Diethoxyphosphorylimine of methyl trifluoropyruvate in cyclocondensation with 1,3-C,N- and -N,N-binucleophiles

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Reaction of diethoxyphosphorylimine of methyl trifluoropyruvate with 1,3-C,N- and -N,N-binucleophiles led to a variety of *N*-phosphorylated fluorine-containing heterocycles, including the fused ones.

Key words: diethoxyphosphorylimine, 1,3-C,N- and -N,N-binucleophiles, *N*-phosphorylated heterocycles, hexahydro-1*H*-pyrrolo[2,4-*d*]pyrimidines, 4,5-dihydro-1*H*-pyrroles, 2,5-dioxoimidazolidine, 4,5-dihydro-1*H*-imidazole, tetrahydroimidazo[2,1-*b*]thiazole, cyclocondensation.

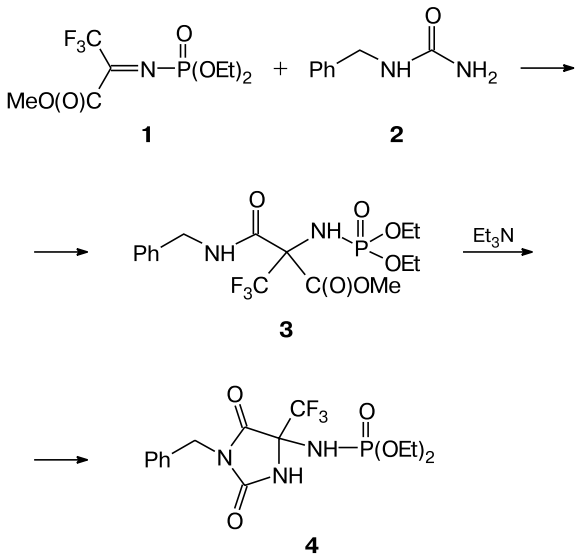
In the preparation of heterocycles containing phosphorus and fluorine, diethoxyphosphorylimine of methyl trifluoropyruvate is a prospective synthon, for example, when it is used in the Mannich reaction with indole,[1] in the aza-Diels—Alder reaction with cyclopentadiene[2] and in the synthesis of *N*-phosphorylated α-(trifluoromethyl)azahistidine.[3] The present communication deals with the application of this compound as the 1,2-bielectrophile in the cyclocondensation reactions with 1,3-C,N- and -N,N-binucleophiles for the synthesis of five-membered heterocycles containing phosphorus and fluorine. The data obtained by us earlier on the reaction of *N*-acylimines of methyl trifluoropyruvate with various 1,3-C,N- and -N,N-binucleophiles, which led to different five- and six-membered fluorine-containing heterocycles,[4—8] served as the prerequisite for this research.

Diethoxyphosphorylimine of methyl trifluoropyruvate (**1**) was used in the reaction with a number of binucleophiles, which proceed according to the two-step scheme: the addition of 1,3-binucleophile at the C=N bond of imine **1** and the subsequent cyclization with elimination of MeOH.

In the case of the reaction of imine **1** with *N*-benzylurea (**2**) (Scheme 1), we isolated and identified the addition product, the corresponding phosphamide **3**, which upon heating in DMF in the presence of catalytic amount of Et_3N for 1 h at 90—100 °C was converted to imidazolidine **4**.

The cyclocondensation of phosphorylimine **1** with other binucleophiles (Scheme 2), *viz.*, methyl 2-aminocrotonate (**5**), *N*-benzylbenzamidine (**7**), 2-aminothiazoline **9**, 6-aminouracils **11a,b**, and 6-aminothiouracils **13a,b**, was carried out upon heating of a mixture of the reagents in DMF for 1 h at 90—100 °C and in the case of the reaction of imine **1** with compounds **11a,b** and **13a,b**, in the presence of catalytic amount of Et_3N.

Scheme 1



Amidophosphates **4**, **6**, **8**, **10**, **12a,b**, and **14a,b**, obtained in 69—83% yield, are solid crystalline substances, their composition and structures were confirmed by elemental analysis and NMR spectroscopy data. A signal of the amide NH proton in form of a doublet with J = 6—7 Hz in the region δ 6—7 is characteristic of the ^{1}H NMR spectra, signals of trifluoromethyl group at δ −1.5—4, of the ^{19}F NMR spectra, and singlets in the region δ 4—6, of the ^{31}P NMR spectra.

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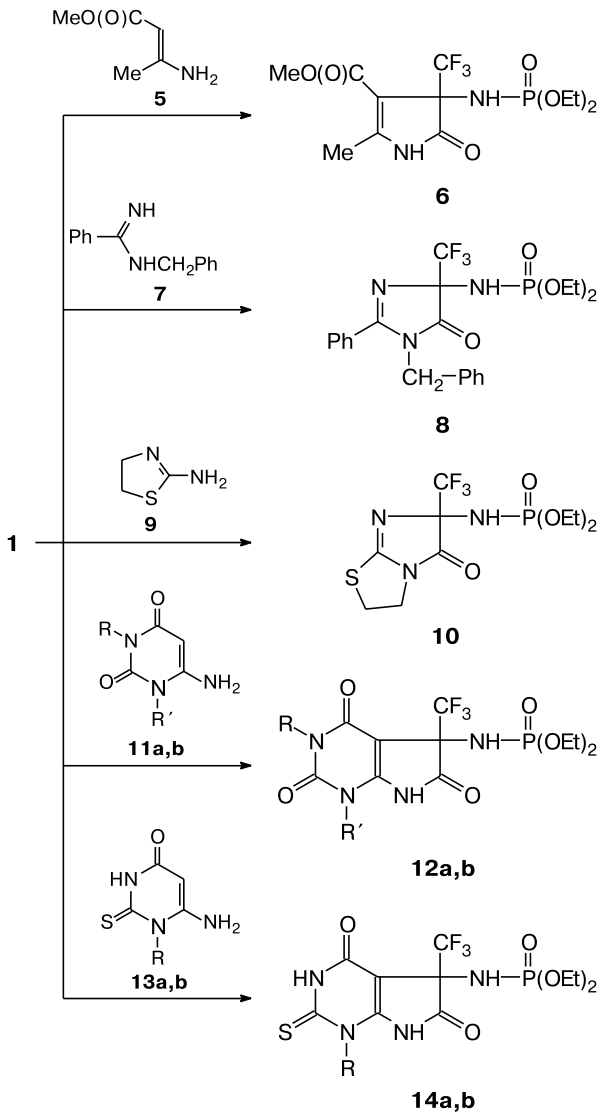
Scheme 2

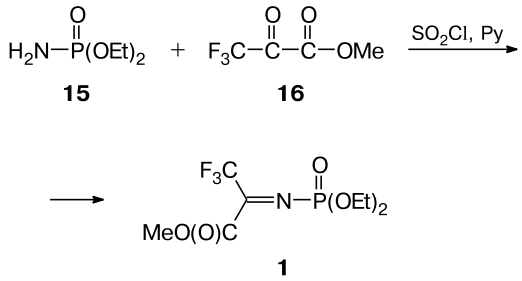


11, 12: R = R′ = Me (**a**); R = H, R′ = 4-FC_6H_4 (**b**)
13, 14: R = CH_2=CH(Me)CH_2 (**a**), 2-FC_6H_4 (**b**)

It should be noted that diethoxyphosphorylimine of methyl trifluoropyruvate (**1**), in contrast to the procedures proposed earlier,[1,2] was synthesized in 73% yield by the one-pot method, including the sequential treatment of a suspension of diethoxyphosphamide **15** in benzene with methyl trifluoropyruvate (**16**), pyridine, and $SOCl_2$ (Scheme 3).

In conclusion, the reaction of diethoxyphosphorylimine of methyl trifluoropyruvate with the mentioned 1,3-C,N- and -N,N-binucleophiles leads to the *N*-phosphorylated fluorine-containing heterocycles of three structural types: imidazolidines, pyrroles, and imidazoles. The experimental date obtained allow one to introduce into the molecules of the phosphorus acid amides various

Scheme 3



(depending on the nature of 1,3-binucleophile used) fluorine-containing heterocycles, including the biologically active ones.

Experimental

^1H, ^{19}F, and ^{31}P NMR spectra were recorded on a Bruker DXP 200 spectrometer (200.13, 188.29, and 81.01 MHz, respectively) relatively to Me_4Si (the internal standard), CF_3COOH and H_3PO_4 (the external standards). Melting points were determined in a glass capillary tube. The starting 6-aminouracils **11a,b** and 6-aminothiouracils **13a,b** were synthesized by the known procedure;[9] *N*-benzylurea (**2**), methyl 2-aminocrotonate (**5**), 2-aminothiazoline **9**, diethoxyphosphamide **15**, and methyl trifluoropyruvate (**16**) (Aldrich) were used without additional purification.

Methyl 2-(diethoxyphosphoryl)imino-3,3,3-trifluoropropionate (1). Methyl trifluoropyruvate **16** (15.6 g, 0.1 mol), pyridine (15.6 g, 0.2 mol), and $SOCl_2$ (11.9 g, 0.1 mol) were sequentially added to a suspension of diethoxyphosphamide **15** (15.3 g, 0.1 mol) in benzene (100 mL). The reaction mixture was stirred for 2 h, the precipitate formed was filtered off, the filtrate was concentrated, the residue fractionally distilled *in vacuo*. Imine **1** (21.3 g, 73%) was obtained, b.p. 95—97 °C (1 Torr). Physicochemical and spectral characteristics are in agreement with those reported in Refs 1, 2.

Methyl 2-(3-benzylureido)-2-(diethoxyphosphoryl)amino-3,3,3-trifluoropropionate (3). Imine **1** (2.91 g, 0.01 mol) was added to a stirred suspension of *N*-benzylurea (**2**) (1.5 g, 0.01 mol) in benzene (20 mL). The reaction mixture was stirred for 1 h, benzene was evaporated, the residue was recrystallized from heptane. Amidophosphate **3** (3.9 g, 88%) was obtained, m.p. 126—128 °C. Found (%): C, 43.38; H, 5.11; N, 9.63. $C_{16}H_{23}F_3N_3O_6P$. Calculated (%): C, 43.64; H, 5.25; N, 9.52. ^1H NMR (DMSO-d_6), δ: 1.21, 1.33 (both t, 3 H each, 4 Me, J = 6.5 Hz); 3.82 (s, 3 H, OMe); 3.85—4.10 (m, 4 H, OCH_2); 4.26 (m, 2 H, NCH_2); 5.19 (d, 1 H, NH, J = 7.0 Hz); 6.94 (t, 1 H, N<u>H</u>CH_2, J = 6.0 Hz); 7.13—7.34 (m, 5 H, CH_{Ar}); 7.37 (s, 1 H, NHCO). ^{19}F NMR (DMSO-d_6), δ: 0.49 (s). ^{31}P NMR (DMSO-d_6), δ: 2.31 (s).

Diethyl [1-benzyl-2,5-dioxo-4-(trifluoromethyl)imidazolidin-4-yl]amidophosphate (4). A solution of compound **3** (2.2 g, 0.005 mol) and Et_3N (0.1 g) in DMF (10 mL) was heated for 1 h at 90—100 °C, diluted with water (50 mL), the precipitate formed was filtered off and recrystallized from 50% aq. EtOH. Amidophosphate **4** (1.6 g, 78%) was obtained, m.p. 124—126 °C.

Found (%): C, 44.19; H, 4.82; N, 10.11. $C_{15}H_{19}F_3N_3O_5P$. Calculated (%): C, 44.02; H, 4.59; N, 10.27. ^{1}H NMR (DMSO-d_6), δ: 1.19 (t, 6 H, 2 Me, J = 5.1 Hz); 3.91 (m, 4 H, OCH_2); 4.52 (AB-system, 2 H, CH_2, J = 17.2 Hz); 6.71 (d, 1 H, NH, J = 6.2 Hz); 6.22 (m, 5 H, CH_{Ar}); 9.34 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: −1.05 (s). ^{31}P NMR (DMSO-d_6), δ: 4.07 (s).

Methyl 4-(diethoxyphosphoryl)amino-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (6). Imine **1** (2.91 g, 0.01 mol) was added to a solution of methyl 2-aminocrotonate (**5**) (1.15 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated for 1 h at 90—100 °C, diluted with water (50 mL), the precipitate formed was filtered off and recrystallized from 50% aq. EtOH. Pyrrole **6** (3.1 g, 83%) was obtained, m.p. 127—129 °C. Found (%): C, 38.35; H, 4.68; N, 7.37. $C_{12}H_{18}F_3N_2O_6P$. Calculated (%): C, 38.51; H, 4.85; N, 7.49. ^{1}H NMR (DMSO-d_6), δ: 1.27, 1.32 (both t, 3 H each, 2 Me, J = 6.7 Hz); 2.38, 3.72 (both s, 3 H each, 2 OMe); 3.93, 4.04 (both m, 2 H each, 2 OCH_2); 5.53 (d, 1 H, NH, J = 6.4 Hz); 10.73 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 2.84 (s). ^{31}P NMR (DMSO-d_6), δ: 5.50 (s).

Diethyl (1-benzyl-5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amidophosphate (8). The product was obtained similarly to compound **6** from benzamidine **7** (2.1 g, 0.01 mol) and imine **1** (2.91 g, 0.01 mol). The yield was 3.8 g (81%), m.p. 116—118 °C. Found (%): C, 53.87; H, 4.78; N, 8.81. $C_{21}H_{23}F_3N_3O_4P$. Calculated (%): C, 53.73; H, 4.94; N, 8.95. ^{1}H NMR (DMSO-d_6), δ: 1.27, 1.32 (both t, 3 H each, 2 Me, J = 6.5 Hz); 4.06 (m, 4 H, OCH_2); 4.56, 4.77 (both d, 1 H each, CH_2, J = 16.1 Hz); 6.90 (d, 1 H, NH, J = 6.6 Hz); 7.15 (m, 2 H, CH_{Ar}); 7.24 (m, 3 H, CH_{Ar}); 7.44 (m, 5 H, CH_{Ar}). ^{19}F NMR (DMSO-d_6), δ: 0.30 (s). ^{31}P NMR (DMSO-d_6), δ: 6.2 (s).

Diethyl (5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazol-6-yl)amidophosphate (10). The product was obtained similarly to compound **6** from 2-aminothiazoline **9** (1.02 g, 0.01 mol) and imine **1** (2.91 g, 0.01 mol). The yield was 2.9 g (80%), m.p. 122—123 °C. Found (%): C, 33.12; H, 4.05; N, 11.49. $C_{10}H_{15}F_3N_3O_4PS$. Calculated (%): C, 33.25; H, 4.18; N, 11.63. ^{1}H NMR (DMSO-d_6), δ: 1.31, 1.33 (both t, 3 H each, 2 Me, J = 4.8 Hz); 3.75 (m, 4 H, NCH_2, SCH_2); 4.01 (m, 4 H, OCH_2); 6.61 (d, 1 H, NH, J = 5.6 Hz). ^{19}F NMR (DMSO-d_6), δ: −0.09 (s). ^{31}P NMR (DMSO-d_6), δ: 6.27 (s).

Diethyl (1,3-dimethyl-5-trifluoromethyl-2,4,6-trioxo-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)amidophosphate (12a). Imine **1** (2.91 g, 0.01 mol) and Et_3N (0.1 mL) were added to a suspension of uracil **11a** (1.55 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated for 1 h at 90—100 °C, diluted with water (50 mL), the precipitate formed was filtered off and recrystallized from 50% aq. EtOH. Amidophosphate **12a** (3.2 g, 77%) was obtained, m.p. 242—244 °C. Found (%): C, 37.52; H, 4.22; N, 13.37. $C_{13}H_{18}F_3N_4O_6P$. Calculated (%): C, 37.69; H, 4.38; N, 13.52. ^{1}H NMR (DMSO-d_6), δ: 1.23, 1.32 (both t, 3 H each, 2 Me, J = 6.5 Hz); 3.26, 3.44 (both s, 3 H each, 2 NMe); 3.92, 4.06 (both m, 2 H each, 2 OCH_2); 6.32 (d, 1 H, NH, J = 7.4 Hz); 11.96 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 3.52 (s). ^{31}P NMR (DMSO-d_6), δ: 4.73 (s).

Diethyl [1-(4-fluorophenyl)-5-trifluoromethyl-2,4,6-trioxo-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]amidophosphate (12b). The product was obtained similarly to compound **12a** from uracil **11b** (2.21 g, 0.01 mol) and imine **1** (2.91 g, 0.01 mol). The yield was 3.2 g (69%), m.p. 181—183 °C. Found (%): C, 42.36; H, 3.42; N, 11.81. $C_{17}H_{17}F_4N_4O_6P$. Calculated (%): C, 42.51; H, 3.57; N, 11.66. ^{1}H NMR (DMSO-d_6), δ: 1.21, 1.25 (both t, 3 H each, 2 Me, J = 6.5 Hz); 4.01 (m, 4 H, OCH_2); 6.64 (d, 1 H, NH, J = 6.7 Hz); 7.41, 7.55 (both m, 2 H each, CH_{Ar}); 11.33, 11.41 (both s, 1 H each, 2 NH). ^{19}F NMR (DMSO-d_6), δ: 4.14 (s, 3 F, CF_3); −34.04 (m, 1 F, CF_{Ar}). ^{31}P NMR (DMSO-d_6), δ: 5.79 (s).

Diethyl [4,6-dioxo-1-(2-methylallyl)-2-thioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]amidophosphate (14a). The product was obtained similarly to compound **12a** from thiouracil **13a** (1.97 g, 0.01 mol) and imine **1** (2.91 g, 0.01 mol). The yield was 3.1 g (68%), m.p. 212—214 °C. Found (%): C, 39.31; H, 4.29; N, 12.12. $C_{15}H_{20}F_3N_4O_5PS$. Calculated (%): C, 39.48; H, 4.42; N, 12.28. ^{1}H NMR (DMSO-d_6), δ: 1.17, 1.23 (both t, 3 H each, 2 Me, J = 6.7 Hz); 2.51 (s, 3 H, Me); 3.95 (m, 4 H, OCH_2); 4.47 (s, 1 H, NCH_2); 4.85 (m, 3 H, $=CH_2$ + NCH_2); 6.76 (d, 1 H, NH, J = 7.2 Hz); 12.11, 12.71 (both s, 1 H each, NH). ^{19}F NMR (DMSO-d_6), δ: 3.47 (s). ^{31}P NMR (DMSO-d_6), δ: 5.32 (s).

Diethyl [1-(2-fluorophenyl)-4,6-dioxo-2-thioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]amidophosphate (14b). The product was obtained similarly to compound **12a** from thiouracil **13b** (2.37 g, 0.01 mol) and imine **1** (2.91 g, 0.01 mol). The yield was 3.1 g (71%), m.p. 204—206 °C. Found (%): C, 41.27; H, 3.59; N, 11.13. $C_{17}H_{17}F_4N_4O_5PS$. Calculated (%): C, 41.14; H, 3.45; N, 11.29. ^{1}H NMR (DMSO-d_6), δ: 1.27 (m, 6 H, 2 Me); 3.93 (m, 4 H, OCH_2); 6.72 (d, 1 H, NH, J = 6.9 Hz); 7.38 (m, 3 H, CH_{Ar}); 7.57 (m, 1 H, CH_{Ar}); 11.55, 12.66 (both s, 1 H each, 2 NH). ^{19}F NMR (DMSO-d_6), δ: 3.23 (s). ^{31}P NMR (DMSO-d_6), δ: 5.21 (s).

References

1. P. P. Onys´ko, Yu. V. Rassukanaya, and A. D. Sinitsa, *Zh. Obshch. Khim.*, 2002, **72**, 1802 [*Russ. J. Gen. Chem.*, 2002, **72** (Engl. Transl.)].
2. N. M. Kobel´kova, S. N. Osipov, and A. F. Kolomiets, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1199 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1298].
3. G. T. Shchetnikov, A. S. Peregudov, and S. N. Osipov, *Synlett*, 2007, 136.
4. V. B. Sokolov, A. Yu. Aksinenko, and I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1064 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1113].
5. V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, and I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 462 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 472].
6. V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, and I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 2755 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 2851].
7. A. Yu. Aksinenko, T. V. Goreva, T. A. Epishina, A. N. Pushin, and V. B. Sokolov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 1014 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1052].
8. V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, A. N. Pushin, and I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1619 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1667].
9. W. Hatzenlaub and W. Pfleiderer, *Liebigs Ann. Chem.*, 1979, 1847.

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