Reactions of ethyl 3-(diethoxyphosphoryl)-3,3-difluoropyruvate with some nucleophilic reagents

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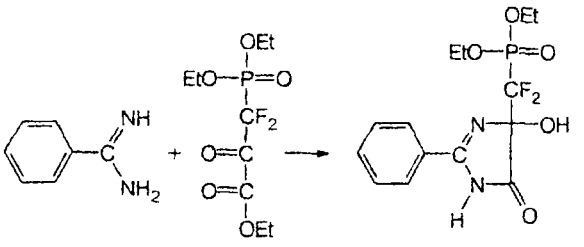
Reactions of ethyl 3-(diethoxyphosphoryl)-3,3-difluoro-2-oxopropionate with a number of nucleophilic reagents were studied. New procedures were developed for the synthesis of difluoromethylphosphonate-substituted nitrogen heterocycles. The ketoester under study is much less reactive in C-hydroxyalkylation of aromatic amines than methyl 3,3,3-trifluoropyruvate.

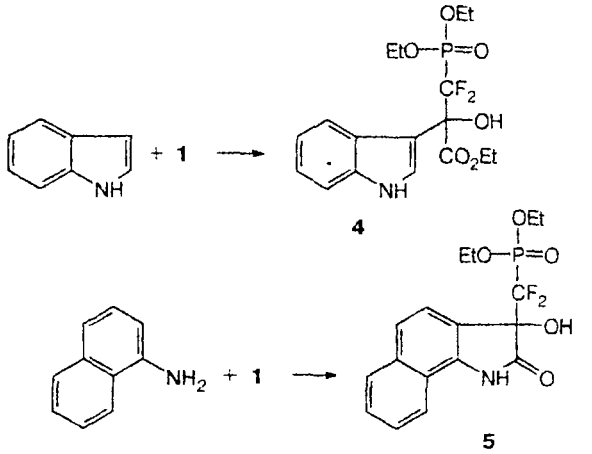
Key words: ethyl 3-(diethoxyphosphoryl)-3,3-difluoro-2-oxopropionate, heterocyclization, C-hydroxyalkylation, N-hydroxyalkylation, difluoromethylphosphonates, imidazolines, indoles, indolines, quinoxalines, phenylhydrazones.

It is known that methyl 3,3,3-trifluoropyruvate vigorously reacts with amidines,[1] *o*-phenylenediamines,[2] and arylamines,[3] is involved into C-hydroxyalkylation of indoles,[4] and reacts with phenylhydrazines to form phenylhydrazones.[5] Great interest in compounds containing the difluoromethylphosphonate group[6] gave impetus to our studies of the reactivity of ethyl 3-(diethoxyphosphoryl)-3,3-difluoropyruvate (**1**),[7] whose chemical properties are virtually unknown. In this work, we studied the reactions of compound **1** with benzamidine, indole, *o*-phenylenediamine, 1-naphthylamine, and phenylhydrazine.

Ketoester **1**, like methyl trifluoropyruvate, exothermically reacts with benzamidine and *o*-phenylenediamine at 20 °C to form the corresponding imidazole and quinoxaline derivatives **2** and **3** in high yields.



Like methyl trifluoropyruvate, ketoester **1** reacts with indole and (more slowly) with 1-naphthylamine to give a product of C-hydroxyalkylation of indole **4** and substituted indolinone **5**, respectively. The reactions with indole at room temperature are completed in 20 min, whereas the reaction with 1-naphthylamine under the same conditions is completed in 48 h, which is indicative of a substantial decrease in the reactivity of **1** in reactions with arylamines compared to methyl trifluoropyruvate,[3] whose reaction with 1-naphthylamine is completed in 1 h. Moreover, under these conditions ester **1**, unlike methyl trifluoropyruvate,[3] is not involved in C-hydroxyalkylation of dialkylanilines at the *para* position. Apparently, this is attributable to the higher stability of hemiaminal, which forms in the case of ketoester **1** as a result of competitive reversible N-hydroxyalkylation of the amino group of the substrate.[8]



When heated, ester **1**, like methyl trifluoropyruvate,[5] gives phenylhydrazone (**6**) as a viscous oil.

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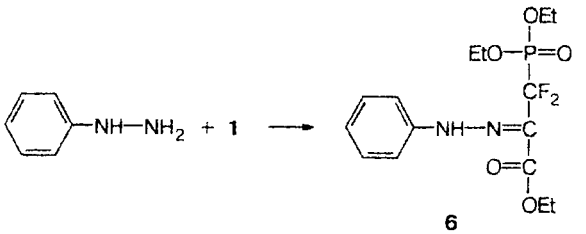

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Therefore, ketoester **1** can be used as a precursor in the synthesis of imidazolones, phenylhydrazones, quinoxalines, indoles, and oxoindolines containing the difluoromethylphosphonate group. It was also found that ester **1** is much less active in C-hydroxyalkylation of arylamines than methyl trifluoropyruvate, which does not contain the phosphoryl group.

The structures of the resulting compounds were confirmed by the data of elemental analysis and ^{1}H, ^{19}F, and ^{31}P NMR spectroscopy.

Experimental

The ^{1}H and ^{31}P NMR spectra were measured on a Bruker AMX-400 instrument operating at 400.13 and 160.62 MHz, respectively. The ^{19}F NMR spectra were recorded on a Bruker WP-200 instrument operating at 188.31 MHz. The chemical shifts in the ^{1}H, ^{19}F, and ^{31}P NMR spectra were measured relative to Me_4Si (internal standard), CF_3COOH (external standard), and 85% H_3PO_4 (external standard), respectively. Ethyl 3-(diethoxyphosphoryl)-3,3-difluoro-2-oxopropionate (**1**) was prepared according to a procedure reported previously.[7]

4-(Diethoxyphosphoryldifluoromethyl)-4-hydroxy-2-phenyl-2-imidazolin-5-one (2). Compound **1** (240 mg, 0.83 mmol) was added with stirring to a solution of benzamidine (100 mg, 0.83 mmol) in MeCN (5 mL) at 20 °C. After 1 h, the precipitate that formed was filtered off, washed with hexane, and dried on a filter. Imidazoline **2** was obtained in a yield of 290 mg (80%) as white crystals, m.p. 166–168 °C. Found (%): C, 46.17; H, 4.38; N, 7.87. $C_{14}H_{17}F_2N_2O_5P$. Calculated (%): C, 46.41; H, 4.73; N, 7.73. ^{1}H NMR (DMSO-d_6), δ: 1.22 (m, 6 H, 2 Me); 4.13 (m, 4 H, 2 CH_2); 7.35 (br.s, 1 H, OH); 7.60–8.00 (m, 5 H, Ph); 11.70 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: −39.4 (d, J_{P-F} = 99.2 Hz). ^{31}P NMR (DMSO-d_6), δ: 7.6 (t, J_{P-F} = 99.2 Hz).

3-(Diethoxyphosphoryldifluoromethyl)-2-hydroxyquinoxaline (3). Compound **1** (280 mg, 0.93 mmol) was added with stirring to a solution of *o*-phenylenediamine (100 mg, 0.93 mmol) in $CHCl_3$ (10 mL) at 20 °C. After 30 min, the solvent was distilled off *in vacuo*. The residue was crystallized from hexane and dried on a filter. Compound **3** was obtained in a yield of 320 mg (99%) as yellowish crystals, m.p. 141–142 °C. Found (%): C, 46.64; H, 4.22; N, 8.07. $C_{13}H_{15}F_2N_2O_4P$. Calculated (%): C, 46.99; H, 4.55; N, 8.43. ^{1}H NMR (DMSO-d_6), δ: 1.33 (t, 6 H, 2 Me, J = 7.4 Hz); 4.32 (m, 4 H, 2 CH_2); 7.40 (m, 2 H, Ar); 7.70 (t, 1 H, Ar, J = 7.6 Hz); 7.83 (d, 1 H, Ar, J = 8.1 Hz); 12.80 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −29.3 (d, J_{P-F} = 99.2 Hz). ^{31}P NMR (DMSO-d_6), δ: 8.0 (t, J_{P-F} = 99.2 Hz).

3-[1-Carbethoxy-(2-diethoxyphosphoryl-2,2-difluoroethyl)-1-hydroxy]indole (4). Compound **1** (290 mg, 1 mmol) was added with stirring to a solution of indole (120 mg, 1 mmol) in $CHCl_3$ (10 mL) at 20 °C. After 20 min, the reaction mixture was filtered and the precipitate was washed with hexane and dried on a filter. Compound **4** was obtained in a yield of 240 mg (59%) as white crystals, m.p. 162 °C. Found (%): C, 50.23; H, 5.33; N, 3.48. $C_{17}H_{22}F_2NO_6P$. Calculated (%): C, 50.37; H, 5.47; N, 3.46. ^{1}H NMR (DMSO-d_6), δ: 1.25 (m, 9 H, 3 Me); 4.19 (m, 6 H, 3 CH_2); 6.60 (br.s, 1 H, OH); 6.90, 7.10 (both t, 1 H each, 2 H(Ar), J = 7.5 Hz); 7.40 (m, 2 H, H(2), H(Ar)); 7.80 (d, 1 H, H(Ar), J = 8.1 Hz); 11.10 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: −31.2 (center of the AB system, J_{P-F} = 99 Hz, J_{FF} = 299 Hz). ^{31}P NMR (DMSO-d_6), δ: 9.9 (t, J_{P-F} = 99 Hz).

3-(Diethoxyphosphoryldifluoromethyl)-3-hydroxy-2,3-dihydrobenzo[*g*]indol-2-one (5). Compound **1** (200 mg, 0.7 mmol) was added with stirring to a solution of 1-naphthylamine (100 mg, 0.7 mmol) in CCl_4 (5 mL) at 20 °C. After 48 h, the precipitate that formed was filtered off, washed with hexane, and dried on a filter. Compound **5** was obtained in a yield of 150 mg (56%) as gray crystals, m.p. 164–165 °C. Found (%): C, 52.70; H, 4.54; N, 3.60. $C_{17}H_{18}F_2NO_5P$. Calculated (%): C, 52.99; H, 4.71; N, 3.64. ^{1}H NMR (DMSO-d_6), δ: 0.98 (t, 3 H, Me, J = 7.15 Hz); 1.07 (t, 3 H, Me, J = 6.98 Hz); 3.67–3.83 (m, 2 H, CH_2); 3.98 (m, 2 H, CH_2); 7.18 (s, 1 H, OH); 7.50–8.08 (m, 6 H, Ar); 11.30 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: −38 (d, J_{P-F} = 99 Hz). ^{31}P NMR (DMSO-d_6), δ: 7.2 (t, J_{P-F} = 99 Hz).

Ethyl 3-diethoxyphosphoryl-3,3-difluoro-2-(phenylhydrazono)propionate (6). Compound **1** (1 g, 3.5 mmol) was added to a solution of freshly distilled phenylhydrazine (370 mg, 3.5 mmol) in benzene (20 mL). The reaction mixture was azeotroped for 2 h. Then the benzene was distilled off *in vacuo*. The residue was dried *in vacuo* (1 Torr) at 50 °C for 15 min. An orange-red oil was obtained in a yield of 1.36 g (100%). Found (%): C, 47.35; H, 5.88; N, 7.28. $C_{15}H_{21}F_2N_2O_5P$. Calculated (%): C, 47.62; H, 5.56; N, 7.41. ^{1}H NMR (benzene-d_6), δ: 1.08 (t, 3 H, Me(CO_2Et), J = 7.14 Hz); 1.14 (t, 6 H, 2 Me(P—OEt), J = 6.98 Hz); 4.04 (q, 2 H, CH_2 (CO_2Et), J = 7.14 Hz); 4.27 (m, 4 H, 2 CH_2, P—OEt); 6.93–7.49 (m, 5 H, Ph); 12.68 (s, 1 H, NH). ^{19}F NMR (benzene-d_6), δ: −27.3 (d, J_{P-F} = 102 Hz). ^{31}P NMR (benzene-d_6), δ: 4.0 (t, J_{P-F} = 102 Hz).

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