



A New Synthetic Route to Perfluoroalkylidene- α,ω -Bisphosphonates

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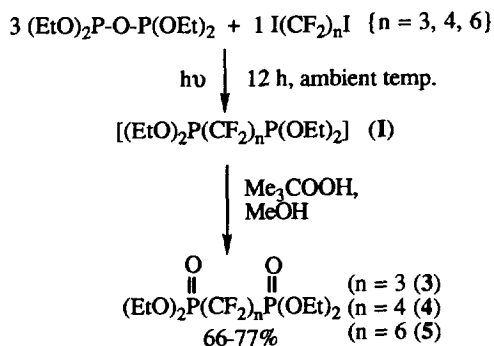
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Abstract. The UV irradiation of a mixture of $(\text{EtO})_2\text{POP}(\text{OEt})_2$ and $\text{I}(\text{CF}_2)_n\text{I}$ ($n = 3, 4, 6$) or $\text{I}(\text{CF}_2)_n\text{P}(\text{O})(\text{OEt})_2$ ($n = 1, 2$) results in the corresponding bisphosphonites or mixed phosphonite-phosphonates, respectively, which on oxidation by Me_3COOH afforded the perfluoroalkylidene- α,ω -bisphosphonates in 64-77% isolated yields.

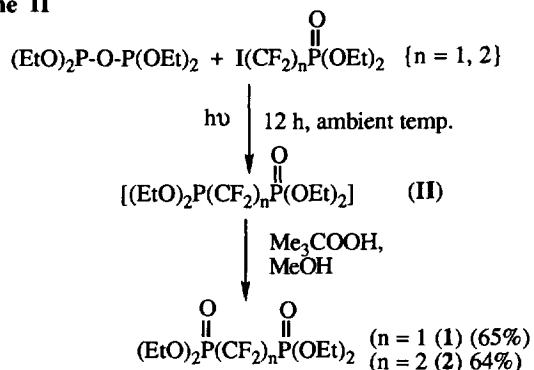
Recently, fluorinated bisphosphonates have gained attention because of their potential as analogues of biologically important pyrophosphates,¹ and as chelating agents in bone resorption studies.² Fluorinated bisphosphonates are also precursors for the corresponding bisphosphonic acids which may find application as fuel cell electrolytes³ since fluorine substitution imparts increased hydrolytic stability as well as oxygen solubility. The synthesis of $(\text{RO})_2\text{P}(\text{O})\text{CF}_2\text{P}(\text{O})(\text{OR})_2$ ($\text{R} = \text{Et}, i\text{-Pr}$) has been described.⁴ Formation of $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CF}_2\text{P}(\text{O})(\text{OEt})_2$ as a by-product in the addition of $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Br}$ to various alkenes has been reported.⁵ Recently, we reported the preparation of novel fluorinated bisphosphonates, $(\text{RO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{P}(\text{O})(\text{OR})_2$ ($\text{R} = \text{Et}$ or $i\text{-Pr}$, $n = 2, 3, 4, 6$) *via* thermally induced radical reaction and metal-mediated reductive coupling.⁶ Herein, we report a new method for the synthesis of a series of perfluoroalkylidene- α,ω -bisphosphonates, $(\text{RO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{P}(\text{O})(\text{OR})_2$ ($\text{R} = \text{Et}$, $n = 1, 2, 3, 4$, and 6) *via* a photochemical approach, in good yields from readily available starting materials.

In 1981, Kato and Yamabe reported the synthesis of F-alkylphosphonates *via* the thermally induced reaction of tetraethylpyrophosphite and R_fI ($\text{R}_f = \text{C}_6\text{F}_{13}, \text{C}_4\text{F}_9, (\text{CF}_3)_2\text{CF}$) in the presence of $\text{Me}_3\text{COOCMe}_3$ in $\text{CF}_2\text{ClCFCl}_2$.⁷ We have found that perfluoroalkylidene- α,ω -bisphosphonates could also be obtained from tetraethylpyrophosphite and the corresponding $\text{I}(\text{CF}_2)_n\text{I}$ ($n = 3, 4, 6$) *via* Kato-Yamabe procedure; however the yields of the bisphosphonates were low and the formation of significant amounts of the by-products, $(\text{EtO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{H}$ and $(\text{EtO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{I}$, could not be avoided.⁶ Also, the procedure involves heating the reaction mixture containing peroxide at elevated temperature. An alternative procedure reported, metal mediated reductive coupling of iodophosphonate, involved the use of toxic cadmium.⁶ The procedure described here involves neither heating a peroxide at high temperature nor the use of a toxic metal. Also, yields of the target bisphosphonates are higher than previously reported.⁶

When a degassed mixture of tetraethylpyrophosphite and $\text{I}(\text{CF}_2)_n\text{I}$ ($n = 3, 4, 6$) (in 3 to 1 ratio) was irradiated at 254 nm at ambient temperature for 15-17 hours, the corresponding mixed P^{III} intermediate, perfluoroalkylidene- α,ω -bisphosphonite (**I**) was formed. **I** was not isolated but identified by ^{19}F and $^{31}\text{P}\{^1\text{H}\}$ NMR spectral analyses; subsequent oxidation of **I** with $\text{Me}_3\text{COOCMe}_3$ afforded the desired bisphosphonates, $(\text{EtO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{P}(\text{O})(\text{OEt})_2$ ($n = 3, 4, 6$) in 66-77% isolated yield (Scheme I). The bisphosphonates (**3**, **4**, **5**) gave the same physical and spectral (^{19}F , $^{31}\text{P}\{^1\text{H}\}$, ^1H and MS) data, as reported in our previous work.⁶

Scheme I

Bisphosphonates containing one and two difluoromethylene groups could be readily prepared by irradiation of tetraethylpyrophosphite and the corresponding iodophosphonate, $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{I}$ ⁶ and $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CF}_2\text{I}$,⁸ respectively; the resultant P^{III}-P^V intermediate (II) (Scheme II) on oxidation afforded the corresponding bisphosphonates $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{P}(\text{O})(\text{OEt})_2$ (**1**) (65%) $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CF}_2\text{P}(\text{O})(\text{OEt})_2$ (**2**) (64%). **1** and **2** exhibited the same physical and spectral data as reported previously.^{4,6}

Scheme II

Irradiation of a degassed mixture of tetraethylpyrophosphite and $\text{ICF}_2\text{CF}_2\text{I}$ resulted in $\text{F}_2\text{C}=\text{CF}_2$ only. This photochemical conversion can be conveniently carried out in glass or quartz vessels. The reduced product, $(\text{EtO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{H}$, formed *via* this procedure is only (~2-3%) (identified by ¹⁹F and ³¹P{¹H} NMR analyses) which can be readily removed under reduced pressure from the product. This procedure is more convenient and yields are higher than reported earlier *via* thermally induced radical reaction or metal mediated reductive coupling.⁶

Table I. Fluorinated Bisphosphonates via Photochemical Reaction

Reactants	Product after oxidation (Isolated Yield)*
1 (EtO) ₂ P(O)CF ₂ I + 1 (EtO) ₂ POP(OEt) ₂	1 (65%)
1 (EtO) ₂ P(O)CF ₂ CF ₂ I + 1 (EtO) ₂ POP(OEt) ₂	2 (64%)
1 I(CF ₂) ₃ I + 3 (EtO) ₂ POP(OEt) ₂	3 (75%)
1 I(CF ₂) ₄ I + 3 (EtO) ₂ POP(OEt) ₂	4 (66%)
1 I(CF ₂) ₆ I + 3 (EtO) ₂ POP(OEt) ₂	5 (77%)

*yields based on the corresponding iodophosphonate or α,ω - diiodide

A representative experimental procedure is as follows: A degassed mixture of I(CF₂)₄I (4.54 g, 10 mmol) and (EtO)₂POP(OEt)₂ (7.74 g, 30 mmol) in a quartz Rotaflo tube (~50 mL capacity) was irradiated (254 nm, Rayonet Photochemical Reactor) at ambient temperature for 15-17 hours. DMF (10 mL) was added to the resultant reaction mixture and the solution was transferred to a 100 mL round-bottomed flask equipped with an addition funnel, nitrogen tee, and a magnetic stir-bar. The flask was cooled by an ice/salt bath (-20°C) and Me₃COOH (60 mmol) in 25 mL MeOH was added drop-wise to the stirred reaction mixture, over a period ~1h. After complete addition, the reaction mixture was stirred for an additional 30 minutes at this temperature, and volatiles were removed under reduced pressure (0.5 mm Hg). The residue was poured into water (~150 mL); the crude bisphosphonate separated as a lower layer {except for (EtO)₂P(O)CF₂P(O)(OEt)₂; in this case the residue was extracted with 125 mL CH₂Cl₂}. The water layer was extracted with 25 mL CH₂Cl₂; the combined CH₂Cl₂ extracts was washed with 20 mL H₂O, dried (MgSO₄), and concentrated on a rotary evaporator. The residue was chromatographed (silica gel column, 1:1 ethylacetate-hexanes) to afford 3.0 g of (EtO)₂P(O)(CF₂)₄P(O)(OEt)₂ (**4**) (66% yield) which exhibited the same spectral data as previously reported.⁶

In summary, a simple, practical synthesis of perfluoroalkylidene- α,ω -bisphosphonates, (EtO)₂P(O)(CF₂)_nP(O)(OEt)₂ {n = 1, 2, 3, 4, 6}, from readily available starting materials *via* photochemical reaction is demonstrated.

Acknowledgement

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References

1. (a) Blackburn, G. M.; England, D.A.; Kolkman, F. J. *Chem. Soc., Chem. Commun.* **1981**, 930. (b) Kent, D. E.; Kolkman, F. J. *Chem. Soc., Chem. Commun.* **1981**, 1188. (c) Blackburn, G. M.; Eckstein, F.; Kent, D. E.; Perree, T.D. *Nucleosides and Nucleotides* **1985**, *4*, 165. (d) Stremmer, K. E.; Poulter, C. D. *J. Am. Chem. Soc.* **1987**, *109*, 5542. (e) Davisson, V. J.; Davis, D. R.; Dixit, V. M.; Poulter, C. D. *J. Org. Chem.* **1987**, *52*, 1794.

2. (a) Fonong, T.; D. J. Burton, D. J.; Pietrzyk, D. J. *Anal. Chem.* **1983**, *55*, 1089. (b) Rowe, D. J.; Burton, D. J.; Pietrzyk, D. J. *J. Dental Research* **1981**, *60*, 596 (Special Issue A).
3. Mahmood, T.; Shreeve, J. M. *Inorg. Chem.* **1986**, *25*, 3128.
4. (a) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1980**, *15*, 263. (b) Blackburn, G. M.; England, D. A.; Kolkmann, F. J. *Chem. Soc., Chem. Commun.* **1981**, 930. (c) McKenna, C. E.; Shen, P. J. *Org. Chem.* **1981**, *46*, 4573. (d) Hutchinson, D. W.; Thornton, D. M. *J. Organomet. Chem.* **1988**, *340*, 93.
5. Hu, C. M.; Chen, J. J. *Chem. Soc. Perkin Trans.* **1993**, *1*, 327.
6. Nair, H. K.; Guneratne, R. D.; Modak, A. S.; Burton, D. J. *J. Org. Chem.* **1994**, *59*, 2393.
7. Kato, Yamabe, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1173.
8. Nair, H. K.; Burton, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6041.

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