Reaction of thiosemicarbazide with *N*-cyanoguanidine: synthesis of 3,5-diamino-1-thiocarbamoyl- and 3,5-diamino-1-thiazol-2-yl-1,2,4-triazoles

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The reaction of thiosemicarbazide with *N*-cyanoguanidine in an acidic medium afforded 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole, whose condensation with α-halo ketones gave 3,5-diamino-1-thiazol-2-yl-1,2,4-triazoles **7a—d**. The latter were also prepared by the independent synthesis from 2-hydrazinothiazoles and *N*-cyanoguanidine. Acylation of compounds **7a,d** under mild conditions and their condensation with aldehydes occur at the C(3′)NH_2 group. The structure of aroyl derivative **11c** was established by X-ray diffraction. Acylation of diaminothiazolyltriazole **7a** in boiling Ac_2O afforded 3,5-diacetylamino-1-(4-phenylthiazol-2-yl)-1,2,4-triazole. Hydrogenation of arylidene derivatives **14b,c** and aroyl derivative **11c** gave the corresponding benzylaminotriazoles **15a,b**.

Key words: thiosemicarbazide, *N*-cyanoguanidine, 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole, 3,5-diamino-1-thiazol-2-yl-1,2,4-triazoles, α-halo ketones, acylation, hydrogenation, X-ray diffraction study.

Thiosemicarbazide derivatives are typical polyfunctional reagents, which can react with 1,3-bielectrophiles to form various heterocyclic compounds.[1,2] Earlier,[3] it has been reported that the reaction of thiosemicarbazide (**1**) with *N*-cyanoguanidines **2a—d** afforded 1-amino-4,6-diiminohexahydro-1,3,5-triazine-2-thiones **3a—d**, whose condensation with phenacyl bromide gave [1,3,5]triazino[2,1-*b*][1,3,4]thiadiazines **4a—d** (Scheme 1). However, it is known[4] that the oxo analog of compound **1**, *viz.*, semicarbazide, reacts with compound **2a** at the hydrazine fragment of the molecule to form 3,5-diamino-1-carbamoyl-1,2,4-triazole. Hence, in our opinion, it cannot be ruled out that the reaction of compound **1** with **2** proceeds analogously.

In the present study, we refined the structure of the reaction product of thiosemicarbazide (**1**) with *N*-cyanoguanidine (**2a**) and the structures of the products of its successive reactions with α-halo ketones.

Heating of compounds **1** and **2a** in concentrated hydrochloric acid afforded a compound (in 40% yield), whose melting point, elemental analysis data, and mass spectrum are identical to those described earlier[3] for structure **3a**. However, the ^{1}H NMR spectrum of this compound is inconsistent with diimino structure **3a**. Two two-proton singlets at δ 5.41 and 8.13 are indicative of the presence of two amino groups in the molecule. Two one-proton singlets (δ 8.07 and 9.02) may be assigned to both the imino groups of the tautomer of triazine structure **3a** and the thiocarbamoyl group in structure **5a**. The ^{13}C NMR spectrum of the reaction product shows signals for carbon atoms whose chemical shifts are close to the corresponding values in alkyl-substituted 3,5-diamino-1-thiocarbamoyl-1,2,4-triazoles.[5] Refluxing of the reaction product with phenacyl bromide (**6a**) in methanol gave a compound whose melting point and elemental composition are identical to those of the product, which has been characterized earlier[3] as structure **4a**. However, the ^{1}H NMR spectrum of this compound shows two two-proton singlets of amino groups (which disappear after deuteration) and it better corresponds to the structure of 3,5-diamino-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (**7a**) (see Scheme 1). The proton-coupled ^{13}C NMR spectrum has two singlets (δ 153.8 and 162.5). Based on the published data,[6] these signals were assigned respectively to the C(3′) and C(5′) atoms of the triazole ring (spin-spin coupling between the C atoms and the protons of the amino groups is not observed due to fast exchange of these protons with solvent molecules[7]). The multiplicities

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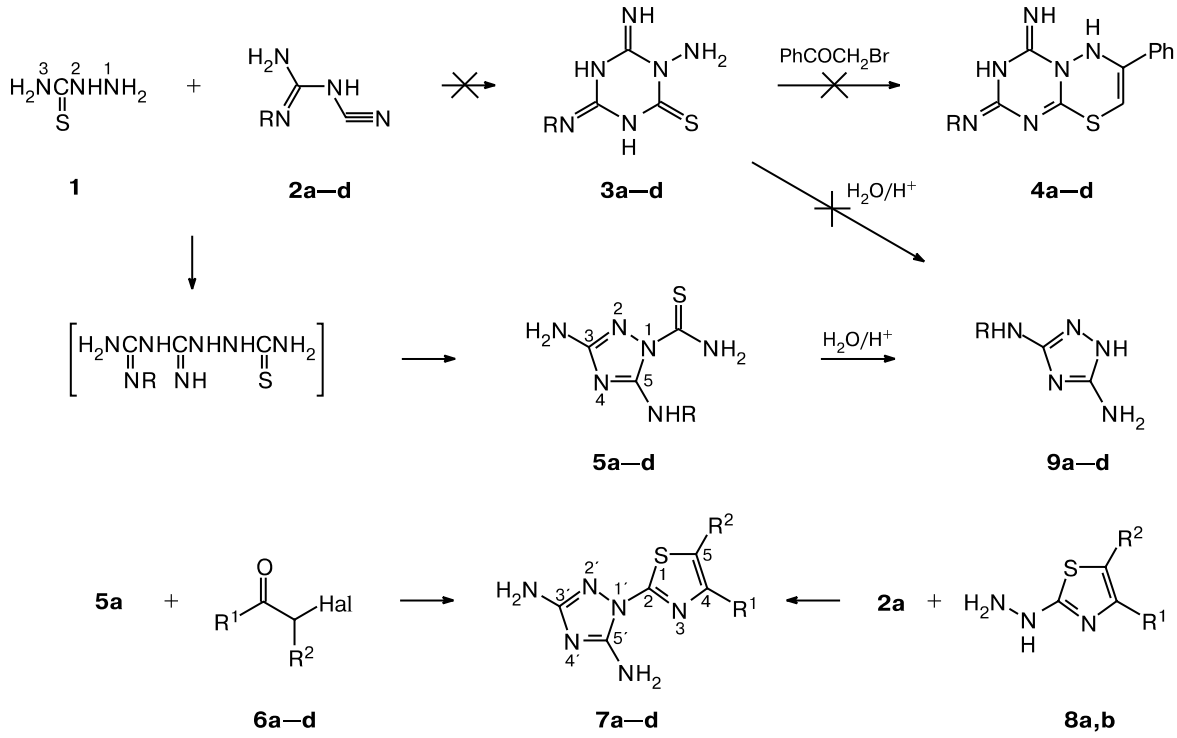
Scheme 1



2—5, 9: R = H (**a**), Ph (**b**), 4-MeC_6H_4 (**c**), 4-ClC_6H_4 (**d**); **6:** Hal = Br (**a—c**), Cl (**d**)
6, 7: R^1 = Ph, R^2 = H (**a**); R^1 = 4-ClC_6H_4, R^2 = H (**b**); R^1 = Me, R^2 = H (**c**); R^1 = Me, R^2 = CO_2Et (**d**)
8: R^1 = Ph, R^2 = H (**a**); R^1 = Me, R^2 = CO_2Et (**b**)

of the other signals correspond to structure **7a**. The structure of compound **7a** was unambiguously proved by its independent synthesis from 2-hydrazino-4-phenyl-1,3-thiazole hydrochloride (**8a**) and nitrile **2a** according to the procedure developed for the synthesis of 1-aryl-3,5-diamino-1,2,4-triazoles.[8] Compounds **7b—d** were synthesized analogously (see Scheme 1).

Therefore, the reaction of thiosemicarbazide (**1**) with compound **2a**, like those of hydrazine and its derivatives,[9,10] involves the nucleophilic addition of the hydrazine fragment at the nitrile group followed by cyclization to give 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole (**5a**).

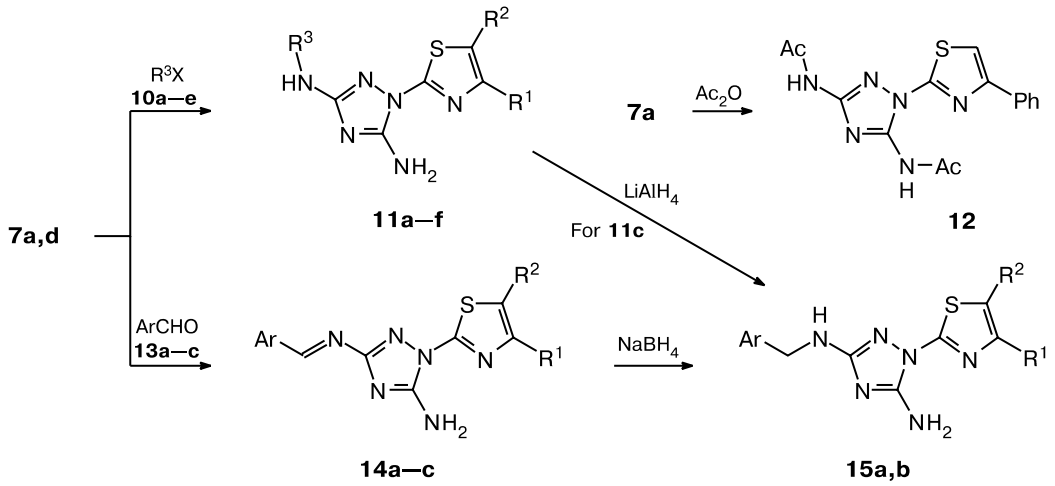
Analysis of the experimental data[3] demonstrated that the reactions of compound **1** with substituted cyanoguanidines **2b—d** also more likely give 3,5-diamino-1-thiocarbamoyl-1,2,4-triazoles **5b—d** rather than triazines **3b—d**. This conclusion is consistent with the results of analysis of fragment ions in the mass spectrum of compound **5b** and the fact that acid hydrolysis of compounds **5b—d** affords triazoles **9b—d** (see Ref. 3 and Scheme 1).

Compounds **7a—d** contain several nucleophilic centers in the molecule and are of interest for studying the reactions with electrophiles. Acylation and sulfonylation of thiazolyltriazoles **7a,d** with compounds **10a—e** in acetonitrile in the presence of pyridine produced derivatives **11a—f** (Scheme 2).

The positions of the acyl and sulfonyl groups in structures **11a—f** were established by analyzing their ^{1}H NMR spectra. It is known[6,10—12] that the signals for the protons of the amino groups in 3,5-diamino-1-R-1,2,4-triazoles appear as two well-resolved singlets, the signal of the amino group at position 5 of the ring being shifted downfield by 1—2 ppm in the spectra of all compounds. The spectra of the starting diamines **7a—d** show signals of the C(3′)NH_2 and C(5′)NH_2 groups at δ 5.5—5.7 and 7.3—7.4, respectively. In the spectra of compounds **11a—f**, the singlet for the protons of the C(3′)NH_2 group disappears, and a broadened singlet for the amide proton appears at δ 10.4—11.1, the signal of the C(5′)NH_2 group being retained and shifted downfield by 0.2—0.4 ppm. Consequently, acylation occurs at the C(3′)NH_2 group. The position of the acyl group in compounds **11** was unambiguously established by X-ray diffraction study of compound **11c** (Fig. 1, Tables 1 and 2).

In the crystals, compound **11c** exists as a crystal solvate with DMF of composition 2 : 3. One DMF molecule occupies a special position on a center of symmetry, which coincides with the position of the nitrogen atom.

Scheme 2



R^1 = Ph (**11a—d**, **14a,b**, **15a**), Me (**11e,f**, **14c**, **15b**); R^2 = H (**11a—d**, **14a,b**, **15a**), CO_2Et (**11e,f**, **14c**, **15b**)
R^3 = Ac (**10a**, **11a**), 4-MeC_6H_4CO (**10b**, **11b**), 2-ClC_6H_4CO (**10c**, **11c**), Ts (**10d**, **11d,f**), PhCO (**10e**, **11e**)
X = OAc (**10a**), Cl (**10b—e**); Ar = 4-$MeOC_6H_4$ (**13a**, **14a**), 2-ClC_6H_4 (**13b**, **14b**, **15a**), 4-ClC_6H_4 (**13c**, **14c**, **15b**)

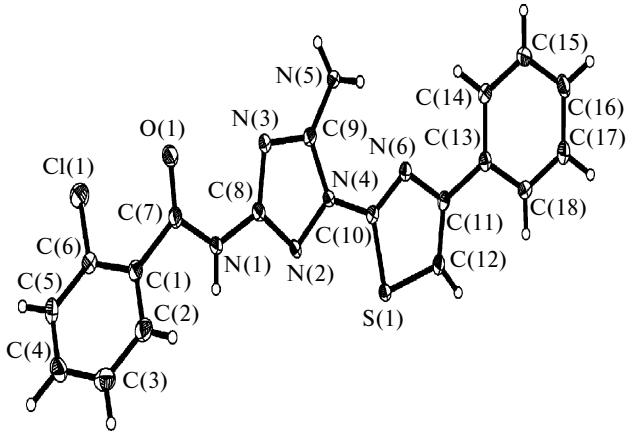


Fig. 1. Structure of compound **11c** (DMF solvate molecules are omitted).

Table 1. Selected bond lengths (*d*) in the structure of **11c**

Bond	*d*/Å	Bond	*d*/Å
Cl(1)—C(6)	1.744(2)	S(1)—C(12)	1.729(1)
S(1)—C(10)	1.730(1)	O(1)—C(7)	1.219(2)
N(1)—C(7)	1.360(2)	N(1)—C(8)	1.395(2)
N(2)—C(8)	1.320(2)	N(2)—N(4)	1.397(2)
N(3)—C(9)	1.335(2)	N(3)—C(8)	1.366(2)
N(4)—C(9)	1.368(2)	N(4)—C(10)	1.390(2)
N(5)—C(9)	1.337(2)	N(6)—C(10)	1.299(2)
N(6)—C(11)	1.393(2)	C(1)—C(6)	1.396(2)
C(1)—C(2)	1.402(2)	C(1)—C(7)	1.509(2)
C(2)—C(3)	1.387(2)	C(3)—C(4)	1.385(2)
C(4)—C(5)	1.385(2)	C(5)—C(6)	1.386(2)
C(11)—C(12)	1.360(2)	C(11)—C(13)	1.480(2)
C(13)—C(14)	1.399(2)	C(13)—C(18)	1.399(2)
C(14)—C(15)	1.389(2)	C(15)—C(16)	1.392(2)
C(16)—C(17)	1.386(2)	C(17)—C(18)	1.392(2)

The trigonal-pyramidal amino group (the sum of the bond angles at the nitrogen atom is 355.3°) and the thiazole ring are linked to each other by the intramolecular N(5)—H(5Na)...N(6) hydrogen bond (2.26 Å), and the N—H...N angle is 128°, which is, apparently, responsible for noncoplanarity of the triazole and thiazole rings (the C(9)—N(4)—C(10)—N(6) torsion angle is 11.1(2)°). The hydrogen bonding also influences the degree of pyramidalization of the amino group. The bond lengths in the triazole ring are consistent with the corresponding values in substituted triazoles studied earlier.[13—15] The carbonyl group of the substituent at the C(8) atom is in the *ap* position with respect to the C(8)—N(2) bond of the triazole ring (the C(7)—N(1)—C(8)—N(2) torsion angle is 167.1(1)°) and is almost coplanar with the N(1)—C(8) bond (the C(8)—N(1)—C(7)—O(1) torsion angle is 5.1(2)°). The *o*-chlorophenyl ring is in the *ap* conformation relative to the N(1)—C(8) bond (the C(8)—N(1)—C(7)—C(1) torsion angle is −172.0(1)°). Repulsion between the chlorine atom and the carbonyl group leads to rotation of the substituent about the C(7)—N(1) bond (the C(2)—C(1)—C(7)—N(1) torsion angle is 57.1(2)°), resulting in the formation of the shortened intramolecular H(1N)...C(2) contact (2.78 Å; the sum of the van der Waals radii is 2.87 Å).[16] The phenyl substituent at the C(11) atom is virtually coplanar with the plane of the thiazole ring (the C(12)—C(11)—C(13)—C(18) torsion angle is −5.1(2)°) in spite of the shortened intramolecular H(14)...N(6) and H(18)...C(12) contacts (2.54 and 2.74 Å, respectively;

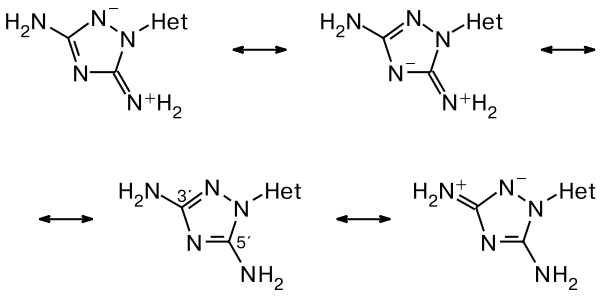
Table 2. Selected bond angles (ω) in the structure of **11c**

Angle	ω/deg	Angle	ω/deg
C(12)—S(1)—C(10)	87.77(7)	C(7)—N(1)—C(8)	126.2(1)
C(8)—N(2)—N(4)	100.7(1)	C(9)—N(3)—C(8)	102.7(1)
C(9)—N(4)—C(10)	129.1(1)	C(9)—N(4)—N(2)	110.0(1)
C(10)—N(4)—N(2)	120.9(1)	C(10)—N(6)—C(11)	109.7(1)
C(6)—C(1)—C(2)	117.9(1)	C(6)—C(1)—C(7)	122.4(1)
C(2)—C(1)—C(7)	119.6(1)	C(3)—C(2)—C(1)	120.8(1)
C(4)—C(3)—C(2)	119.8(2)	C(3)—C(4)—C(5)	120.7(1)
C(4)—C(5)—C(6)	119.1(1)	C(5)—C(6)—C(1)	121.7(1)
C(5)—C(6)—Cl(1)	118.2(1)	C(1)—C(6)—Cl(1)	120.1(1)
O(1)—C(7)—N(1)	125.0(1)	O(1)—C(7)—C(1)	121.4(1)
N(1)—C(7)—C(1)	113.6(1)	N(2)—C(8)—N(3)	117.1(1)
N(2)—C(8)—N(1)	118.4(1)	N(3)—C(8)—N(1)	124.6(1)
N(3)—C(9)—N(5)	126.4(1)	N(3)—C(9)—N(4)	109.5(1)
N(5)—C(9)—N(4)	124.1(1)	N(6)—C(10)—N(4)	122.2(1)
N(6)—C(10)—S(1)	116.7(1)	N(4)—C(10)—S(1)	121.0(1)
C(12)—C(11)—N(6)	114.6(1)	C(12)—C(11)—C(13)	127.0(1)
N(6)—C(11)—C(13)	118.4(1)	C(11)—C(12)—S(1)	111.2(1)
C(14)—C(13)—C(18)	118.8(1)	C(14)—C(13)—C(11)	120.5(1)
C(18)—C(13)—C(11)	120.7(1)	C(15)—C(14)—C(13)	120.4(1)
C(14)—C(15)—C(16)	120.5(1)	C(17)—C(16)—C(15)	119.4(1)
C(16)—C(17)—C(18)	120.6(1)	C(17)—C(18)—C(13)	120.3(1)

the corresponding sums of the van der Waals radii are 2.67 and 2.87 Å).

The amino group at position 5′ is less nucleophilic and is not subjected to acylation under conditions of the synthesis of compounds **11** due, apparently, to the electron-withdrawing effect of two "pyridine" nitrogen atoms of the triazole ring, which are linearly conjugated with this amino group (Scheme 3). The C(3′)NH_2 group is conjugated with only one "pyridine" nitrogen atom and is, consequently, more nucleophilic.

Scheme 3



In spite of low nucleophilicity of the C(5′)NH_2 group, we succeeded in synthesizing diacetyl derivative **12** by refluxing diamine **7a** in acetic anhydride.

Heating of compounds **7a,d** with substituted benzaldehydes **13a—c** in DMF led to condensation at the C(3′)NH_2 group giving rise to arylidene derivatives **14a—c** (see Scheme 2). We failed to prepare diarylidene derivatives according to this procedure. The structures of compounds **14a—c** were confirmed by spectroscopic data, elemental analysis, and the synthesis of benzyl derivatives **15a,b** based on these compounds. In the ^{1}H NMR spectra of compounds **14a—c**, the signal for the protons of the C(3′)NH_2 group is absent, whereas the singlet of the C(5′)NH_2 group persists (δ 7.6—7.8). The spectra of benzyl derivatives **15a,b** show signals of the A_2X system of the protons of the C(3′)$NHCH_2$ fragment. In the proton-coupled ^{13}C NMR spectra of compounds **14b** and **15a,b**, the signal for the C(5′) atom is observed as a singlet at δ 154.0—154.5. The signal for the C(3′) atom (δ 161.5—163.7) is split due to spin-spin coupling with the methine and methylene protons of the benzylidene and benzyl groups, respectively, to form a doublet (J = 11.1 Hz (**14b**)) and a triplet (J = 3.1 Hz (**15a**), J = 2.8 Hz (**15b**)). The pathway of condensation of diamines **7** with aldehydes was additionally confirmed by the independent synthesis of compound **15a** by reduction of aroyl derivative **11c** with lithium aluminum hydride (see Scheme 2).

The above-described transformations show that compounds **7**, as a whole, behave in the reactions with electrophiles analogously to 3,5-diamino-1-aryl-1,2,4-triazoles, in which the amino group at position 5 of the triazole ring has a low nucleophilicity.[12,17]

Experimental

The ^{1}H and ^{13}C NMR spectra were measured on Varian Unity-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) and Varian Mercury VX-200 (200 MHz for ^{1}H) spectrometers in DMSO-d_6 with Me_4Si as the internal standard. The IR spectra were recorded on a Specord IR-75 instrument in Nujol mulls. The mass spectra were obtained on a Varian 1200L spectrometer (direct inlet, EI, 70 eV). The melting points are uncorrected. Compounds **8a** [18] and **8b** [19] were synthesized according to procedures described earlier.

3,5-Diamino-1-thiocarbamoyl-1,2,4-triazole (5a) was prepared by the reaction of compounds **1** and **2a** in concentrated hydrochloric acid according to a known procedure.[3] The yield was 40%, m.p. 163—165 °C (*cf.* lit. data[3]: m.p. 170 °C). Found (%): C, 22.81; H, 3.81; N, 53.16; S, 20.20. $C_3H_6N_6S$. Calculated (%): C, 22.78; H, 3.82; N, 53.13; S, 20.27. IR, ν/cm^{-1}: 3400 (NH), 3260 (NH), 1290 (C=S). ^{1}H NMR, δ: 5.41 (br.s, 2 H, C(3)NH_2); 8.07 (br.s, 1 H, CSNH_2); 8.13 (br.s, 2 H, C(5)NH_2); 9.02 (br.s, 1 H, CSNH_2). ^{13}C NMR, δ: 157.1 (C(5)), 159.7 (C(3)), 174.0 (C=S). MS, m/z (I_{rel} (%)): 158 [M]$^+$ (100), 124 (14).

Synthesis of 3,5-diamino-1-thiazol-2-yl-1,2,4-triazoles 7a—d (general procedure). ***A.*** A mixture of compound **5a** (0.91 g, 5.75 mmol) and halo ketone **6a—d** (5.75 mmol) in methanol (20 mL) was refluxed for 2 h. Then the reaction mixture was cooled and neutralized with a saturated NaOAc solution. The precipitate that formed was filtered off, washed with water, and crystallized.

B. A mixture of compound **2a** (2.4 g, 2.85 mmol) and 2-hydrazinothiazole hydrochloride **8a,b** (2.85 mmol) in H_2O

(100 mL) was refluxed for 1 h. The product was isolated as described in the method *A*.

3,5-Diamino-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (7a). The yield was 80% (method *A*) and 41% (method *B*), m.p. 224—225 °C (from EtOH) (*cf.* lit. data[3]: m.p. 225 °C). Found (%): C, 51.21; H, 3.86; N, 32.39; S, 12.38. $C_{11}H_{10}N_6S$. Calculated (%): C, 51.15; H, 3.90; N, 32.54; S, 12.41. IR, ν/cm^{-1}: 3420 (NH). ^{1}H NMR, δ: 5.73 (br.s, 2 H, C(3′)NH_2); 7.31—7.47 (m, 3 H, H arom.); 7.41 (br.s, 2 H, C(5′)NH_2); 7.70 (s, 1 H, H(5)); 7.93—7.97 (m, 2 H, H arom.). ^{13}C NMR, δ: 107.9 (C(5)), 125.9 (*m*-C arom.), 128.1 (*p*-C arom.), 128.7 (*o*-C arom.), 133.5 (*i*-C arom.), 151.0 (C(4)), 153.8 (C(5′)), 159.1 (C(2)), 162.5 (C(3′)). MS, *m/z* (I_{rel} (%)): 258 [M]$^+$ (61), 174 (45), 102 (88).

3,5-Diamino-1-(4-*p*-chlorophenylthiazol-2-yl)-1,2,4-triazole (7b). The yield was 78% (method *A*), m.p. 265—266 °C (from an AcOH—EtOH mixture). Found (%): C, 45.17; H, 3.21; N, 28.89; S, 11.00. $C_{11}H_9ClN_6S$. Calculated (%): C, 45.13; H, 3.10; N, 28.71; S, 10.95. IR, ν/cm^{-1}: 3470 (NH). ^{1}H NMR, δ: 5.72 (br.s, 2 H, C(3′)NH_2); 7.39 (br.s, 2 H, C(5′)NH_2); 7.47 (m, 2 H, H arom.); 7.76 (s, 1 H, H(5)); 8.01 (m, 2 H, H arom.). MS, *m/z* (I_{rel} (%)): 292 [M]$^+$ (100), 258 (19), 208 (22), 173 (37), 136 (43).

3,5-Diamino-1-(4-methylthiazol-2-yl)-1,2,4-triazole (7c). The yield was 50% (method *A*), m.p. 251—252 °C (from EtOH). Found (%): C, 36.88; H, 4.20; N, 42.51; S, 16.31. $C_6H_8N_6S$. Calculated (%): C, 36.72; H, 4.11; N, 42.83; S, 16.34. IR, ν/cm^{-1}: 3460 (NH). ^{1}H NMR, δ: 2.27 (s, 3 H, Me); 5.62 (br.s, 2 H, C(3′)NH_2); 6.82 (s, 1 H, H(5)); 7.30 (br.s, 2 H, C(5′)NH_2). MS, *m/z* (I_{rel} (%)): 196 [M]$^+$ (100), 154 (20), 112 (59).

3,5-Diamino-1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-1,2,4-triazole (7d). The yield was 8% (method *A*) and 60% (method *B*), m.p. 222—224 °C (from an AcOH—MeCN mixture). Found (%): C, 40.07; H, 4.62; N, 31.50; S, 12.10. $C_9H_{12}N_6O_2S$. Calculated (%): C, 40.29; H, 4.51; N, 31.32; S, 11.95. IR, ν/cm^{-1}: 3390 (NH), 1710 (C=O). ^{1}H NMR, δ: 1.25 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.55 (s, 3 H, Me); 4.21 (q, 2 H, $OC\underline{H}_2CH_3$); 5.88 (br.s, 2 H, C(3′)NH_2); 7.50 (br.s, 2 H, C(5′)NH_2). MS, *m/z* (I_{rel} (%)): 268 [M]$^+$ (30), 112 (35).

3-Acylamino-5-amino-1-thiazol-2-yl-1,2,4-triazoles 11a—c,e and 5-amino-3-tosylamino-1-thiazol-2-yl-1,2,4-triazoles 11d,f (general procedure). A solution of acylating agent **10a—e** (2.6 mmol) in MeCN (1 mL) was added to a mixture of compound **7a** or **7d** (2 mmol), MeCN (1 mL), and pyridine (1 mL). The reaction mixture was refluxed for 10 min. The precipitate that formed after cooling was filtered off and crystallized.

3-Acetylamino-5-amino-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (11a). The yield was 65%, m.p. 294 °C (from a DMF—EtOH mixture). Found (%): C, 60.10; H, 4.11; N, 28.12; S, 10.57. $C_{13}H_{12}N_6OS$. Calculated (%): C, 51.99; H, 4.03; N, 27.98; S, 10.68. IR, ν/cm^{-1}: 3440 (NH), 3300 (NH), 1670 (C=O). ^{1}H NMR, δ: 2.06 (s, 3 H, Me); 7.34—7.48 (m, 3 H, H arom.); 7.67 (br.s, 2 H, NH_2); 7.84 (s, 1 H, H(5)); 8.01 (m, 2 H, H arom.); 10.42 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 300 [M]$^+$ (32), 258 (100), 216 (22), 174 (25), 134 (36).

5-Amino-3-(*p*-methylbenzoylamino)-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (11b). The yield was 70%, m.p. 299—300 °C (from a DMF—EtOH mixture). Found (%): C, 60.49; H, 4.26; N, 22.22; S, 8.61. $C_{19}H_{16}N_6OS$. Calculated (%): C, 60.62; H, 4.28; N, 22.32; S, 8.52. IR, ν/cm^{-1}: 3410 (NH), 3310 (NH), 1670 (C=O). ^{1}H NMR, δ: 2.41 (s, 3 H, Me); 7.20—7.42 (m, 5 H, H arom.); 7.62 (s, 1 H, H(5)); 7.85 (br.s, 2 H, NH_2); 7.87—7.93 (m, 4 H, H arom.); 10.59 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 376 [M]$^+$ (22), 348 (17), 119 (100).

5-Amino-3-(*o*-chlorobenzoylamino)-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (11c). The yield was 65%, m.p. 271—272 °C (from a DMF—EtOH mixture). Found (%): C, 54.33; H, 3.36; N, 22.11; S, 8.01. $C_{18}H_{13}ClN_6OS$. Calculated (%): C, 54.48; H, 3.30; N, 21.18; S, 8.08. ^{1}H NMR, δ: 7.35—7.50 (m, 7 H, H arom.); 7.70 (br.s, 2 H, NH_2); 7.85 (s, 1 H, H(5)); 8.00—8.07 (m, 2 H, H arom.); 11.07 (br.s, 1 H, NH). ^{13}C NMR, δ: 109.6 (C(5)), 126.0, 127.0, 128.3, 128.7, 128.9, 129.5, 129.9, 131.1, 133.3, 136.1, 151.2 (C(4)), 153.6 (C(5′)), 155.0 (C(3′)), 158.9 (C(2)), 164.2 (C=O). MS, *m/z* (I_{rel} (%)): 398 (16), 396 (50), 368 (37), 361 (100), 216 (39), 187 (69).

5-Amino-1-(4-phenylthiazol-2-yl)-3-(*p*-toluenesulfonyl)amino-1,2,4-triazole (11d). The yield was 80%, m.p. 300 °C (decomp.) (from a DMF—MeCN mixture). Found (%): C, 52.69; H, 4.00; N, 20.50; S, 15.72. $C_{18}H_{16}N_6O_2S_2$. Calculated (%): C, 52.41; H, 3.91; N, 20.37; S, 15.55. IR, ν/cm^{-1}: 3450 (NH), 3340 (NH), 1160 (SO_2). ^{1}H NMR, δ: 2.41 (s, 3 H, Me); 7.26—7.40 (m, 5 H, H arom.); 7.59 (s, 1 H, H(5)); 7.62 (br.s, 2 H, NH_2); 7.85—7.89 (m, 4 H, H arom.); 11.03 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 412 [M]$^+$ (14), 216 (66), 215 (87), 162 (39), 160 (90).

5-Amino-3-benzoylamino-1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-1,2,4-triazole (11e). The yield was 60%, m.p. 258—260 °C (from an AcOH—MeCN mixture). Found (%): C, 51.68; H, 4.25; N, 22.49; S, 8.47. $C_{16}H_{16}N_6O_3S$. Calculated (%): C, 51.60; H, 4.33; N, 22.57; S, 8.61. IR, ν/cm^{-1}: 3410 (NH), 3370 (NH), 1710 (C=O), 1670 (C=O). ^{1}H NMR, δ: 1.34 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.65 (s, 3 H, Me); 4.30 (q, 2 H, $OC\underline{H}_2CH_3$); 7.40—7.58 (m, 3 H, H arom.); 7.72 (br.s, 2 H, NH_2); 7.87—8.01 (m, 2 H, H arom.); 10.78 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 372 [M]$^+$ (82), 344 (73), 292 (24), 226 (28).

5-Amino-1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-3-(*p*-toluenesulfonyl)amino-1,2,4-triazole (11f). The yield was 60%, m.p. 288—290 °C (from a DMF—EtOH mixture). Found (%): C, 45.60; H, 4.34; N, 20.02; S, 15.31. $C_{16}H_{18}N_6O_4S_2$. Calculated (%): C, 45.49; H, 4.29; N, 19.89; S, 15.18. IR, ν/cm^{-1}: 3380 (NH), 3250 (NH), 1690 (C=O), 1160 (SO_2). ^{1}H NMR, δ: 1.36 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.40 (s, 3 H, Me); 2.60 (s, 3 H, C(4)Me); 4.30 (q, 2 H, $OC\underline{H}_2CH_3$); 7.31 (m, 2 H, H arom.); 7.65 (br.s, 2 H, NH_2); 7.84 (m, 2 H, H arom.); 11.15 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 422 [M]$^+$ (22), 284 (22), 226 (59), 225 (83), 200 (87).

3,5-Diacetylamino-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (12). A mixture of compound **7a** (1 g, 3.9 mmol) and Ac_2O (3 mL) was refluxed for 4 h. Then EtOH (3 mL) was added, the solvent was distilled off, and the residue was treated with water and recrystallized. The yield was 1.2 g (90%), m.p. 240—242 °C (from a AcOH—MeCN mixture). Found (%): C, 52.49; H, 4.16; N, 24.63; S, 9.40. $C_{15}H_{14}N_6O_2S$. Calculated (%): C, 52.62; H, 4.12; N, 24.55; S, 9.36. ^{1}H NMR, δ: 2.08 and 2.27 (both s, 3 H each, Me); 7.38—7.50 (m, 3 H, H arom.); 7.92 (m, 2 H, H arom.); 8.00 (s, 1 H, H(5)); 10.84 and 10.91 (both br.s, 1 H each, NH). MS, *m/z* (I_{rel} (%)): 342 [M]$^+$ (7), 300 (20), 258 (83), 216 (68), 174 (34).

5-Amino-3-(*p*-methoxybenzylideneamino)-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (14a). A mixture of compound **7a** (0.5 g,

1.9 mmol), DMF (2 mL), and *p*-methoxybenzaldehyde (0.31 g, 2.3 mmol) was refluxed for 5 min and then cooled. Ethanol (5 mL) was added and the precipitate that formed was filtered off. The yield was 0.5 g (70%), m.p. 261—262 °C (from a DMF—EtOH mixture). Found (%): C, 60.68; H, 4.14; N, 22.53; S, 8.64. $C_{19}H_{16}N_6OS$. Calculated (%): C, 60.62; H, 4.28; N, 22.32; S, 8.52. ^{1}H NMR, δ: 3.88 (s, 3 H, OMe); 7.01 (m, 2 H, H arom.); 7.28—7.43 (m, 4 H, H arom.); 7.61 (br.s, 2 H, NH_2); 7.90—7.93 (m, 4 H, H arom., H(5)); 9.03 (s, 1 H, CH=N). MS, *m/z* (I_{rel} (%)): 376 $[M]^+$ (48), 242 (19), 176 (19), 159 (34), 146 (39).

Compounds **14b,c** were prepared analogously.

5-Amino-3-(*o*-chlorobenzylideneamino)-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (14b). The yield was 69%, m.p. 272—273 °C (from a DMF—EtOH mixture). Found (%): C, 56.51; H, 3.52; N, 22.21; S, 8.40. $C_{18}H_{13}ClN_6S$. Calculated (%): C, 56.77; H, 3.44; N, 22.07; S, 8.42. ^{1}H NMR, δ: 7.34—7.64 (m, 6 H, H arom.); 7.85 (br.s, 2 H, NH_2); 7.93 (s, 1 H, H(5)); 8.05 (m, 2 H, H arom.); 8.24 (m, 1 H, H arom.); 9.53 (s, 1 H, CH=N). ^{13}C NMR, δ: 110.1 (C(5)), 126.0, 127.9, 128.4, 128.8, 130.3, 131.8, 133.2, 134.0, 135.9, 151.4 (C(4)), 154.4 (C(5′)), 158.9 (C(2)), 161.0 (CH=N), 163.8 (C(3′)). MS, *m/z* (I_{rel} (%)): 380 $[M]^+$ (95), 345 (100), 337 (17), 303 (15), 242 (35), 176 (38), 134 (63).

5-Amino-3-(*p*-chlorobenzylideneamino)-1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-1,2,4-triazole (14c). The yield was 60%, m.p. 253—254 °C (from a AcOH—EtOH mixture). Found (%): C, 48.98; H, 3.96; N, 21.82; S, 8.32. $C_{16}H_{15}ClN_6O_2S$. Calculated (%): C, 49.17; H, 3.87; N, 21.50; S, 8.20. ^{1}H NMR, δ: 1.28 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.63 (s, 3 H, Me); 4.28 (q, 2 H, $OC\underline{H}_2CH_3$); 7.60 (m, 2 H, H arom.); 7.83 (br.s, 2 H, NH_2); 8.01 (m, 2 H, H arom.); 9.09 (s, 1 H, CH=N). MS, *m/z* (I_{rel} (%)): 392 $[M]^+$ (53), 390 (81), 347 (18), 186 (13), 181 (24).

5-Amino-3-(*o*-chlorobenzylamino)-1-(4-phenylthiazol-2-yl)-1,2,4-triazole (15a). ***A.*** Sodium borohydride (0.1 g, 2.6 mmol) was added portionwise with stirring to a suspension of compound **14b** (0.5 g, 1.3 mmol) in EtOH (5 mL) at 50—70 °C. The reaction mixture was refluxed for 10 min and then H_2O (30 mL) was added. The precipitate that formed was washed with water and recrystallized. The yield was 0.3 g (42%), m.p. 221—223 °C (from a DMF—EtOH mixture). Found (%): C, 56.52; H, 4.01; N, 21.64; S, 8.41. $C_{18}H_{15}ClN_6S$. Calculated (%): C, 56.47; H, 3.95; N, 21.95; S, 8.37. ^{1}H NMR, δ: 4.39 (d, 2 H, CH_2, J = 6.2 Hz); 6.94 (t, 1 H, NH, J = 6.2 Hz); 7.23—7.46 (m, 7 H, H arom.); 7.50 (br.s, 2 H, C(5′)NH_2); 7.71 (s, 1 H, H(5)); 7.97 (m, 2 H, H arom.). ^{13}C NMR, δ: 43.4 (CH_2), 108.0 (C(5)), 125.8, 126.9, 128.1, 128.2, 128.6, 128.7, 128.9, 131.8, 133.5, 137.4, 151.0 (C(4)), 154.0 (C(5)), 159.1 (C(2)), 162.5 (C(3′)). MS, *m/z* (I_{rel} (%)): 382 $[M]^+$ (31), 347 (29), 242 (55), 173 (50), 160 (29), 134 (40), 125 (100).

B. A mixture of compound **11c** (1.0 g, 2.6 mmol) and $LiAlH_4$ (0.3 g, 7.9 mmol) in THF (10 mL) was refluxed for 12 h. Then $LiAlH_4$ (0.3 g, 7.9 mmol) was added, the reaction mixture was refluxed for 12 h, H_2O (3 mL) was added, and the solvent was distilled off. The residue was dissolved with heating in 10% HCl (5 mL). The precipitate that formed upon cooling was filtered off, washed with a small amount of water, and treated with a 5% NaOH solution (10 mL) at high temperature. The precipitate was filtered off and recrystallized from a DMF—EtOH mixture. The yield was 0.1 g (10%). The properties of the reaction product were identical to those of the product prepared according to the method *A*.

5-Amino-3-(*p*-chlorobenzylamino)-1-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-1,2,4-triazole (15b) was prepared by reduction of compound **14c** (0.5 g, 1.3 mmol) as described above for the synthesis of compound **15a** according to method *A*. The yield was 0.3 g (59%), m.p. 168—170 °C (from a DMF—EtOH mixture). Found (%): C, 49.08; H, 4.29; N, 21.42; S, 8.20. $C_{16}H_{17}ClN_6O_2S$. Calculated (%): C, 48.92; H, 4.36; N, 21.39; S, 8.16. ^{1}H NMR, δ: 1.30 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.60 (s, 3 H, C(4)Me); 4.26 (q, 2 H, $OC\underline{H}_2CH_3$); 4.28 (d, 2 H, $NHC\underline{H}_2$, J = 5.8 Hz); 6.80 (t, 1 H, NH, J = 5.8 Hz); 7.22—7.36 (m, 4 H, H arom.); 7.48 (br.s, 2 H, C(5′)NH_2). ^{13}C NMR, δ: 14.1 ($OCH_2\underline{C}H_3$), 17.2 (C(4)$\underline{C}H_3$), 44.9 (CH_2NH), 60.8 ($O\underline{C}H_2CH_3$), 114.5 (C(5)), 128.0, 129.0, 131.1, 139.27, 154.5 (C(5′)), 158.1 (C(4)), 159.8 (C(2)), 161.5 (C=O), 162.9 (C(3′)). MS, *m/z* (I_{rel} (%)): 392 $[M]^+$ (17), 200 (23), 181 (74).

X-ray diffraction study. Single crystals of compound **11c** were grown by crystallization from a DMF—ethanol mixture. Crystals of **11c** are triclinic, $C_{18}H_{13}ClN_6OS \cdot 1.5C_3H_7NO$, at −173 °C a = 10.104(1) Å, b = 11.033(1) Å, c = 11.641(1) Å, α = 72.04(1)°, β = 74.16(1)°, γ = 79.85(1)°, V = 1181.6(1) Å^3, M_r = 506.50, Z = 2, space group $P\bar{1}$, d_{calc} = 1.424 g cm^{-3}, μ(Mo-Kα) = 0.290 mm^{-1}, F(000) = 528. The unit cell parameters and intensities of 14994 reflections (4019 independent reflection, R_{int} = 0.019) were measured on a Xcalibur-3 diffractometer (Mo-Kα radiation, CCD detector, graphite monochromator, ω scanning technique, $2\theta_{max} = 50°$). The structure was solved by direct methods using the SHELXTL program package.[20] The positions of the hydrogen atoms were located from difference electron density maps and refined isotropically. The structure was refined by the full-matrix least-squares method against F^2 with anisotropic displacement parameters for all nonhydrogen atoms to wR_2 = 0.077 using 3971 reflections (R_1 = 0.030 for 3792 reflections with $F > 4\sigma(F)$, S = 1.051). The atomic coordinates in the structure of **11c** and complete tables of the bond lengths and bond angles were deposited with the Cambridge Structural Database. Selected bond lengths and bond angles are given in Tables 1 and 2, respectively.

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