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LETTERS TO THE EDITOR

Methyl Trifluoropyruvate in Cyclocondensation Reactions with *N*-Substituted Ureas

V. B. Sokolov[a] and A. Yu. Aksinenko[a]*

[a] *Institute of Physiologically Active Compounds of the Russian Academy of Sciences, Severnyi proezd 1, Chernogolovka, 142432 Russia*
**e-mail: alaks@ipac.ac.ru*

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Abstract—The transformations of methyl trifluoropyruvate in cyclocondensation reactions with N-substituted ureas, leading to 3-substituted 5-hydroxy- or 5-methoxy-5-trifluoromethylimidazolidine-2,4-diones, were studied. The possibility of using 5-hydroxy-3-(prop-2-in-1-yl)-5-trifluoromethylimidazolidine-2,4-dione for modifying phenothiazine with a copper-catalyzed alkyne-azide 1,3-dipolar cycloaddition was shown.

Keywords: methyl trifluoropyruvate, N-substituted ureas, 5-trifluoromethylimidazolidine-2,4-diones, phenothiazine, 1,3-dipolar cycloaddition

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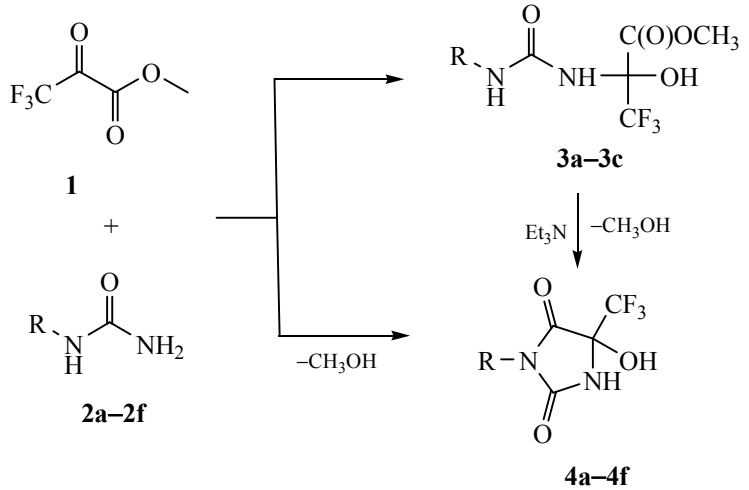
The study of the transformations of methyl trifluoropyruvate *N*-substituted imines in cyclocondensation reactions with 1,3-binucleophiles [1–3] allowed us to propose a synthetic approach to various trifluoromethyl containing five- and six-membered heterocycles. This method allows modification of drugs, for example, piracetam [4] and acetazolamide [5], which are subunits of methyl trifluoropyruvate imines molecules. The purpose of this study is to study the synthetic possibilities of cyclocondensation of methyl trifluoropyruvate with *N*-substituted ureas for the preparation of 3-substituted 5-trifluoromethylimidazolidine-2,4-diones.

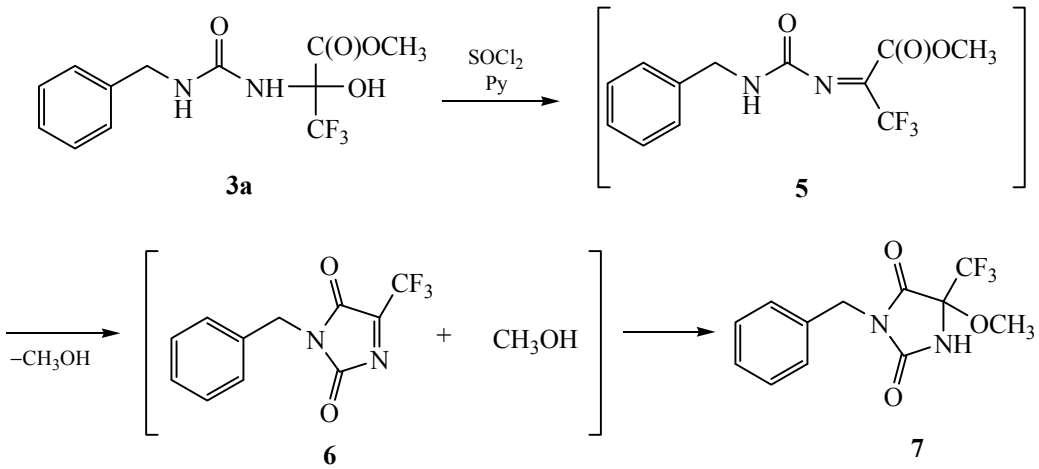
Methyl trifluoropyruvate **1** reacted readily with *N*-substituted ureas **2a–2c** to give the corresponding 3,3,3-trifluoro-2-hydroxypropionates **3a–3c** with a yield of 80–85%. The obtained 3,3,3-trifluoro-2-hydroxy-

Scheme 1.



R = $C_6H_5CH_2$ (**a**), $C_6H_5CH_2CH_2$ (**b**), prop-2-yn-1-yl (**c**), (pyridin-2-yl)methyl (**d**), (pyridin-3-yl)methyl (**e**), (pyridin-4-yl)-methyl (**f**).

Scheme 2.



propionates were converted to 5-hydroxy-5-trifluoromethylimidazolidine-2,4-diones **4a–4c** in 76–81% yield when heated (40°C) in the presence of catalytic amounts of triethylamine (Scheme 1).

N-Pyridyl ureas **2d–2f** underwent cyclocondensation with methyl trifluoropyruvate **1** in the absence of triethyl amine to form 3-pyridyl-5-hydroxy-5-trifluoromethylimidazolidine-2,4-diones **4d–4f** in 76–81% yield. The intermediate reaction products could not be isolated; apparently, in this case, the sufficiently basic ureas **3d–3f** themselves act as catalysts.

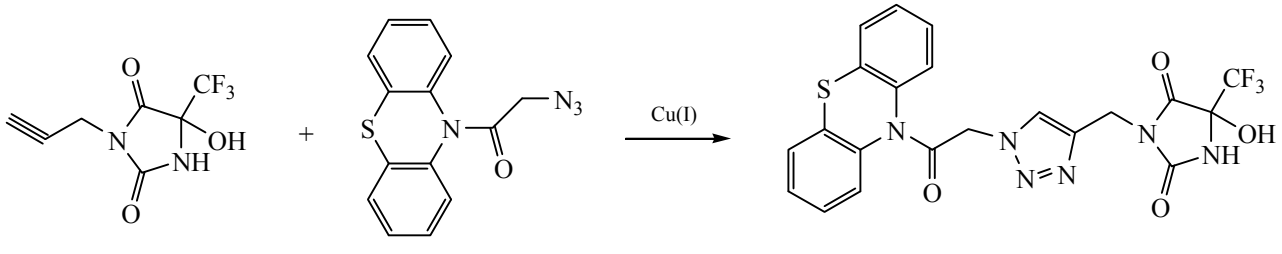
An attempt to obtain imine **5** by dehydrating the adduct of *N*-benzylurea and methyltrifluoropyruvate **3a** unexpectedly led to the formation of 3-benzyl-5-methoxy-5-trifluoromethylimidazolidine-2,4-dione **7** in 73% yield (Scheme 2). Probably, the reaction occurs through heterocyclization of the resulting imine **5** to imidazole-2,5-dione **6** followed by the addition of methanol released during the cyclocondensation process.

5-Hydroxy-3-(prop-2-yn-1-yl)-5-trifluoromethylimidazolidin-2,4-dione **4c** was found to be a promising fluorine-containing precursor in the reaction of the copper-catalyzed alkyne azide 1,3-dipolar cycloaddition [6]. Thus, in the presence of catalytic amounts of Cu(I), imidazolidine-2,4-dione **4c** reacted with azide-containing phenothiazine to produce 1,4-substituted 1,2,3-triazole **9** with high yield (Scheme 3).

Composition and structure of the obtained compounds were confirmed by elemental analysis and NMR spectroscopy data. In the ^{19}F NMR spectra, the singlet signals of the CF_3 group in the range of 3–6 ppm are characteristic. The ^{1}H NMR spectrum of conjugate **9** represents the superposition of the spectra of the phenothiazine and imidazolidin-2,4-dione fragments and contains the characteristic singlet signal of the CH-proton of the triazole ring at 7.93 ppm.

In conclusion, depending on the reaction conditions, cyclocondensation of methyl trifluoropyruvate with *N*-substituted ureas afforded 3-substituted 5-hyd-

Scheme 3.



roxy- or 5-methoxy-5-trifluoromethylimidazolidine-2,4-diones. The use of functionally substituted ureas in these transformations allows one to obtain precursors for the subsequent modification of biologically active substances, for example, phenothiazine.

N-Substituted ureas **2a**–**2f** [3] and azide **8** [4] were obtained by the known methods.

Methyl 2-(benzylureido)-3,3,3-trifluoro-2-hydroxypropionate (3a). To a solution of 2 mmol of urea **2a** in 20 mL of acetonitrile was added 2 mmol of methyl trifluoropyruvate **1**. The reaction mixture was stirred for 2 h at 20°C, then 50 mL of water was added. The precipitate was filtered and recrystallized from 50% ethanol. Yield 0.5 g (82%), mp 153–155°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.88 s (3H, MeO), 4.20–4.46 m (2H, CH_2), 5.74 s (1H, OH), 6.59 s (1H, NH), 7.19–7.40 m (5H, CH_{Ar}), 7.49 s (1H, NH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.47 ppm. Found, %: C 47.34; H 4.07; N 8.96. $C_{12}H_{13}F_3N_2O_4$. Calculated, %: C 47.06; H 4.28; N 9.15.

Methyl 2-hydroxy-2-(2-phenetylureido)-3,3,3-trifluoropropionate (3b) was prepared similarly. Yield 0.51 g (80%), mp 135–137°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.66 t (2H, CH_2, $^3J_{HH}$ = 4.4), 3.18–3.33 m (2H, CH_2), 3.72 s (3H, MeO), 5.74 s (1H, OH), 5.92 s (1H, NH), 6.85–7.10 m (5H, CH_{Ar}), 7.18 s (1H, NH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.44 ppm. Found, %: C 48.54; H 4.57; N 8.97. $C_{13}H_{15}F_3N_2O_4$. Calculated, %: C 48.75; H 4.72; N 8.75.

Methyl 2-hydroxy-2-[3-(prop-2-yn-1-yl)ureido]-3,3,3-trifluoropropionate (3c) was obtained similarly. Yield 0.43 g (85%), mp 113–155°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.12 t (1H, CH, $^3J_{HH}$ = 2.1), 3.51 s (3H, MeO), 3.56–3.62 m (3H, CH_2 + OH), 5.90 s (1H, NH), 7.23 s (1H, NH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.89 ppm. Found, %: C 37.64; H 3.38; N 8.96. $C_8H_9F_3N_2O_4$. Calculated, %: C 37.80 H, 3.57; N 9.12.

3-Benzyl-5-hydroxy-5-trifluoromethylimidazolidine-2,4-dione (4a). To a solution of 1 mmol of urea **3a** in 20 mL of acetonitrile was added 0.1 g of triethylamine. The reaction mixture was stirred for 3 h at 40°C, then 50 mL of water was added. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 0.22 g (80%), mp 154–156°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.57 s (2H, CH_2), 7.10–7.39 m (5H, CH_{Ar}), 8.56 s (1H, NH), 9.79 s (1H, OH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –2.98 ppm. Found, %: C 48.34; H 3.07; N 9.96. $C_{11}H_9F_3N_2O_3$. Calculated, %: C 48.18; H 3.31; N 10.22.

5-Hydroxy-5-trifluoromethyl-3-(2-phenethyl)imidazolidine-2,4-dione (4b) was prepared similarly. Yield 0.22 g (76%), mp 161–163°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.80 t (2H, CH_{Ar}, $^3J_{HH}$ = 7.1), 3.61 t (2H, CH_{Ar}, $^3J_{HH}$ = 7.1), 7.01–7.32 m (5H, CH_{Ar}), 8.39 s (1H, NH), 9.60 s (1H, OH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.62 ppm. Found, %: C 50.19; H 3.68; N 9.96. $C_{12}H_{11}F_3N_2O_3$. Calculated, %: C 50.01; H 3.85; N 9.72.

5-Hydroxy-3-(prop-2-yn-1-yl)-5-trifluoromethylimidazolidine-2,4-dione (4c) was prepared similarly. Yield 0.18 g (81%), mp 108–110°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.30 t (1H, CH, $^3J_{HH}$ = 2.1), 4.31 d (2H, CH_2, $^3J_{HH}$ = 2.2), 5.68 br. s (2H, OH + NH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –6.22 ppm. Found, %: C 37.63; H 2.48; N 12.80. $C_7H_5F_3N_2O_3$. Calculated, %: C 37.85; H 2.27; N 12.61.

5-Hydroxy-3-(pyridin-2-yl)methyl-5-trifluoromethylimidazolidine-2,4-dione (4d). To a solution of 1 mmol of urea **2a** in 20 mL of acetonitrile was added 1 mmol of methyl trifluoropyruvate **1**. The reaction mixture was stirred for 3 h at 40°C, then 50 mL of water was added. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 0.22 g (80%), mp 197–198°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.67 s (2H, CH_2), 7.10–7.39 m (5H, CH_{Ar}), 8.56 s (1H, NH), 9.79 s (1H, OH). ^{19}F NMR spectrum ($CDCl_3$): δ_F -–4.68 ppm. Found, %: C 43.44; H 3.18; N 15.44. $C_{10}H_8F_3N_3O_3$. Calculated, %: C 43.65; H 2.93; N 15.27.

5-Hydroxy-3-(pyridin-3-yl)methyl-5-trifluoromethylimidazolidine-2,4-dione (4e) was prepared similarly. Yield 0.2 g (73%), mp 239–241°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.63 s (2H, CH_2), 7.28–7.43 m (1H, CH_{Ar}), 7.60 s (1H, CH_{Ar}, $^3J_{HH}$ = 8.1), 8.39–8.52 m (2H, CH_{Ar}), 8.57 s (1H, NH), 9.65 s (1H, OH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.79 ppm. Found, %: C 43.44; H 2.78; N 15.42. $C_{10}H_8F_3N_3O_3$. Calculated, %: C 43.65; H 2.93; N 15.27.

5-Hydroxy-3-(pyridin-4-yl)methyl-5-trifluoromethylimidazolidine-2,4-dione (4f) was prepared similarly. Yield 0.21 g (76%), mp 237–239°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.64 s (2H, CH_2), 6.85 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.9), 7.19 d (2H, CH_{Ar}, $^3J_{HH}$ = 4.8), 8.64 s (1H, NH), 9.92 s (1H, OH). ^{19}F NMR spectrum ($CDCl_3$): δ_F –4.71 ppm. Found, %: C 43.48;

H 3.18; N 15.24. $C_{10}H_8F_3N_3O_3$. Calculated, %: C 43.65; H 2.93; N 15.27.

3-Benzyl-5-methoxy-5-trifluoromethylimidazolidine-2,4-dione (7). To a solution of 1 mmol of urea **3a** in 20 mL of acetonitrile were added 2 mmol of pyridine and 1 mmol of $SOCl_2$. The reaction mixture was stirred for 3 h at 40°C, then 50 mL of water was added. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 0.21 g (73%), mp 126–128°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.25 s (3H, MeO), 4.71 s (2H, CH_2), 6.72 s (1H, NH), 7.32 s (5H, CH_{Ar}). ^{19}F NMR spectrum ($CDCl_3$): δ_F –3.72 ppm. Found, %: C 49.88; H 3.78; N 9.54. $C_{12}H_{11}F_3N_2O_3$. Calculated, %: C 50.01; H 3.85; N 9.72.

5-Hydroxy-5-trifluoromethyl-3-({4-[(10*H*-phenothiazin-10-yl)methyl]-1*H*-1,2,3-triazol-1-yl}methyl)-imidazolidine-2,4-dione (9). To a solution of 0.5 mmol of imidazolidine-2,4-dione **4c** in 20 mL of methylene chloride were added 0.5 mmol of phenothiazine **8**, 0.1 mmol of $CuSO_4$ in 1 mL of H_2O and 0.1 mmol of sodium ascorbate in 1 mL of H_2O. The reaction mixture was stirred for 6 h at 40°C, then washed with 10 mL of a 1% ammonia aqueous solution. The organic layer was separated, methylene chloride was evaporated, the residue was chromatographed on silica gel (60 mesh, methanol–chloroform, 1 : 10). Yield 0.21 g (88%), mp 198–199°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.68 s (2H, CH_2), 5.54 s (2H, CH_2), 7.22–7.53 m (4H, CH_{Ar}), 7.58–7.83 m (4H, CH_{Ar}), 7.93 (1H, =CHNN), 8.61 s (1H, OH), 9.82 s (1 H, NH). Спектр ЯМР ^{19}F ($CDCl_3$): δ_F –4.41 ppm. Found, %: C 50.28; H 3.38; N 17.43. $C_{20}H_{15}F_3N_6O_3S$. Calculated, %: C 50.42; H 3.17; N 17.64.

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13 and 188.0 MHz, respectively, relative to internal $SiMe_4$ or external CF_3COOH. Melting points were determined in a glass capillary.

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CONFLICT OF INTEREST

No conflict of interests was declared by the authors.

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