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Cyclocondensation of Methyl 2-(5-Methylisoxazol-3-yl)imino-3,3,3-trifluoropropionate with 1,3- Binucleophiles

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Abstract—Cyclocondensation of methyl 2-(5-methylisoxazol-3-yl)imino-3,3,3-trifluoropropionate with 1,3-binucleophiles such as benzamidines, aminothiazoline, and 2-aminocrotonic acid nitrile results in trifluoromethyl-containing 3,5-dihydro-4-ones, 2,3-dihydro-6*H*-imidazo[2,1-*b*]thiazol-5-one, and 4,5-dihydro-1*H*-pyrrole-3-carbonitrile.

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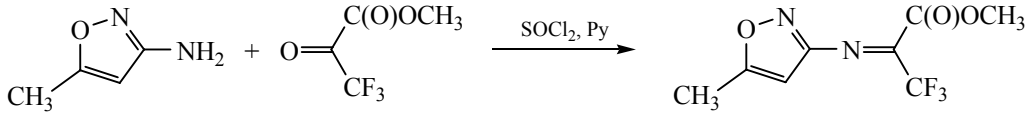
Imines of *N*-substituted methyl trifluoropyruvates react with 1,3-binucleophiles to form trifluoromethyl-containing five-membered heterocycles [1–4]. In this work we report on the synthetic approach to prepare heterocycles from trifluoromethyl-containing 1,2-biselectrophiles. The previously unknown 2-(5-methylisoxazol-3-yl)imino-3,3,3-trifluoropropionate **III** was used as the fluorine-containing component in the studied cyclocondensation.

The proposed method to obtain imine **III** consisted in the sequential addition of equimolar amounts of pyridine, methyl trifluoropyruvate **II**, and $SOCl_2$ to solution of 2-amino-5-methylisoxazole **I**.



I **II** **III**

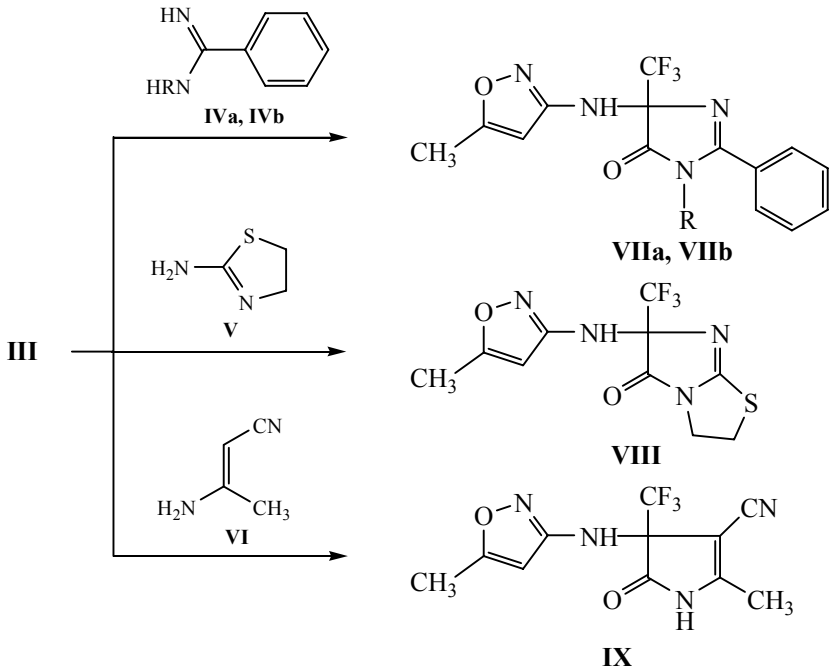
Imine **III** was a high-boiling compound, its composition and structure being confirmed by elemental analysis and NMR spectroscopy. ^{19}F NMR spectra of **III** contained the signal of trifluoromethyl group at the azomethine bond (δ_F 7.02 ppm) [5].

N-(Isoxazol-3-yl)imine of methyl trifluoropyruvate **III** reacted exothermically with highly reactive 1,3-*N*,*N*- and 1,3-*C*,*N*-binucleophiles (such as benzamidines **IVa** and **IVb**, 2-aminothiazoline **V**, and 3-aminocrotonate **VI**) via cyclocondensation: 1,3-addition of the binucleophile at the C=N bond of **III** followed by cyclization and elimination of methanol. In order to reach complete conversion, short-time heating at 50°C was necessary, the products being the corresponding 5-(5-methylisoxazol-3-ylamino)-2-phenyl-5-trifluoromethyl-3,5-dihydroimidazol-4-ones **VIIa** and **VIIb**, 6-(5-methylisoxazol-3-ylamino)-6-trifluoromethy-2,3-dihydro-6*H*-imidazo[2,1-*b*]-thiazol-5-one **VIII**, and 2-methyl-4-(5-methylisoxazol-3-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile **IX** with yields of 72–80% (see Scheme 1).

The prepared 5-trifluoromethyl-3,5-dihydroimidazol-4-ones **VIIa** and **VIIb**, 6-trifluoromethyl-2,3-dihydro-6*H*-imidazo[2,1-*b*]thiazol-5-one **VIII**, and 5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile **IX** were colorless crystalline solids. In the ^1H NMR spectra of **VII**–**IX**, the CH protons of isoxazole ring resonated at 5.6–5.8 ppm; the NH protons signals of benzamide substituent were observed at 9–10 ppm. The ^{19}F NMR spectra contained the signals of CF_3 group at 0.4–3.9 ppm.

To conclude, we have proposed a novel synthetic approach to functionalize 2-amino-5-methylisoxazole using various trifluoromethyl-containing five-membered

Scheme 1.



IV, VII: R = H (**a**), cyclo-C_6H_{11} (**b**).

heterocycles via cyclocondensation of 2-(5-methylisoxazol-3-yl)imino-3,3,3-trifluoropropionate with 1,3-binucleophiles.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra were registered with Bruker DPX 200 spectrometer at 200.13 and 188.29 MHz, respectively; relative to TMS (internal reference) and CF_3COOH (external reference), respectively. Melting points were determined in glass capillaries. Benzamidines **IVa** and **IVb**, 2-aminothiazoline **V**, and 3-aminocrotonic acid nitrile **VI** (Aldrich) were used as received.

Methyl 2-(5-methylisoxazol-3-yl)imino-3,3,3-trifluoropropionate (III). Mixture of 0.1 mol of compound **I** in 50 mL of benzene, 0.2 mol of pyridine, and 0.1 mol of **II** was stirred at 20°C during 30 min. Then, 0.1 mol of $SOCl_2$ was added, and the mixture was stirred during 1 h. The formed precipitate was filtered off. After the solvent removal, the residue was fractionated. Yield 18.5 g (78%), bp 79–80°C (1 Torr). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.32 s (3H, Me), 3.69 s (3H, MeO), 5.77 s (1H, CH_{Ar}). ^{19}F NMR spectrum ($CDCl_3$): δ_F 7.02 ppm. Found, %: C 40.51; H 2.82; N 11.66. $C_8H_7F_3N_2O_3$. Calculated, %: C 40.69; H 2.99; N 8.68.

5-(5-Methylisoxazol-3-ylamino)-2-phenyl-5-trifluoromethyl-3,5-dihydroimidazol-4-one (VIIa). Mixture of 5 mmol of compound **III** in 10 mL of DMF and 5 mmol of **VIa** was stirred at 50°C during 1 h, cooled down, and poured into 50 mL H_2O. The precipitate was recrystallized from 50% EtOH. Yield 1.3 g (80%), mp 205–207°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.21 s (3H, Me), 5.72 s (1H, CH_{Ar}), 7.46–7.72 m (3H, CH_{Ar}), 7.91 s (1H, NH), 7.98 d (2H, CH_{Ar}, J 7.1 Hz), 12.21 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 1.15 ppm. Found, %: C 51.99; H 3.59; N 17.10. $C_{14}H_{11}F_3N_4O_2$. Calculated, %: C 51.86; H 3.42; N 17.28.

3-Benzyl-5-(5-methylisoxazol-3-ylamino)-2-phenyl-5-trifluoromethyl-3,5-dihydroimidazol-4-one (VIIb) was prepared similarly. Yield 73%, mp 168–170°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.22 s (3H, Me), 4.55–4.77 m (2H, CH_2), 5.61 s (1H, CH_{Ar}), 6.87–7.07 m (5H, CH_{Ar}), 7.14–7.24 m (4H, CH_{Ar}), 7.26–7.33 m (1H, CH_{Ar}), 7.82 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 2.12 ppm. Found, %: C 60.62; H 4.32; N 13.30. $C_{21}H_{17}F_3N_4O_2$. Calculated, %: C 60.81; H 4.14; N 13.52.

6-(5-Methylisoxazol-3-ylamino)-6-trifluoromethyl-2,3-dihydro-6*H*-imidazo[2,1-*b*]thiazol-5-one (VIII) was prepared similarly. Yield 76%, mp 216–218°C. ^{1}H

NMR spectrum (DMSO-d_6), δ, ppm: 2.19 s (3H, Me), 3.51–3.70 m (1H, CH_2), 3.73–3.86 m (2H, CH_2), 3.88–3.03 m (1H, CH_2), 5.72 s (1H, CH_{Ar}), 7.98 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 0.2 ppm. Found, %: C 39.03; H 3.18; N 19.45. $C_{10}H_9F_3N_4O_2S$. Calculated, %: C 39.22; H 2.96; N 18.29.

2-Methyl-4-(5-methylisoxazol-3-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (IX) was prepared similarly. Yield 72%, mp 223–225°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.21 s (3H, Me), 2.26 s (3H, Me), 5.78 s (1H, CH_{Ar}), 7.91 s (1H, NH), 11.38 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6): δ_F 2.27 ppm. Found, %: C 43.33; H 3.38; N 19.29. $C_{11}H_9F_3N_4O_2$. Calculated, %: C 46.16; H 3.17; N 19.58.

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