Convenient method for the synthesis and some transformations of the lithium salt of bis(diethoxyphosphoryl)fluoromethane*

B. I. Martynov, V. B. Sokolov, A. Yu. Aksinenko, T. V. Goreva, T. A. Epishina, and A. N. Pushin*

Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 (095) 292 6511. E-mail: chelex@ipacl.sherna.msk.su

A convenient method was developed for the synthesis of the lithium salt of 1,1-bis(diethoxyphosphoryl)fluoromethane from available *O,O*-diethyl (chlorofluoromethyl)phosphonate, and some transformations of the resulting salt were studied.

Key words: bis(diethoxyphosphoryl)fluoromethane, *O,O*-diethyl (chlorofluoromethyl)phosphonate, 1,1-bis(diethoxyphosphoryl)-1-fluoroethane, *O,O*-diethyl (1-fluorobut-1-enyl)phosphonate.

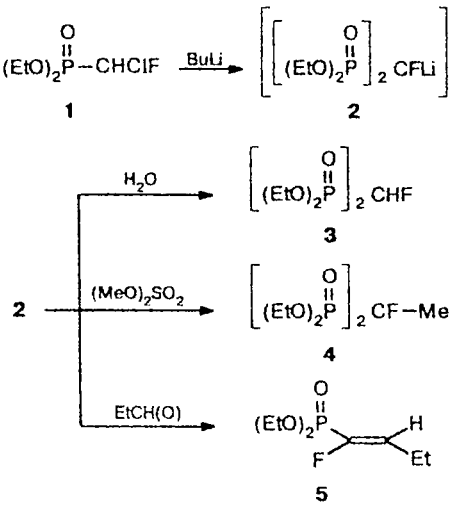
Fluorine-containing derivatives of vinyl fluoride belong to irreversible inhibitors of enzymatic reactions.[1] Therefore, these compounds are of interest as physiologically active compounds. One of the methods for the synthesis of these compounds involves olefination of carbonyl compounds with the lithium salt of bis(diethoxyphosphoryl)fluoromethane.[2] However, a known procedure for the preparation of bis(diethoxyphosphoryl)fluoromethane by fluorination of bis(diethoxyphosphoryl)methane with $FClO_3$ does not allow one to consider this compound as an available reagent for preparative purposes. In this connection, we developed a convenient procedure for the synthesis of bis(diethoxyphosphoryl)fluoromethane and its lithium salt from readily available reagents and studied transformations of the resulting compounds.

It was established that the reaction of *O,O*-diethyl (chlorofluoromethyl)phosphonate (**1**) with BuLi taken in a ratio of 1 : 1.2 in dilute solutions at −70 °C yielded the lithium salt of bis(diethoxyphosphoryl)fluoromethane (**2**) as the major phosphorus-containing product, whose structure was unambiguously confirmed by its subsequent transformations. For example, when compound **2** was treated with water, dimethyl sulfate, or propionaldehyde, bis(diethoxyphosphoryl)fluoromethane (**3**), bis(diethoxyphosphoryl)fluoroethane (**4**), and α-fluorovinyl phosphonate **5** were formed, respectively (Scheme 1).

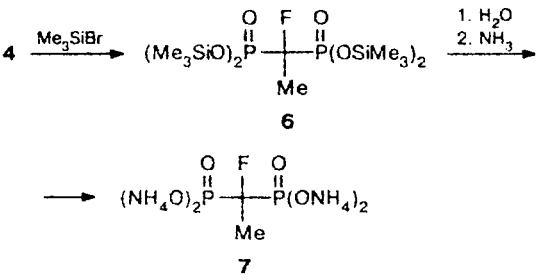
The compositions and the structures of the resulting compounds were established by ^1H, ^{19}F, and ^{31}P NMR spectroscopy and by elemental analysis. The composition and the structure of compound **4** were established based on its chemical transformations.

For example, the reaction of fluoroethane **4** with four equivalents of bromotrimethylsilane afforded the corresponding silyl ether **6**, the subsequent treatment of which with aqueous NH_3 yielded ammonium salt **7** (Scheme 2).

Scheme 1



Scheme 2



* Dedicated to the memory of Academician M. I. Kabachnik on his 90th birthday.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 10, pp. 2039—2040, October, 1998.

1066-5285/98/4710-1983 $20.00

To summarize, a convenient method was developed for the synthesis of the lithium salt of bis(diethoxyphosphoryl)fluoromethane from readily available (chlorofluoromethyl)phosphonate, which was confirmed by subsequent chemical transformations.

Experimental

The ^1H, ^{19}F, and ^{31}P NMR spectra were recorded on a Bruker CXP-200 instrument (at 200, 188, and 81 MHz, respectively); $SiMe_4$ was used as the internal standard; CF_3COOH and a 85% H_3PO_4 solution were used as the external standards. The melting points were determined in glass tubes.

Bis(diethoxyphosphoryl)fluoromethane (3). A 3 *N* BuLi solution (7.5 mL, 0.025 mol) was added with stirring to a solution of compound **1** (4.08 g, 0.02 mol) in anhydrous ether (50 mL) at −70 °C. The reaction mixture was stirred at −40 °C for 30 min. Then the mixture was warmed to room temperature and a 5% HCl solution (10 mL) was added. The ethereal layer was separated, dried over Na_2SO_4, and concentrated. Fractionation of the residue afforded compound **3** in a yield of 2.39 g (39%), b.p. 128—130 °C (1 Torr). Found (%): C, 35.56; H, 6.70. $C_9H_{21}FO_6P_2$. Calculated (%): C, 35.30; H, 6.91. ^1H NMR ($CDCl_3$), δ: 1.30 (t, 12 H, $\underline{CH_3}CH_2$); 4.22 (m, 8 H, CH_2O); 5.04 (dt, 1 H, CHF, J_{HP} = 13.5 Hz, J_{HF} = 46 Hz). ^{19}F NMR ($CDCl_3$), δ: −151 (dt, J_{FP} = 64 Hz, J_{FH} = 46 Hz). ^{31}P NMR ($CDCl_3$), δ: 11.62 (d, J_{PF} = 64 Hz).

1,1-Bis(diethoxyphosphoryl)-1-fluoroethane (4). A 3 *N* BuLi solution (7.5 mL, 0.025 mol) was added with stirring to a solution of compound **1** (4.08 g, 0.02 mol) in anhydrous ether (50 mL) at −70 °C. The reaction mixture was stirred at −40 °C for 30 min. Then dimethyl sulfate (2.5 g, 0.02 mol) was added. The reaction mixture was warmed to room temperature and kept overnight. Then a 5% HCl solution was added. The ethereal layer was separated, dried over Na_2SO_4, and concentrated. Fractionation of the residue afforded compound **4** in a yield of 2.37 g (37%), b.p. 151—152 °C (1 Torr). Found (%): C, 37.66; H, 7.37. $C_{10}H_{23}FO_6P_2$. Calculated (%): C, 37.51; H, 7.24. ^1H NMR ($CDCl_3$), δ: 1.33 (t, 12 H, $\underline{CH_3}CH_2$); 1.80 (dt, 3 H, CH_3CF, J_{HP} = 19 Hz, J_{HF} = 26 Hz); 4.18 (m, 8 H, CH_2O). ^{19}F NMR ($CDCl_3$), δ: −109 (tq, J_{FP} = 72.5 Hz, J_{FH} = 26 Hz). ^{31}P NMR ($CDCl_3$), δ: 14.85 (d, J_{PF} = 71 Hz).

***O,O*-Diethyl (1-fluorobut-1-enyl)phosphonate (5).** A 3 *N* BuLi solution (7.5 mL, 0.025 mol) was added with stirring to a solution of compound **1** (4.08 g, 0.02 mol) in anhydrous ether (50 mL) at −70 °C. The reaction mixture was stirred at −40 °C for 30 min. Then a solution of EtC(O)H (1.12 g, 0.02 mol) in ether (10 mL) was added. The mixture was warmed to room temperature and kept overnight. Then a 5% HCl solution (10 mL) was added. The ethereal layer was separated, dried over Na_2SO_4, and concentrated. The residue was fractionated, and compound **5** was obtained in a yield of 1.78 g (42.4%) **5**, b.p. 128—130 °C (20 Torr). Found (%): C, 45.56; H, 7.48. $C_8H_{16}FO_3P$. Calculated (%): C, 45.72; H, 7.67. ^1H NMR ($CDCl_3$), δ: 1.05 (t, 3 H, $\underline{CH_3}CH_2CH$=); 1.35 (t, 6 H, $\underline{CH_3}CH_2O$); 2.30 (m, 2 H, CH_2CH=); 4.15 (m, 4 H, CH_2O); 6.00 (dq, 1 H, CH=, J_{HH} = J_{HP} = 4 Hz, J_{HF} = 40 Hz). ^{19}F NMR ($CDCl_3$), δ: −55.35 (dd, J_{FP} = 102 Hz, J_{FH} = 40 Hz). ^{31}P NMR ($CDCl_3$), δ: 5.9 (d, J_{PF} = 102 Hz).

1,1-Bis[bis(trimethylsilyloxyphosphoryl)-1-fluoroethane (6). Me_3SiBr (9.3 mL, 0.06 mol) was added with stirring to compound **4** (2.9 g, 0.01 mol). The reaction mixture was stirred for one day and fractionated. Compound **6** was obtained in a yield of 3.08 g (62%) **6**, b.p. 157—158 °C (0.1 Torr). Found (%): C, 33.65; H, 7.78. $C_{14}H_{39}FO_6P_2Si_4$. Calculated (%): C, 33.85; H, 7.91. ^1H NMR ($CDCl_3$), δ: 0.36 (d, 36 H, CH_3Si, J_{HP} = 1.2 Hz); 1.75 (dt, 3 H, CH_3CF, J_{HP} = 20 Hz, J_{HF} = 25 Hz). ^{19}F NMR ($CDCl_3$), δ: −106 (tq, J_{FP} = 76 Hz, J_{FH} = 25 Hz). ^{31}P NMR ($CDCl_3$), δ: −2.98 (d, J_{PF} = 76 Hz).

Tetraammonium 1-fluoroethylidene-1,1-bis(phosphonate) (7). A 25% aqueous NH_3 solution (1 mL) was added to a solution of compound **6** (2.35 g, 0.005 mol) in acetone (20 mL). The reaction mixture was stirred for 1 h. The solvent was evaporated. The residue was recrystallized from aqueous alcohol, and compound **7** was obtained in a yield of 0.99 g (72%), m.p. 181—183 °C. Found (%): C, 8.55; H, 7.12; N, 20.46. $C_2H_7FO_6P_2 \cdot 4NH_3$. Calculated (%): C, 8.70; H, 6.94; N, 20.29. ^1H NMR (D_2O), δ: 1.82 (d.t, 3 H, CH_3CF, J_{HP} = 18 Hz, J_{HF} = 26 Hz). ^{19}F NMR (D_2O), δ: −104 (t.q, J_{FP} = 78 Hz, J_{FH} = 26 Hz). ^{31}P NMR (D_2O), δ: 0.6 (d, J_{PF} = 78 Hz).

References

1. B. I. Martynov, V. B. Sokolov, T. A. Epishina, O. V. Korenchenko, T. V. Goreva, A. Yu. Aksinenko, A. N. Pushin, and G. A. Shataeva, in *14th Intern. Symp. on Med. Chem., Maastricht, The Netherlands, 8—12 September, 1996, Abstracts*, 1996, P-5.51.
2. G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1417.

Received March 10, 1998