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New Heterocyclic Derivatives of Trifluoroalanine

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Abstract—A new method of the synthesis of heterocyclic derivatives of trifluoroalanine based on the cyclocondensation of methyl trifluoropyruvate *tert*-butoxycarbonylimine with *C*,*N*- and *N*,*N*-binucleophiles, like *N*-substituted ureas, 1-benzyl-6-aminouracil, benzamidine, and 3-aminocrotononitrile, followed by hydrolysis of the resulting Boc-derivatives to 5-amino-5-trifluoromethylimidazolidine-2,4-diones, 5-amino-5-trifluoromethyl-1-benzyl-5,7-dihydropyrrolo[2,3-*d*]-pyrimidine-2,4,6-3*H*-trione, 4-amino-2-methyl-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile, or 5-amino-5-trifluoromethyl-2-phenyl-3,5-dihydroimidazol-4-one, respectively, was developed.

Keywords: methyl trifluoropyruvate, binucleophiles, cyclocondensation, imidazolones, *tert*-butyl carbamate

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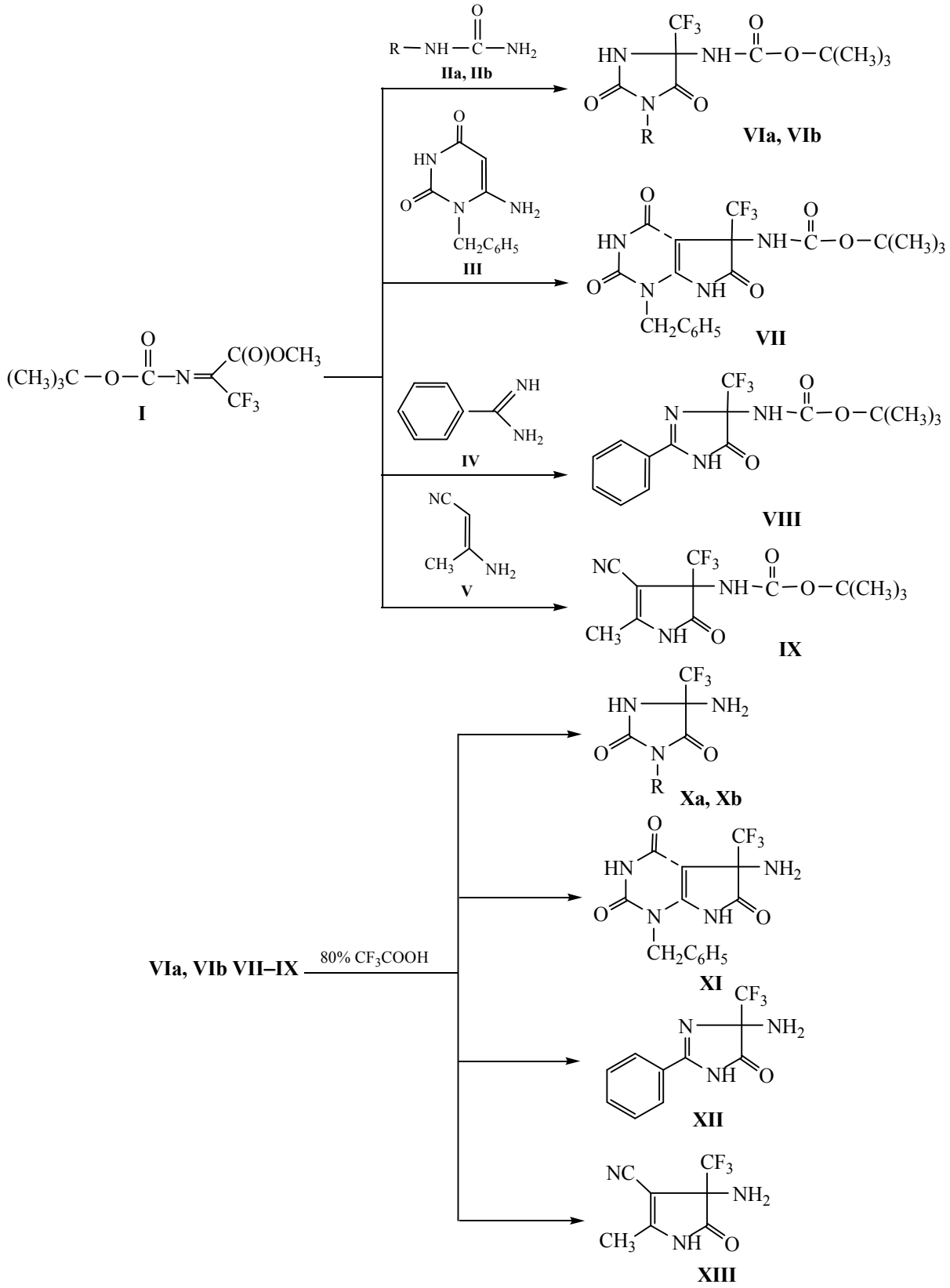
Fluorine-containing amino acids, including trifluoromethyl-containing amino acids, are a promising class of biologically active substances [1]. The introduction of these unnatural bioisosters into the peptide molecules improves usually their metabolic stability [2, 3] due to the low binding affinity [4] and creates the possibility of additional interactions with enzymes or receptor sites [5] in comparison with their natural counterparts. The purpose of this study is to develop a synthetic approach to heterocyclic derivatives of trifluoroalanine that may be of interest as potential biologically active substances, as well as new building blocks. Prerequisite for the study was the data on the cyclocondensation of *N*-substituted imines of methyl trifluoropyruvate with 1,3-binucleophiles [6–12] and on the synthesis of α-substituted aliphatic trifluoroalanines [13–15].

A synthetic approach to heterocyclic derivatives of trifluoroalanine consists in the cyclocondensation of methyl *tert*-butoxycarbonylimino-3,3,3-trifluoropropionate **I** with *C*,*N*- and *N*,*N*-1,3-binucleophiles, like *N*-substituted ureas **IIa** and **IIb**, 1-benzyl-6-aminouracil **III**, benzamidine **IV**, 3-aminocrotononitrile **V**, followed by hydrolysis of the corresponding Boc-derivatives (2,5-dioxo-4-trifluoromethylimidazolidines **VIa** and **VIa**, 2,4,6-trioxo-5-trifluoromethyl-1,2,3,4,5,6-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidine **VII**, 5-oxo-4-trifluoromethyl-2-phenyl-4,5-dihydro-1*H*-imidazole **VIII**, and 5-methyl-2-oxo-3-trifluoromethyl-4-cyano-2,3-dihydro-1*H*-pyrrole **IX**). Nature of the 1,3-binucleophile governs the cyclocondensation conditions. Thus, compound **I** reacts with equimolar amounts of **IIa**, **IIb**, and **III** in DMF in the presence of catalytic amounts of Et_3N under heating at 90°C for 3 h. The cyclocondensation of **IV** and **V** requires brief heating at 90°C for 20 min in the absence of a catalyst. Compounds **VI–IX** transformed into the corresponding derivatives at short (20 min) heating at 90°C in an excess of 80% CF_3COOH (Scheme 1).

The synthesized compounds **VI–XIII** were colorless crystalline substances. Their ^1H NMR spectra contained singlet signals of *tert*-butoxy groups in the range of 1.26–1.38 ppm (**VI–IX**) and of the amino group, at 3.08–4.93 ppm (**X–XIII**). In their ^{19}F NMR spectra the singlet signal of CF_3-group was observed in the ranges of 0.15–4.52 (**VI–IX**) or –2.20–4.18 ppm (**X–XIII**).

Thus we developed a new synthetic approach to the previously unknown heterocyclic derivatives of trifluoroalanine of four structural types via cyclocondensation of methyl trifluoropyruvate *tert*-butoxycarbonylimine with 1,3-binucleophiles followed by hydrolysis of the obtained Boc-derivatives.

Scheme 1.



II, VI, X, R = $C_6H_5CH_2$ (**a**), $C_6H_5CH_2CH_2$ (**b**).

EXPERIMENTAL

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (200.13, 188.29 MHz), internal reference tetramethylsilane or external reference CF_3COOH, respectively. Melting points were determined in glass capillaries.

Methyl *tert*-butoxycarbonylimino-3,3,3-trifluoropropionate **I** was prepared according to [16], 1-benzyl-6-aminouracil **III**, according to [17]. *N*-Substituted ureas **IIa** and **IIb**, benzamidine **IV**, 3-aminocrotononitrile **V** (Aldrich) were used without further purification.

***tert*-Butyl (1-benzyl-2,5-dioxo-4-trifluoromethylimidazolidin-4-yl)carbamate (VIa).** To a solution of 5 mmol of compound **I** in 10 mL of DMF under stirring at 20°C was added 5 mmol of **IIa**. The reaction mixture was stirred for 1 h at 90°C. Next, 0.1 g of NEt_3 was added and the mixture was heated for 3 h at 90°C, then cooled and poured into 50 mL of H_2O. The formed precipitate was filtered off and crystallized from 50% EtOH. Yield 1.2 g (85%), mp 169–171°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 s (9H, Me), 4.59 s (2H, CH_2), 7.16–7.36 m (5H, CH_{Ar}), 9.04 s (1H, NH), 9.54 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 0.21 ppm. Found, %: C 51.65; H 4.69; N 11.12. $C_{16}H_{18}F_3N_3O_4$. Calculated, %: C 51.48; H 4.86; N 11.26.

***tert*-Butyl [2,5-dioxo-4-trifluoromethyl-1-(2-phenylethyl)imidazolidin-4-yl]carbamate (VIb)** was obtained similarly. Yield 1.5 g (78%), mp 153–155°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 s (9H, Me), 2.78 t (2H, CH_2, *J* 6.6 Hz), 3.56 t (2H, CH_2, *J* 6.7 Hz), 6.84–7.07 m (5H, CH_{Ar}), 8.66 s (1H, NH), 9.05 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 0.15 ppm. Found, %: C 52.89; H 5.02; N 11.09. $C_{17}H_{20}F_3N_3O_4$. Calculated, %: C 52.71; H 5.20; N 10.85.

***tert*-Butyl (1-benzyl-2,4,6-trioxo-5-trifluoromethyl-2,3,4,5,6-hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)carbamate (VII)** was obtained similarly. Yield 1.8 g (82%), mp 181–183°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 s (9H, Me), 4.70–4.91 m (2H, CH_2), 6.81–7.06 m (5H, CH_{Ar}), 8.40 s (1H, NH), 10.71 s (1H, NH), 11.62 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 4.52 ppm. Found, %: C 53.07; H 4.21; N 12.88. $C_{19}H_{19}F_3N_4O_5$. Calculated, %: C 52.81; H 4.35; N 12.72.

***tert*-Butyl (5-oxo-4-trifluoromethyl-2-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)carbamate (VIII).** To a solution of 5 mmol of compound **I** in 10 mL of DMF under stirring at 20°C was added 5 mmol of **IV**. The reaction mixture was stirred for 20 min at 90°C, then cooled, and poured into 50 mL of H_2O. The formed precipitate was filtered off and crystallized from 50% EtOH. Yield 1.4 g (82%), mp 208–210°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 s (9H, Me), 7.12–7.37 m (3H, CH_{Ar}), 7.64 d (2H, CH_{Ar}, *J* 6.9 Hz), 8.48 s (1H, NH), 11.53 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 1.01 ppm. Found, %: C 52.31; H 4.49; N 12.49. $C_{15}H_{16}F_3N_3O_3$. Calculated, %: C 52.48; H 4.70; N 12.24.

***tert*-Butyl (5-methyl-2-oxo-3-trifluoromethyl-4-cyano-2,3-dihydro-1*H*-pyrrol-3-yl)carbamate (IX)** was obtained similarly. Yield 1.3 g (81%), mp 196–198°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 t (9H, Me), 2.18 (3H, Me), 8.51 s (1H, NH), 10.80 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 3.21 ppm. Found, %: C 48.59; H 5.13; N 13.33. $C_{13}H_{17}F_3N_3O_3$. Calculated, %: C 48.75; H 5.35; N 13.12.

5-Amino-3-benzyl-5-trifluoromethylimidazolidine-2,4-dione (Xa). A mixture of 3 mmol of **VIa** in 3 mL of 80% CF_3COOH was heated for 30 min at 90°C, then cooled, poured into 10 mL of H_2O, and neutralized with 10% aqueous NaOH. The formed precipitate was filtered off and crystallized from 50% EtOH. Yield 0.7 g (85%), mp 125–127°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.21 s (2H, NH_2), 4.45 s (2H, CH_2), 6.86–7.17 m (5H, CH_{Ar}), 9.01 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F –2.03 ppm. Found, %: C 48.49; H 3.43; N 15.21. $C_{11}H_{10}F_3N_3O_2$. Calculated, %: C 48.36; H 3.69; N 15.38.

5-Amino-5-trifluoromethyl-3-(2-phenethyl)imidazolidine-2,4-dione (Xb) was obtained similarly. Yield 0.7 g (81%), mp 113–115°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.77 t (2H, CH_2, *J* 6.7 Hz), 3.08 s (2H, NH_2), 3.51 t (2H, CH_2, *J* 6.7 Hz), 6.82–7.09 m (5H, CH_{Ar}), 8.82 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F –2.20 ppm. Found, %: C 49.99; H 3.98; N 14.45. $C_{12}H_{12}F_3N_3O_2$. Calculated, %: C 50.18; H 4.21; N 14.63.

5-Amino-1-benzyl-5-trifluoromethyl-5,7-dihydropirrolo[2,3-*d*]pyrimidine-2,4,6-3*H*-trione (XI) was obtained similarly. Yield 0.9 g (88%), mp 144–146°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.75 s (2H, NH_2), 6.82–7.13 m (5H, CH_{Ar}), 7.94 (1H, NH), 9.56 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 4.18 ppm. Found, %: C 49.29; H 3.03; N 16.25. $C_{14}H_{11}F_3N_4O_3$. Calculated, %: C 49.42; H 3.26; N 16.47.

5-Amino-5-trifluoromethyl-2-phenyl-3,5-dihydroimidazol-4-one (XII) was obtained similarly. Yield 0.6 g (82%), mp 207–209°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.93 s (2H, NH_2), 7.15–7.32 m (5H, CH_{Ar}), 9.94 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 1.05 ppm. Found, %: C 49.21; H 3.13; N 17.11. $C_{10}H_8F_3N_3O$. Calculated, %: 49.39; H 3.32; N 17.28.

4-Amino-2-methyl-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (XIII) was obtained similarly. Yield 0.5 g (76%), mp 152–154°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.08 s (3H, Me), 2.79 s (2H, NH_2), 10.59 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 0.82 ppm. Found, %: C 43.49; H 3.93; N 19.24. $C_8H_9F_3N_3O$. Calculated, %: C 43.64; H 4.12; N 19.08.

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