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A High Yielding Synthesis of Diethyl 1-Fluoromethylphosphonate in pure form

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Abstract We describe a high yielding synthesis of the title compound (**2**) in pure form. The synthesis consists of : a) a Michaelis-Arbuzov reaction between triethylphosphite and fluorotribromomethane in hexane at 50°C giving diethyl dibromofluoromethylphosphonate (**1**) in 79-85% yield and b) a halogen-metal exchange reaction between (**1**) and *n*-BuLi-CISiMe₃ at -90°C yielding (**2**) in 94% yield.

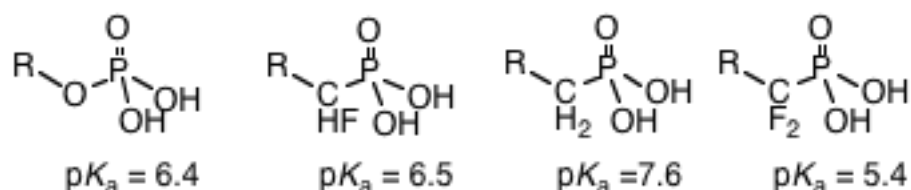
Une synthèse efficace du diéthyl 1-fluorométhylphosphonate
de grande pureté

Résumé Nous avons mis au point une préparation efficace du diéthyl 1-fluorométhylphosphonate (**2**) pur. Elle comprend: a) une réaction de Michaelis-Arbuzov entre le triéthylphosphite et le fluorotribromométhane dans l'hexane à 50°C conduisant à (**1**) (79-85%) puis b) une réaction de double échange halogène-métal en présence de *n*-BuLi-CISiMe₃ à -90°C convertissant (**1**) en (**2**) avec un rendement de 94%

Version française abrégée

Le diéthyl 1-fluorométhylphosphonate **2** est un réactif très utile dans la préparation d'analogues stables de phosphates d'intérêt biologique (Schéma 1). Les voies d'accès à **2**, essentiellement par réaction électrophile, sont peu efficaces et conduisent régulièrement à des mélanges de produits mono et difluorés. Nous avons mis au point une préparation efficace de **2** pur que nous décrivons en détail. Le procédé se décompose en deux étapes. La première conduit au diéthyl dibromofluorométhylphosphonate **1** (79-85%) par réaction de Michaelis-Arbuzov entre $(\text{EtO})_3\text{P}$ et CFBr_3 dans l'hexane à 50°C (Schéma 2) . La seconde est un double échange halogène-métal réalisé à -90°C entre **1** et le $n\text{-BuLi}$ en présence de ClSiMe_3 . Après éthanolyse et distillation **2** est isolé non contaminé de composés phosphorés indésirables et avec un excellent rendement (94%). A notre connaissance cette préparation de **2** est la seule qui, actuellement, conduise efficacement à un produit pur.

Difluoro- and monofluoromethylenephosphonates, (CF₂-phosphonate) and (CHF-phosphonate), are currently being explored as phosphatase stable phosphate mimics for biological systems (1). The pK_a of the second deprotonation (ca. 6.4 for a phosphate group) is generally considered to be an important electronic factor in the binding of such compounds to enzymes. The CH₂-phosphonate has a pK_a of ca. 7.6, less acidic than the phosphate, when the CHF-phosphonate has a pK_a of ca. 6.5, almost identical to that of the natural phosphate (2) (Scheme 1).



Scheme 1

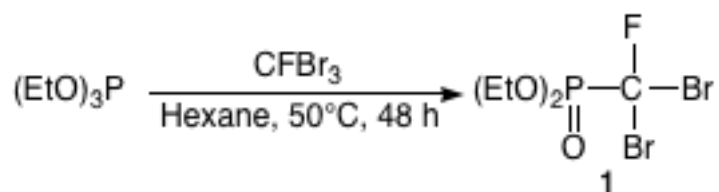
The introduction of fluorine on the carbon in the α -position to phosphorus has been shown to be a useful operation, reducing the disparity in important physical properties between alkylphosphonates and phosphates leading to isopolar, isosteric analogues of biological phosphates (3). This advantage of CHF-phosphonate over CH₂-phosphonate suggests that it is of interest to master a good synthetic approach to CHF-phosphonate on preparative scale and in pure form. We report here a high yielding synthesis of the parent compound, the 1-fluoromethyl-phosphonate **2** which is a valuable synthetic intermediate.

Previous methods for incorporating fluorine into a phosphonate moiety are based on two main procedures (4). The first involves P-CF bond formation using CH₂FCI or CH₂FBr and dialkylphosphite anions (5). The yields of **2** are generally modest (45%) and moreover this route has been abandoned since the two starting reagents are no longer commercially available. The second involves PC-F bond formation. This can be accomplished by fluorination of phosphonate carbanions by reagent sources of positive halogen which are frequently hazardous fluorinating reagents. The preferred reagents for these reactions were found to be perchloryl fluoride (FCIO₃) (3b), and N-fluorobenzenesulfonimide ((C₆H₅SO₂)₂NF) (6). With the former the yields of monofluorinated phosphonates are modest (43%), with the latter the yields are significantly lower (11%). Full utilization of this chemistry is handicapped by the competitive formation of the CF₂-phosphonates resulting from an acid-base equilibrium during the reaction. Another method of access to CHF-phosphonates is based on the reaction of diethylaminosulphur trifluoride (Et₂NSF₃)

(DAST) (3a) with 1-hydroxymethylphosphonates, however these intermediates are not easily obtained in good yields.

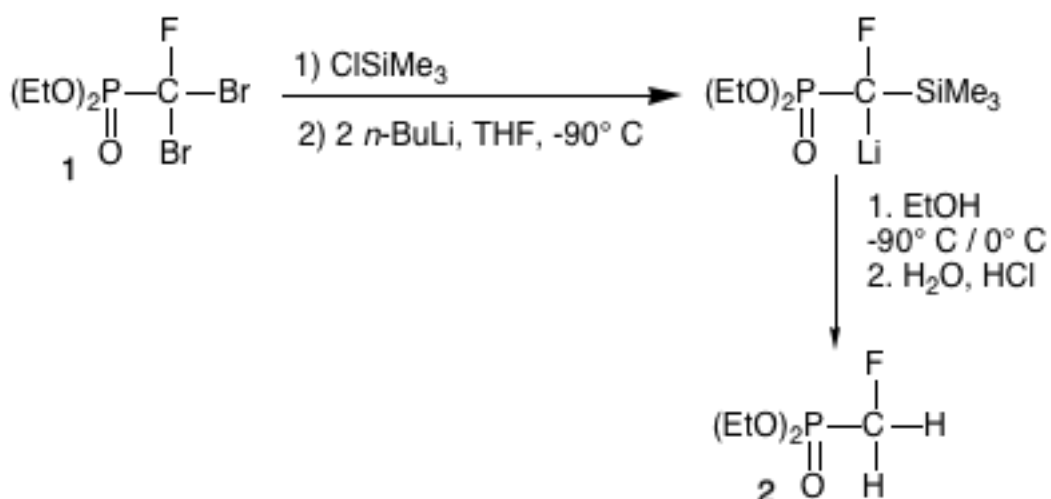
Our synthetic approach to **2**, based on the P-CF approach, exploited a halogen-metal exchange reaction with the diethyl dibromofluoromethyl-phosphonate **1** obtained by a Michaelis-Arbuzov reaction. Each of the two steps has been tested under a wide range of conditions with the aim of improving the reaction conditions and isolating compounds on preparative scale with the highest purity and in high yield (7).

Several variations on the preparation of **1** from $(\text{EtO})_3\text{P}$ and CFBr_3 including, time, solvent, thermally or photolytically conditions have been reported (8). CFBr_3 is an expensive reagent and its consumption has thus to be complete. Best yields are obtained when the reaction is realized in a solvent in order to minimize the competitive halophilic attack of **1** by $(\text{EtO})_3\text{P}$. Use of polar solvents, such as diethyl ether or THF, leads to notable proportion of byproducts. These disadvantages are overcome in nonpolar solvent where the formation of byproducts is negligible, but reaction time is far too long (15-20 days) at room temperature. Hexane is particularly suited to the reaction and heating the reaction mixture at 50°C for 48h offers a shorter and more convenient route to **1** in 79-85%. With these conditions there is no isomerization of triethylphosphite and the only byproducts are the triethylphosphate and a phosphorus compound containing fluorine at low field (Scheme 2).



Scheme2

The second step is the key step (Scheme 3). The halogen-metal exchange reaction is realized in THF at low temperature in the presence of chlorotrimethylsilane as trapping agent. The intermediate carbenoid species has to be generated at low temperature where the carbon-lithium bond has mainly a covalent character and behaves as an ordinary nucleophile. It has been found more efficient to accomplish the reaction at -90°C rather than -78°C . The reaction is fast and clean and after ethanolysis with an excess of anhydrous ethanol and cleavage of the C-Si bond, **2** is isolated in pure form as a colorless liquid and distilled in almost quantitative yield.



Scheme 3

The procedure described herein for the preparation of **2** is representative of a general method for the synthesis of α -fluoromethyl and α -fluoroalkylphosphonates previously reported on a small scale (9). It is characterized by good chemical yield, simple operation and ready availability of the starting materials. To the best of our knowledge it is presently the sole available preparative access to **2** in pure form and high yield.

Experimental Section

Diethyl 1,1-dibromo-1-fluoromethylphosphonate **1**. An oven dried, 500 mL pressure bottle purged with nitrogen is charged with 100 mL of hexane triethylphosphite (29 g, 0.175 mol) and fluorotribromomethane (50 g, 0.184 mol). The pressure bottle is carefully closed with a rubber stopper and immersed in a water bath at 50°C . On heating the hexane solution a yellow colour appears. After heating during 48 h the pressure bottle is cooled to 0°C and opened. Hexane is evaporated on a rotary evaporator and the yellow crude liquid (56-57g) is transferred to a pear-shaped flask fitted with a short column and distilled under reduced pressure to give 45-48.5 g (79-85%) of diethyl 1,1-dibromo-1-fluoromethylphosphonate **1** as a colorless liquid, b.p. $62\text{-}64^\circ\text{C} / 0.05 \text{ mmHg}$.

Product **1** displays the following spectroscopic data: ^{31}P NMR (CDCl_3) d: +1.6 (d, $^2J_{\text{PF}}$ 76.5); ^{19}F NMR (CDCl_3) d: -51.2 (d, $^2J_{\text{FP}}$ 76.4); ^1H NMR (CDCl_3) d: 1.38 (t, 6H, $^3J_{\text{HH}}$ 7.1, $\text{CH}_3\text{CH}_2\text{O}$), 4.37 (qd, 4H, $^3J_{\text{HP}}$ 8.2, $^3J_{\text{HH}}$ 7.1, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (CDCl_3) 16.5 (d, $^3J_{\text{CP}}$ 5.8, $\text{CH}_3\text{CH}_2\text{O}$), 67.0 (d, $^2J_{\text{CP}}$ 6.5, $\text{CH}_3\text{CH}_2\text{O}$), 88.4 (dd, 1J 333.6, 1J 202.3, PCFBr_2).

Diethyl 1-fluoromethylphosphonate **2**. An oven-dried, 1-L, four-necked, round-bottomed flask is fitted with an efficient mechanical stirrer, a thermometer, a reflux condenser surmounted with a bubbler, and a 200 ml pressure equalizing dropping funnel with a nitrogen inlet. Under a gentle flow of nitrogen the flask is charged with 150 mL of THF. The dropping funnel is charged with 135 mL of a 1.56 M solution of *n*-butyllithium in hexane (0.210 mol). The flask is cooled to -70°C with a Dewar partially filled with liquid nitrogen, stirring is started, and *n*-butyllithium is added to THF over a few minutes. At -90°C a solution of diethyl 1,1-dibromo-1-fluoromethylphosphonate **1** (32.8 g, 0.100 mol) and chlorotrimethylsilane (12 g, 0.110 mol) in THF (50 mL) is added dropwise from the dropping funnel over 15 min. The resulting clear slightly yellow solution is stirred for an additional 10 min at -90°C. The reaction mixture is then treated at this temperature by a dropwise addition of a solution of anhydrous ethanol (16 g, 0.35 mol) in THF (10 mL). The resulting mixture is then allowed to warm up gently to 0°C in 45 min. At this temperature the reaction mixture is poured into a beaker containing a stirred mixture of 3N hydrochloric acid (50 mL), an equal volume of crushed ice and CH₂Cl₂ (60 mL). The solution became completely colourless. The organic layer is then separated, and the aqueous layer is extracted with CH₂Cl₂ (2 x 60 mL). The extracts are combined with the original organic layer and dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration and the solvents are evaporated on a rotary evaporator. The crude liquid is transferred to a pear-shaped flask fitted with a short column and distilled under reduced pressure to give 15.98 g (94%) of diethyl 1-fluoromethylphosphonate **2** as a colorless liquid, b.p. 40-45°C / 0.1 mm Hg.

Product **2** displays the following spectroscopic data: ³¹P NMR (CDCl₃) d: +14.2, (d, ²J_{PF} 63.5); ¹⁹F NMR (CDCl₃) d: -223.5, (d, ²J_{FP}62); ¹H NMR (CDCl₃) d: 1.20 (t, 6H, ³J_{HH} 7.1, CH₃CH₂O), 4.0 (qd, 4H, ³J_{HP} 8.1, ³J_{HH} 7.1, CH₃CH₂O), 6.08 (dd, 2H, ²J_{PH} 4.7, ²J_{FH} 46.8, PCH₂F); ¹³C NMR (CDCl₃) 16.0 (d, ³J_{CP} 4.8, CH₃CH₂O), 62.1 (d, ²J_{CP} 6.1, CH₃CH₂O), 76.2 (dd, ¹J_{CF} 179.9, ¹J_{CP} 169.2, PCH₂F).

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