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# Methyl Benzothiazol-2-yliminotrifluoropyruvates in the Diels-Alder Aza-reaction with Cyclopentadiene and Cyanoamines

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**Abstract**—Methyl trifluoropyruvate benzothiazol-2-ylimines exhibit both a heterodiene and a dienophile properties in the Diels–Alder aza-reaction with cyclopentadiene and cyanoamines, leading to the formation of 4-substituted 2-trifluoromethyl-2*H*-[1,3,5]triazine[2,1-*b*][1,3]benzothiazole and 2-benzothiazol-2-yl-3-trifluoromethyl-2-azabicyclo[2.2.1]hept-5-ene, respectively.

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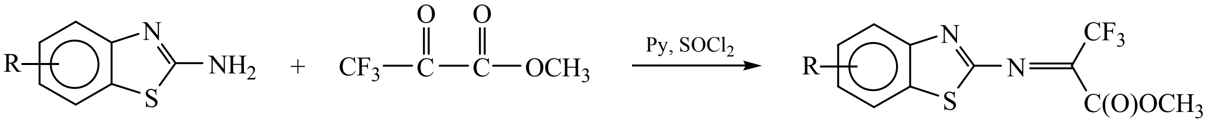
The Diels–Alder reaction is one of the key methods for the synthesis of heterocycles [1]. Use in this reaction of the reagents exhibiting the properties of dienes and dienophiles is particularly fruitful and expands the diversity of the synthesized heterocycles. From this point of view, N-substituted hexafluoroacetone imines and methyl trifluoropyruvate are of great interest. The hexafluoroacetone acylimines and methyl trifluoropyruvates react with dienophiles exhibiting the properties of the electron-rich heterodienes, and react with dienes as the electron-deficient dienophiles, to form the corresponding products of (2+4) cycloaddition [2–8]. Examples are known of the use of hexafluoroacetone benzothiazol-2-ylimines and pyrimidin-2-ylimines [9], as well as a N-substituted hexafluoroacetone imine obtained from 2-chloro-*N*-(2,6-dimethylphenyl)benzamidine, as heterodienes [10–13]. The purpose of this study was to investigate the behavior of methyl benzothiazol-2-yliliminotrifluoropyruvates in the Diels–Alder aza-reaction with cyanoamines and cyclopentadiene, leading to the formation of trifluoromethyl-substituted heterocycles with a 2-aminobenzothiazolyl fragment. The latter is present in the molecules of biologically active substances, like inhibitors of nitric oxide syntase agonists, as a substructural cluster [14].

Methyl benzothiazol-2-yliminotrifluoropyruvates **IIIa–IIId** were synthesized by condensation of 2-aminobenzothiazoles **Ia–Id** with methyl trifluoropyruvate **II** using a one-pot technique, by consecutive adding pyridine, methyl trifluoropyruvate, and $SOCl_2$ to a solution or suspension of **Ia–Id** in benzene.

Methyl benzothiazol-2-iminotrifluoropyruvates **IIIa–IIId** were less reactive in the reactions of (2+4)-cycloaddition with cyanoamines than hexafluoro-acetone acylimines and methyl trifluoropyruvate, which react exothermically with the cyanoamines. To complete the reaction of imines **IIIa–IIId** and cyanoamines **IVa–IVd** refluxing of equimolar mixture of reactants in benzene for 5 h was necessary, resulting in the formation of the corresponding triazinobenzothiazoles **Va–Vf** in 67–82% yield. To complete the reaction of imine **IIIa** with cyclopentadiene **VI** refluxing of equimolar mixture of the reactants in benzene for 2 h was required.

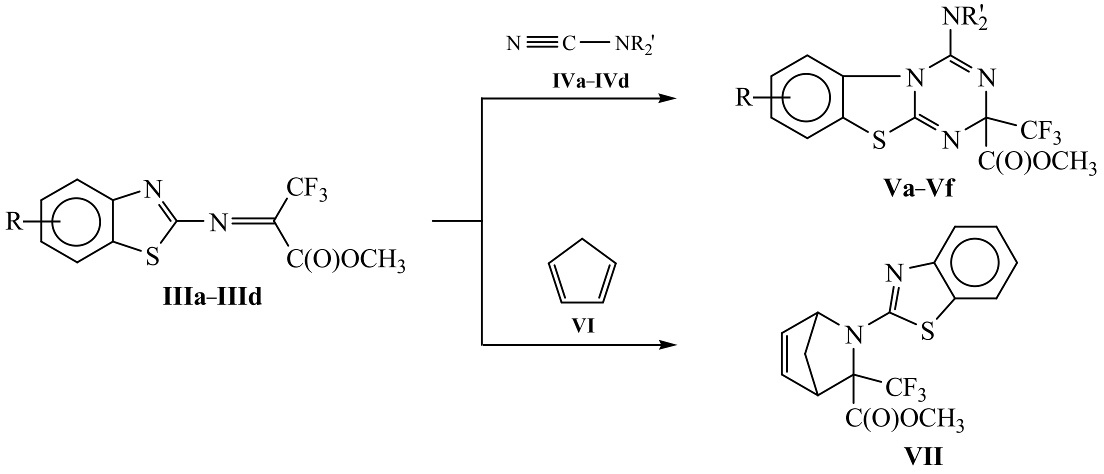
The synthesized triazinobenzothiazoles **Va–Vf** and azabicyclo[2.2.1]hept-5-ene **VII** are crystalline solids. Their composition and structure were proved by



**Ia–Id** **II** **IIIa–IIId**

**I, III**: R = H (**a**), 6-Cl (**b**), 6-$NO_2$ (**c**), 6-$CH_3SO_2$ (**d**).

elemental analysis and $^1$H and $^{19}$F NMR spectroscopy. In the $^{19}$F NMR spectra there are signals in the region of δ 0.2–0.6 ppm characteristic of compounds **Va–Vf** and 15.3 ppm, of compound **VII**.



**IV**: R' = Me (**a**), Et (**b**), $R_2'$ = $(CH_2)_5$ (**c**), $CH_2CH_2OCH_2CH_2$ (**d**); **V**: R = H, R' = Et (**a**); $R_2'$ = $(CH_2)_5$ (**b**); R = 8-Cl, R' = Me (**c**); R = 8-$NO_2$, $R_2'$ = $(CH_2)_5$ (**d**); $R_2'$ = $CH_2CH_2OCH_2CH_2$ (**e**); R = $MeSO_2$, R' = Me (**f**).

Thus, we have developed new fluorine-containing reagents for the Diels–Alder reaction: methyl benzothiazol-2-yliminotrifluoropyruvates, which exhibit the heterodiene and dienophile properties in the considered transformations.

## EXPERIMENTAL

The $^1$H and $^{19}$F NMR spectra were recorded on a Bruker DPX 200 instrument at a frequency of 200.13 and 188.29 MHz, respectively, relative to internal tetramethylsilane and external $CF_3COOH$. Melting points were determined in a glass capillary. Initial 2-aminobenzothiazoles **Ia–If**, methyl trifluoropyruvate **II**, cyanoamines **IVa–IVd,** and cyclopentadiene **VI** from Aldrich were used without pretreatment, methyl benzothiazol-2-yliminotrifluoropyruvate **Ia** we synthesized and described previously [15].

**Methyl 2-(6-chlorbenzothiazol-2-yl imino-3,3,3-trifluoropropanoate (IIIb)**. To a solution of 0.05 mol of compound **Ib** in 50 ml of benzene at 20°C while stirring were successively added 0.1 mol of pyridine and 0.05 mol of compound **II**. The reaction mixture was stirred for 30 min, 0.05 mol of $SOCl_2$ was then added, and the stirring was continued for 1 h. Then the mixture was filtered and the filtrate was evaporated, the residue was crystallized from hexane. Yield 12.3 g (76%), mp 152–154°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.96 s (3H, MeO), 7.18 d (1H, $CH_{Ar}$, $J$ 7.8 Hz) 7.37 d (1H, $CH_{Ar}$, $J$ 7.8 Hz), 7.58 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 8.22 s. Found, %: C 40.82, H 1.75, N 8.56. $C_{11}H_6ClF_3N_2O_2S$. Calculated, %: C 40.94, H 1.87, N 8.68.

**Methyl 2-(6-nitrobenzothiazol-2-yl)imino-3,3,3-trifluoropropanoate (IIIc)** was obtained similarly to **IIIb**. Yield 1.12 g (73%), mp 185–186°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.94 s (3H, MeO), 8.08 d (1H, $CH_{Ar}$, $J$ 8.1 Hz) 8.41 d (1H, $CH_{Ar}$, $J$ 8.1 Hz), 8.86 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 8.07 s. Found, %: C 39.77, H 1.68, N 12.49. $C_{11}H_6F_3N_3O_4S$. Calculated, %: C 39.65, H 1.81, N 12.61.

**Methyl 2-(6-methylsulfonylbenzothiazol-2-yl) imino-3,3,3-trifluoropropanoate (IIId)** was obtained similarly to **IIIb**. Yield 8.12 g (70%), mp 191–193°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.13 s (3H, $MeSO_2$), 3.93 s (3H, MeO), 8.11 m (2H, $CH_{Ar}$), 8.58 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 8.11 s. Found, %: C 39.12, H 2.31, N 7.47. $C_{12}H_9F_3N_2O_4S_2$. Calculated, %: C 39.34, H 2.48, N 17.65.

**Methyl 4-diethylamino-2-trifluoromethyl-2*H*-[1,3,5]-triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Va).** A solution of 0.01 mol of compound **IIIa** and 0.01 mol of compound **IVa** in 20 ml of benzene was refluxed for 5 h, evaporated, and the residue was recrystallized from hexane. Yield 3.2 g (82%), mp 116–118°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 m (6H, $MeCH_2$), 1.3 m (4H, $CH_2N$), 3.79 s (3H, MeO), 7.19 m (2H, $CH_{Ar}$), 7.65 m (2H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 0.65 s. Found, %: C 49.61, H 4.29, N 14.63. $C_{16}H_{17}F_3N_4O_2S$. Calculated, %: C 49.74, H 4.43, N 14.50.

**Methyl 4-(piperidin-1-yl)-2-trifluoromethyl-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Vb)** was obtained analogously to compound **Va**. Yield 3.1 g (78%), mp 142–144ºC. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.62 m (6H, $CH_2$), 2.61 m (1H, $CH_2$), 3.14 m (2H, $CH_2$), 3.45 m (1H, $CH_2$) , 3.78 s (3H, MeO), 7.31 m (2H, $CH_{Ar}$), 7.68 d (1H, $CH_{Ar}$, *J* 7.9 Hz) 7.72 d (1H, $CH_{Ar}$, *J* 7.9 Hz). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 0.21 s. Found, %: C 51.13, H 4.18, N 14.22. $C_{17}H_{17}$·$F_3N_4O_2S$. Calculated, %: C 51.25, H 4.30, N 14.06.

**Methyl 4-dimethylamino-2-trifluoromethyl-8-chloro-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Vc)** was obtained analogously to compound **Va**. Yield 2.9 g (74%), mp 175–177ºC. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.41 s (6H, Me), 3.79 s (3H, MeO), 7.73 d and 8.21 d (1H, $CH_{Ar}$, *J* 7.7 Hz), 8.59 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 0.32 s. Found, %: C 42.63, H 2.88, N 14.07. $C_{14}H_{12}$·$ClF_3N_4O_2S$. Calculated, %: C 42.81, H 3.08, N 14.26.

**Methyl 8-nitro-4-(piperidin-1-yl)-2-trifluoromethyl-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Vd)** was obtained analogously to compound **Va**. Yield 3.1 g (70%), mp 152–154ºC. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.69 m (6H, $CH_2$), 2.68 m (1H, $CH_2$), 3.11 m (2H, $CH_2$), 3.38 m (1H, $CH_2$), 3.76 s (3H, MeO), 7.84 d and 8.23 d (1H, $CH_{Ar}$, *J* 7.9 Hz), 8.61 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 0.43 s. Found, %: C 46.19, H 3.51, N 15.66. $C_{17}H_{16}F_3$·$N_5O_4S$. Calculated, %: C 46.05, H 3.64, N 15.79.

**Methyl 4-(morpholin-4-yl)-8-nitro-2-trifluoromethyl-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Ve)** was obtained analogously to compound **Va**. Yield 3.0 g (68%), mp 165–167ºC. $^1$H NMR spectrum ($CDCl_3$) δ, ppm: 2.84 m (1H, $CH_2N$), 2.27 m (3H, $CH_2N$), 3.76 m (4H, $CH_2O$), 3.81 s (3H, MeO), 7.94 d (1H, $CH_{Ar}$, *J* 9.9 Hz) 8.29 d.d (1H, $CH_{Ar}$, $J_1$ 9.9 Hz, $J_2$ 3.5 Hz), 8.59 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$) δ, ppm: 0.53 s. Found, %: C 43.03, H 3.28, N 15.58. $C_{16}H_{14}F_3N_5O_2S$. Calculated, %: C 43.15, H 3.17, N 15.72.

**Methyl 4-dimethylamino-8-methylsulfonyl-2-trifluoromethyl-2*H*-[1,3,5]triazino[2,1-*b*][1,3]benzothiazole-2-carboxylate (Vf)** was obtained analogously to compound **Va**. Yield 3.4 g (78%), mp 182–184ºC. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.44 s (6H, Me), 3.73 s (3H, MeO), 7.81 d and 8.25 d (1H, $CH_{Ar}$, *J* 7.8 Hz), 8.65 s (1H, $CH_{Ar}$). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 0.26 s. Found, %: 41.47, H 3.27, N 12.66. $C_{15}H_{15}$·$F_3N_4O_4S_2$. Calculated, %: C 41.28, H 3.46, N 12.84.

**Methyl 2-(benzothiazol-2-yl)-3-trifluoromethyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (VII).** A solution of 0.01 mol of compound **IIIa** and 0.01 mol of cyclopentadiene **VI** in 20 ml of benzene was refluxed for 2 h, evaporated, and the residue was recrystallized from hexane. Yield 2.8 g (79%), mp 132–134ºC. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 2.54 m (2H, $CH_2$), 3.41 q (1H, CH, *J* 8.1 Hz), 3.79 s (3H, MeO), 4.68 d (1H, CH, *J* 8.1 Hz), 8.6 m (1H, CH), 6.34 m (1H, CH), 7.01 m (2H, $CH_{Ar}$), 7.22 m (1H, $CH_{Ar}$), 7.40 d (1H, $CH_{Ar}$, *J* 8.2 Hz). $^{19}$F NMR spectrum ($CDCl_3$), δ, ppm: 15.3 s. Found. %: C 54.12, H 3.58, N 7.78. $C_{16}H_{13}F_3N_2O_2S$. Calculated, %: C 54.23, H 3.70, N 7.91.

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