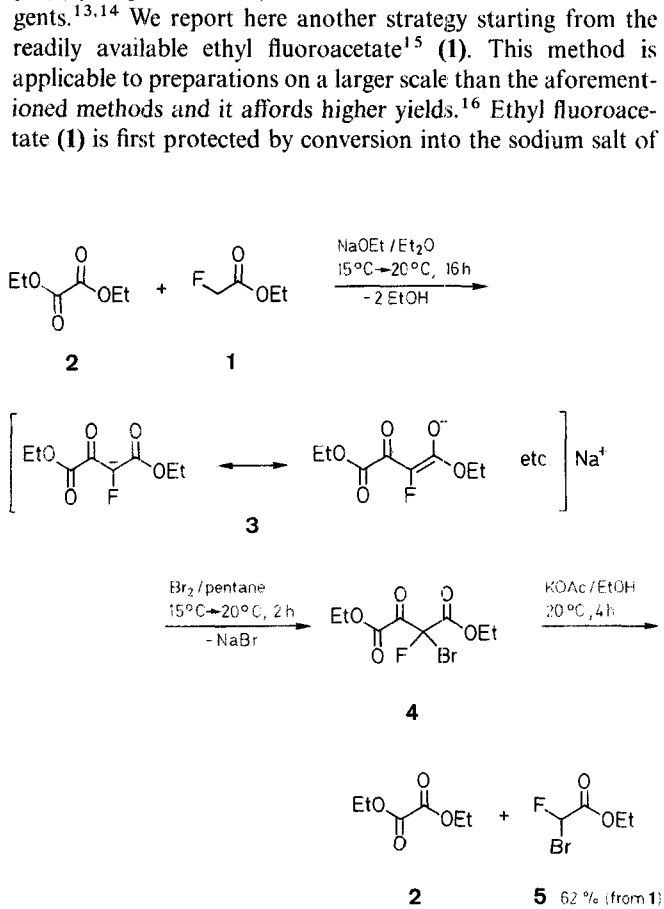
A Convenient Synthesis of Ethyl (Diethoxyphosphoryl) fluoroacetate from Ethyl Fluoroacetate

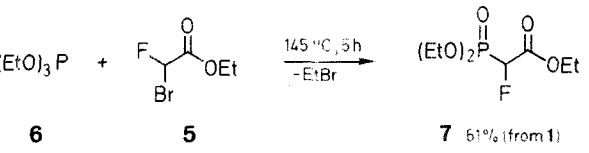
Elias Elkik, Michèle Imbeaux*

Ecole Normale Supérieure, Département de Chimie, UA1110 du CNRS, Laboratoire de l'Activation Moléculaire, Laboratoire de l'Université Pierre et Marie Curie, 24 rue Lhomond, F-75231 Paris Cedex 05, France

A new synthesis of ethyl (diethoxyphosphoryl)fluoroacetate starting from ethyl fluoroacetate is described for a mole scale. This synthesis does not require the use of special equipment for fluorine chemistry since no hydrogen fluoride is evolved.

Organic compounds bearing a fluorine atom in a specific position have found a large number of biological and pharmaceutical applications.[1,2] In particular, fluoroalkenes are widely used. Since the work of Machleidt et al.,[3,4] the Wittig–Horner reaction using ethyl (diethoxyphosphoryl)fluoroacetate [**7**; ethyl(diethylphosphono)fluoroacetate] represents an efficient route to fluorolefins. Moreover, by varying the experimental conditions the stereochemistry of the double bond formed can be controlled.[5,6] Reagent **7** is usually synthesized from ethyl bromofluoroacetate (**5**) and triethyl phosphite (**6**) by the Arbusov reaction. Although ethyl halofluoroacetates are commercially available, they are currently expensive reagents.[7] The usual preparation of bromofluoroacetic esters[8,9,10] follows a procedure similar to that originally described for the synthesis of chlorofluoroacetic esters.[11,12] This method, which uses bromotrifluoroethylene as starting material, is rather tedious since it involves the use of a gaseous reagent and two moles of hydrogen fluoride per mole of product are evolved. An alternative approach is the dediazoniative bromofluorination of ethyl diazoacetate using liquid hydrogen fluoride or pyridinium poly(hydrogen fluoride) and *N*-bromosuccinimide as reagents.[13,14] We report here another strategy starting from the readily available ethyl fluoroacetate[15] (**1**). This method is applicable to preparations on a larger scale than the aforementioned methods and it affords higher yields.[16] Ethyl fluoroacetate (**1**) is first protected by conversion into the sodium salt of ethyl ethoxalylfluoroacetate (**3**; diethyl 2-fluoro-3-oxobutanedioate). This *C*-protection prevents dibromination and results in a concomitant increase of the acidity of the CH bond. The reaction is performed by condensing ethyl fluoroacetate (**1**) with diethyl oxalate (**2**) in presence of one equivalent of sodium ethoxide.[17] The sodium salt **3** is not isolated but is directly brominated in the same flask. The crude diethyl 2-bromo-2-fluoro-3-oxobutanedioate (**4**) is then cleaved to afford ethyl bromofluoroacetate (**5**) by treating the crude reaction mixture with potassium acetate. (Acidic cleavage of **4** has been reported[17] to give bromofluoropyruvic acid or its ethyl ester, depending on the conditions used, in analogy to the acidic cleavage of **3** protonated which affords fluoropyruvic acid[18]). This three-step one-pot reaction is routinely performed in our laboratory on a mole scale. The crude ethyl bromofluoroacetate (**5**) may be either purified by distillation or transformed into ethyl (diethoxyphosphoryl)fluoroacetate (**7**) in 60% overall yield (from **1**) by reaction with triethyl phosphite (**6**) under the usual conditions.[3,19]





6 **5** **7** 61% (from 1)

Microanalyses were performed by the Service Central d'Analyse du Centre National de la Recherche Scientifique, Vernaison, France. GLC-MS experiments were carried out with a glass capillary column CPSIL5 (50 m, 0.3 mm ID; program: 100–300°C, 5°C/min) from Chrompack Co. (Netherlands) on a NERMAG R10-10C mass spectrometer. ^{1}H-NMR spectra were recorded on a Cameca 250 MHz or a Bruker AM 400 spectrometer, ^{13}C-NMR spectra on a Bruker AM 400 spectrometer operating at 100 MHz, ^{19}F-NMR spectra on a Bruker WH 90 spectrometer operating at 84.66 MHz, and ^{31}P-NMR spectra on a Bruker WH 90 spectrometer operating at 36.44 MHz.

Pentane was dried by distillation from P_2O_5. Diethyl ether was dried by distillation from Na-benzophenone just before use. Absolute EtOH "Normapur" grade from Prolabo (France) was used as recieved. Ethyl fluoroacetate and NaH (60% suspension in mineral oil) were purchased from Janssen Co. and used without further purification. Triethyl phosphite from Janssen Co. was distilled just before use. Diethyl oxalate was purchased from Prolabo Co. and distilled just before use.

Ethyl Bromofluoroacetate (5) or Ethyl (Diethoxyphosphoryl)fluoroacetate (7):

Caution: Ethyl fluoroacetate (**1**) is extremely toxic! All manipulations should be performed under a well ventilated hood.

A 4 L reactor equipped with a mechanical stirrer is charged with 60% NaH suspension (42 g, 1.05 mol) in mineral oil and flushed with N_2. Then, the NaH is washed with anhydrous pentane to remove the mineral oil (this step may be omitted, but the formation of sticky precipitates makes the following reactions troublesome), anhydrous Et_2O (800 mL) is added, and thereafter a mixture of absolute EtOH (52 g, 1.13 mol) and anhydrous Et_2O (200 mL) is added dropwise with stirring. When hydrogen evolution has ceased (about 1 h), a mixture of freshly distilled diethyl oxalate (**2**; 150 g, 1.03 mol) and anhydrous Et_2O (200 mL) is added at such a rate as to maintain the temperature at 20–25°C. Stirring is continued for 30 min, the solution is then cooled to 15°C, and a mixture of ethyl fluoroacetate (**1**; 106 g, 1.00 mol) (extreme *caution!* see above) and anhydrous Et_2O (200 mL) is added dropwise; stirring is continued for 2 h and the solution is kept at room temperature overnight. During this time, a precipitate of the sodium enolate **3** appears. The mixture is stirred and cooled to 15°C, a solution of Br_2 (160 g, 51.3 mL, 1.00 mol) in anhydrous pentane (200 mL) is added dropwise, and stirring is continued for 2 h at r.t. A suspension of anhydrous KOAc (100 g, 1.02 mol) in absolute EtOH (400 mL) is added in one portion, stirring is continued for 4 h, and the mixture is allowed to stand at r.t. overnight. Then, H_2O (500 mL) is added, the organic layer is separated, and the aqueous layer is extracted with Et_2O (3 × 250 mL). If an emulsion is formed, more H_2O (500 mL) should be

added. The organic layers are combined, washed with sat. aq. $NaHCO_3$ (350 mL), dried ($MgSO_4$), and concentrated using a rotary evaporator. The remaining EtOH is removed by distillation at atmospheric pressure. The residual liquid is distilled under reduced pressure to afford the following fractions: (1) bp 35–65 °C/95 Torr, 3.3 g; (2) bp 65–114 °C/95 Torr, 173.6 g; (3) bp 114–125 °C/95 Torr, 97 g. The second fraction contains the majority of the ethyl bromofluoroacetate **(5)**, the third fraction is mainly diethyl oxalate **(2)**.

If *ethyl bromofluoroacetate* **(5)** is the target product, the second fraction is fractionally distilled; yield: 115.2 g (62%, from **1**); bp 94–98 °C/95 Torr (Lit.[9] bp 98.5 °C/138 Torr; Lit.[13] bp 68 °C/34 Torr).

$C_4H_6BrFO_2$ (185.0)

MS (EI, 70 eV); *m/z* = 187 (1.2%); 186 (5.8); 185 (2.7); 184 (M^+, 4.2); 113 (82); 111 (80); 109 (26); 107 (26); 81 (14); 79 (13); 73 (12); 72 (8); 61 (100); 60 (99); 57 (11).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.36 (t, 3 H, J = 7 Hz, CH_3); 4.4 (q, 2 H, J = 7 Hz, CH_2OCO); 6.64 (d, 1 H, J_{HF} = 50 Hz, CHFBr).

^{19}F-NMR ($CDCl_3$/$CFCl_3$): δ = −151.27 (d, J_{FH} = 50 Hz)

If *ethyl (diethoxyphosphoryl)fluoroacetate* **(7)** is the target product, the second fraction and freshly distilled triethyl phosphite (**6**; 250 g, 1.50 mol) are placed in a 500 mL Claisen flask and this mixture is gently heated at 145 °C for 5 h with simultaneous distillation of EtBr (49.5 g, 0.45 mol). The mixture is then distilled under reduced pressure to give the following fractions: (1) bp 25–80 °C/20 Torr, 52.8 g, mainly triethyl phosphite **(6)**; (2) bp 80–95 °C/20 Torr, 135.3 g, diethyl oxalate and diethyl ethylphosphonate. The remaining liquid is then fractionally distilled at 0.3 Torr to afford, after a low-boiling fraction (9.6 g), pure ethyl (diethoxyphosphoryl)fluoroacetate **(7)**; yield: 149.0 g (61%, from **1**); bp 107–109 °C/0.3 Torr (Lit.[3] bp 75 °C/0.01 Torr). Product **7** thus obtained is analytically pure [one peak in GLC-MS using a 50 m capillary column; no impurity detectable by ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz)].

$C_8H_{16}FO_5P$	calc.	C 39.68	H 6.66	P 12.79
(242.2)	found	39.67	6.73	12.78

MS (EI, 70 eV): *m/z* 243 (0.1%); 242 (M^+, 0.2); 215 (7); 214 (15); 213 (8); 197 (22); 187 (9); 186 (14); 183 (6); 159 (46); 158 (13); 155 (18); 143 (11); 141 (12); 138 (9); 137 (14); 131 (22); 130 (20); 127 (17); 121 (9); 115 (15); 114 (52); 113 (6); 111 (11); 110 (13); 109 (53); 106 (14); 99 (23); 96 (14); 93 (30); 91 (14); 82 (14); 81 (53); 78 (26); 77 (13); 65 (100); 60 (29).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.35 (t, 3 H, J = 7 Hz, CH_3); 1.38 (t, 3 H, J = 7 Hz, CH_3); 1.39 (t, 3 H, J = 7 Hz, CH_3); 4.20–4.32 [m, 4 H; by CH_3 irradiation: 4.26 (d, 1 H, J_{HP} = 8 Hz, CH_2OP); 4.27 (d, 1 H, J_{HP} = 8 Hz, CH_2OP); 4.28 (d, 2 H, J_{HP} = 8 Hz, CH_2OP)]; 4.36 (q, 2 H, J = 7 Hz, CH_2OCO); 5.22 (dd, 1 H, J_{HF} = 47 Hz, J_{HP} = 12.5 Hz, CHF).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.61 (CH_3); 15.90 (d, 2 CH_3, J_{CP} = 6 Hz); 61.98 (CH_2); 63.77 (d, CH_2, J_{CP} = 6 Hz); 63.83 (d, CH_2, J_{CP} = 6 Hz); 84.56 (dd, CHF, J_{CF} = 195 Hz, J_{CP} = 158 Hz); 164.40 (d, CO, J_{CF} = 21 Hz).

^{19}F-NMR ($CDCl_3$/$CFCl_3$): δ = −211.15 (dd, J_{FP} = 72 Hz, J_{FH} = 47 Hz).

^{31}P-NMR ($CDCl_3$/H_3PO_{4ext}, ^{1}H decoupled): δ = +9.88 (d, J_{PF} = 72 Hz).

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