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5-AMINO-3,4-DIHYDRO-2H-1,2,4-TRIAZOLE-3-THIONES. SYNTHESIS AND CHEMOSENSOR PROPERTIES

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The reaction of 4-arylalkyl- and 4-arylthiosemicarbazides with aroyl isothiocyanates gave substituted 1,2-bis(thiocarbamoyl)hydrazines, which readily cyclize to give previously unreported 4-aroyl 5-arylalkyl- and 4-aroyl-5-arylamino-2H-1,2,4-triazole-3-thiones, respectively. A spectral study of 9-anthrylmethylthiosemicarbazides and derived dihydrotriazolethione indicated the chemosensor activity of these compounds relative to a cation series.

Keywords: 4-arylalkyl- and 4-arylthiosemicarbazides, aroyl and hetaroyl isothiocyanates, 1,2,4-triazole-3-thiones, fluorescent chemosensors.

Derivatives of 1,2,4-triazole have found common use in medicine [1-3] and as efficient corrosion inhibitors [4], catalysts [5], ligands [6], and chemosensors [7], Various pathways and methods exist for the synthesis and modification of both 1,2,4-triazole [8-10] and its 3-thio derivatives [11-13]. Greatest interest is found for one- and two-step methods for the preparation of similar structures. Hydrazides of acids and 4-substituted thiosemicarbazides in combination with isothiocyanates or cyanamides are often used for the synthesis of 1,2,4-triazole-3-thiones as the starting compounds.

In previous work [14], we have shown the feasibility of using thioureas containing a 9-anthrylmethyl fragment as highly efficient chemosensors for the Hg^{2+} cation. In a search for new, highly efficient sulfur-containing anion and cation sensors, 4-(9-anthrylmethyl)thiosemicarbazide (**1a**) was obtained starting from 9-aminomethylanthracene according to Kazakov and Postovskii [15]. In order to increase the number of coordination sites, we carried out the reaction of compound **1a** with *p*-chlorobenzoyl isothiocyanate (**2a**) obtained *in situ* from *p*-chlorobenzoyl chloride and ammonium thiocyanate in acetonitrile. However, 1,2,4-triazole-3-thione (**4a**) was obtained as the major product instead of the expected substituted 1,2-bis(thiocarbamoyl)hydrazine **3a**. This result can probably be attributed to the thermal cyclization of initially formed compound **3a** upon its recrystallization from 1-butanol. Cyclic products **4b-h** were also obtained in the reaction of 4-arylalkyl- and 4-arylthiosemicarbazides **1b-d** with aroyl and hetaroyl isothiocyanates **2b-f** (see Scheme).

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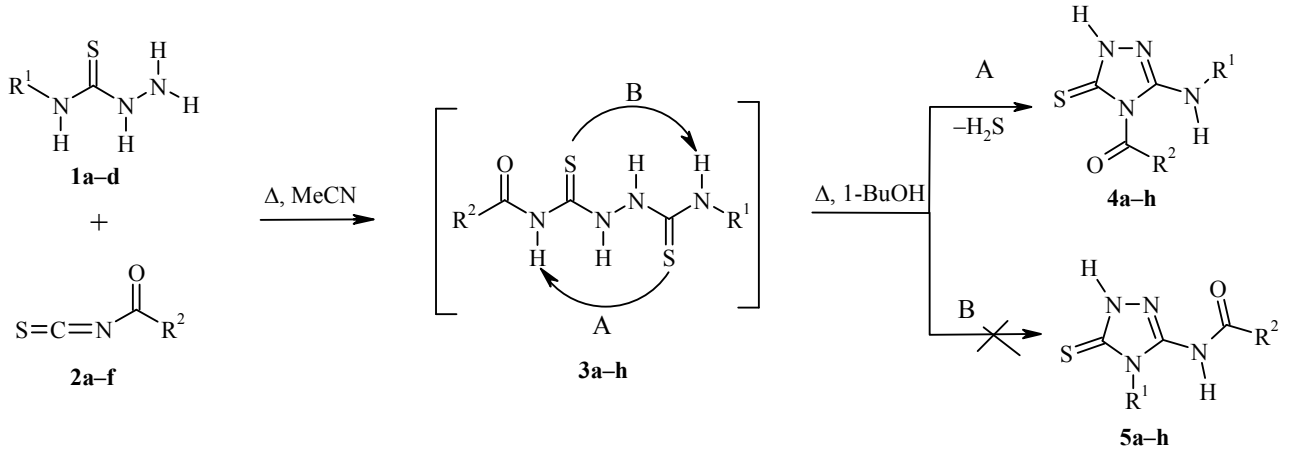
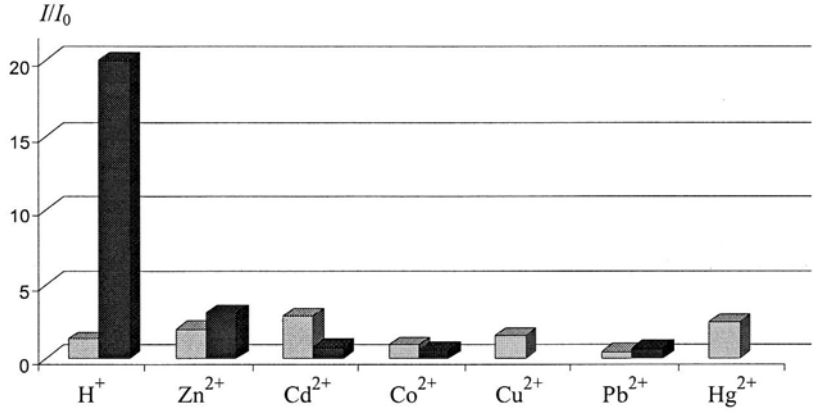


1–5 a R^1 = 9-anthrylmethyl, R^2 = C_6H_4Cl-*p*; **b** R^1 = CH_2Ph, R^2 = C_6H_4F-*p*; **c** R^1 = CH_2CH_2Ph, R^2 = C_6H_4F-*m*; **d** R^1 = C_6H_4OMe-*o*, R^2 = $C_6H_4CMe_3$-*p*; **2–5 e** R^1 = CH_2Ph, R^2 = C_6H_4Me-*p*; **f** R^1 = C_6H_4OMe-*o*, R^2 = thien-2-yl; **3–5 g** R^1 = CH_2Ph, R^2 = C_6H_4Cl-*p*; **h** R^1 = CH_2CH_2Ph, R^2 = C_6H_4Cl-*p*

The cyclization of substituted bis(thiocarbamoyl)hydrazines **3** may take place through alternative pathways: 1) Formation of 4-aroyl-5-arylalkylamino- or 4-aroyl-5-arylamino-1,2,4-triazole-3-thiones **4a-h** or 2) Formation of N-[4-arylalkyl- or N-[4-aryl-5-thioxo-1,2,4-triazol-3-yl]carboxamides **5a-h**. However, the spectral evidence indicates the formation only of a compounds corresponding to thione structure **4**, i.e., the cyclization proceeds through pathway A and not through alternative pathway B, which would have given products with structure **5** (see Scheme). Thus, the ^{1}H NMR spectra of the products obtained feature broad single-proton signals for the ring NH group at 12-13 ppm and signals for the CH_2 group (in **4a-c**, **4e**,**g**,**h**) as a doublet or quartet at 3-6 ppm, indicating intereaction with the NH group protons and the protons of the adjacent CH_2 groups (in **4c**,**h**). The IR spectra of **4a-h** have NH group stretching bands at 3300-3400 and 3100-3200 cm^{-1} and C=O group stretching bands at 1640-1670 cm^{-1}. In the case of compounds **4d**,**f**, the NH group signal is found at 9.10-9.20 ppm as a singlet. Such a downfield shift is characteristic for some derivatives of N-aryl-N-(1,2,4-triazol-3-yl)amines [13].



1a	1.3	2.0	2.9	0.9	1.6	0.5	2.5
4a	20.1	3.1	0.8	0.6	–	0.7	–

Fig. 1. Relative change in the fluorescence intensity (I/I_0) for compounds **1a** and **4a** ($c = 5\cdot10^{-6}$ mol/l) in acetonitrile upon the addition of various cations ($c = 2.5\cdot10^{-5}$ mol/l). "–" indicates the absence of fluorescence. □ – **1a**, ■ – **4a**.

The structure of intermediates **3** was demonstrated for thiosemicarbazide **3e**, which could be separated and characterized. The ^{1}H NMR spectrum of **3e** has characteristic signals for the protons of the four NH groups at 8.76 (t, J = 5.8 Hz), 10.38 (br. s), 11.37 (s), and 13.72 ppm (br. s) as well as a doublet for the CH_2 group protons at 4.74 ppm (d, J = 5.8 Hz). In all the other cases, intermediates **3** underwent cyclization during purification.

Anthrylthiosemicarbazide **1a** and anthryl-1,2,4-triazole-3-thione **4a** were studied relative to their chemosensor properties. The chemisensor properties of these compounds were evaluated relative to the fluorescence spectra data (λ_{max} = 390 nm) before and after addition of trifluoroacetic acid or metal (Zn^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Pd^{2+}, Hg^{2+}) acetates to their solutions.

Thiosemicarbazide **1a** showed low sensitivity and selectivity as a chemosensor relative to the cation series studied (Fig. 1). In this case, the PET effect was the major condition for realizing sensor properties [16].

The addition of divalent transition metal (Cu, Hg) acetates to a solution of **4a** in acetonitrile caused extinction of the local anthracene emission, while the addition of H^+ and Zn^{2+} ions led to an increase in its intensity by factors of 20 and 3, respectively (Fig. 1).

Thus, a method has been developed for the synthesis of previously unreported derivatives of 5-amino-3,4-dihydro-2H-1,2,4-triazole-3-thione and we have shown that 5-[(9-anthrylmethyl)amino]-4-(*p*-chlorobenzoyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione displays chemosensor properties toward acids and a series of transition metal cations.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer for vaseline mulls. The electronic absorption spectra were taken on a Varian Cary 100 spectrometer. The fluorescence spectra were taken on a Hitachi 650-60 spectrofluorimeter. The ^{1}H NMR spectra were taken on a Varian Unity 300 spectrometer at 300 MHz and a Bruker 600 spectrometer at 600 MHz in DMSO-d_6. The residual DMSO signals served as the internal standard (δ 2.50 ppm). The melting points were determined in glass capillaries on a PTP(M) instrument. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform as the eluent and development by iodine vapor in a moist chamber. The starting thiosemicarbazides **1a-d** were obtained according to Kazakov and Postovskii [15].

Synthesis of Compounds 3a-h and 4a-h (General Method). NH_4NCS (18 mmol) was dissolved in acetonitrile (100 ml) at 60-70°C. The solution was cooled to 35-40°C and aroyl chloride (12 mmol) was added with stirring. The suspension obtained was stirred for 15-20 min and then a solution of corresponding thiosemicarbazide **1a-d** (10 mmol) in acetonitrile (50 ml) was added. Stirring was continued for 30 min at 45-50°C. The reaction mixture was diluted with cold water. The precipitate of product **3a-h** was filtered off, washed with water, and dried in the air. Then, amide **3a-h** (5 mmol) in 1-butanol (100 ml) was heated at reflux for 4-6 h and cooled to room temperature. The precipitate of product **4a-h** was filtered off, washed with hot methanol, dried in the air, and crystallized from a suitable solvent. Products **4a-h** were obtained analogously by heating amides **3a-h** in 2-butanol, 2-methyl-1-propanol, 2-methyl-2-butanol, 3-methyl-1-butanol, and 1-pentanol.

N(1)-Benzylaminothioxo-N(4)-(*p*-methylbenzoyl)thiosemicarbazide (3e) was obtained in 81% yield; mp >120°C (acetonitrile, cyclization). IR spectrum, ν, cm^{-1}: 3400, 1640, 1500, 1460. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.60 (3H, s, CH_3), 4.74 (2H, d, J = 5.8, CH_2); 7.10-8.00 (9H, m, H arom); 8.76 (1H, br. s, R^{1}NH); 10.38 (1H, br. s, NH); 11.37 (1H, br. s, NH); 13.72 (1H, br. s, NH). Found, %: C 56.89; H 5.00; N 15.71; S 17.91. $C_{17}H_{18}N_4OS_2$. Calculated, %: C 56.96; H 5.06; N 15.63; S 17.89.

5-[(9-Anthrylmethyl)amino]-4-(*p*-chlorobenzoyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (4a) was obtained in 67% yield; mp 290-291°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 1650, 1540, 1500, 1465. ^{1}H NMR spectrum, δ, ppm (J, Hz): 5.42 (2H, d, J = 5.4, CH_2); 7.35-8.62 (14H, m, H arom, R^{1}NH); 12.46 (1H,

br. s, NH ring). Found, %: C 64.77; H 3.88; Cl 8.02; N 12.55; S 7.27. $C_{24}H_{17}ClN_4OS$. Calculated, %: C 64.79; H 3.85; Cl 7.97; N 12.59; S 7.21.

5-(Benzylamino)-4-(*p*-fluorobenzoyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (4b) was obtained in 79% yield; mp 272-273°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 3375, 1645, 1535, 1500, 1470. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.46 (2H, d, *J* = 6.7, CH_2); 7.10-7.44 (7H, m, H arom); 7.67 (1H, t, *J* = 6.7, R^1NH); 8.05-8.24 (2H, m, H arom); 12.38 (1H, br. s, NH ring). Found, %: C 58.59; H 3.95; F 5.72; N 17.11; S 9.76. $C_{16}H_{13}FN_4OS$. Calculated, %: C 58.52; H 3.99; F 5.79; N 17.06; S 9.73.

4-(*m*-Fluorobenzoyl)-5-[(2-phenylethyl)amino]-3,4-dihydro-2H-1,2,4-triazole-3-thione (4c) was obtained in 76% yield; mp 235-236°C (1-BuOH). IR spectrum, ν, cm^{-1}: 3380, 1640, 1495, 1460. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.90 (2H, t, *J* = 7.5, $PhC\underline{H}_2$); 3.50 (2H, q, $PhCH_2C\underline{H}_2$); 7.00-8.00 (10H, m, H arom, R^1NH); 12.47 (1H, br. s, NH ring). Found, %: C 59.68; H 4.44; F 5.51; N 16.41; S 9.34. $C_{17}H_{15}FN_4OS$. Calculated, %: C 59.63; H 4.42; F 5.55; N 16.36; S 9.37.

4-(*p*-*tert*-Butylbenzoyl)-5-[(*o*-methoxyphenyl)amino]-3,4-dihydro-2H-1,2,4-triazole-3-thione (4d) was obtained in 72% yield; mp 242-243°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 1650, 1490, 1465. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, CH_3); 3.80 (3H, s, OCH_3); 6.90-8.50 (8H, m, H arom); 9.10 (1H, s, R^1NH); 12.45 (1H, br. s, NH ring). Found, %: C 62.76; H 5.82; N 14.70; S 8.32. $C_{20}H_{22}N_4O_2S$. Calculated, %: C 62.80; H 5.80; N 14.65; S 8.38.

5-(Benzylamino)-4-(*p*-methylbenzoyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (4e) was obtained in 67% yield; mp 260-261°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 3345, 1640, 1490, 1460. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3); 4.46 (2H, d, *J* = 6.0, CH_2); 7.11-7.45 (7H, m, H arom); 7.65 (1H, t, *J* = 6.0, R^1NH); 7.86-8.07 (2H, m, H arom); 12.18 (1H, br. s, NH ring). Found, %: C 62.90; H 4.91; N 17.35; S 9.93. $C_{17}H_{16}N_4OS$. Calculated, %: C 62.94; H 4.97; N 17.27; S 9.88.

5-[(*o*-Methoxyphenyl)amino]-4-(thien-2-ylcarbonyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (4f) was obtained in 78% yield; mp 257-258°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 3370, 1645, 1530, 1495, 1315. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.90 (3H, s, OCH_3); 6.80-8.45 (7H, m, H arom); 9.20 (1H, s, R^1NH); 12.57 (1H, br. s, NH ring). Found, %: C 50.64; H 3.60; N 16.91; S 19.33. $C_{14}H_{12}N_4O_2S_2$. Calculated, %: C 50.59; H 3.64; N 16.86; S 19.29.

5-(Benzylamino)-4-(*p*-chlorobenzoyl)-3,4-dihydro-2H-1,2,4-triazole-3-thione (4g) was obtained in 81% yield; mp 258-259°C (4:1 1-BuOH–DMF). IR spectrum, ν, cm^{-1}: 3365, 1640, 1495, 1465. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.47 (2H, d, *J* = 6.8, CH_2); 7.12-7.52 (7H, m, H arom); 7.70 (1H, t, *J* = 6.8, R^1NH); 8.03-8.15 (2H, m, H arom); 12.45 (1H, br. s, NH ring). Found, %: C 55.70; H 3.74; Cl 10.34; N 16.27; S 9.22. $C_{16}H_{13}ClN_4OS$. Calculated, %: C 55.73; H 3.80; Cl 10.28; N 16.25; S 9.30.

4-(*p*-Chlorobenzoyl)-5-[(2-phenylethyl)amino]-3,4-dihydro-2H-1,2,4-triazole-3-thione (4h) was obtained in 76% yield; mp 165-166°C *t*-BuOH). IR spectrum, ν, cm^{-1}: 3350, 1640, 1505, 1460. ^{1}H NMR spectrum, δ, ppm (*J*, Hz); 2.88 (2H, t, *J* = 7.1, $PhC\underline{H}_2$); 3.54 (2H, q, $PhCH_2C\underline{H}_2$); 6.95-7.90 (10H, m, H arom); R^1NH); 12.45 (1H, br. s, NH ring). Found, %: C 56.92; H 4.20; Cl 9.94; N 15.66; S 8.90. $C_{17}H_{15}ClN_4OS$. Calculated, %: C 56.90; H 4.21; Cl 9.88; N 15.61; S 8.94.

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