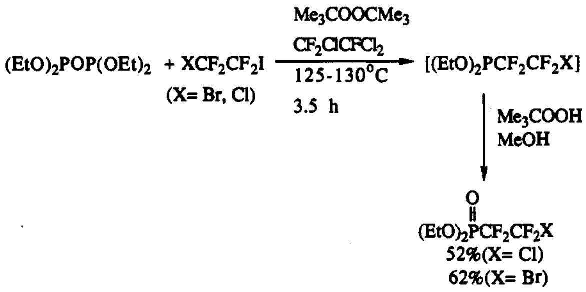
(50%)



$$(RO)_3P + CF_2Br_2 \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}CF_2Br + RBr \quad (2)$$

(95%)

Our initial attempts for the synthesis of dialkyl (β-halotetrafluoroethyl)phosphonate was *via* Kato–Yamabe[15] thermally induced radical reaction. Thus, when a mixture of ICF_2CF_2I, $(EtO)_2POP(OEt)_2$, and di-*tert*-butyl peroxide in $CF_2ClCFCl_2$ was heated at 125–130 °C, under degassed conditions for 3.5 h, only $F_2C{=}CF_2$ was observed; $BrCF_2CF_2Br$ did not react at all under similar experimental conditions. However, when $BrCF_2CF_2I$ was employed, formation of the corresponding phosphonite, $[(EtO)_2PCF_2CF_2Br]$, was observed (eq 3). Though this intermediate was not isolated, its characterization was accomplished



$$(EtO)_2POP(OEt)_2 + \underset{(X=\,Br,\,Cl)}{XCF_2CF_2I} \xrightarrow[\substack{125\text{-}130\,^\circ C \\ 3.5\ h}]{\substack{Me_3COOCMe_3 \\ CF_2ClCFCl_2}} [(EtO)_2PCF_2CF_2X] \xrightarrow{\substack{Me_3COOH \\ MeOH}} (EtO)_2\overset{O}{\overset{\|}{P}}CF_2CF_2X \quad (3)$$

52%(X= Cl)
62%(X= Br)

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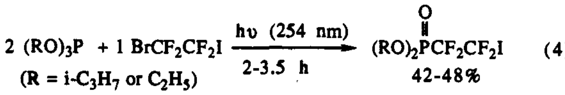
by ^{19}F and ^{31}P{^{1}H} NMR analyses.[16] The resultant [$(EtO)_2PCF_2CF_2Br$] upon oxidation with Me_3COOH in MeOH readily afforded the target phosphonate, $(EtO)_2P(O)CF_2CF_2Br$,[17] in 62% isolated yield. Similarly, the corresponding chloro derivative was obtained from $ClCF_2CF_2I$, in 52% yield (eq 3).

As an alternative to the thermally induced radical reaction, we focused our attention on a photochemical approach. Previously, it was reported that UV irradiation of a mixture of triethyl phosphite and CF_3I or C_6F_5I afforded $CF_3P(O)(OR)_2$ or $C_6F_5P(O)(OR)_2$ (R = C_2H_5), respectively.[18] We chose to explore the photochemical reaction of ICF_2CF_2X (X = Br, I) and trialkyl phosphite. Thus, when a degassed mixture of ICF_2CF_2I and triethyl or triisopropyl phosphite was subjected to UV irradiation (254 nm, Rayonet Photochemical apparatus) for 2–3.5 h at ambient temperature, only the formation of C_2F_4 was observed. However, when $BrCF_2CF_2I$ was employed, an interesting and unique transformation resulted; $(RO)_2P(O)CF_2CF_2I$[17] (R = Et or *i*-Pr) was formed (42–48% isolated yields) (eq 4) with no detectable amount of the bromo derivative, $(RO)_2P(O)CF_2CF_2Br$![19] We found the yield of $(RO)_2P(O)CF_2CF_2I$ optimum when the ratio of trialkyl phosphite to $BrCF_2CF_2I$ was 2:1.

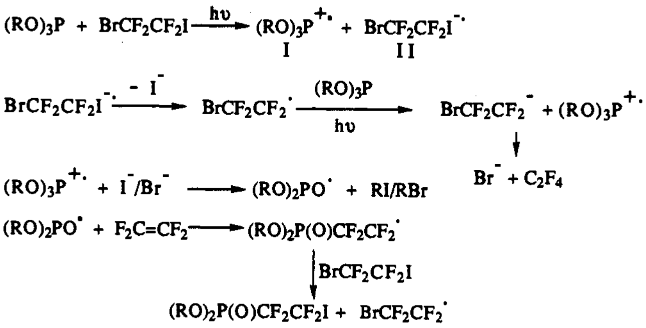


$$2\,(RO)_3P + 1\,BrCF_2CF_2I \xrightarrow[2\text{-}3.5\ h]{h\upsilon\ (254\ nm)} (RO)_2\overset{O}{\overset{\|}{P}}CF_2CF_2I \qquad (4)$$

(R = i-C_3H_7 or C_2H_5) 42-48%

Byproducts observed from the above reaction were EtBr, EtI, $BrCF_2CF_2H$, and unreacted $BrCF_2CF_2I$,[20] besides $(RO)_2P(O)CF_2CF_2H$ (5–10%). Irradiation for a longer time did not improve the yield of $(RO)_2P(O)CF_2CF_2I$.[21] The reaction of XCF_2CF_2I (X = Br or I) with $(RO)_3P$ (R = *i*-C_3H_7 or C_2H_5) (at 100 °C, under degassed conditions) or with $(EtO)_2PO^-Na^+$ were also investigated; in both cases, neither $(RO)_2P(O)CF_2CF_2I$ nor $(RO)_2P(O)CF_2CF_2Br$ was observed, but $F_2C{=}CF_2$.[22] Also, triphenyl phosphite, a poor nucleophilic substrate, on irradiation with $BrCF_2CF_2I$ afforded $F_2C{=}CF_2$ as the only fluorine-containing product. Our proposed mechanism for this remarkable transformation is illustrated in Scheme 1.

Scheme 1



Photoinduced electron transfer between the phosphite and 1-bromo 2-iodotetrafluoroethane produces the radical cation, **I**,[23,24] and radical anion, **II**, respectively. A second electron transfer to **II** affords the unstable $BrCF_2CF_2^-$, which eliminates Br^- to generate $F_2C{=}CF_2$. Phosphoryl radical results on dealkylation of **I** by either I^- or Br^-. Subsequent addition of phosphoryl radical to the tetrafluoroethylene[25] results in the formation of $(RO)_2P(O)CF_2CF_2^{\bullet}$, which in the last step abstracts an iodine atom from the starting ethane to afford $(RO)_2P(O)CF_2CF_2I$ and $BrCF_2CF_2^{\bullet}$; the latter continues the chain process.

In summary, we have demonstrated the facile preparation of new fluorinated phosphonates, $(RO)_2P(O)CF_2CF_2X$ (X = Cl, Br, or I), for the *first* time from readily available precursors. We anticipate that ready accessibility of these interesting phosphonates makes them attractive targets for biochemical studies and precursors for fuel cell electrolytes.

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Supplementary Material Available: Detailed experimental procedures and spectral data for $(RO)_2P(O)CF_2CF_2X$ (X = Cl, Br, I) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) $(EtO)_2PCF_2CF_2Cl$: ^{19}F ($CDCl_3$) δ −67.3 (dt, 2F), −122.6 (dt, 2F) ppm; ^{31}P{^{1}H} δ 144.8 (tt) ppm ($^{2}J_{PF}$ = 80 Hz, $^{3}J_{PF}$ = 17 Hz, $^{3}J_{FF}$ = 10 Hz). $(EtO)_2PCF_2CF_2Br$: ^{19}F ($CDCl_3$) δ −61.3 (dt, 2F), −119.6 (dt, 2F) ppm; ^{31}P{^{1}H} δ 145.6 (tt) ppm ($^{2}J_{PF}$ = 82 Hz, $^{3}J_{PF}$ = 19 Hz, $^{3}J_{FF}$ = 10 Hz). The ^{31}P{^{1}H} and ^{19}F δ values are consistent with the previously reported values for *F*-alkylphosphonites.[15]

(17) The new phosphonates were fully characterized by spectral (^{19}F, ^{31}P{^{1}H}, ^{1}H, ^{13}C{^{1}H}, IR, and MS) and elemental analyses; see supplementary material.

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(19) We could detect $(EtO)_2P(O)CF_2CF_2Br$, in a mixture of $(EtO)_2P(O)CF_2CF_2Br$ (1%, 0.0137 M) and $(EtO)_2P(O)CF_2CF_2I$ (99%) in $CDCl_3$, *via* ^{19}F NMR (at 90 MHz) spectroscopy since ^{19}F NMR δ values of these two phosphonates differ by 5.2 ppm; cf. supplementary material. Thus, if any $(EtO)_2P(O)CF_2CF_2Br$ is formed, it is <1%.

(20) GC analysis of the volatiles from the reaction mixture indicated the presence of $BrCF_2CF_2H$, EtBr, EtI, and $BrCF_2CF_2I$ in the ratio 15:49:34:2, respectively; the identities of these compounds were established by spectral (^{1}H and ^{19}F NMR and GC–MS) analysis. EtI and EtBr were further confirmed with authentic samples.

(21) Irradiation for a longer time (~6 h) resulted in many new resonances (−110 to −140 ppm) in the ^{19}F NMR spectrum, with gradual reduction of $(RO)_2P(O)CF_2CF_2I$.

(22) Under degassed conditions, the fluorine-containing product identified in the ^{19}F NMR spectrum from the reaction of $(EtO)_2PO^-Na^+$ and XCF_2CF_2I (X = Cl, Br, or I) in the ratio 2 (or excess) to 1 was $F_2C{=}CF_2$ only; no resonance attributable to a $(EtO)_2P(O)CF_2CF_2X$ species was evident.

(23) ESR studies on radical cations, $P(OMe)_3^{\bullet+}$ and $HP(OMe)_2^{\bullet+}$, have been reported. See: (a) Hasegawa, A.; McConnachie, G. D. G.; Symons, M. C. R. *J. Chem. Soc., Faraday Trans. 1*, **1984**, *80*, 1005. (b) Janes, R.; Symons, M. C. R. *J. Chem. Soc., Faraday Trans. 1*, **1990**, *86*, 2173. Recently, the formation of triethyl phosphite radical cation under photochemical conditions has been reported.[24]

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