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PREPARATION OF TRIETHYL 2-FLUORO-2-PHOSPHONOACETATE

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Abstract : Triethyl 2-fluoro-2-phosphonoacetate was prepared in one step from dibromofluoromethylphosphonate and ethyl chloroformate.

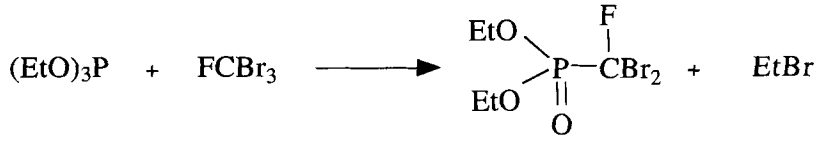
α-Fluoro α,β-unsaturated esters are valuable building blocks especially involved in the synthesis of monofluorinated retinoids,[1] fluorinated analogues of *insect sex pheromones*[2] and pyrethroids.[3] Since the work of Machleidt et al.[4] the Wittig-Horner reaction using triethyl 2-fluoro-2-phosphonoacetate **4** has represented an efficient method for the preparation of α-fluoro α,β-unsaturated esters. Later a careful investigation of the experimental conditions was carried out[5]

in order to control the stereochemistry of the so-formed double bond and to improve the scope of the reaction.

In spite of these examinations the development of the phosphonic method depends upon the availability of the α-fluorinated phosphonoacetates. The ethyl ester is usually prepared via a Michaelis-Arbuzov reaction between triethylphosphite and ethyl bromofluoroacetate.[5] Although ethyl bromofluoroacetate is commercially avaible it remains an expensive and toxic starting material and for that reason several preparative approaches have been described.[6] It is also important to take notice that the yield of triethyl 2-fluoro-2-phosphonoacetate via the Michaelis-Arbuzov reaction does not exceed 60-64%.

We report here a new preparation of **4** starting from the readily available dibromofluoromethylphosphonate.[7] This method is applicable to the large scale preparation of α-fluorophosphonoacetates and routinely affords good yields.

Diethyl dibromofluoromethylphosphonate **1** [δ ^{31}P ($CDCl_3$) +2.0, d, J_{PF} 76.6] was obtained in good yield (90-95%) by the action of triethylphosphite on tribromofluoromethane in hexane. The ease of obtention of **1** renders its use particularly attractive (Scheme 1).

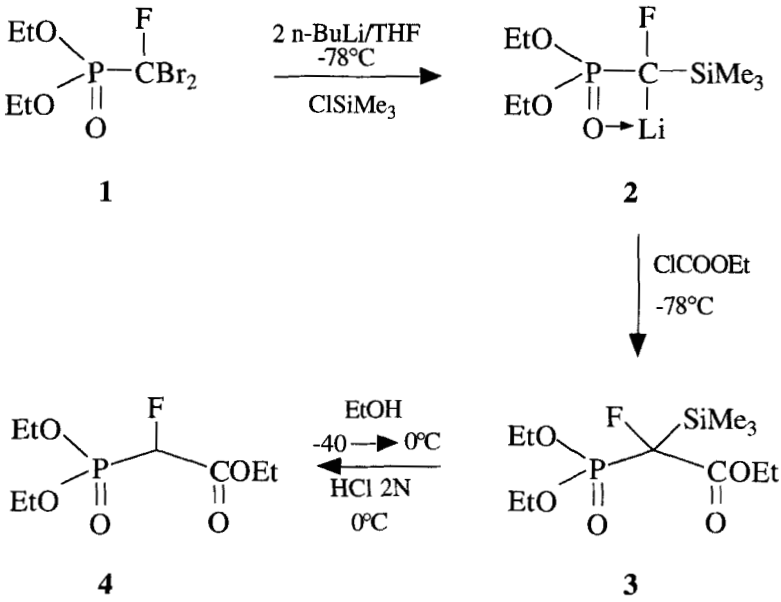


1

Scheme 1

Dibromofluoromethylphosphonate **1** was first condensed with chlorotrimethylsilane in presence of two equivalents of n-BuLi at low temperature.[8] The presence

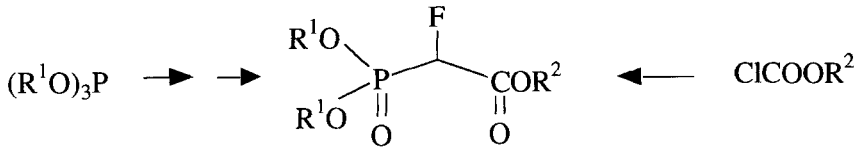
of two bromine atoms resulted in a quantitative and highly selective double halogen-metal exchange. Formation of carbanion **2** was easily monitored by ^{31}P NMR spectroscopy at low temperature [δ ^{31}P (THF) +53.3, d, J_{PF} 65.2]; it was directly treated at low temperature with ethyl chloroformate to give triethyl 2-fluoro-2-silyl-2-phosphonoacetate **3** [δ ^{31}P (THF) +25.8, d, J_{PF} 75.5] which is very sensitive in basic medium. Compound **3** was not isolated but directly treated with dry ethanol in the same flask to afford **4** [δ ^{31}P (THF) +11.7, d, J_{PF} 72.6] which was isolated after acidic hydrolysis (Scheme 2).



Scheme 2

This expeditious one-pot preparation of **4** is routinely performed on a 100 mmol-scale. The crude 2-fluoro-2-phosphonoacetate was purified by distillation using a bulb to bulb apparatus; it is thermally stable and underwent the operation without damage.

This convergent preparation of triethyl 2-fluoro-2-phosphonoacetate has several advantages. First the starting dibromofluoromethylphosphonate can be prepared in high yield and second the preparation of **4** can be easily extended to ester groups at phosphorus and carbon other than ethyl using the suitable trialkylphosphite $(R^1O)_3P$ and chloroformate $(ClCOOR^2)$ respectively (Scheme 3).



Scheme 3

Experimental procedure

All reactions were carried out under inert atmosphere; THF was distilled from benzophenone sodium prior to use. n-BuLi was titrated with a solution of benzylic alcohol in toluene with 2,2'-biquinoline as a color indicator. All other commercially available compounds were used without purification. NMR spectra were recorded on a spectrometer operating at 81.02 MHz (^{31}P) and 200.13 MHz for (^1H). Chemical shifts are in parts per million with $CDCl_3$ as internal standard (^1H) and with 85% H_3PO_4 as external standard (^{31}P). Coupling constants are quoted in Hz.

Triethyl 2-fluoro-2-phosphonoacetate **4**

To a stirred solution of n-BuLi in hexane (1.6 M, 79 ml, 126 mmol) and THF (80 ml) at -78°C was added dropwise a mixture of **1** (19.7 g, 60 mmol) and chlorotrimethylsilane (6.90 g, 63 mmol) in THF (50 ml). The reaction was exothermic. The solution remained limpid and colorless. After 5 min ethylchloroformate (8.5 g, 78 mmol) was added dropwise at -78°C. Stirring was continued for 30 min at that temperature, then the solution was allowed to warm to

-40°C. It was treated with anhydrous ethanol (20 ml) then poured into a baker containing 2 N HCl (40 ml) crushed ice and CH_2Cl_2 (50 ml). The aqueous phase was extracted with CH_2Cl_2 (3x30 ml) and the combined organic layers dried ($MgSO_4$), concentrated under reduced pressure and distilled on a bulb to bulb apparatus (Büchi GKR-50). Yield 89-92%; b.p. (16 mmHg) 190-200°C; $\delta^{31}P$ ($CDCl_3$) +10.65, J_{PF} 72.7; δ ^1H ($CDCl_3$) 1.35 (t, J_{HH} 7, 3H); 1.37 (t, 3H); 1.38 (t, 3H); 4.27 (m, 4H); 4.35 (q, 2H); 5.21 (dd, J_{HF} 47, J_{HP} 12.5, 1H). δ ^{13}C ($CDCl_3$) 13.2 (CH_3); 15.62 (d, J_{CP} 5.7, CH_3); 61.41 (CH_2); 62.71 (d, J_{CP} 5.9, CH_2); 63.30 (d, J_{CP} 6.8, CH_2); 84.11 (dd, J_{CF} 195.3, J_{CP} 158.5, CHF); 164.26 (d, J_{CF} 21.8, CO).

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