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REACTIONS OF MALONOTHIOAMIDE DERIVATIVES WITH AZIDES*

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The reactions of primary and tertiary malonothioamides with aryl and sulfonyl azides can take place in three directions, depending on the nature of the thioamides and azides. Ethoxycarbonylthioacetamide reacts with aryl azides with the formation of ethyl 5-amino-1-aryl-1,2,3-triazole-4-carboxylates. In reaction with aryl azides tertiary thioamides of cyanoacetic acid form 5-amino-1-aryl-1,2,3-triazole-4-carbothioamides, and in reaction with tosyl azide they form 5-amino-4-carboxamidino-1,2,3-thiadiazoles. Hypothetical mechanisms for the transformations are discussed.

Keywords: aryl azides, malonothioamides, 1,2,3-thiadiazoles, 1,2,3-triazoles, cyclocondensation, rearrangements.

The ability of 1,2,3-triazoles and 1,2,3-thiadiazoles to undergo various changes, particularly transformations and mutual rearrangements, has always attracted the attention of research workers [1-9]. 1,2,3-Triazole and 1,2,3-thiadiazole rings form part of the structure of many compounds having biological activity, and this has stimulated interest in the synthesis of new derivatives of this series. The 1,2,3-triazole ring forms the structural basis of antibacterial, anti-inflammatory, and hypotensive medications, neuroleptics, antiHIV agents, and pesticides [1, 2]. Selective inhibitors of HIV-1 protease and histone deacetylase, which are prospective antitumor agents, have been found among the derivatives of 1,2,3-triazole [10-14]. A broad spectrum of biological activity is also characteristic of 1,2,3-thiadiazole derivatives. Most interesting from the practical standpoint are substances having antiviral, herbicidal, and fungicidal activity and agents for the protection and growth regulation of plants [6, 9, 15, 16].

There are four main methods for the synthesis of 1,2,3-triazoles: condensation of amines with α-diazocarbonyl compounds; cyclization of bishydrazones of α-dicarbonyl compounds; cycloaddition of azides to substituted acetylenes and olefins; reaction of azides with CH-active compounds [1, 2]. In the last case, trisubstituted triazoles were obtained by the condensation of azides (aromatic, aliphatic, heterocyclic) and

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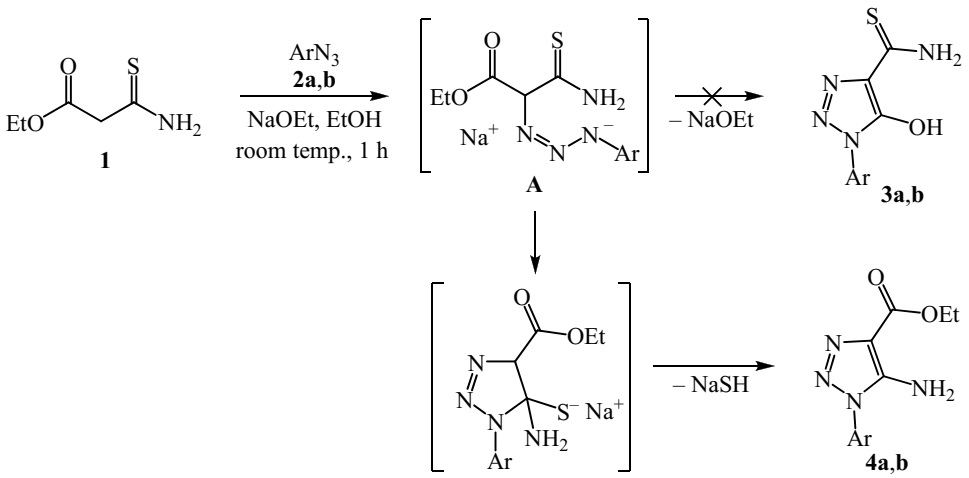
compounds with an active methylene group in the presence of a base. Depending on the nature of the activating group, the reactions can take place either as nucleophilic addition of a carbanion to the azide or by a concerted mechanism as cycloaddition of the azide to the intermediate olefin (enol).

There are many examples of the reaction of azides with various carbonyl and cyano derivatives of acetic acid as well as the so-called Dimroth reaction in the literature [2, 14, 17-21]. Only one example of the use of malonothioamides in the reaction is known – the cyclization of cyanothioacetamide in reaction with aryl azides, where the thioamide group remains unchanged [19]. This example by no means exhausts the rich chemical potentialities of thioamides, their ability to react with various electrophilic reagents and participate in various condensations [22] and rearrangements [7-9].

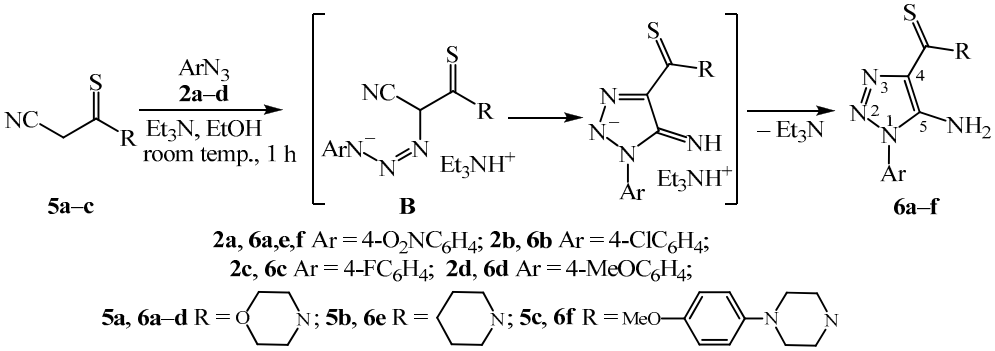
In order to develop new methods for the synthesis of 1,2,3-triazole and 1,2,3-thiadiazole by bringing the thioamide group into reaction with azides, we investigated the reactions of primary and tertiary thioacetamides with aryl and tosyl azides. On the basis of published data [2] we expected the reaction of ethyl 2-thiocarbamoylacetate (**1**) with aryl azides **2a**,**b** in the presence of a base to lead to the formation of 1-aryl-4-hydroxy-1,2,3-triazole-4-carbothioamides **3a**,**b** as a result of addition of the electrophilic azide to the active methylene group with subsequent cyclocondensation of the intermediate triazine **A** and elimination of the ethoxide ion at the last stage of the process.



a Ar = 4-$O_2NC_6H_4$, **b** Ar = 4-ClC_6H_4

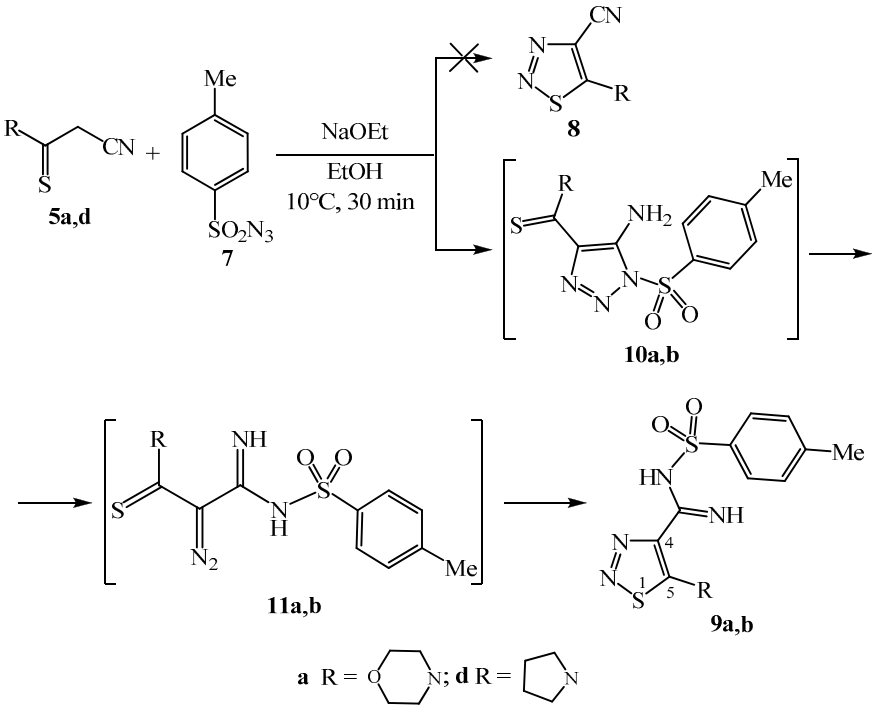
Instead we found that the reaction of the thioamide **1** with the azides **2a**,**b** in the presence of sodium ethoxide at room temperature takes place selectively with the formation of a different type of compound. Ethyl 5-amino-1-aryl-1,2,3-triazole-4-carboxylates **4a**,**b**, the structure of which was established on the basis of data from IR and NMR spectroscopy and mass spectrometry, were isolated from the reaction mixture with moderate yields. In the IR spectrum of compound **4a** there were bands for the stretching vibrations of the ester C=O group (1733 cm^{-1}) and bands for the amino group (3447, 3276 cm^{-1}). In the ^1H NMR spectrum there were signals for the protons of the ethyl group and a singlet for the protons of the amino group at 6.76 ppm. The synthesis of similar 5-amino-1,2,3-triazole-4-carboxylates by other methods was described earlier [2, 23, 24]. The reaction of the 2-thiocarbamoylacetate ester **1** with the aryl azides **2** evidently takes place through intramolecular condensation of the intermediate triazene **A** with participation of the thioamide group. The reaction is the first example of a Dimroth reaction in which the concluding stage is elimination of a hydrosulfide ion.

The reactions of *N*,*N*-disubstituted cyanothioacetamides **5a**-**c** with aryl azides **2a**-**d** in the presence of triethylamine at room temperature also take place selectively with the formation of 5-amino-1-aryl-1,2,3-triazole-4-carbothioamides **6a**-**f**. It can be supposed that in this case intramolecular attack of the anionic center at the nitrogen atom of the triazene **B**, formed in the first stage, occurs more quickly at the electrophilic carbon atom of the cyano group than attack at the thioamide group.



Evidence for the structure of the triazoles **6a-f** was obtained by analysis of the NMR spectra. Thus, the presence of the thioamide group was confirmed by a signal for the amino group protons in the form of a singlet at 7.30 ppm in the ^{1}H NMR spectrum and by a characteristic signal for the thiocarbonyl carbon at 184.6 ppm in the ^{13}C NMR spectrum.

Whereas the reactions of malonothioamides with aryl azides are little known the reaction of malonothioamides with sulfonyl azides is widely used for the production of 1,2,3-thiadiazole derivatives [16]. Therefore, the formation of 5-amino derivatives of 1,2,3-thiadiazole-4-carbonitrile **8** could be expected primarily in the reaction of thioamides **5a**,**d** with tosyl azide **7** in the presence of sodium ethoxide.



In order to exclude possible rearrangements of the 1,2,3-thiadiazoles, the reaction was conducted at reduced temperature (10°C). However, derivatives of the *N*-tosyl-1,2,3-thiadiazole-4-carboxamidine **9a**,**b** and not the expected 1,2,3-thiadiazole-4-carbonitriles **8** were obtained with good yields (80 and 82%, respectively) as a result of the experiment.

The data from ^{1}H and ^{13}C NMR spectroscopy and also mass spectrometry of compounds **9a**,**b** agree well with the *N*-tosylcarboxamidine structure. The ^{1}H NMR spectrum of compound **9a** contains signals for the protons of the tosyl and morpholine fragments and also two singlets for the NH protons at 8.39 and 9.16 ppm. Signals for the carbon atoms of the methyl groups (20.9 ppm), the morpholine (52.9 and 61.9 ppm) and

aromatic (126.2, 129.5, 139.0, and 141.8 ppm) rings, the carbon atom of the amidine group at 136.3 ppm, and the two carbon atoms of the 1,2,3-thiadiazole ring at 156.6 and 170.2 ppm were recorded in the ^{13}C NMR spectrum. The 1,2,3-thiadiazole structure and not the 1,2,3-triazole-4-carbothioamide **10a** is also favored by the absence of a signal for the C=S carbon atom of the thioamide group in the region of 185 ppm. The values of the chemical shifts of the signals for the C-4 and C-5 carbon atoms of the 1,2,3-thiadiazoles **9a**,**b** agree with data from ^{13}C NMR spectroscopy of other derivatives of 5-amino-1,2,3-thiadiazole [3, 4].

The final identification of 5-morpholino-*N*-tosyl-1,2,3-thiadiazole-4-carboxamidine (**9a**) was made by means of two-dimensional NMR spectroscopy on the basis of the results from HMBC and HSQC experiments. Thus, the HMBC spectrum of compound **9a** is characterized by cross peaks of the signals of the C-5 carbon atom (170.2 ppm) and the protons of the morpholine ring (3.20-3.25 ppm) and also by correlation of the signals of the C-3 carbon atom (136.3 ppm) with the NH group protons (8.39 and 9.16 ppm) in the amidine fragment. Cross peaks of all the signals of the carbon and the protons having direct coupling are observed in the HSQC spectrum of compound **9a**.

It is likely that cyclization of the *N*,*N*-disubstituted cyanothioacetamides during the action of tosyl azide takes place as a three-step process: 5-amino-1-tosyl-1*H*-1,2,3-triazole-4-carbothioamides **10a**,**b** are formed at the first stage, and they then undergo a two-stage rearrangement of the Cornforth type to 1,2,3-thiadiazole-4-carboxamidines **9a**,**b** through the intermediate diazo compounds **11a**,**b**.

Thus, in the present work it was shown that various types of heterocyclization are realized in the reactions of azides with thioacetamides derivatives, depending on the nature of the initial reagents, and either esters and thioamides of 5-amino-1-aryl-1,2,3-triazole-4-carboxylic acid or 4-carboxamidine derivatives of 5-amino-1,2,3-thiadiazoles are formed.

EXPERIMENTAL

IR spectra were recorded on a Bruker Alpha Fourier spectrometer with ATIR (ZnSe) for samples of the compounds in powder form. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 and 100 MHz, respectively) in solution of 1:1 DMSO-d_6–CCl_4 with TMS as internal standard. Mass spectra with EI ionization were recorded on a Varian MATT 311A instrument, accelerating potential 3 kV, ionization energy 70 eV. The mass spectrum of compound **9a** with electrospray ionization was recorded on a Bruker Daltonics instrument. Elemental analysis was performed on a Perkin Elmer CHNS 2400 II analyzer. The reactions and the individuality of the obtained compounds were monitored by thin-layer chromatography on Sorbfil UV-254 plates in 9:1 chloroform–hexane and 7:1 chloroform–benzene solvent systems.

The thioamides **1**, **5a-d** were synthesized by the described methods [7, 25] and the tosylamide **7** by the method [25]. The azides **2a-d** were obtained by the method [21] and corresponded to the characteristics given in [26, 27].

Ethyl 5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (4a). The thioamide **1** (0.300 g, 2.00 mmol) was suspended in a solution of sodium ethoxide, prepared from sodium (0.046 g, 2.0 mmol) and absolute ethanol (10 ml), and azide **2a** (0.320 g, 2.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and cooled to 10°C, and the precipitate was filtered off and crystallized from ethanol. Yield 0.371 g (67%). Colorless crystals, mp 174-176°C. IR spectrum, ν, cm^{-1}: 3447, 3276 (NH), 1733 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (3H, t, *J* = 8.0, CH_3); 4.36 (2H, q, *J* = 8.0, CH_2); 6.79 (2H, s, NH_2); 7.90 (2H, d, *J* = 8.6, H Ar); 8.43 (2H, d, *J* = 8.6, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 277 $[M]^+$ (75), 231 (42), 130 (100), 102 (43), 76 (61). Found, %: C 47.57; H 4.12; N 25.39. Calculated, %: C 47.66; H 4.00; N 25.26.

Ethyl 5-Amino-1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylate (4b). This compound was obtained by a similar method. Yield 60%. Colorless crystals, mp 158-160°C. IR spectrum, ν, cm^{-1}: 3438, 3277 (NH), 1732 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 8.0, CH_3); 4.34 (2H, q, *J* = 8.0, CH_2);

6.76 (2H, s, NH_2); 7.9 (2H, d, *J* = 8.2, H Ar); 8.42 (2H, d, *J* = 8.2, H Ar). Found, %: C 49.74; H 4.02; N 20.92. Calculated, %: C 49.54; H 4.16; N 21.01.

Preparation of 5-Amino-1,2,3-triazoles 6a-f (General Method). Equimolar amounts of the azide **2a-d** and triethylamine were added to the thioamide **5a-c** (1.0 mmol) in ethanol. The reaction mixture was stirred at room temperature for 1 h and cooled to 10°C, and the precipitate was filtered off and crystallized from ethanol.

[5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl](morpholin-1-yl)methanethione (6a). Yield 80%. Colorless crystals, mp 164-167°C. IR spectrum, ν, cm^{-1}: 3432, 3292 (NH), 3041 (Ar); 2987, 2857 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.75-3.85 (4H, m, $2CH_2$); 4.20-4.6 (4H, m, $2CH_2$); 7.30 (2H, s, NH_2); 7.92 (2H, d, *J* = 6.2, H Ar); 8.45 (2H, d, *J* = 6.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 49.9 (CH_2), 54.0 (CH_2), 66.6 (CH_2); 66.7 (CH_2); 125.6 (=CH); 125.7 (=CH); 126.6 (C-5); 140.3 (=C); 147.1 (C-4); 147.5 (=C); 184.6 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 334 $[M]^+$ (33), 103 (11), 86 (100), 76 (24). Found, %: C 46.98; H 4.12; N 25.47; S 11.61. $C_{13}H_{14}N_6O_3S$. Calculated, %: C 46.70; H 4.22; N 25.13; S 11.89.

[5-Amino-1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl](morpholin-1-yl)methanethione (6b). Yield 71%. Colorless crystals, mp 168-171°C. IR spectrum, ν, cm^{-1}: 3367, 3226 (NH), 3040 (Ar), 2928, 2862 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.65-3.85 (4H, m, $2CH_2$); 4.25-4.55 (4H, m, $2CH_2$); 7.07 (2H, s, NH_2); 7.60 (4H, s, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 323 $[M]^+$ (27), 210 (100), 153 (67), 111 (34), 76 (14). Found, %: C 48.38; H 4.15; N 21.54; S 9.87. $C_{13}H_{14}N_5OSCl$. Calculated, %: %: C 48.22; H 4.36; N 21.63; S 9.90.

[5-Amino-1-(4-fluorophenyl)]-1*H*-1,2,3-triazol-4-yl](morpholin-1-yl)methanethione (6c). Yield 53%. Colorless crystals, 136-138°C. IR spectrum, ν, cm^{-1}: 3340, 3246 (NH), 3046 (Ar); 2916, 2849 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.65-3.85 (4H, m, $2CH_2$); 4.20-4.55 (4H, m, $2CH_2$); 7.04 (2H, s, NH_2); 7.35-7.42 (2H, m, H Ar); 7.60-7.83 (2H, m, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 307 $[M]^+$ (33), 194 (100), 137 (77), 95 (99), 86 (50), 75 (36). Found, %: C 50.64; H 4.38; N 22.59; S 10.26. $C_{13}H_{14}N_5FOS$. Calculated, %: C 50.80; H 4.54; N 22.79; S 10.43.

[5-Amino-1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl](morpholin-1-yl)methanethione (6d). Yield 67%. Colorless crystals, mp 155-158°C. IR spectrum, ν, cm^{-1}: 3347, 3235 (NH), 3010 (Ar); 2916, 2856 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.65-3.82 (4H, m, $2CH_2$); 3.89 (3H, s, OCH_3); 4.20-4.65 (4H, m, $2CH_2$); 6.92 (2H, s, NH_2); 7.15 (2H, d, *J* = 6.7, H Ar); 7.45 (2H, d, *J* = 6.7, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 319 $[M]^+$ (16), 206 (100), 191 (48), 149 (68), 108 (20), 77 (52). Found, %: C 52.39; H 5.22; N 21.72; S 10.26. $C_{14}H_{17}N_5O_2S$. Calculated, %: C 52.65; H 5.36; N 21.93; S 10.04.

[5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl](piperidin-1-yl)methanethione (6e). Yield 44%. Colorless crystals, mp 167-170°C. IR spectrum, ν, cm^{-1}: 3434, 3293 (NH), 3085 (Ar); 2903, 2857 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70-1.90 (6H, m, CH_2); 4.13 (4H, s, CH_2); 7.18 (2H, s, NH_2); 7.95 (2H, d, *J* = 8.9, H Ar); 8.45 (2H, d, *J* = 8.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 27.4; 50.7; 54.1 (CH_2); 125.6 (=CH); 127.0 (C-5); 140.4 (=C); 147.0 (C-4); 147.5 (=C); 183.6 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 332 $[M]^+$ (19), 111 (15), 84 (100). Found, %: C50.95; H 4.32; N 25.59; S 10.01. $C_{14}H_{16}N_6O_2S$. Calculated, %: C 50.54; H 4.85; N 25.28; S 9.65.

[5-Amino-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl][4-(4-methoxyphenyl)piperazin-1-yl]methanethione (6f). Yield 58%. Colorless crystals, mp 201-203°C. IR spectrum, ν, cm^{-1}: 3396, 3249 (NH), 3081 (Ar), 2905, 2829 (CH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.02-3.38 (4H, m, $2CH_2$); 3.74 (3H, s, OCH_3); 4.25-4.65 (4H, m, $2CH_2$); 7.25 (2H, s, NH_2); 6.75-6.90 (4H, m, H Ar); 7.95 (2H, d, *J* = 7.9, H Ar); 8.49 (2H, d, *J* = 7.9, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 439 $[M]^+$ (16), 190 (19), 175 (21), 162 (100), 134 (73), 108 (17), 77 (20). Found, %: C 54.49; H 4.57; N 22.09; S 7.23. $C_{20}H_{21}N_7O_3S$. Calculated, %: C 54.66; H 4.82; N 22.34; S 7.50.

5-(Morpholin-4-yl)-*N*-tosyl-1,2,3-thiadiazole-4-carboxamidine (9a). The thioamide **5a** (0.31 g, 2.0 mmol) was suspended in a solution of sodium ethoxide prepared from sodium (0.046 g, 2.0 mmol) and absolute ethanol (10 ml), and toluenesulfanyl azide **8** (0.39 g, 2.0 mmol) was added at 10°C with stirring. The precipitate that separated after 30 min was filtered off and recrystallized from ethanol. Yield 80%. Colorless crystals, mp 123-125°C. IR spectrum, ν, cm^{-1}: 3400, 3291 (NH), 2960 (CH); 2859 (CH_2); 1143 (S=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.20-3.25 (4H, m, CH_2); 3.50-3.53 (4H, m, CH_2); 7.39 (2H, d,

J = 8.2, H Ar); 7.79 (2H, d, J = 8.2, H Ar); 8.39 (1H, s, NH); 9.16 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 20.9 (CH_3); 53.0 (CH_2); 64.0 (CH_2); 126.2 (=CH); 129.5 (=CH); 136.3 (C=NH); 139.1 (C–SO_2); 142.8 (C–Me); 156.6 (C-4); 170.2 (C-5). Mass spectrum, m/z (I_{rel}, %): 368 $[M+H]^+$. Found, %: C 45.59; H 4.78; N 18.88; S 17.45. $C_{14}H_{17}N_5O_3S_2$. Calculated, %: C 45.77; H 4.63; N 19.07; S 17.43.

5-(Pyrrolidin-1-yl)-*N*-tosyl-1,2,3-thiadiazole-4-carboxamidine (9b). This compound was obtained by a similar method. Yield 82%. Colorless crystals, mp 163-165°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.87 (4H, s, $2CH_2$); 2.38 (3H, s, CH_3); 3.21 (4H, s, $2CH_2$); 7.38 (4H, d, J = 8.2, H Ar); 7.80 (4H, d, J = 8.2, H Ar); 8.26 (1H, s, NH); 9.08 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 26.0 (CH_2); 55.8 (CH_2); 126.8 (=CH); 129.8 (=CH); 134.7 (C=NH); 139.9 (CSO_2); 142.7 (CMe); 157.2 (C-4); 165.3 (C-5). Mass spectrum, m/z (I_{rel}, %): 351 $[M]^+$ (12), 196 (40), 91 (64), 72 (28), 70 (100). Found, %: C 47.69; H 4.72; N 19.81; S 18.45. $C_{14}H_{17}N_5O_2S_2$. Calculated, %: C 47.85; H 4.88; N 19.93; S 18.25.

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