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CHEMISTRY

Methyl Trifluoropyruvate in Cyclocondensation with 1,3-Bis(nucleophiles)

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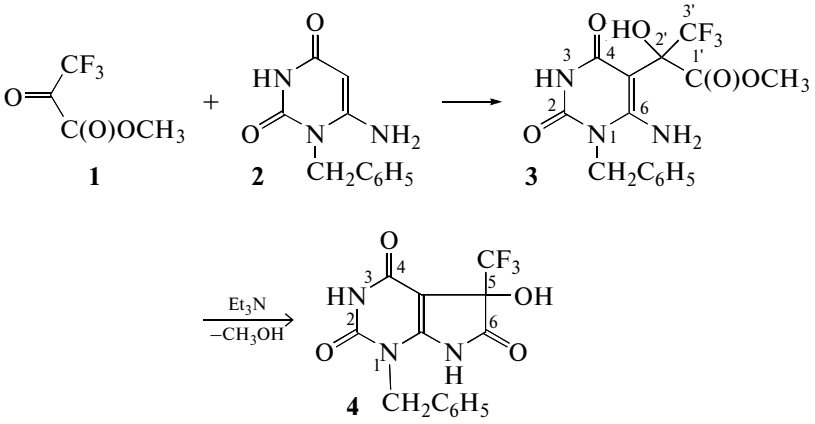
The directed synthesis of five-membered heterocyclic systems by the cyclocondensation of 1,2-bis(electrophiles) with 1,3-bis(nucleophiles) is a topical task of organic chemistry in spite of the well developed but continuously updated by new data methodology of these transformations. In our opinion, the present study is a new original evolution of this synthetic practice as applied to the synthesis of trifluoromethyl-containing five-membered heterocyclic compounds.

Methyl trifluoropyruvate (MTFP) derivatives, in particular its N-substituted imines, are well studied in cyclocondensation reactions, for the synthesis of biologically active compounds including [1–6]. However, the question on the direct use of MTFP **1** in these reactions—except for the reaction of **1** with phenols [7], anilines [8], 2-aminophenols [9], and 2-mercaptophenol [10] resulting in five- and six-membered heterocyclic compounds—remained open. The aim of this work is a declaration of synthetic possibilities of MTFP **1** as available fluorine-containing 1,2-bis(electrophile) in cyclocondensation reactions with 1,3-bis(nucleophiles) resulting in various heterocyclic derivatives of trifluoro-2-hydroxypropionic acid.

The reaction of compound **1** with 1,3-bis(nucleophiles) was accomplished as a two-stage cyclocondensation reaction: addition of bis(nucleophile) at highly electrophilic C=O bond followed by heterocyclization with methanol elimination. 6-Amino-1-benzyluracil (**2**), 3-aminocyclohexenones (**5a**, **5b**), 3-aminocrotononitrile (**6**), and *N*-substituted benzamidines (**7a**, **7b**) were used in these transformations as 1,3-bis(nucleophiles). In the reaction of **1** with compound **2**, we isolated in a pure state and characterized a primary reaction product, 6-aminouracil (**3**), which undergoes heterocyclization on heating at 90–100°C in DMF for 2 h in the presence of catalytic amounts of Et_3N to give dihydro-1H-pyrrolo[2,3-*d*]pyrimidin-2,4,6-trione (**4**).



3-Aminocrotononitrile **6** and *N*-substituted benzamidines **7a** and **7b** combine with MTFP **1** in the absence of catalyst to form 4,5-dihydro-1H-pyrrole (**9**) and 4,5-dihydroimidazol-5-ones (**10a**, **10b**). Less nucleophilic 3-aminocyclohexenones **5a**, **5b** undergo cyclocondensation with **1** in the presence of catalytic amounts of Et_3N to yield 4,5,6,7-tetrahydro-1H-indole-2,4-diones (**8a**, **8b**).

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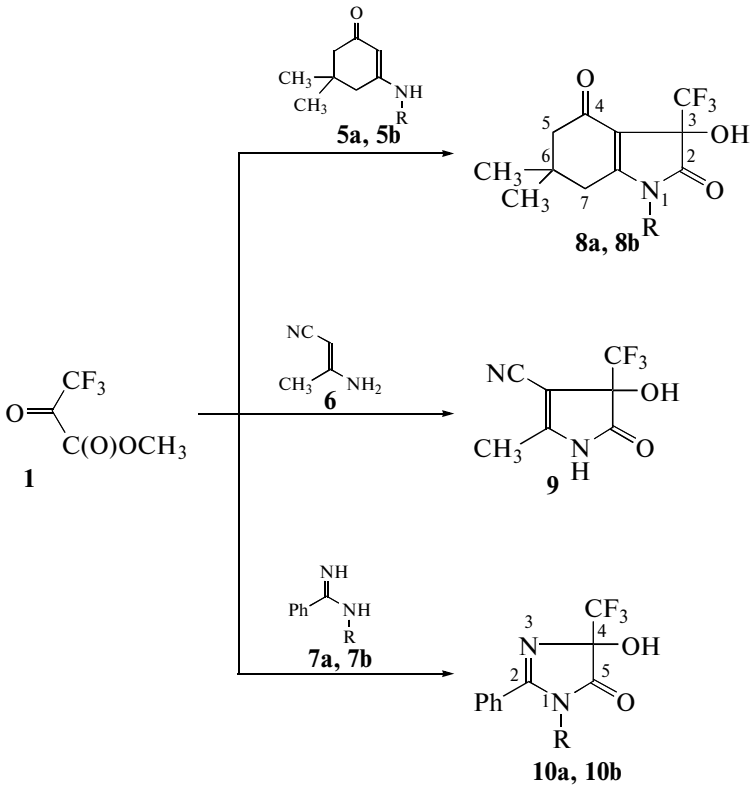
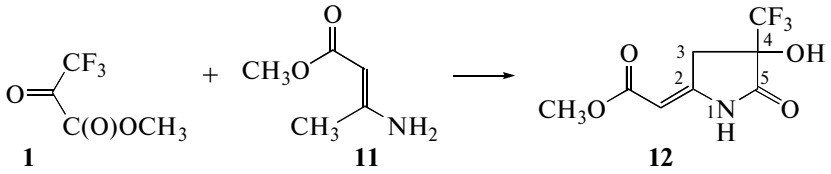


5, **8**: R = $CH_2C_6H_5$ (**a**), 3,4-$(CH_3)_2C_6H_3$ (**b**);
7, **10**: R = C_3H_7 (**a**), $CH_2CH_2C_6H_5$ (**b**).

Methyl 3-aminocrotonate (**11**) undergoes cyclocondensation with MTFP **1** to produce pyrrolidine (**12**), which is anomalous in comparison with considered above 1,3-C,N-bis(nucleophiles).



The composition and structure of all obtained compounds were proved by the data of elemental analysis and ^1H and ^{19}F NMR spectra. ^{19}F NMR spectra show typical signals of trifluoromethyl group at 1.11 ppm for **4**, 1.1–1.3 ppm for **8a**, **8b**, 2.2 ppm for **9**, −1.8 to −2.0 ppm for **10a**, **10b**, and **12**.

Thus, MTFP **1** can be successfully used as 1,2-bis(electrophilic) reagent in the cyclocondensation with 1,3-bis(nucleophiles) to obtain trifluoromethyl-containing five-membered heterocyclic derivatives of trifluoro-2-hydroxypropionic acid.

EXPERIMENTAL

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer operating at 200.13 and 188.29 MHz, respectively, using tetramethylsilane as an internal reference and CF_3COOH as an external reference, respectively. Melting points were determined in a glass capillary. Initial 6-amino-1-benzyluracil **2** and 3-aminocyclohexenones **5a**, **5b** were obtained by procedures [11, 12], 3-aminocrotononitrile **6** and *N*-substituted benzamidines **7a**, **7b** (Aldrich) were used as received.

Methyl 2-(6-amino-1-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3',3',3'-trifluoro-2'-hydroxypropionate (3). Uracil **2** (2.17 g, 0.01 mol) was added to a solution of 1.56 g (0.01 mol) of methyl trifluoropyruvate **1** in 20 mL of DMF with stirring, the reaction mixture was stirred for 30 min and poured into 50 mL of water. The resultant precipitate was separated by filtration and recrystallized from 50% EtOH

to give 3.4 g (91%) of the title compound, mp 133–135°C.

^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 3.71 (s, 3H, MeO), 5.17 (AB system, 2H, CH_2, $J = 17.6$), 6.97 (s, 2H, NH_2), 7.32 (m, 5H, CH_{Ar}), 8.04 (s, 1H, OH), 10.70 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm): –0.64 s.

For $C_{15}H_{14}F_3N_3O_5$ anal. calcd. (%): C, 48.26; H, 3.78; N, 11.26.

Found (%): C, 48.45; H, 3.95; N, 11.42.

1-Benzyl-5-hydroxy-5-trifluoromethyl-5,6-dihydro-1H-pyrrolo[2,3-*d*]pyrimidin-2,4,6-trione (4). A solution of 3.73 g (0.01 mol) of compound **3** and 0.1 g of Et_3N in 20 mL of DMF was heated for 2 h at 90–100°C and poured into 50 mL of water. The resultant precipitate was separated by filtration and recrystallized from 50% EtOH to give 3.0 g (88%) of the title compound, mp 158–159°C.

^{1}H NMR (DMSO-d_6, δ, ppm): 5.03 (s, 2H, CH_2), 7.05 (s, 1H, OH), 7.18–7.42 (m, 5H, CH_{Ar}), 10.96 (s, 1H, NH), 11.62 (s, 1H, NH).

^{19}F NMR ($CDCl_3$, δ, ppm): 1.11 s.

For $C_{14}H_{10}F_3N_3O_4$ anal. calcd. (%): C, 49.28; H, 2.95; N, 12.31.

Found (%): C, 49.47; H, 3.13; N, 12.23.

1-Benzyl-3-hydroxy-6,6-dimethyl-3-trifluoromethyl-4,5,6,7-tetrahydro-1H-indole-2,4-dione (8a). 3-Aminocyclohexenone **5a** (2.29 g, 0.01 mol) was added to a solution of 1.56 g (0.01 mol) of methyl trifluoropyruvate **1** in 20 mL of DMF with stirring, the reaction mixture was stirred for 30 min, 0.1 g of Et_3N was added, the mixture was heated for 2 h at 90–100°C and poured into 50 mL of water. The resultant precipitate was separated by filtration and recrystallized from 50% EtOH to give 2.9 g (82%) of the title compound, mp 93–95°C.

^{1}H NMR (DMSO-d_6, δ, ppm): 1.04 (s, 3H, Me), 1.08 (s, 3H, Me), 2.21 (s, 2H, CH_2), 2.45–2.53 (m, 2H, CH_2), 4.73–4.92 (m, 2H, CH_2), 7.22 (m, 2H, CH_{Ar}), 7.25 (s, 1H, OH), 7.28–7.40 (m, 3H, CH_{Ar}).

^{19}F NMR ($CDCl_3$, δ, ppm): 1.39 s.

For $C_{18}H_{18}F_3NO_3$ anal. calcd. (%): C, 61.19; H, 5.13; N, 3.96.

Found (%): C, 61.35; H, 5.26; N, 4.15.

3-Hydroxy-1-(3,4-dimethylphenyl)-6,6-dimethyl-3-trifluoromethyl-4,5,6,7-tetrahydro-1H-indole-2,4-dione (8b). The compound was obtained similarly to **8a**.

Yield 3.0 g (82%), mp 138–140°C.

^{1}H NMR (DMSO-d_6, δ, ppm): 1.09 (s, 3H, Me), 1.12 (s, 3H, Me), 2.18–2.43 (m, 10H, 2Me + 2CH_2), 6.95–7.05 (m, 2H, CH_{Ar}), 7.23 (s, 1H, OH), 7.31 (s, 1H, CH_{Ar}).

^{19}F NMR (DMSO-d_6, δ, ppm): 1.32 s.

For $C_{19}H_{20}F_3NO_3$ anal. calcd. (%): C, 62.12; H, 5.49; N, 3.81.

Found (%): C, 62.30; H, 5.31; N, 3.66.

4-Hydroxy-2-methyl-5-oxo-4-trifluoromethyl-3-cyano-4,5- dihydro-1H-pyrrol (9). 3-Aminocrotononitrile **6** (0.82 g, 0.01 mol) was added to a solution of 1.56 g (0.01 mol) of methyl trifluoropyruvate **1** in 20 mL of DMF with stirring, the reaction mixture was heated for 2 h at 90–100°C and poured into 50 mL of water. The resultant precipitate was separated by filtration and recrystallized from 50% EtOH to give 1.6 g (78%) of the title compound, mp 88–90°C.

^{1}H NMR ($CDCl_3$, δ, ppm): 2.20 (s, 3H, Me), 7.79 (s, 1H, OH), 11.09 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm): –0.63 s.

For $C_7H_5F_3N_2O_2$ anal. calcd. (%): C, 40.79; H, 2.45; N, 13.59.

Found (%): C, 40.96; H, 2.31; N, 13.40.

4-Hydroxy-1-propyl-2-phenyl-4-trifluoromethyl-4,5-dihydroimidazol-5-one (10a) was obtained similarly to compound **9**. Yield 2.4 g (84%), mp 123–125°C.

^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 0.8 (t, 3H, Me, $J = 7.4$), 1.43 (q, 2H, CH_2, $J = 7.4$), 3.55 (t, 2H, CH_2, $J = 7.4$), 7.60 (m, 3H, CH_{Ar}), 7.72 (m, 2H, CH_{Ar}), 7.88 (s, 1H, OH).

^{19}F NMR (DMSO-d_6, δ, ppm): –1.95 s.

For $C_{13}H_{13}F_3N_2O_2$ anal. calcd. (%): C, 54.55; H, 4.58; N, 9.79.

Found (%): C, 54.66; H, 4.75; N, 9.91.

4-Hydroxy-2-phenyl-1-phenylethyl-4-trifluoromethyl-4,5-dihydroimidazol-5-one (10b) was obtained similarly to compound **10a**. Yield 2.8 g (80%), mp 112–114°C.

^{1}H NMR (DMSO-d_6, δ, ppm, *J*, Hz): 2.77 (td, 2H, CH_2, $J_t = 7.1$, $J_d = 2.8$), 3.78 (t, 2H, CH_2, $J = 7.1$), 6.98 (m, 2H, CH_{Ar}), 7.18 (m, 3H, CH_{Ar}), 7.52 (m, 5H, CH_{Ar}), 7.90 (s, 1H, OH).

^{19}F NMR ($CDCl_3$, δ, ppm): –1.86 s.

For $C_{18}H_{15}F_3N_2O_2$ anal. calcd. (%): C, 62.07; H, 4.34; N, 8.04.

Found (%): C, 62.22; H, 4.53; N, 8.18.

Methyl 4-hydroxy-5-oxo-4-trifluoromethylpyrrolidin-(2*E*)-ylideneacetate (12). Methyl 3-aminocrotonate **11** (1.15 g, 0.01 mol) was added to a solution of 1.56 g (0.01 mol) of methyl trifluoropyruvate **1** in

20 mL of DMF with stirring, the reaction mixture was heated for 2 h at 90–100°C and poured into 50 mL of water. The resultant precipitate was separated by filtration and recrystallized from 50% EtOH to give 1.9 g (71%) of the title compound, mp 95–97°C.

^{1}H NMR (DMSO-d_6, δ, ppm): 3.04 (s, 2H, CH_2), 3.70 (s, 3H, MeO), 5.08 (s, 1H, C=CH), 7.38 (s, 1H, OH), 10.41 (s, 1H, NH).

^{19}F NMR ($CDCl_3$, δ, ppm): –1.82 s.

For $C_8H_8F_3NO_4$ anal. calcd. (%): C, 40.18; H, 3.37; N, 5.86.

Found (%): C, 40.33; H, 3.52; N, 5.99.

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