

A Highly Selective Synthesis of α -Monofluoro- and α -Monochloro-benzylphosphonates Using Electrophilic Halogenation of Benzylphosphonates Carbanions

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Abstract: The selective electrophilic monofluorination and monochlorination of a wide variety of diethyl benzylphosphonates have been realized in a one-pot procedure. The monohalogenation was accomplished by intermediate of a benzylic carbanion protected with TMSCl using N-fluorobenzenesulfonimide (NFBS) and hexachloroethane, respectively. After mild removal of protecting group, this procedure delivers the α -monohalogenobenzylphosphonates in high yields (68–97%) and pure form. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The α -monofluoro- and α -monochlorophosphonates are recognized as important and useful compounds for independent reasons. The first ones behave as phosphate mimics for biological systems.¹ Due to the fluorine electronegativity, the monofluorophosphonate function has a pK_a almost identical to that of the corresponding phosphates. These analogues could be complexed similarly to the natural ligands but could not be hydrolyzed.² By contrast, the monochlorophosphonates are widely utilized synthetic reagents and especially as ideal precursors for the generation of symmetrical or unsymmetrical acetylenic compounds in mild conditions by the Wittig-Horner reaction.³

The preparation of monohalogenophosphonates by selective electrophilic halogenation at the α -CH₂ position by carbanionic way is a delicate and difficult to control process. This reaction generates unavoidably a monohalogenated derivative more acidic than the initial phosphonate, thus inducing an acid-base equilibrium which evolves toward the formation of a mixture of mono- and dihalogenophosphonates.⁴ This methodology has been successfully exploited lately to prepare the α,α -difluorinated phosphonates^{5a-c} or to introduce fluorine on a tertiary carbon.⁶ The α,α -difluorinated phosphonates can also be obtained by a CuCl promoted coupling reaction between aryl iodides and difluoromethylcadmium reagents.^{5d}

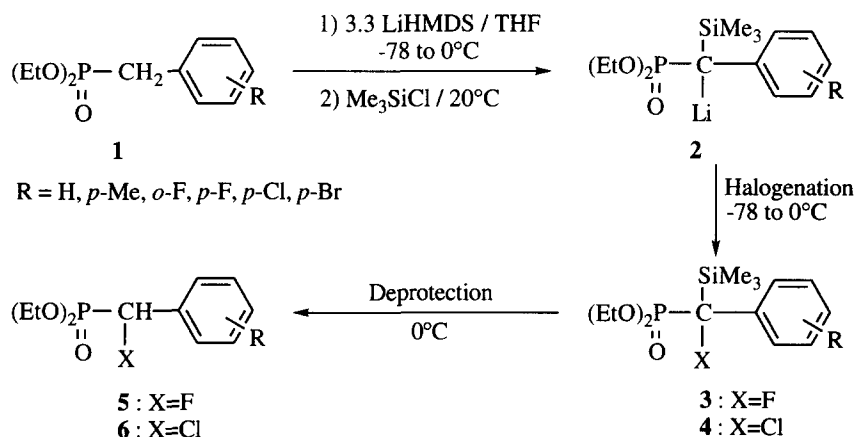
We report here a highly selective and attractive one-pot procedure for the synthesis of diethyl α -monofluoro- **5** and α -monochloro- **6** benzylphosphonates from diethyl benzylphosphonates **1**, based on the electrophilic halogenation of a benzylic carbanion transiently protected by a trimethylsilyl group. The starting

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materials **1** are commercially available or prepared on laboratory scale by the Michaelis-Arbuzov reaction between triethyl phosphite and corresponding benzyl bromides or chlorides.⁷⁻¹¹

We chose N-fluorobenzenesulfonimide (NFBS)⁴ as fluorinating agent and hexachloroethane as chlorinating agent because they are stable, crystalline, easy to handle and commercially available reagents. Moreover, the by-product of chlorination is volatile and easy to eliminate.

The diethyl benzylphosphonates **1** are first deprotonated with lithium hexamethyldisilazane (LiHMDS) 3.3 eq. at low temperature to give stable benzylic anions which are reacted at room temperature with Me₃SiCl (TMSCl) to afford quantitatively silylated benzylic anions **2** ($\delta^{31}\text{P}(\text{THF})=+45\text{--}47$ ppm). At low temperature, the resulting carbanions **2** undergo halogenation reaction to give the protected diethyl α -fluoro- **3** and α -chloro- **4** benzylphosphonates which, after deprotection, produce the desired fluorinated **5 a-f** and chlorinated **6 a-f** materials (Scheme 1). To explore the scope and applicability of this method, the synthesis was monitored by ³¹P-NMR spectrometry.



Scheme 1

We chose LiHMDS as base because HMDS, after regeneration in the reaction medium, is compatible with TMSCl even at room temperature, whereas both diisopropylamine and tetramethylpiperidine react with TMSCl, generating a chlorhydrate able to protonate the carbanions **2**.

We observed that silylation takes place completely only at room temperature with 1.1 eq. of TMSCl. The use of an excess of TMSCl has a detrimental effect since it reacts with NFBS inducing an halogen exchange.

While the first deprotonation is a fast reaction at low temperature, it appears that the second is slow and for complete generation of **2** it is necessary to operate with an excess of LiHMDS (3.3 eq.). In these conditions, carbanions **2** are obtained quickly and cleanly at room temperature. The need for an excess of base was confirmed independently by metallation of diethyl α -(trimethylsilyl)benzylphosphonate, which was achieved with at least 2 eq. of LiHMDS. This result confirms that the second deprotonation is slowed down by the low nucleophilicity and steric requirements of LiHMDS.

The halogenation with NFBS or hexachloroethane (1.2 eq.) is efficiently and rapidly carried out at -78°C in THF. Thereafter, the reaction mixture is warmed up to room temperature. In the case of the chlorination, the resulting compounds **4** are treated *in situ* with an excess of EtOLi in anhydrous EtOH which effects the facile and clean removal of the trimethylsilyl group. We found that this methodology was not suited for the fluorinated

Table 1. Diethyl α -fluorobenzylphosphonates **5**



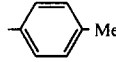

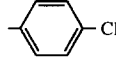
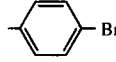



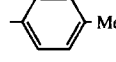
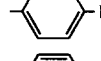
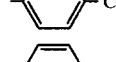
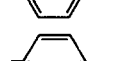

5		Rdt. (%)	$\delta^{31}\text{P}$ (ppm) (CDCl_3)	$\delta_{\text{CHF}}^{19}\text{F}$ (ppm)(CDCl_3)	$\delta_{\text{CHF}}^1\text{H}$ (ppm) (CDCl_3)	$\delta_{\text{CHF}}^{13}\text{C}$ (ppm) (CDCl_3)
a		97	13.0 (d, $^2J_{\text{PF}}=85.6$)	-200.6 (d, $^2J_{\text{PF}}=85.6$)	5.75 (dd, $^2J_{\text{PH}}=7.9$, $^2J_{\text{FH}}=44.6$)	89.9 (dd, $^1J_{\text{PC}}=170.5$, $^1J_{\text{FC}}=184.2$)
b		90	13.5 (d, $^2J_{\text{PF}}=87.7$)	-199.2 (d, $^2J_{\text{PF}}=86.9$)	5.70 (dd, $^2J_{\text{PH}}=7.5$, $^2J_{\text{FH}}=44.4$)	89.6 (dd, $^1J_{\text{PC}}=172.4$, $^1J_{\text{FC}}=183.2$)
c		68	12.9 (d, $^2J_{\text{PF}}=85.6$)	-199.2 (d, $^2J_{\text{PF}}=85.8$)	5.62 (dd, $^2J_{\text{PH}}=7.5$, $^2J_{\text{FH}}=44.5$)	88.7 (dd, $^1J_{\text{PC}}=171.5$, $^1J_{\text{FC}}=183.9$)
d		74	12.6 (d, $^2J_{\text{PF}}=83.3$)	-201.4 (d, $^2J_{\text{PF}}=83.6$)	5.70 (dd, $^2J_{\text{PH}}=7.3$, $^2J_{\text{FH}}=44.5$)	88.9 (dd, $^1J_{\text{PC}}=172.9$, $^1J_{\text{FC}}=184.0$)
e		76	14.4 (d, $^2J_{\text{PF}}=85.1$)	-199.7 (d, $^2J_{\text{PF}}=85.4$)	5.77 (dd, $^2J_{\text{PH}}=8.0$, $^2J_{\text{FH}}=44.6$)	89.1 (dd, $^1J_{\text{PC}}=171.0$, $^1J_{\text{FC}}=184.6$)
f		68	12.6 (dd, $^2J_{\text{PF}}=88.6$, $^4J_{\text{PF}}=5.2$)	-204.0 (d, $^2J_{\text{PF}}=90.4$)	6.10 (dd, $^2J_{\text{PH}}=8.0$, $^2J_{\text{FH}}=44.2$)	83.5 (ddd, $^1J_{\text{PC}}=177.0$, $^1J_{\text{FC}}=180.1$, $^3J_{\text{FC}}=3.0$)

Table 2. Diethyl α -chlorobenzylphosphonates **6**

6		Rdt. (%)	$\delta^{31}\text{P}$ (ppm) (CDCl_3)	$\delta_{\text{CHCl}}^1\text{H}$ (ppm) (CDCl_3)	$\delta_{\text{CHCl}}^{13}\text{C}$ (ppm) (CDCl_3)
a		93	18.2 (s)	4.87 (d, $^2J_{\text{PH}}=14.1$)	53.2 (d, $^1J_{\text{PC}}=159.6$)
b		90	17.5 (s)	4.90 (d, $^2J_{\text{PH}}=13.9$)	53.3 (d, $^1J_{\text{PC}}=161.2$)
c		94	17.0 (s)	4.75 (d, $^2J_{\text{PH}}=14.1$)	53.1 (d, $^1J_{\text{PC}}=160.6$)
d		93	16.4 (s)	4.79 (d, $^2J_{\text{PH}}=14.3$)	53.3 (d, $^1J_{\text{PC}}=160.2$)
e		93	16.4 (s)	4.75 (d, $^2J_{\text{PH}}=14.3$)	53.1 (d, $^1J_{\text{PC}}=159.5$)
f		92	16.6 (s)	5.20 (d, $^2J_{\text{PH}}=14.3$)	45.0 (d, $^1J_{\text{PC}}=163.3$)

derivatives **3** despite the total cleavage of the C-Si bond, because the resulting N-ethylbenzenesulfonimide is very difficult to separate from the desired products. Thus, we replaced this treatment by an hydrolysis with an aqueous solution of LiOH 1M which affords at the same time a smooth, immediate removal of the trimethylsilyl moiety and the best way to retain the benzenesulfonimide in the aqueous layer. Employment of NaOH 1M is however not so satisfying because the benzenesulfonimide is not completely retained in water in these conditions. After acidic work-up and extraction, the desired α -halogenobenzylphosphonates **5 a-f** and **6 a-f** are isolated in good to excellent yields. Examination of the spectral data (^{31}P , ^{19}F , ^1H , ^{13}C -RMN) shows that further purifications (distillation or chromatography) are not necessary. A clear illustration of the advantages of this novel synthetic procedure is provided by some representative examples collected in Tables 1 and 2.

We are currently extending this methodology to the synthesis of α -monobromo- and α -monoiodo-benzylphosphonates as well as heterocyclic analogs.

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References

1. (a) Bergmann, E.D.; Shahak, I.; Appelbaum, J. *Isr.J.Chem.* **1968**, 6, 73. (b) McCarthy, J.R.; Jarvi, E.T.; Matthews, M.L.; Prakash, N.J.; Bowlin, T.L.; Mehdi, S.; Sunkara, P.S.; Bey, P. *J. Amer. Chem. Soc.* **1989**, 111, 1127. (c) Tsai, H.J. *Tetrahedron Lett.* **1996**, 37, 629.
2. O'Hagan, D.; Rzepa, H. S. *Chem. Comm.* **1997**, 7, 645.
3. (a) Zimmer, H.; Bercz, P.J.; Maltenieks, O.J.; Moore, M.W. *J. Amer. Chem. Soc.* **1965**, 87, 2777. (b) Gallagher, M.J.; Noerdin, H. *Aust. J. Chem.* **1985**, 38, 997. (c) Kondo, K.; Ohnishi, N.; Takemoto, K.; Yoshida, H.; Yoshida, K. *J.Org.Chem.* **1992**, 57, 1622.
4. (a) Differding, E.; Ofner, H. *Synlett* **1991**, 187. (b) Differding, E.; Duthaler, R. O.; Kreiger, A.; Rüegg, G. M.; Schmit, C. *Synlett* **1991**, 395.
5. (a) Taylor, S.D.; Dinaut, A.N.; Thadani, A. T.; Huang, Z. *Tetrahedron Lett.* **1996**, 37, 8089. (b) Chen, W.; Flavin, M. T.; Filler, R.; Xu, Z.-Q. *Tetrahedron Lett.* **1996**, 37, 8975. (c) Taylor, S.D.; Kotoris, C.C.; Dinaut, A.N.; Chen, M.-J. *Tetrahedron* **1998**, 54, 1691. (d) Qiu, W.; Burton, D.J. *Tetrahedron Lett.* **1996**, 37, 2745.
6. Burke Jr., T.R.; Ye, B.; Akamatsu, M.; Ford Jr., H.; Yan, X.; Kole, H. K.; Wolf, G.; Shoelson, S. E.; Roller, P. P. *J. Med. Chem.* **1996**, 39, 1021.
7. (a) Saunders, B. C.; Stacey, G. J.; Wild, F.; Wilding, I. G. E. *J. Chem. Soc.* **1948**, 699. (b) Gronowitz, S.; Stenhammar, K.; Svensson, L. *Heterocycles* **1981**, 947. (c) Cabares, J.; Mavoungou-Gomes, L. *Bull. Soc. Chim. Fr.* **1986**, 3, 401. (d) Mouysset, G.; Bellan, J.; Payard, M.; Tisne-Versailles, J.; *Farmaco Ed. Sci.* **1987**, 42, 805.
8. Williams, A.; Naylor, R. A.; Collyer, S. G. *J. Chem. Soc., Perkin Trans. 2* **1973**, 25.
9. Brettle, R.; Dunmur, D. A.; Hindley, N. J.; Marson, C. M. *J. Chem. Soc., Chem. Commun.* **1992**, 410.
10. Nasser, J.; About-Jaudet, E.; Collignon, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, 54, 171.
11. (a) Savignac, P.; Lavielle, G. *Bull. Soc. Chim. Fr.* **1974**, 1506. (b) Kennedy, G.; Perboni, A. D.; *Tetrahedron Lett.* **1996**, 37, 7611.