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

3*. Piracetam in the three-component reaction with methyl trifluoropyruvate and 1,3-binucleophiles

V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, and I. V. Martynov*

Institute of Physiologically Active Substances, Russian Academy of Sciences, 1 Severnyi proezd, Chernogolovka, 142432 Moscow Region, Russian Federation. Fax: +7 (496) 524 9508. E-mail: alaks@ipac.ac.ru

Three-component reaction of Piracetam, methyl trifluoropyruvate and 1,3-binucleophiles, such as 6-aminouracils, 6-aminothiouracils, 4-(4-tolylamino)pent-3-en-2-one and *N*-substituted ureas, has been studied. This reaction resulted in fluorinated heterocyclic derivatives of Piracetam.

Key words: Piracetam, methyl trifluoropyruvate, imines of methyl trifluoropyruvate, 6-aminouracils, 6-aminothiouracils, 4-(*p*-tolylamino)pent-3-en-2-one, *N*-substituted ureas, fluorinated imidazolidines, dihydropyrroles, hexahydropyrrolopyrimidines, cyclocondensation.

Nowadays in therapy of various diseases of central nervous system, a great importance attached to nootropic drugs, which affect the neuron metabolism and possess vasoactive and antihy action. The nootropics improve the stability of the central nervous system to various injury, information exchange in the brain, learning and memory.[2] Among nootropics, the large group is represented by pharmaceuticals with metabolite action, such as cyclic derivatives of γ-aminobutyric acid (Piracetam, Oxiracetam, Aniracetam, Fenotropil and *etc.*). The distinctive feature of these compounds is 2-(2-oxopyrrolidin-1-yl)acetamide fragment in the structure. The latest generation of nootropics represented by the compounds, which were derived from the parent structure (Piracetam) by introduction of different functionality at 2-oxopyrrolodin-1-yl fragment or at amide nitrogen.[3]

The aim of the present work was a modification of the known nootropic pharmaceutical — Piracetam (2-(2-oxopyrrolidin-1-yl)acetamide (**1**)). The functionalization was carried out using trifluoromethyl-substituted heterocycles under conditions of multicomponent reactions of **1** with methyl pyruvate (**2**) and 1,3-*N,N*- or 1,3-*C,N*-binucleophiles. The premise of present work were the data obtained in detailed study of the cyclocondensations of methyl trifluoropyruvate related acylimines with 1,3-*N,N*- or 1,3-*C,N*-binucleophiles, which yielded five-membered trifluoromethyl-substituted heterocycles.[4—9]

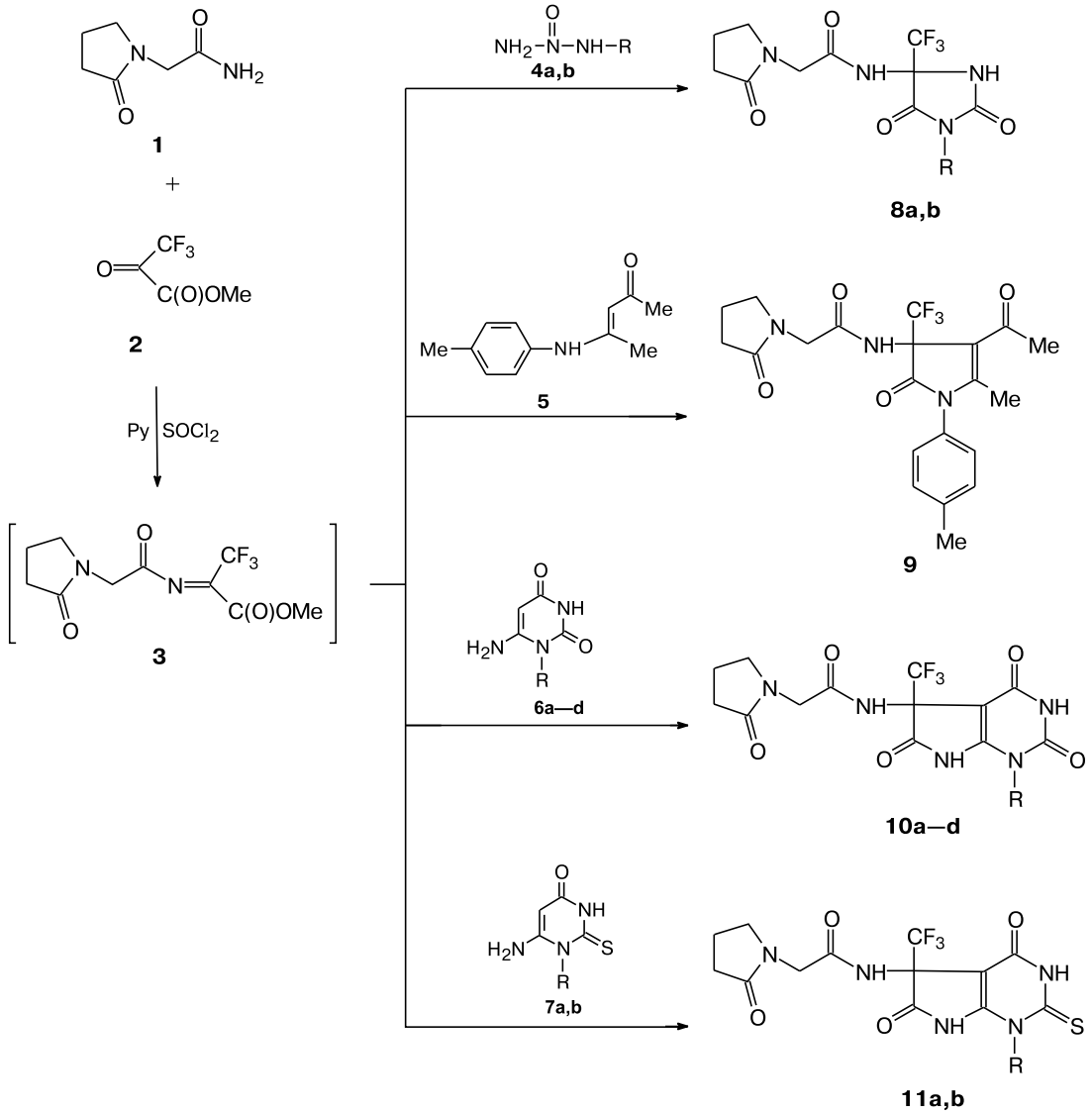
All attempts to synthesize the starting binucleophile, methyl 2-(2-oxopyrrolidin-1-yl)-acetylimino-3,3,3-trifluoropropionate (**3**), in an individual state applying the known protocols for the related *N*-substituted imines[4] failed. Therefore, the imine **3** was generated *in situ* by successive addition of pyridine, methyl trifluoropyruvate (**2**) and thionylchloride to a solution of Piracetam (**1**) in DMF (Scheme 1). The formation of imine **3** was confirmed by the data from the ^{19}F NMR spectra of the reaction mixture. The ^{19}F NMR spectra exhibited the signals of trifluoromethyl group in the range of δ 4.1 characteristic of methyl trifluoropyruvate related imines.[7] In the reactions under study, *N*-substituted ureas **4a,b**, 4-(*p*-tolylamino)pent-3-en-2-one (**5**), 6-aminouracils **6a,b** and 6-aminothiouracils **7a,b** were used as 1,3-binucleophiles. The reaction of imine **3** with 1,3-binucleophiles **4—7** were carried out in DMF at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N. The cyclocondensation of imine **3** with nucleophiles **4—7** yielded the corresponding heterocyclic derivatives of Piracetam: 2,5-dioxo-4-trifluoromethylimidazolidines **8a,b**, 4-trifluorometyl-4,5-dihydro-1*H*-pyrrole **9**, 2,4,6-trioxo-5-trifluorometyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo-[2,3-*d*]pyrimidines **10a—d**, 4,6-dioxo-2-thioxo-5-trifluorometyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-pyrimidines **11a,b**.

In summary, three-component reaction of Piracetam, methyl trifluoropyruvate and 1,3-*C,N*- or 1,3-*N,N*-binucleophiles are convenient synthetic approach to a variety of trifluoromethyl-substituted heterocyclic derivatives of

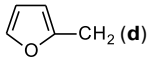
* For Part 1, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 281—283, January, 2010.

Scheme 1



4, **8**: R = *cyclo*-C_5H_9 (**a**); $PhCH_2$ (**b**)

6, **10**: R = $PhCH_2$ (**a**); $PhCH_2CH_2$ (**b**); 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (**c**);  (**d**)

7, **11**: R = Ph (**a**); 3-Me-C_6H_4 (**b**)

Piracetam and for the introduction of heterocyclic function at the amide nitrogen.

Experimental

The ^1H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 instrument at 200.13 MHz and 188.29 MHz relative to tetramethylsilane (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in open capillaries. The starting 4-(*p*-tolylamino)pent-3-en-2-one **5** was synthesized in accordance with the known method,[10] 6-aminouracils **7a,b** and **8** were prepared by the known procedure.[11] *N*-Substituted ureas **9a,b**, 2-(2-oxopyrrolidin-1-yl)-acetamide (**1**) and methyl trifluoropyruvate (**2**) were used as purchased (Aldrich).

***N*-[1-(Cyclopentylimidazolidin-4-yl)-2,5-dioxo-4-trifluoromethyl]-2-(2-oxopyrrolidin-1-yl)acetamide (8a).** To solution of 2-(2-oxopyrrolidin-1-yl)acetamide (**1**) (0.01 mol, 1.42 g) in DMF (20 mL) 1.56 г (0.01 mol) pyridine (0.01 mol, 1.56 g) and methyl trifluoropyruvate **2** (0.01 mol, 1.56 g) were successively added with stirring. The reaction mixture was stirred for 30 min, then $SOCl_2$ (0.01 mol, 1.19 g) was added. After 1 h of stirring the urea **4a** (0.01 mol, 1.28 g) was added and stirring was continued for 1 h at room temperature. Then Et_3N (0.1 g) was added and the resulted mixture was heated at 90—100 °C for 2 h. The reaction mixture was cooled to room temperature, poured into 10% aqueous NaCl, the precipitate formed was filtered off and recrystal-

lized from 50% EtOH to give acetamide **8a** in 73% yield (2.74 g), m.p. 168—170 °C. ^{1}H NMR (DMSO-d_6), δ: 1.47—1.71 (m, 2 H, CH_2); 1.75—2.18 (m, 8 H, CH_2); 2.20—2.38 (m, 2 H, CH_2); 3.42 (m, 2 H, CH_2); 3.81 and 4.11 (both d, 2 H, CH_2, J = 17.2 Hz); 4.33 (m, H, CH); 9.16 (s, 1 H, NH); 9.61 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –0.84 s. Found (%): C, 47.69; H, 5.31; N, 14.65. $C_{15}H_{19}F_3N_4O_4$. Calculated (%): C, 47.87; H, 5.09; N, 14.89.

***N*-(1-Benzyl-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (8b)** was synthesized in accordance with the procedure above in a yield of 3.06 г (77%), m.p. 208—210 °C. ^{1}H NMR (DMSO-d_6), δ: 1.93—2.14 (m, 2 H, CH_2); 2.21—2.36 (m, 2 H, CH_2); 3.45 (m, 2 H, CH_2); 4.02 (AB-system, 2 H, CH_2, J = 19.8 Hz); 4.64 (m, 2 H, CH_2); 7.29 (s, 5 H, CH_{Ar}); 9.38 (s, 1 H, NH); 9.75 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –0.59 s. Found (%): C, 51.07; H, 4.52; N, 13.85. $C_{17}H_{17}F_3N_4O_4$. Calculated (%): C, 51.26; H, 4.30; N, 14.06.

***N*-[4-Acetyl-5-methyl-1-(4-methylphenyl)-2-oxo-3-trifluoromethyl-2,3-dihydro-1*H*-pyrrol-3-yl]-2-(2-oxopyrrolidin-1-yl)acetamide (9)** was synthesized by the procedure described for **8a** in a yield of 3.54 g (81%), m.p. 182—184 °C. ^{1}H NMR (DMSO-d_6), δ: 1.97—2.16 (m, 2 H, CH_2); 2.17—2.37 (m, 8 H, CH_2 + Me + Me); 2.45 (s, 3 H, Me); 3.47 (m, 2 H, CH_2); 4.04 (AB-system, 2 H, CH_2, J = 16.6 Hz); 7.16 (d, 2 H, CH_{Ar}, J = 9.3 Hz); 7.33 (d, 2 H, CH_{Ar}, J = 9.3 Hz); 9.89 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.45 s. Found (%): C, 57.45; H, 5.24; N, 9.83. $C_{21}H_{22}F_3N_3O_4$. Calculated (%): C, 57.66; H, 5.07; N, 9.61.

***N*-(1-Benzyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (10a)** was synthesized by the general procedure in a yield of 4.0 g (86%), m.p. 227—229 °C. ^{1}H NMR (DMSO-d_6), δ: 1.88—2.08 (m, 2 H, CH_2); 2.24 (t, 2 H, CH_2, J = 7.7 Hz); 2.91 (t, 2 H, CH_2, J = 6.7 Hz); 3.38 (m, 2 H, CH_2); 3.96 (m, 2 H, CH_2); 4.06 (m, 2 H, CH_2); 7.12—7.35 (m, 5 H, CH_{Ar}); 9.70 (s, 1 H, NH); 11.00 (s, 1 H, NH); 12.21 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.23 s. Found (%): C, 51.81; H, 4.11; N, 15.75. $C_{20}H_{18}F_3N_5O_5$. Calculated (%): C, 51.62; H, 3.90; N, 15.50.

***N*-(1-Phenylethyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (10b)** was synthesized in accordance with the general procedure in a yield of 4.07 g (85%), m.p. 233—235 °C. ^{1}H NMR (DMSO-d_6), δ: 1.88—2.08 (m, 2 H, CH_2); 2.24 (t, 2 H, CH_2, J = 7.7 Hz); 2.91 (t, 2 H, CH_2, J = 6.7 Hz); 3.38 (m, 2 H, CH_2); 3,96 (m, 2 H, CH_2); 4,06 (m, 2 H, CH_2); 7.12—7.35 (m, 5 H, CH_{Ar}); 9.70 (s, 1 H, NH); 11.00 (s, 1 H, NH); 12.21 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.03 s. Found (%): C, 52.84; H, 4.39; N, 14.38. $C_{21}H_{20}F_3N_5O_5$. Calculated (%): C, 52.61; H, 4.20; N, 14.61.

***N*-{1-[2-(3,4-Dimethoxyphenyl)ethyl]-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)}-2-(2-oxopyrrolidin-1-yl)acetamide (10c)** was synthesized by the general procedure in a yield of 4.26 g (79%), m.p. 231—233 °C. ^{1}H NMR (DMSO-d_6), δ: 1.86—2.15 (m, 2 H, CH_2); 2.23 (t, 2 H, CH_2, J = 9.1 Hz); 2.81 (m, 2 H, CH_2); 3.34 (m, 2 H, CH_2); 3.75 (s, 6 H, MeO); 3.89—4.08 (m, 4 H, CH_2); 6.67—6.82 (m, 3 H, CH_{Ar}); 9.72 (s, 1 H, NH); 10.99 (s, 1 H, NH); 12.06 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.30 s. Found (%): C, 51.39; H, 4.21; N, 13.16. $C_{23}H_{24}F_3N_5O_7$. Calculated (%): C, 51.21; H, 4.48; N, 12.98.

***N*-[1-(Furan-2-yl)methyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-2-(2-oxopyrrolidin-1-yl)acetamide (10d)** was synthesized by the general procedure in a yield of 3.87 g (85%), m.p. 190—192 °C. ^{1}H NMR (DMSO-d_6), δ: 1.86—2.09 (m, 2 H, CH_2); 2.26 (t, 2 H, CH_2, J = 7.1 Hz); 3.37 (m, 2 H, CH_2); 3.97 (m, 2 H, CH_2); 5.06 (AB-system, 2 H, CH_2, J = 15.4 Hz); 6.39 (m, 2 H, CH_{Ar}); 7,52 (m, 1 H, CH_{Ar}); 9.73 (s, 1 H, NH); 11.11 (s, 1 H, NH); 12.17 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 3.93 s. Found (%): C, 47.65; H, 3.33; N, 15.61. $C_{18}H_{16}F_3N_5O_6$. Calculated (%): C, 51.26; H, 4.30; N, 14.06.

***N*-(4,6-Dioxo-1-phenyl-2-thioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (11a)** was synthesized in accordance with the general procedure in a yield of 3.83 g (82%), m.p. 221—223 °C. ^{1}H NMR (DMSO-d_6), δ: 1.87—2.09 (m, 2 H, CH_2); 2.25 (t, 2 H, CH_2, J = 7.4 Hz); 3.38 (m, 2 H, CH_2); 3.97 (AB-system, 2 H, CH_2, J = 16.6); 7.30 (m, 2 H, CH_{Ar}); 7.52 (m, 3 H, CH_{Ar}); 9.84 (s, 1 H, NH); 11.46 (s, 1 H, NH); 12.63 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.24 s. Found (%): C, 48.61; H, 3.23; N, 15.17. $C_{19}H_{16}F_3N_5O_4S$. Calculated (%): C, 48.82; H, 3.45; N, 14.98.

***N*-(4,6-Dioxo-1-(3-methylphenyl)-2-thioxo-5-trifluoromethyl-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-pyrimidin-5-yl)-2-(2-oxopyrrolidin-1-yl)acetamide (11b)** was synthesized by the general procedure in a yield of 3.85 g (80%), m.p. 232—234 °C. ^{1}H NMR (DMSO-d_6), δ: 1.91—2.16 (m, 2 H, CH_2); 2.18—2.36 (m, 2 H, CH_2); 2.47 (s, 3 H, Me); 3.42 (m, 2 H, CH_2); 4.01 (AB-system, 2 H, CH_2, J = 16.8 Hz); 7.09 (m, 2 H, CH_{Ar}); 7.24—7.51 (m, 2 H, CH_{Ar}); 9.82 (s, 1 H, NH); 11.34 (s, 1 H, NH); 12.54 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 4.25 s. Found (%): C, 50.12, H, 3.52; N, 14.71. $C_{20}H_{18}F_3N_5O_4S$. Calculated (%): C, 49.90; H, 3.77; N, 14.55.

This work was financially supported by Russian Academy of Sciences (program «Medicinal and Biomedicinal Chemistry» of the Department of Chemistry and Material Sciences) and the Russian Foundation for Basic Research (Project 08-04-12074).

References

1. V. B. Sokolov, A. Yu. Aksinenko, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 193 [*Russ. Chem. Bull., Int. Ed.*, 2010, **58**, No. 1].
2. M. A. Mashkovsky, *Lekarstvennye Sredstva* [*Pharmaceuticals*], Meditsina, Moscow, 1994 (in Russian).
3. S. O. Bachurin, *Meditsinskaya khimia napravlennogo poiska preparatov dlya preduprezhdeniya neyroderenerativnykh zabolevaniy na primere bolezni Alzgeimera* v sb. *Neuro-degenerativnye bolezni i starenie* [*Medicinal chemistry of direct search of drugs for therapy and prevention of nuerodegenerative diseases on the example of Alzheimer's disease*, in *Neurodegenerative disease and aging*], Moscow, 2001, 399 pp. (in Russian).
4. S. N. Osipov, A. F. Kolomiets, A. V. Fokin, *Usp. Khim.*, 1992, **61**, 1457 [*Russ. Chem. Rev.* (*Engl. Transl.*), 1992, **61**].

5. V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, 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, A. N. Pushin, I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1619 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1667].
7. Yu. Aksinenko, T. V. Goreva, T. A. Epishina, A. N. Pushin, V. B. Sokolov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 1014 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1052].
8. V. B. Sokolov, A. Yu. Aksinenko, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2176 [*Russ. Chem. Bull.*, *Int. Ed.*, 2007, **56**, 2252].
9. V. B. Sokolov, A. Yu. Aksinenko, I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2171 [*Russ. Chem. Bull.*, *Int. Ed.*, 2007, **56**, 2247].
10. O. Edafiogho, C. N. Hinko, H. Chang, J. A. Moore, D. Mulzac, J. M. Nicholson, K. R. Scott. *J. Med. Chem.* 1992, **35**, 2798.
11. W. Hatzenlaub, W. Pfleiderer, *Lieb. Ann. Chem.* 1979, 1847.

Received December 18, 2008;
in revised form April 9, 2009