The First Synthesis of Diethyl α,α-Chlorofluorobenzylphosphonates

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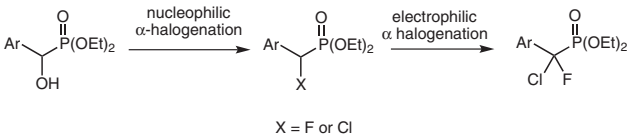
Abstract: Starting from α-hydroxyphosphonates, a wide variety of diethyl α,α-chlorofluorobenzylphosphonates have been obtained in pure form in a two-step procedure. The first step was chlorination of α-hydroxyphosphonates with Ph_3P and CCl_4, while the second step was fluorination with *N*-fluorobisbenzenesulfonimide.

Key words: fluorinated phosphonates, chlorination, fluorination, diethyl α,α-chlorofluorobenzylphosphonates

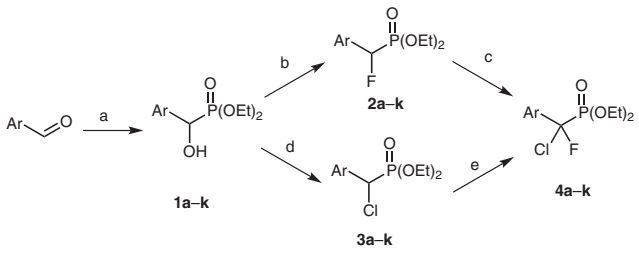
Fluorinated phosphonates have attracted considerable attention in the field of biology, pharmacology, and organic chemistry in recent years.[1] Due to their structural and electronic similarities to the parent phosphate groups,[2] α-monofluorophosphonates and α,α-difluorophosphonates are often designed as phosphate mimics and used as chelating agents,[3] enzyme inhibitors, and metabolite probes.[4] A lot of methods are available to prepare fluorinated phosphonates. For example, α-monofluoro- and α,α-difluorophosphonates have been prepared by Arbuzov reactions,[5] electrophilic fluorination of phosphonate-stabilized anions with the *N*-fluorobisbenzenesulfonimide (NFSI), Selectfluor and other electrophilic fluorinating reagents,[6] nucleophilic fluorination of α-hydroxyphosphonates or α-oxophosphonates with Et_2NSF_3 (DAST) and other nucleophilic fluorinating reagents,[7] and radical reactions through addition of phosphonyl radical onto 1,1-difluoroolefins.[8] However, structurally more complicated α-chloro-α-fluorophosphonates have not been well explored.[9] In our ongoing project of synthesizing probe library of protein tyrosine phosphatases (PTPs), some α-chloro-α-fluorophosphonate molecules were included. Modeling results indicated that α-chloro-α-fluorophosphonates as enzyme inhibitors and phosphate mimics will have their own special advantages. Therefore it is desirable to develop a useful synthetic method. Herein, we wish to report the first synthesis of α-chloro-α-fluorobenzylphosphonate compounds from α-hydroxyphosphonates which are easily prepared from commercially available materials.

The strategy to synthesize diethyl α-chloro-α-fluorobenzylphosphonates included a two-step halogenation procedure (Scheme 1). The starting material, α-hydroxyphosphonates, can be easily prepared from corresponding aldehydes and diethyl phosphite.



Scheme 1 Preparation of diethyl α-chloro-α-fluorobenzylphosphonates

In our initial investigation, we adopted the route starting from step b to c (Scheme 2). The starting materials **1** were prepared on laboratory scale by the Pudovik reaction between diethyl phosphite and corresponding aldehyde in excellent yields. The α-monofluorophosphonates were successfully synthesized by nucleophilic fluorination of α-hydroxyphosphonates **1** with DAST in the CH_2Cl_2 in good yield. However, the subsequent electrophilic α-chlorination of α-monofluorophosphonates with hexachloroethane ($C1_3CCC1_3$) and sodium hexamethyldisilazide (NaHMDS) in THF did not proceed as smoothly as expected.[10] The conversion rates were quite low, and the reaction mixture contained a large amount of starting material together with small amount of products. The failure of the α-chlorination was both probably related to the weak nucleophilicity of intermediate phosphonate carbanions which were counteracted by the electron withdrawing F-substituent and the weak electrophilicity of the hexachloroethane. In order to solve the problem of low conversion rates, we adopted a series of means such as increasing the number of equivalents of base and hexachloroethane, prolonging reaction time, and increasing reaction temperature. Unfortunately, there was no obvious improvement.



Scheme 2 *Reagents and conditions*: (a) $HP(O)(OEt)_2$, NaOEt, CH_2Cl_2, –35 °C; (b) DAST, CH_2Cl_2, –78 °C to r.t.; (c) C_2Cl_6, NaHMDS, –78 °C to 30 °C; (d) Ph_3P, CCl_4, 80 °C; (e) NFSI, NaHMDS, –78 °C to 30 °C.

The above results prompted us to investigate the possibility of the process from step d to e that exchanged the sequence of halogenations (Scheme 2). Treatment of α-hydroxyphosphonates with triphenylphosphine in CCl_4

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Table 1 Spectroscopic Data of Diethyl α-Chlorobenzylphosphonates **3**

	Ar	^{1}H NMR ($CDCl_3$) $\delta_{\alpha\ CH}$ ($^2J_{PH}$)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha\ CH}$ ($^1J_{PC}$)	Isolated yield (%)
3a	Ph	4.91 (d, $^2J_{PH}$ = 14.1 Hz)	53.7 (d, $^1J_{PC}$ = 158.7 Hz)	85
3b	4-MeC_6H_4	4.87 (d, $^2J_{PH}$ = 13.9 Hz)	53.6 (d, $^1J_{PC}$ = 159.7 Hz)	80
3c	4-$MeOC_6H_4$-	4.86 (d, $^2J_{PH}$ = 13.7 Hz)	53.9 (d, $^1J_{PC}$ = 162.0 Hz)	79
3d	4-NCC_6H_4	4.97 (d, $^2J_{PH}$ = 15.0 Hz)	52.7 (d, $^1J_{PC}$ = 156.8 Hz)	80
3e	4-$BnOOCC_6H_4$	4.94 (d, $^2J_{PH}$ = 14.7 Hz)	53.0 (d, $^1J_{PC}$ = 157.0 Hz)	72
3f	4-FC_6H_4	4.88 (d, $^2J_{PH}$ = 14.1 Hz)	53.1 (d, $^1J_{PC}$ = 160.6 Hz)	83
3g	4-ClC_6H_4	4.87 (d, $^2J_{PH}$ = 14.3 Hz)	52.7 (d, $^1J_{PC}$ = 159.2 Hz)	87
3h	4-BrC_6H_4	4.85 (d, $^2J_{PH}$ = 14.3 Hz)	52.7 (d, $^1J_{PC}$ = 159.0 Hz)	81
3i	2-$O_2NC_6H_4$	6.18 (d, $^2J_{PH}$ = 16.0 Hz)	47.0 (d, $^1J_{PC}$ = 157.4 Hz)	74
3j	3-$O_2NC_6H_4$	5.00 (d, $^2J_{PH}$ = 14.7 Hz)	52.1 (d, $^1J_{PC}$ = 157.4 Hz)	77
3k	4-$O_2NC_6H_4$	5.00 (d, $^2J_{PH}$ = 15.2 Hz)	52.5 (d, $^1J_{PC}$ = 156.4 Hz)	76

was found to provide, via oxyphosphonium intermediates, the appropriate α-chlorophosphonates generally in high yields (**3a–k**, Table 1).[11]

We next focused our attention on the substitution of single hydrogen for fluorine in α-chlorophosphonates by treating a solution of the respective compound **3** in THF with excess NaHMDS (1.5 equiv) and NFSI (1.3 equiv) at –78 °C to room temperature. Fortunately, this procedure worked well, and a wide variety of chlorofluorophenylmethanephosphonate derivatives (**4a–k**, Table 2) were obtained in reasonable to good yields (30–92%).[12] The results indicated that an array of both electron-withdrawing and electron-donating functional groups (such as ester, ether, nitro, alkyl, halogen, and cyano) on aromatic rings could be tolerated. But inferior results were displayed when the substrates **3** with electron-donating groups attached on aromatic rings were employed. Although the mechanism for this messy outcome was not clear,[13] we reasoned that the electron-donating group might contribute to an increased electron density of the aromatic ring, which made it difficult to form intermediate phosphonate carbanions or radicals during the reaction process. Meanwhile, increasing the electron density of aromatic rings generally favored aromatic ring fluorination. For example, **4a** and **4b** were generated in 52% and 50% yield of product, respectively, when aryl-substituted (Ar = Ph, 4-MeC_6H_4) α-chlorophosphonates **3a** and **3b** were employed in the reactions.

Table 2 Spectroscopic Data of Diethyl α,α-Chlorofluorobenzylphosphonates **4**

	Ar	^{13}C NMR ($CDCl_3$) $\delta_{\alpha\ CCl}$ ($^1J_{PC}$, $^1J_{FC}$)	^{31}P NMR ($CDCl_3$) $\delta_{\alpha\ CCl}$ ($^2J_{PF}$)	Isolated yield (%)
4a	Ph	106.9 (dd, $^1J_{PC}$ = 196.0 Hz, $^1J_{FC}$ = 258.2 Hz)	6.16 (d, $^2J_{PF}$ = 91.2 Hz)	52
4b	4-MeC_6H_4	107.3 (dd, $^1J_{PC}$ = 197.3 Hz, $^1J_{FC}$ = 258.1 Hz)	6.24 (d, $^2J_{PF}$ = 92.5 Hz)	50
4c	4-$MeOC_6H_4$	107.3 (dd, $^1J_{PC}$ = 199.4 Hz, $^1J_{FC}$ = 258.2 Hz)	6.25 (d, $^2J_{PF}$ = 93.5 Hz)	76
4d	4-NCC_6H_4	105.7 (dd, $^1J_{PC}$ = 193.9 Hz, $^1J_{FC}$ = 259.0 Hz)	5.23 (d, $^2J_{PF}$ = 88.1 Hz)	70
4e	4-$BnOOCC_6H_4$	106.4 (dd, $^1J_{PC}$ = 195.0 Hz, $^1J_{FC}$ = 258.6 Hz)	6.50 (d, $^2J_{PF}$ = 89.7 Hz)	73
4f	4-FC_6H_4	106.6 (dd, $^1J_{PC}$ = 197.5 Hz, $^1J_{FC}$ = 258.4 Hz)	5.89 (d, $^2J_{PF}$ = 91.1 Hz)	69
4g	4-ClC_6H_4	106.5 (dd, $^1J_{PC}$ = 196.4 Hz, $^1J_{FC}$ = 258.4 Hz)	5.75 (d, $^2J_{PF}$ = 90.7 Hz)	66
4h	4-BrC_6H_4	106.6 (dd, $^1J_{PC}$ = 196.3 Hz, $^1J_{FC}$ = 258.4 Hz)	5.63 (d, $^2J_{PF}$ = 90.7 Hz)	62
4i	2-$O_2NC_6H_4$	105.3 (dd, $^1J_{PC}$ = 194.2 Hz, $^1J_{FC}$ = 259.9 Hz)	3.32 (d, $^2J_{PF}$ = 80.5 Hz)	30
4j	3-$O_2NC_6H_4$	105.5 (dd, $^1J_{PC}$ = 195.3 Hz, $^1J_{FC}$ = 258.8 Hz)	6.63 (d, $^2J_{PF}$ = 89.7 Hz)	92
4k	4-$O_2NC_6H_4$	105.6 (dd, $^1J_{PC}$ = 193.4 Hz, $^1J_{FC}$ = 259.1 Hz)	5.13 (d, $^2J_{PF}$ = 88.1 Hz)	77

Compound **3j** (Ar = 3-$O_2NC_6H_4$) reacted with NFSI leading to the corresponding product **4j** in 92% yield. A similar result was observed when substrate **3k** (Ar = 4-$O_2NC_6H_4$) was utilized in the reaction. Other explanation for this observation cannot be derived from our current knowledge of the mechanism, but the phenomenon may stem from that (a) a carbene formation might be involved or (b) NFSI might act to abstract chloride anion (forming FCl) in a halophilic process leading to the monofluorobenzylphosphonate product.[14]

We also investigated the influence of steric hindrance of the substituents. The reaction was general for substituents on 4- and 3-position of aromatic rings such as 4-methyl, 4-fluoro, 4-chloro, 4-bromo, 4-methoxy, 3- and 4-nitro which did not interfere with the fluorination process. However, these substituents had a significant influence

when they were at the 2-position of aromatic rings. For example, there was a decrease in yield of the 2-nitro derivative **4i** (30%) compared to the 3-nitro **4g** and 4-nitro **4k** derivatives (92% and 77%, respectively). This decrease in yield could be attributed to the increased steric demands of the 2-substituted phosphonates. Under these conditions, the step of deprotonation to form carbanions was slowed down because of a difficult approach of NaHMDS in a highly crowded position.

In summary, we have developed an efficient and practical approach for the preparation of diethyl α-chloro-α-fluorobenzylphosphonates from simple carbonyl compounds. These compounds can be converted into various useful quaternary carbon-containing α-fluorophosphonates by using nucleophilic substitution. Attempts toward the asymmetric version of the reaction as well as the extension of this method are currently under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **General Procedure for the Preparation of α-Chlorobenzylphosphonates from α-Hydroxyphosphonates**
A solution of **1k** (1.00 g, 3.46 mmol, 1.0 equiv) and Ph_3P (1.36 g, 5.19 mmol, 1.5 equiv) in dry CCl_4 (10 mL) is refluxed for 8 h under argon. Then, the mixture is evaporated under reduced pressure, and the semisolid residue is extracted with PE. The combined extracts are filtered, and the solvent is removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel to yield **3k** as yellow oil (0.81 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H), 4.00–4.14 (m, 2 H), 4.15–4.28 (m, 2 H), 5.00 (d, $^2J_{PH}$ = 15.2 Hz, 1 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 8.25 (d, *J* = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{PC}$ = 5.6 Hz), 16.4 (d, $^3J_{PC}$ = 5.7 Hz), 52.5 (d, $^1J_{PC}$ = 156.4 Hz), 64.1 (d, $^2J_{PC}$ = 7.0 Hz), 64.6 (d, $^2J_{PC}$ = 7.0 Hz), 123.6, 129.8, 141.4, 148.0 ppm.

(12) **General Procedure for the Preparation of α,α-Chlorofluorobenzylphosphonates from α-Chlorophosphonates**
To a solution of the α-chlorophosphonates **3k** (0.31 g, 0.94 mmol, 1.0 equiv) in dry THF (10 mL) at –78 °C was added dropwise a solution of NaHMDS (1.69 mmol, 2.0 M in THF, 1.5 equiv) in dry THF (5 mL) under argon. The resulting dark green solution was stirred for 1 h at –78 °C. A solution of NFSI (0.41 g, 1.31 mmol, 1.3 equiv) in dry THF (5 mL) was added over a period of 10 min. After addition, the solution was stirred for 1 h and then allowed to warm to –30 °C. The reaction was quenched with 0.01 N HC1, and the resulting solution was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude material was purified via flash column chromatography on silica gel to yield **4k** as yellow oil (0.24 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H), 1.41 (t, *J* = 7.0 Hz, 3 H), 4.05–4.19 (m, 2 H), 4.32–4.41 (m, 2 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 8.29 (d, *J* = 8.6 Hz, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (d, $^3J_{PC}$ = 15.0 Hz), 65.3 (d, $^2J_{PC}$ = 7.2 Hz), 66.2 (d, $^2J_{PC}$ = 7.1 Hz), 105.6 (dd, $^1J_{PC}$ = 193.4 Hz, $^1J_{FC}$ = 259.1 Hz), 123.4, 127.5 (d, $^3J_{PC}$ = 8.4 Hz), 142.5 (d, $^2J_{PC}$ = 21.0 Hz), 148.7 ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 5.13 (d, $^2J_{PF}$ = 88.1 Hz) ppm.

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