Modification of biologically active amides and amines with fluorine-containing heterocycles

6.* Methyl 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate in cyclocondensation with 1,3-binucleophiles

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A reaction of methyl 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate with 1,3-binucleophiles (*N*-benzylurea, *N*-substituted 3-aminocrotonates, *N*-substituted 3-aminocyclohexenones, and 6-aminouracyls), leading to the formation of fluorine-containing heterocyclic 3-methyl-1-phenylpyrazol-5-one derivatives, was studied.

Key words: 3-methyl-1-phenylpyrazol-5-one, methyl trifluoropyruvate, *N*-benzylurea, 3-aminocrotonates, 3-aminocyclohexenones, 6-aminouracyls, fluorine-containing imidazolidine-2,4-diones, dihydro-1*H*-pyrroles, tetrahydro-1*H*-indole-2,4-diones, dihydro-1*H*-pyrrolo-[2,3-d]pyrimidine-2,4,6-triones.

Dihydro-4*H*-pyrazol-3-one derivatives belong to an important class of physiologically active substances. Among them were found non-narcotic analgesics and antipyrenes,[2] antineoplastics,[3—5] substances possessing antimicrobal,[6—8] parasiticide,[9] and antiviral[10] activity. Many of these compounds are successfully used in medical practice, for example, aminophenazone, phenylbutazone, analgene.[11]

A general approach to the molecular design of dihydro-4*H*-pyrazol-3-ones consists in the introduction of substituents at position 4 of the heterocycle. The purpose of the present studies is to modify 3-methyl-1-phenylpyrazol-5-one with trifluoromethyl-containing five-membered heterocycles by means of the reactions of the condensation product of pyrazolone and methyl trifluoropyruvate, *i.e.*, methyl 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate (**1**), with 1,3-binucleophiles: *N*-benzylurea, *N*-substituted 3-aminocrotonates, *N*-substituted 3-aminocyclohexenones, and 6-aminouracyls. The present work was prompted by the data obtained during the systematic studies of the behavior of imines of methyl trifluoropyruvate in the cyclocondensation reactions with 1,3-binucleophiles, leading to the formation of five-membered trifluoromethyl-containing heterocycles.[12—18]

Methyl 3,3,3-trifluoro-2(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate (**1**) exothermically reacted with *N*-benzylurea (**2**) according to the scheme of cyclocondensation reaction: the addition of 1,3-binucleophile at the highly electrophilic C=C bond with the formation of methyl ester of 2-(3-benzylureido)-3,3,3-trifluoro-2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)propionic acid (**3**), which was isolated and characterized in the individual state, and the cyclization of the latter in the presence of catalytic amounts of Et_3N to 3-benzyl-5-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-trifluoromethylimidazolidine-2,4-dione (**4**) (Scheme 1).

The reactions of methyl 3,3,3-trifluoro-2-(3-methyl-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate (**1**) with *N*-substituted 3-aminocrotonates **5a**,**b**, *N*-substituted 3-aminocyclohexenones **6a**—**c**, and 6-aminouracyls **7a**,**b** were carried out without isolation of the intermediate products upon heating of a mixture of reagents in DMF at 80 °C during 2 h, in the presence of catalytic amounts of Et_3N in the case of **6a**—**c** and **7a**,**b**. The cyclocondensation of **1** with **5a**,**b**, **6a**—**c**, and **7a**,**b** resulted in the formation of the corresponding heterocyclic derivatives of 3-methyl-1-phenylpyrazol-5-one: 2-methyl-4-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrroles **8a**,**b**, 6,6-dimethyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-phenyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-diones **9a**—**c**, 5-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-d]pyrimidine-2,4,6-triones **10a**,**b** (Scheme 2).

The thus obtained fluorine-containing heterocyclic derivatives of 3-methyl-1-phenylpyrazol-5-one, *viz.*, com-

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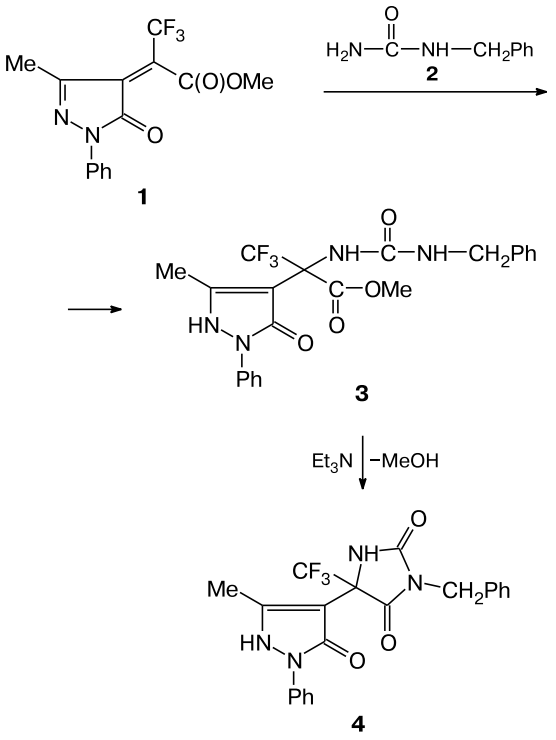
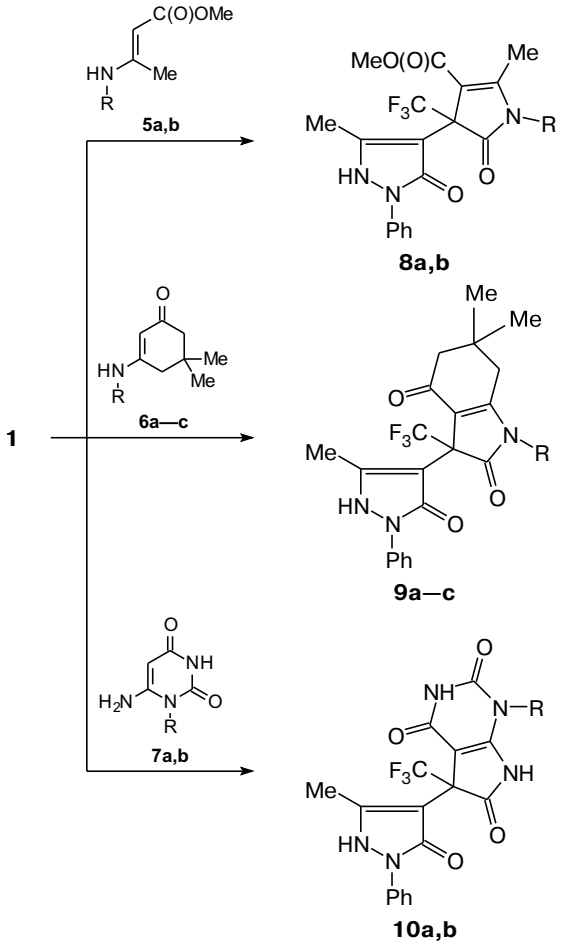
Scheme 1



Scheme 2



pounds **4**, **8a**,**b**, **9a**—**c**, and **10a**,**b**, are solid crystalline substances, their composition and structure were confirmed by the elemental analysis data and ^{1}H and ^{19}F NMR spectroscopy. The ^{19}F NMR spectra are characterized by the signals in the region of δ 2.8 for the **4** and δ 11—12 for the **8a**,**b**, **9a**—**c** and **10a**,**b**.

The suggested cyclocondensation reaction of methyl ester of 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionic acid with 1,3-binucleophiles is one of the promising synthetic approaches to the modification of biologically active dihydro-4*H*-pyrazol-3-ones with various trifluoromethyl-containing five-membered heterocycles.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (200.13 and 188.29 MHz, respectively) relative to tetramethylsilane (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined using a glass capillary tube. The starting reagents were obtained according to the known procedures:[19—21] methyl 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate (**1**) (see Ref. 19), 3-aminocyclohexenones **6a**—**c** (see Ref. 20), 6-aminouracyls **7a**,**b** (see Ref. 21). *N*-benzylurea (**2**) and 3-aminocrotonates **5a**,**b** (Aldrich) were used without additional purification.

Methyl 2-(3-benzylureido)-3,3,3-trifluoro-2-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)propionate (3). Urea **2** (1.5 g, 10 mmol) was added to a solution of compound **1** (3.12 g, 10 mmol) in DMF (20 mL). The reaction mixture was stirred for 2 h at 20 °C, poured into water, a precipitate formed was filtered off and recrystallized from 50% aqueous EtOH to obtain compound **3** (4.3 g, 93%), m.p. 115—117 °C. Found (%): C, 57.32; H, 4.41; N, 12.29. $C_{22}H_{21}F_3N_4O_4$. Calculated (%): C, 57.14; H, 4.58; N, 12.12. ^{1}H NMR (DMSO-d_6), δ: 2.10 (s, 3 H, Me); 3.71 (s, 3 H, MeO); 4.20 (s, 2 H, CH_2); 7.09—7.31 (m, 7 H, CH_{Ar} + NH); 7.42 (t, 2 H, CH_{Ar}, J = 7.9 Hz); 7.72 (d, 2 H, CH_{Ar}, J = 7.9 Hz); 7.89 (s, 1 H. NH); 9.01 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 2.01 s.

3-Benzyl-5-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-trifluoromethylimidazolidine-2,4-dione (4). Triethylamine (0.1 g) was added to a solution of compound **3** (2.3 g, 5 mmol) in DMF (10 mL). The reaction mixture was heated for 2 h at 80 °C, poured into water, a precipitate formed was filtered off and recrystallized from 50% aq. EtOH to obtain compound **4** (1.7 g, 79%), m.p. 211—213 °C. Found (%): C, 58.82; H, 4.15; N, 13.21. $C_{21}H_{17}F_3N_4O_3$. Calculated (%): C, 58.61; H, 3.98; N, 13.02. ^{1}H NMR (DMSO-d_6), δ: 2.32 (s, 3 H, Me); 4.63

(s, 2 H, CH_2); 7.13—7.36 (m, 7 H, CH_{Ar} + NH); 7.45 (t, 2 H, CH_{Ar}, J = 7.9 Hz); 7.48 (d, 2 H, CH_{Ar}, J = 7.9 Hz); 9.33 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 2.82 s.

Methyl 2-methyl-4-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (8a). Methyl 3-aminocrotonate **5a** (0.58 g, 5 mmol) was added to a solution of compound **1** (1.56 g, 5 mmol) in DMF (20 mL). The reaction mixture was stirred for 2 h at 20 °C, then heated for 2 h at 80 °C, poured into water, a precipitate formed was filtered off and recrystallized from 50% aq. EtOH to obtain compound **8a** (1.6 g, 81%), m.p. 248—250 °C. Found (%): C, 54.87; H, 4.22; N, 10.44. $C_{18}H_{16}F_3N_3O_4$. Calculated (%): C, 54.69; H, 4.08; N, 10.63. ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 3 H, Me); 2.38 (s, 3 H, Me); 3.61 (s, 3 H, MeO); 7.12 (t, 1 H, CH_{Ar}, J = 8.1 Hz); 7.36 (t, 2 H, CH_{Ar}, J = 8.1 Hz); 7.72 (d, 2 H, CH_{Ar}, J = 8.1 Hz); 10.75 (s, 1 H, NH); 11.16 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.12 s.

Methyl 1-isopropyl-2-methyl-4-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (8b) was obtained similarly to compound **8a** from compound **1** (1.56 g, 5 mmol) and compound **5b** (0.78 g, 5 mmol). The yield was 1.7 g (78%), m.p. 189—191 °C. Found (%): C, 57.87; H, 5.18; N, 9.78. $C_{21}H_{22}F_3N_3O_4$. Calculated (%): C, 57.66; H, 5.07; N, 9.61. ^{1}H NMR (DMSO-d_6), δ: 1.40 (dd, 6 H, Me, J = 7.2 Hz); 2.28 (s, 3 H, Me); 2.55 (s, 3 H, Me); 3.61 (s, 3 H, MeO); 4.19 (septet, 1 H, CH, J = 7.1 Hz); 7.17 (t, 1 H, CH_{Ar}, J = 7.4 Hz); 7.41 (t, 2 H, CH_{Ar}, J = 7.4 Hz); 7.69 (d, 2 H, CH_{Ar}, J = 7.4 Hz); 11.33 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.01 s.

6,6-Dimethyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-phenyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (9a). 3-Aminocyclohexenone **6a** (1.08 g, 5 mmol) was added to a solution of compound **1** (1.56 g, 5 mmol) in DMF (20 mL). The reaction mixture was stirred for 2 h at 20 °C, followed by the addition of Et_3N (0.1 g), then heated for 2 h at 80 °C, poured into water, a precipitate formed was filtered off and recrystallized from 50% aq. EtOH to obtain compound **8a** (2 g, 80%), m.p. 269—271 °C. Found (%): C, 65.66; H, 4.71; N, 8.31. $C_{27}H_{24}F_3N_3O_3$. Calculated (%): C, 65.45; H, 4.88; N, 8.48. ^{1}H NMR (DMSO-d_6), δ: 1.03 and 1.11 (both s, 6 H, Me); 2.06—2.64 (m, 7 H, CH_2 + Me); 7.14 (t, 1 H, CH_{Ar}, J = 8.1 Hz); 7.39 (t, 2 H, CH_{Ar}, J = 8.2 Hz); 7.45—7.56 (m, 2 H, CH_{Ar}); 7.66—7.86 (m, 5 H, CH_{Ar}); 11.45 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.61 s.

1-(4-Methoxyphenyl)-6,6-dimethyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (9b) was obtained similarly to compound **9a** from compound **1** (1.56 g, 5 mmol) and compound **6b** (1.23 g, 5 mmol). The yield was 2.1 g (79%), m.p. 253—255 °C. Found (%): C, 63.80; H, 5.18; N, 8.17. $C_{28}H_{26}F_3N_3O_4$. Calculated (%): C, 63.99; H, 4.99; N, 8.00. ^{1}H NMR (DMSO-d_6), δ: 1.02 and 1.10 (both s, 6 H, Me); 2.07—2.47 (m, 4 H, CH_2); 2.41 (s, 3 H, Me); 3.84 (s, 3 H, MeO); 7.03 (d, 2 H, CH_{Ar}, J = 9.1 Hz); 7.16 (t, 1 H, CH_{Ar}, J = 7.6 Hz); 7.28—7.47 (m, 4 H, CH_{Ar}); 7.74 (d, 2 H, CH_{Ar}, J = 9.1 Hz); 11.40 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.64 s.

6,6-Dimethyl-3-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-trifluoromethyl-1-(3-(trifluoromethyl)phenyl)-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (9c) was obtained similarly to compound **9a** from compound **1** (1.56 g, 5 mmol) and compound **6a** (1.42 g, 5 mmol). The yield was 2.2 g (78%), m.p. 252—254 °C. Found (%): C, 59.89; H, 4.33; N, 7.62. $C_{28}H_{23}F_6N_3O_3$. Calculated (%): C, 59.68; H, 4.11; N, 7.46. ^{1}H NMR (DMSO-d_6), δ: 1.01 and 1.12 (both s, 6 H, Me); 2.07—2.38 (m, 4 H, CH_2); 2.42 (s, 3 H, Me); 7.10 (t, 1 H, CH_{Ar}, J = 7.7 Hz); 7.32—7.62 (m, 6 H, CH_{Ar}); 7.75 (d, 2 H, CH_{Ar}, J = 8.1 Hz); 11.44 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.73 s; 11.92 s.

1-Benzyl-5-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-d]-pyrimidine-2,4,6-trione (10a) was obtained similarly to compound **9a** from compound **1** (1.56 g, 5 mmol) and compound **7a** (1.09 g, 5 mmol). The yield was 1.9 g (76%), m.p. 261—263 °C. Found (%): C, 57.74; H, 3.79; N, 14.22. $C_{24}H_{18}F_3N_5O_4$. Calculated (%): C, 57.95; H, 3.65; N, 14.08. ^{1}H NMR (DMSO-d_6), δ: 2.41 (s, 3 H, Me); 5.10 (m, 2 H, CH_2); 7.17 (t, 1 H, CH_{Ar}, J = 7.0 Hz); 7.25—7.48 (m, 7 H, CH_{Ar}); 7.77 (d, 2 H, CH_{Ar}, J = 8.1 Hz); 10.96 (s, 1 H, NH); 11.41 (s, 1 H, NH); 12.12 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 10.91 s.

5-(5-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1-(2-phenylethyl)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo-[2,3-d]pyrimidine-2,4,6-trione (10b) was obtained similarly to compound **9a** from compound **1** (1.56 g, 5 mmol) and compound **7b** (1.16 g, 5 mmol). The yield was 1.9 g (74%), m.p. 251—253 °C. Found (%): C, 58.89; H, 4.12; N, 13.87. $C_{25}H_{20}F_3N_5O_4$. Calculated (%): C, 58.71; H, 3.94; N, 13.69. ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 3 H, Me); 2.90 (t, 2 H, CH_2, J = 7.2 Hz); 4.04 (t, 2 H, CH_2, J = 7.2 Hz); 7.08—7.31 (m, 6 H, CH_{Ar}); 7.41 (t, 2 H, CH_{Ar}, J = 7.9 Hz); 7.70 (d, 2 H, CH_{Ar}, J = 7.9 Hz); 10.93 (s, 1 H, NH); 11.51 (s, 1 H, NH); 12.07 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 11.09 s.

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