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# Cyclocondensation of Methyl 2-(1,3-Benzothiazol-2-ylimino)-3,3,3-trifluoropropionate with C,N-Binucleophiles

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**Abstract**—Reactions of methyl 2-(1,3-benzothiazol-2-ylimino)-3,3,3-trifluoropropionate with 1,3-C,N-binucleophiles, methyl 2-aminobut-2-enoate, 2-aminobut-2-enenitrile and N-substituted 6-aminouracils and 3-aminocyclohex-2-en-1-ones, led to the formation of trifluoromethyl-substituted heterocycles, dihydro-1*H*-pyrroles, hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6-triones, and hexahydro-1*H*-indole-2,4-diones.

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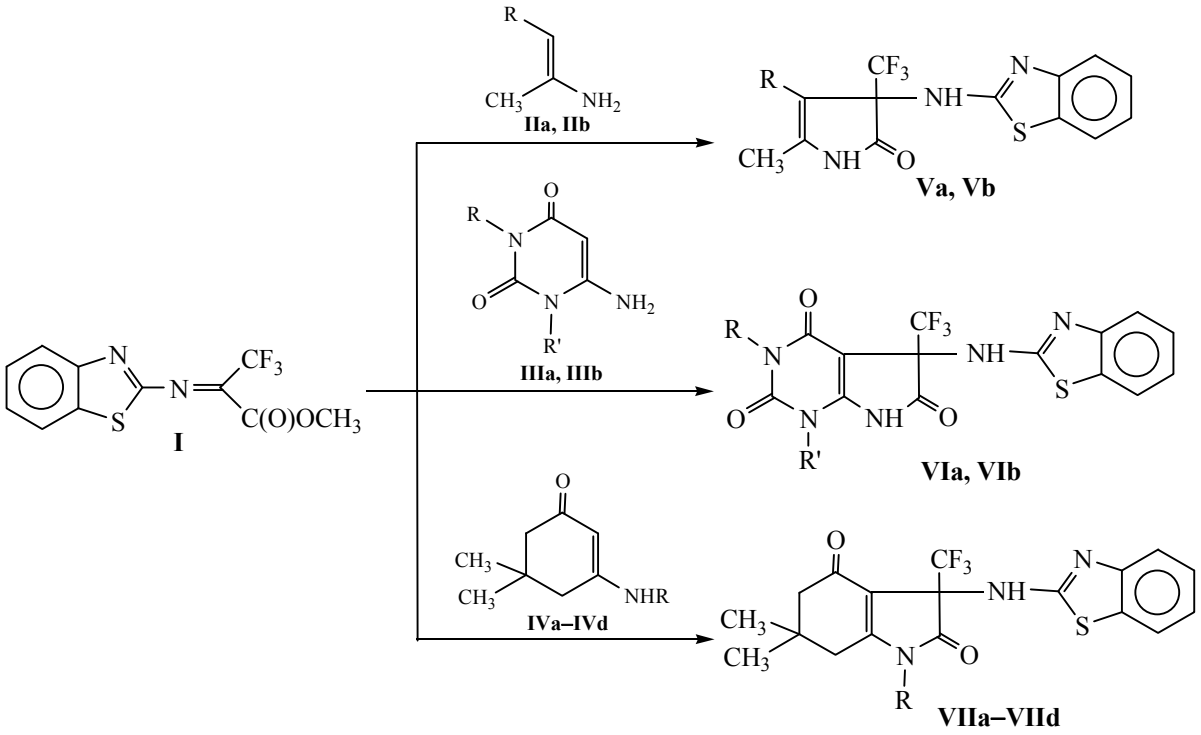
Cyclocondensations of N-substituted methyl 2-imino-3,3,3-trifluoropropionates with difunctional nucleophiles underlie effective methods for the synthesis of novel trifluoromethyl-substituted five-membered heterocycles [1–4]. While developing studies in this line, in the present communication we report on transformations of methyl 2-(1,3-benzothiazol-2-ylimino)-3,3,3-trifluoropropionate (**I**), which was synthesized by us previously [5], in cyclocondensations with 1,3-binucleophiles to obtain trifluoromethyl-containing heterocyclic N-substituted 2-aminobenzothiazole derivatives. It should be noted that 2-aminobenzothiazole




**II**, **V**, R = MeOC(O) (**a**), CN (**b**); **III**, **VI**, R = R′ = Me (**a**), R = H, R′ = $PhCH_2$ (**b**); **IV**, **VII**, R = Ph (**a**), $PhCH_2$ (**b**), pyridin-3-ylmethyl (**c**), 4-$MeOC_6H_4$ (**d**).

fragment is a structural unit of molecules of some biologically active substances, e.g., nitric oxide synthase inhibitors [6] and anticonvulsants [7].

Methyl 2-(1,3-benzothiazol-2-ylimino)-3,3,3-trifluoropropionate (**I**) turned out to be less reactive toward 1,3-C,N-binucleophiles, as compared to N-substituted analogs studied previously [8]. Compound **I** reacted with methyl 2-aminobut-2-enoate (**IIa**) and 2-aminobut-2-enenitrile (**IIb**) at 90°C (reaction time 1 h) to give the corresponding 4-(benzothiazol-2-ylamino)-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid derivatives **Va** and **Vb**. The reactions of **I** with 6-aminouracils **IIIa** and **IIIb** and 3-aminocyclohex-2-en-1-ones **IVa**–**IVd** required heating of the reaction mixtures for 6 h at 90°C in the presence of a catalytic amount of triethylamine to be complete. As a result, hexahydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6-triones **VIa** and **VIb** and hexahydro-1*H*-indole-2,4-diones **VIIa**–**VIId** were obtained in 66–78% yield.

5-Oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrroles **V**, 5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6-trionyes **VI**, and 3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-diones **VII** were isolated as crystalline substances which displayed characteristic signals in the NMR spectra. The NH proton at $C^2$ in the benzothiazole fragment resonated in the $^1$H NMR spectra of **V**–**VII** at δ 9–10 ppm, and the $CF_3$ signal was located at $\delta_F$ 0.4–3.9 ppm in the $^{19}$F NMR spectra.

Thus we have proposed a novel synthetic approach to 2-aminobenzothiazole derivatives having different trifluoromethyl-containing five-membered heterocyclic substituents on the exocyclic nitrogen atom via cyclocondensation of methyl 2-(1,3-benzothiazol-2-ylimino)-3,3,3-trifluoropropionate with 1,3-C,N-binucleophiles.

## EXPERIMENTAL

The $^1$H and $^{19}$F NMR spectra were recorded on a Bruker DPX-200 spectrometer at 200.13 and 188.29 MHz, respectively, using tetramethylsilane ($^1$H, internal) or $CF_3COOH$ ($^{19}$F, external) as reference. The melting points were determined by heating samples in glass capillaries. Methyl 2-(1,3-benzothiazol-2-ylimino)-3,3,3-trifluoropropionate (**I**) was synthesized according to the procedure reported in [5]. Initial 6-aminouracils **IIIa** and **IIIb** were prepared as described in [9], 3-aminocyclohex-2-en-1-ones **IVa**–**IVd** were obtained according to [10], and methyl 3-aminobut-2-enoate (**IIa**) and 3-aminobut-2-enenitrile were commercial products (Aldrich) which were used without preliminary purification.

**Methyl 4-(1,3-benzothiazol-2-ylamino)-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (Va).** Compound **I**, 5 mmol, was dissolved in 10 ml of DMF, 5 mmol of compound **IIa** was added under stirring at 20°C, and the mixture was stirred for 1 h at 90°C, cooled, and poured into 50 ml of water. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 1.3 g (70%), mp 123–125°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 2.37 s (3H, Me), 3.57 s (3H, MeO), 6.97 t (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.13 t (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.24 d (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.55 d (1H, $H_{arom}$, $J$ = 7.7 Hz), 9.04 s (1H, NH), 10.95 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 0.49 ppm. Found, %: C 48.39; H 3.13; N 11.19. $C_{15}H_{12}F_3N_3O_3S$. Calculated, %: C 48.52; H 3.26; N 11.22.

**4-(1,3-Benzothiazol-2-ylamino)-2-methyl-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (Vb)** was synthesized in a similar way. Yield 68%. mp 131–132°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 2.27 s (3H, $CH_3$), 7.05 t (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.20 t (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.35 d (1H, $H_{arom}$, $J$ = 7.7 Hz), 7.60 d (1H, $H_{arom}$, $J$ = 7.7 Hz), 9.40 s (1H, NH), 11.33 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 2.50 ppm. Found, %: C 49.48; H 2.91; N 17.08. $C_{14}H_9F_3N_4OS$. Calculated, %: C 49.70; H 2.68; N 16.85.

**5-(1,3-Benzothiazol-2-ylamino)-1,3-dimethyl-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione (VIa).** Compound **IIIa**, 5 mmol, was added under stirring at 20°C to a solution of 5 mmol of compound **I** in 10 ml of DMF. The mixture was stirred for 1 h at 90°C, 0.1 g of triethylamine was added, and the mixture was heated for 6 h at 90°C, cooled, and poured into 50 ml of water. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 1.6 g (78%), mp 233–235°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 3.12 s and 3.48 s (3H each, MeN), 6.92 t (1H, $H_{arom}$, $J$ = 7.4 Hz), 7.19 t (1H, $H_{arom}$, $J$ = 7.4 Hz), 7.26 d (1H, $H_{arom}$, $J$ = 7.4 Hz), 7.49 d (1H, $H_{arom}$, $J$ = 7.4 Hz), 9.43 s (1H, NH), 12.19 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.91 ppm. Found, %: C 46.58; H 2.81; N 17.16. $C_{16}H_{12}F_3N_5O_3S$. Calculated, %: C 46.72; H 2.94; N 17.02.

Compounds **VIb** and **VIIa–VIId** were synthesized in a similar way.

**5-(1,3-Benzothiazol-2-ylamino)-1-benzyl-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione (VIb).** Yield 73%. mp 215–216°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 5.14 m (2H, $CH_2$), 7.13 m (3H, $H_{arom}$), 7.38 m (5H, $H_{arom}$), 7.62 d (1H, $H_{arom}$, $J$ = 7.9 Hz), 9.56 s (1H, NH), 11.07 s (1H, NH), 12.36 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.88 ppm, s. Found, %: C 53.12; H 2.85; N 14.66. $C_{21}H_{14}F_3N_5O_3S$. Calculated, %: C 53.28; H 2.98; N 14.79.

**3-(1,3-Benzothiazol-2-ylamino)-6,6-dimethyl-1-phenyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (VIIa).** Yield 66%. mp 218–220°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.97 s and 1.11 s (3H each, Me), 2.71 m (4H, $CH_2$), 7.07 t (1H, $H_{arom}$, $J$ = 6.7 Hz), 7.26 m (2H, $H_{arom}$), 7.59 m (6H, $H_{arom}$), 9.64 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.78 ppm. Found, %: C 61.25; H 4.11; N 8.77. $C_{24}H_{20}F_3N_3O_2S$. Calculated, %: C 61.14; H 4.28; N 8.91.

**3-(1,3-Benzothiazol-2-ylamino)-1-benzyl-6,6-dimethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (VIIb).** Yield 69%. mp 206–208°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.97 s and 1.08 s (3H each, Me), 2.11 m (2H, $CH_2$), 2.41 m (2H, $CH_2$), 4.93 m (2H, $CH_2$), 6.99 m (1H, $H_{arom}$), 7.05 d (2H, $H_{arom}$, $J$ = 7.1 Hz), 7.37 m (5H, $H_{arom}$), 7.57 d (1H, $H_{arom}$, $J$ = 8.3 Hz), 9.46 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.74 ppm. Found, %: C 68.71; H 4.44; N 8.53. $C_{25}H_{22}F_3N_3O_2S$. Calculated, %: C 68.85; H 4.57; N 8.65.

**3-(1,3-Benzothiazol-2-ylamino)-6,6-dimethyl-1-(pyridin-3-ylmethyl)-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (VIIc).** Yield 66%. mp 229–231°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.99 s and 1,12 s (3H each, Me), 2.17 m (2H, $CH_2$), 2.52 m (2H, $CH_2$), 5.01 m (2H, $CH_2$), 7.07 t (1H, $H_{arom}$, $J$ = 8.0 Hz), 7.23 m (2H, $H_{arom}$), 7.33 m (1H, $H_{arom}$), 7.58 d (1H, $H_{arom}$, $J$ = 8.2 Hz), 7.85 d (1H, $H_{arom}$, $J$ = 8.2 Hz), 8.56 d (1H, $H_{arom}$, $J$ = 7.2 Hz), 8.79 s (1H, $H_{arom}$), 9.49 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.75 ppm. Found, %: C 59.13; H 4.22; N 11.39. $C_{24}H_{21}F_3N_4O_2S$. Calculated, %: C 59.25; H 4.35; N 11.52.

**3-(1,3-Benzothiazol-2-ylamino)-1-(4-methoxyphenyl)-6,6-dimethyl-3-trifluoromethyl-3,5,6,7-tetrahydro-1*H*-indole-2,4-dione (VIId).** Yield 71%. mp 245–246°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm): 0.96 s and 1.12 s (3H each, Me), 2.25 m (2H, $CH_2$), 2.54 m (2H, $CH_2$), 3.91 s (3H, MeO), 7.09 m (3H, $H_{arom}$), 7.22 t (1H, $H_{arom}$, $J$ = 8.1 Hz), 7.63 d (1H, $H_{arom}$, $J$ = 8.1 Hz), 7.24 m (3H, $H_{arom}$), 9.62 s (1H, NH). $^{19}$F NMR spectrum (DMSO-$d_6$): $\delta_F$ 3.81 ppm. Found, %: C 59.75; H 4.31; N 8.26. $C_{25}H_{22}F_3N_3O_3S$. Calculated, %: C 59.87; H 4.42; N 8.38.

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