Convenient way to 5-Substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones

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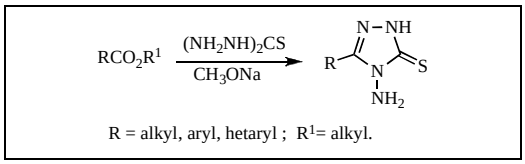

Various 4-amino-2,3-dihydro-4*H*-triazoles with aromatic, aliphatic and heterocyclic substituents at the C(5) position were synthesized from corresponding esters and thiocarbohydrazide. This method allows the synthesis these heterocycles in a short time and at reduced expenses.

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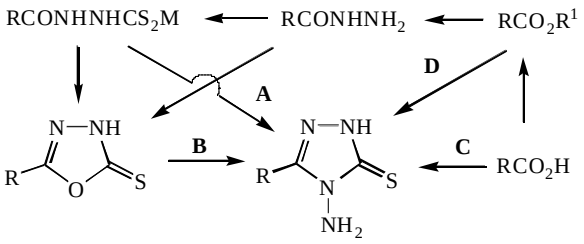
INTRODUCTION

Substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones are interesting compounds due to their chemical and biological properties. First, polyfunctionality of these heterocycles gives the possibility to synthesize a variety of derivatives, and second, among these compounds there are several representatives with various biological activities, such as antibacterial [1-7], antifungal [1-3,5,8], antiparasitic [5,6,9], anti-inflammatory [10-12], analgesic [12], and anticancer [7,13,14]. Some of these derivatives can also act as selective ligands for serotonine receptors [15]. Noticeable are also other properties such as resistance to gamma irradiation [8] and the ability to form complexes with transition metals [16]. These diverse features make that class of heterocyclic compounds important in respect to the synthesis of biologically valuable derivatives.

The common pathways for 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones are reactions of 3-acyldithiocarbazates [17,18] or 1,3,4-oxadiazole-2-thiones [19] with hydrazine (Scheme 1, directions **A**, **B**). An alternative way to the mentioned aminotriazolethiones is the fusion of a carboxylic acid and thiocarbohydrazide [20] (Scheme 1, direction **C**). The latter is applicable for aliphatic [20] and some aromatic acids [21] and is more convenient than the precedent methods because it avoids additional steps, *i.e.*, the preparation of hydrazides, dithiocarbazates, oxadiazolethiones, or even the esters, if they are not commercially available. However melting points of the carboxylic acids should be low enough to avoid the thiocarbohydrazide decomposition above 171ºC [22].

This problem is partly eliminated for the esters, whose melting points usually are much lower than for acids (Scheme 1, direction **D**). Surprisingly, even

Scheme 1



R = alkyl, aryl, hetaryl; R^1 = alkyl; M = Na, K, alkyl.

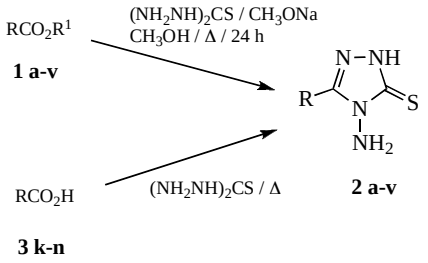
orthoesters are less reactive in the reaction with thiocarbohydrazide than corresponding acids or amides, what is reflected on much lower yields [20]. Another rare example of such type of reaction is the synthesis of the 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones from 1,5-lactones and thiocarbohydrazide in pyridine [23]. We have found that interaction of ethyl (6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)-acetate with thiocarbohydrazide in the presence of sodium methoxide yields the corresponding 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thione [24]. This method, which is similar to the mentioned above synthesis from acids, produces the desirable heterocycles directly from esters. Thus avoiding the preparation of hydrazides, carbazates or 1,3,4-oxadiazole-2-thiones, and already was applied for the synthesis of 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones with other heterocyclic substituents at the C(5)-position [25]. Performing the reaction without sodium ethoxide gives only half the yield. The method described by us [24] was applied only for synthesis of a few 5-substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones [25], thus we

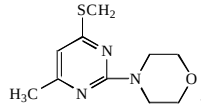
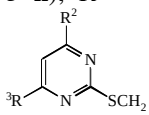
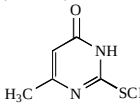
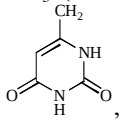
decided to extend it for the preparation of other C(5)-substituted heterocycles.

RESULTS AND DISCUSSION

We provided several reactions of ethylbenzoate (**1 a**) with thiocarbohydrazide and found that the best yield (45%) of 4-amino-5-phenyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (**2 a**) was achieved when a double excess of thiocarbohydrazide and sodium methoxide was used at a reaction time of 24 h. Employing the same reaction conditions to other aromatic esters **1 b-i** (except **1 h**, see below), we synthesized the corresponding compounds **2 b-i** (Scheme 2).

Scheme 2

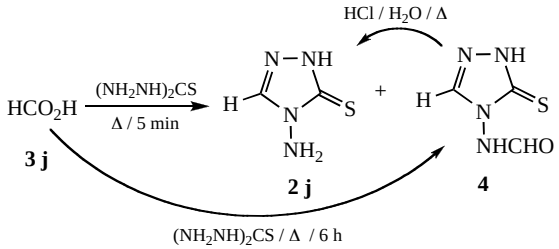


R = C_6H_5, R^1 = C_2H_5 (**1-2 a**), R = 2-$CH_3OC_6H_4$, R^1 = CH_3 (**1-2 b**), R = 3-$CH_3OC_6H_4$, R^1 = CH_3 (**1-2 c**), R = 4-$CH_3OC_6H_4$, R^1 = CH_3 (**1-2 d**), R = 3-BrC_6H_4, R^1 = CH_3 (**1-2 e**), R = 4-ClC_6H_4, R^1 = CH_3 (**1-2 f**), R = 4-$NH_2C_6H_4$, R^1 = CH_3 (**1-2 g**), R = 4-$CH_3O_2CC_6H_4$, R^1 = CH_3 (**1-2 h**), R = 4-pyridyl, R^1 = $CH_2C_6H_5$ (**1-2 i**), R = H, R^1 = C_4H_9 (**1-2 j**), R = CH_3, R^1 = C_2H_5 (**1-3 k**), R = C_3H_7, R^1 = C_2H_5 (**1-3 l**), R = C_6H_{13}, R^1 = CH_3 (**1-3 m**), R = $C_6H_5CH_2$, R^1 = C_2H_5 (**1-3 n**), R =  , R^1 = CH_3 (**1-2 o**), R =  , R^2 = R^3 = CH_3, R^1 = CH_3 (**1-2 p**), R^2 = R^3 = OCH_3, R^1 = CH_3 (**1-2 r**), R^2 = CH_3, R^3 = $N(CH_3)_2$, R^1 = CH_3 (**1-2 s**), R =  , R^1 = CH_3 (**1-2 t**), R =  , R^1 = C_5H_{11} (**1-2 u**).

Yields were moderate (44-54% - for **2 b-f**, 35% - for **2 i**), and only in two cases low (27% - for **2 h**, and 18% - **2 g**). As a reason for the lower yield of compound **2 h** may be the use of equimolar amounts of thiocarbohydrazide and sodium methoxide to ester, to avoid both ester groups participate in the reaction. The same was observed for the synthesis of compound **2 a**, when a similar ratio of reagents was used. In the reaction of methyl 4-aminobenzoate (**1 g**), apparently, the electron-donating effect of the amino group influenced the reactivity of the ester and, consequently, gave a lower yield.

The next step of our research was the synthesis of aminotriazolethiones **2 j-n** from the corresponding aliphatic esters **1 j-m** and ethyl phenylacetate (**1 n**) (Scheme 2). Yields varied from moderate (58-60% - for **2 l-n**) to high (77-78% - for **2 j**, **k**). The same compounds **2 j-n** we synthesized alternatively from the corresponding acids **3 j-n** and thiocarbohydrazide using well-known method [20]. Surprisingly, reaction of formic acid and thiocarbohydrazide yielded not only the desirable 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (**2 j**), but also its N-formyl derivative **4** (Scheme 3) in ratio **2 j**:**4** = 2:1 (according to the ^{1}H-NMR spectrum) (Scheme 3).

Scheme 3



Further hydrolysis of the residue after crystallization increased the yield of **2 j** from 47% to 77%. When the reaction of formic acid with thiocarbohydrazide was prolonged to 6 h instead of 5 min, only the formyl derivative **4** was isolated.

Because of our particular interest in the synthesis and investigation of pyrimidines with five-membered heterocyclic substituents [24,26-28], such as thiadiazoles, oxadiazoles, and triazoles in the side chain, we successfully synthesized aminotriazolethiones **2 o-u** from the corresponding esters by employing the synthetic method described here. Yields of the mentioned compounds **2 o-v** varied from 39% to 59%.

For comparison, the preparation of 4-amino-5-aryl-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones from potassium 3-aroyldithiocarbazates and hydrazine gives **2a** in 78% [1], or 87% [18], **2 b** - 68% [18], **2 d** – 59%, **2 e** – 58%, **2 f** – 65%, and **2 g** – 50% [1] yield, which are 11% to 38% higher than ours. Similar or even lower yields of 4-amino-5-aryl-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones were observed when the synthesis was performed from corresponding 5-substituted 2,3-dihydro-1,3,4-oxadiazole-3-thiones [18,19,24,25]. Synthesis of 5-substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones from

hydrazides, generating corresponding dithiocarbazate *in situ*, gives products in moderate yields (60% [3], 32-57% [15]). In comparison to the discussed above synthetic procedures, our method is more convenient and efficient, as it is shorter, cheaper and quicker. If we compare it to synthesis from carboxylic acids and thiocarbohydrazide, the last one is shorter, but only acceptable for acids with low melting points. So, for most aromatic and heterocyclic acids it can not be applied, contrary to the method described here, which was and can be successfully adopted for the synthesis of various 5-substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones.

The characteristic chemical shifts of NH_2 and NH protons of the aminotriazolthione fragment of compounds **2 a-k**, **n-u** was observed at 5.46-5.85 ppm (for NH_2) and 13.28-14.10 ppm (for NH). The chemical shifts for analogous groups protons of aminotriazolethiones **2 l, m** are located down-field compared to that of **2 a-k**, **n-u**,- 4.77 ppm (**2 l**) and 4.70 ppm (**2 m**) for NH_2, and 12.06 ppm (**2 l**) and 11.73 ppm (**2 m**) for NH. In the IR spectra of compounds **2 a-u** the absorbtion bands of C=S (1476-1509 cm^{-1}), C=N (1532-1598 cm^{-1}), NH_2 (1605-1665 cm^{-1}) are observed. Also the characteristic absorbtion of NH_2 and NH groups are found in the regions of the strongest waves - 3233-3317, 3073-3192 and 2920-2959 cm^{-1}. For the derivative **4** besides absorbtion of NH (2943, 3123, 3256 cm^{-1}), C=N (1553 cm^{-1}), and C=S (1473 cm^{-1}) groups, characterictic absorbtion of C=O is observed (1690 cm^{-1}).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were measured in KBr tablets on a Spectrum BX II FT-IR (Perkin-Elmer, Sweden). ^{1}H nmr spectra were recorded with a Varian Inova 300 spectrometer (300 MHz) using TMS as internal standard.

Synthesis of 5-Substituted 4-Amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones 2 a-u from esters.

4-Amino-5-phenyl-2,3-dihydro-4H-1,2,4-triazole-3-thione (2 a). Method A. To the solution of 1.19 g (0.022 mol) sodium methoxide in 40 ml methanol 2.33 g (0.022 mol) thiocarbohydrazide was added and the mixture was refluxed for 5 min. Then 3.18 ml (3.28 g, 0.02 mol) of ethylbenzoate (**1 a**) was added, and the reaction mixture was refluxed for 14 h, cooled to room temperature and evaporated to dryness. The residue was dissolved in 40 ml H_2O and acidified with conc. HCl to pH ~ 4-5. The precipitate was collected by filtration, washed with cold H_2O, dried and recrystallized from butylacetate to yield 1.04 g (27%), mp 210-212°C; (mp 204-205°C (ethanol-water), Ref. [17]); ir: 3300, 3113, 2943 (NH_2, NH), 1633 (NH_2), 1532 (C=N), 1498 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.81 (s, 2H, NH_2), 7.55 (m, 3H, 3,4,5-H_3), 8.04 (m, 2H, 2,6-H_2), 13.95 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_8N_4S$ (192.24): C, 49.98; H, 4.19; N, 29.14. Found: C, 50.00; H, 3.94; N, 29.42.

Method B. The same procedure as *A*, but the reaction was carried out for 24 h. It yielded 1.31 g (34%) of compound **2 a**.

Method C. The same procedure as *B*, except 2.16 g (0.04 mol) sodium methoxide and 4.42 g (0.04 mol) of thiocarbohydrazide were used. It yielded 1.73 g (45%) of compound **2 a**.

5-Substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones 2 b-u (general procedure). To a solution of 2.16 g (0.04 mol) (for **1 h -** 1.08 g (0.02 mol), for **1 u** – 3.24 g (0.06 mol)) sodium methoxide in 40 ml methanol 4.42 g (0.04 mol) (for **1 h -** 2.12 g (0.02 mol)) thiocarbohydrazide was added and the mixture was refluxed for 5 min. Then 0.02 mol of corresponding ester **1 b-u** was added, the reaction mixture was refluxed for 24 h and cooled to room temperature. In the case of compounds **2 b-g, i, n-u** the reaction mixture was evaporated to dryness, the residue was dissolved in 40-80 ml H_2O and acidified with conc. HCl to pH ~ 4-5. The precipitate was collected by filtration, washed with cold H_2O, dried and recrystallized from the appropriate solvent. In the case of compounds **2 h, j-m** the reaction mixture was acidified with conc. HCl to pH ~ 4-5, evaporated to dryness and the residue was recrystallized from the appropriate solvent.

4-Amino-5-(2-methoxyphenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 b). This compound was obtained in 2.40 g (54%) yield, mp 217-220°C (butylacetate); (mp 216-219°C (ethanol), Ref. [18]); ir: 3289, 3120, 2933 (NH_2, NH), 2839 (CH_3), 1614 (NH_2), 1585 (C=N), 1508 (C=S), 1257, 1020 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 5.46 (s, 2H, NH_2), 7.08 (ddd, ^{4}J=0,9 Hz (4-6), ^{3}J=7.5 Hz (4-3, 4-5), 1H, 4-H), 7.20 (dd, ^{4}J=0,9 Hz (6-4),^{3}J=8.4 Hz (6-5), 1H, 6-H), 7.41 (dd, ^{4}J=1.7 Hz (3-5), ^{3}J=7.5 Hz (3-4), 1H, 3-H), 7.57 (ddd, ^{4}J=1.7 Hz (5-3), ^{3}J=7.5 Hz (5-4), ^{3}J=8.4 Hz (5-6), 1H, 5-H), 13.87 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{10}N_4OS$ (222.26): C, 48.64; H, 4.53; N, 25.31. Found: C, 48.68; H, 4.83; N, 25.11.

4-Amino-5-(3-methoxyphenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 c). This compound was obtained in 2.18 g (49%) yield, mp 204-206°C (butylacetate); ir: 3300, 3119, 2943 (NH_2, NH), 2836 (CH_3), 1627 (NH_2), 1583 (C=N), 1497 (C=S), 1250, 1023 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 5.82 (s, 2H, NH_2), 7.13 (dd, ^{4}J=1.5 Hz (4-2, 4-6), ^{3}J=8.4 Hz (4-5), 1H, 4-H), 7.46 (dd, ^{3}J=7.7 Hz (5-6), ^{3}J=8.4 Hz (5-4), 1H, 5-H), 7.61 (dd, ^{4}J=1.5 Hz (6-2, 6-4), ^{3}J=7.7 Hz (5-6), 1H, 6-H) 7.62 (d, ^{4}J=1.5 Hz (2-4, 2-6), 1H, 2-H), 13.97 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{10}N_4OS$ (222.26): C, 48.64; H, 4.53; N, 25.31. Found: C, 48.80; H, 4.65; N, 25.03.

4-Amino-5-(4-methoxyphenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 d). This compound was obtained in 2.27 g (51%) yield, mp 208-210°C (butylacetate); (mp 205-206°C (ethanol), Ref. [17]); ir: 3309, 3140, 2959 (NH_2, NH), 2833 (CH_3), 1626 (NH_2), 1581 (C=N), 1508 (C=S), 1254, 1032 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 5.78 (s, 2H, NH_2), 7.09 (dd, ^{4}J=2.4 Hz (3-5), ^{3}J=9.3 Hz (3-2, 5-6), 2H, 3,5-H_2), 7.99 (dd, ^{4}J=2.4 Hz (2-6), ^{3}J=9.3 Hz (2-3, 6-5), 2H, 2,6-H_2), 13.84 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{10}N_4OS$ (222.26): C, 48.64; H, 4.53; N, 25.31. Found: C, 48.91; H, 4.58; N, 25.41.

4-Amino-5-(3-bromophenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 e). This compound was obtained in 2.55 g (47%) yield, mp 235-237°C (butylacetate); (mp: 223-235°C (ethanol), Ref. [1]); ir: 3306, 3116, 2947 (NH_2, NH), 1625 (NH_2), 1569 (C=N), 1498 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.82 (s, 2H, NH_2), 7.52 (dd, ^{3}J=8 Hz (5-4, 5-6), 1H, 5-H), 7.77 (dd, ^{4}J=1.7

Hz (4-6, 4-2), ^{3}J=8 Hz (4-5), 1H, 4-H), 8.03 (dd, ^{4}J=1.7 Hz (6-4, 6-2), ^{3}J=8 Hz (6-5), 1H, 6-H), 8.30 (dd, ^{4}J=1.7 Hz (2-4, 2-6), 1H, 2-H), 14.05 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_7BrN_4S$ (271.13): C, 35.44; H, 2.60; N, 20.66. Found: C, 35.29; H, 2.53; N, 20.74.

4-Amino-5-(4-chlorophenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 f). This compound was obtained in 1.98 g (44%) yield, mp 211-213°C (butylacetate); (m.p.: 210-211°C (ethanol), Ref. [1]); ir: 3246, 3149, 2935 (NH_2, NH), 1638 (NH_2), 1598 (C=N), 1498 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.81 (s, 2H, NH_2), 7.64 (dd, ^{4}J=2.3 Hz (3-5), ^{3}J=8.9 Hz (3-2, 5-6), 2H, 3,5-H_2), 8.08 (dd, ^{4}J=2.3 Hz (2-6), ^{3}J=8.9 Hz (2-3, 6-5), 2H, 2,6-H_2), 14.00 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_7ClN_4S$ (226.68): C, 42.39; H, 3.11; N, 24.72. Found: C, 42.54; H, 3.03; N, 24.70.

4-Amino-5-(4-aminophenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 g). This compound was obtained in 0.75 g (18%) yield, mp 258-260°C (methanol); (m.p.: 260-261°C (ethanol), Ref. [1].); ir: 3352, 3270, 3180, 2928 (NH_2, NH), 1612 (NH_2), 1582 (C=N), 1504 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.64 (s, 2H, (C_6H_4)NH_2), 5.72 (s, 2H, NH_2), 6.64 (d, ^{3}J=8.6 Hz (3-2, 5-6), 2H, 3,5-H_2), 7.74 (d, ^{3}J=8.6 Hz (2-3, 6-5), 2H, 2,6-H_2), 13.63 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_9N_5S$ (207.25): C, 46.36; H, 4.38; N, 33.79. Found: C, 46.13; H, 4.43; N, 33.64.

4-Amino-5-(4-methoxycarbonylphenyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 h). This compound was obtained in 1.35 g (27%) yield, mp 197-200°C (methanol); ir: 3317, 3108, 2943 (NH_2, NH), 1727 (C=O), 1632 (NH_2), 1579 (C=N), 1484 (C=S), 1285 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.90 (s, 3H, CH_3), 5.85 (s, 2H, NH_2), 8.10 (dd, ^{4}J=1.7 Hz (3-5), ^{3}J=8.5 Hz (3-2, 5-6), 2H, 3,5-H_2), 8.23 (dd, ^{4}J=1.7 Hz (2-6), ^{3}J=8.5 Hz (2-3, 6-5), 2H, 2,6-H_2), 14.10 (s, 1H, NH) ppm. *Anal.* Calcd for $C_{10}H_{10}N_4O_2S$ (250.27): C, 47.99; H, 4.03; N, 22.39. Found: C, 47.83; H, 3.90; N, 22.58.

4-Amino-5-(3-pyridyl)-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 i). This compound was obtained in 1.35 g (35%) yield, mp 216-217°C (methanol); ir: 3233, 3149 (NH_2, NH), 1653 (NH_2), 1566 (C=N), 1486 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.83 (s, 2H, NH_2), 7.59 (ddd, ^{5}J=0.9 Hz (5-2), ^{3}J=4.8 Hz (5-6), ^{3}J=8 Hz (5-4), 1H, 5-H), 8.39 (ddd, ^{4}J=1.8 Hz (4-6), ^{4}J=2.2Hz (4-2), ^{3}J=8 Hz (4-5), 1H, 4-H), 8.74 (dd, ^{4}J=1.7 Hz (6-4), ^{3}J=4.8Hz (6-5), 1H, 6-H), 9.17 (dd, ^{5}J=0.9 Hz (2-5), ^{4}J=2.2 Hz (2-4), 1H, 2-H), 14.08 (s, 1H, NH) ppm. *Anal.* Calcd for $C_7H_7N_5S$ (193.23): C, 43.51; H, 3.65; N, 36.24. Found: C, 43.46; H, 3.58; N, 36.48.

4-Amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 j). This compound was obtained in 1.81 g (78%) yield, mp 169-171°C (butylacetate); (m.p.: 167-168°C (ethanol), Ref. [20]); ir: 3276, 3172, 2941 (NH_2, NH), 1605 (NH_2), 1561 (C=N), 1496 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.69 (s, 2H, NH_2), 8.46 (s, 1H, CH), 13.65 (s, 1H, NH) ppm. *Anal.* Calcd for $C_2H_4N_4S$ (116.14): C, 20.68; H, 3.47; N, 48.24. Found: C, 20.88; H, 3.41; N, 48.13.

4-Amino-5-methyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 k). This compound was obtained in 2 g (77%) yield, m.p.: 208-210°C (butylacetate); (m.p.: 201-202°C (water), Ref. [20]); ir: 3272, 3116, 2948 (NH_2, NH), 1631 (NH_2), 1577 (C=N), 1509 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 5.53 (s, 2H, NH_2), 13.41 (s, 1H, NH) ppm. *Anal.* Calcd for $C_3H_6N_4S$ (130.17): C, 27.68; H, 4.68; N, 43.04. Found: C, 27.87; H, 4.47; N, 42.95.

4-Amino-5-propyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 l). This compound was obtained in 1.76 g (56%) yield, mp 108-109.5°C (toluene); ir: 3292, 3140, 2942 (NH_2, NH), 1625 (NH_2), 1572 (C=N), 1502 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.02 (t, J=7.4 Hz, 3H, CH_3), 1.78 (sx, J=7.4 Hz, 2H, $CH_2CH_2CH_3$), 2.76 (t, J=7.4 Hz, 2H, $CH_2CH_2CH_3$), 4.77 (s, 2H, NH_2), 12.06 (s, 1H, NH) ppm. *Anal.* Calcd for $C_5H_{10}N_4S$ (158.22): C, 37.96; H, 6.37; N, 35.41. Found: C, 38.15; H, 6.55; N, 35.11.

4-Amino-5-hexyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 m). This compound was obtained in 2.4 g (60%) yield, mp 111-113°C (toluene); ir: 3285, 3152, 2949 (NH_2, NH), 1623 (NH_2), 1564 (C=N), 1485 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 0.91 (t, J=7 Hz, 3H, CH_3), 1.33-1.38 (m, 6H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.74 (td, J=7.3 Hz, J=15.4 Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.77 (t, J=7.5 Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 4.70 (s, 2H, NH_2), 11.73 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_{16}N_4S$ (200.30): C, 47.97; H, 8.05; N, 27.97. Found: C, 48.17; H, 8.26; N, 27.69.

4-Amino-5-benzyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 n). This compound was obtained in 2.39 g (58%) yield, mp 181-183°C (butylacetate); (m.p.: 179-180°C (ethanol), Ref. [1]); ir: 3287, 3150, 2935 (NH_2, NH), 1624 (NH_2), 1567 (C=N), 1495 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.05 (s, 2H, CH_2), 5.57 (s, 2H, NH_2), 7.32 (m, 5H, C_6H_5), 13.56 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{10}N_4S$ (206.27): C, 52.41; H, 4.89; N, 27.16. Found: C, 52.23; H, 4.94; N, 26.92.

4-Amino-5-(6-methyl-2-*N*-morpholino-4-pyrimidin-yl)-sulfanylmethyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thi-one (2 o). This compound was obtained in 4 g (59%) yield, mp 217-219°C (butylacetate); ir: 3253, 3130, 2959 (NH_2, NH), 1618 (NH_2), 1553 (C=N), 1505 (C=S), 1119 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 3.64 (t, J=5 Hz, 4H, N(CH_2)$_2$), 3.70 (t, J=5 Hz, 4H, O(CH_2)$_2$), 4.43 (s, 2H, SCH_2), 5.62 (s, 2H, NH_2), 6.56 (s, 1H, CH), 13.63 (s, 1H, NH) ppm. *Anal.* Calcd for $C_{12}H_{17}N_7OS_2$ (339.43): C, 42.46; H, 5.05; N, 28.89. Found: C, 42.56; H, 4.94; N, 28.84.

14-Amino-5-(4,6-dimethyl-2-pyrimidinyl)sulfanyl-methyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 p). This compound was obtained in 2.58 g (48%) yield, mp 194-197°C (butylacetate); ir: 3236, 3118, 2950 (NH_2, NH), 1654 (NH_2), 1578 (C=N), 1497 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.37 (s, 6H, (CH_3)$_2$), 4.47 (s, 2H, SCH_2), 5.62 (s, 2H, NH_2), 7.00 (s, 1H, CH), 13.54 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{12}N_6S_2$ (268.35): C, 40.28; H, 4.51; N, 31.32. Found: C, 40.30; H, 4.36; N, 31.06.

4-Amino-5-(4,6-dimethoxy-2-pyrimidinyl)sulfanyl-methyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 r). This compound was obtained in 2.88 g (48%) yield, mp 158-160°C (butylacetate); ir: 3263, 3192, 2956 (NH_2, NH), 1619 (NH_2), 1579 (C=N), 1504 (C=S), 1266, 1051 (COC) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.88 (s, 6H, (CH_3O)$_2$), 4.47 (s, 2H, SCH_2), 5.63 (s, 2H, NH_2), 5.99 (s, 1H, CH), 13.28 (s, 1H, NH) ppm. *Anal.* Calcd for $C_9H_{12}N_6O_2S_2$ (300.35): C, 35.99; H, 4.03; N, 27.98. Found: C, 35.75; H, 4.07; N, 28.22.

4-Amino-5-(4-*N*,*N*-dimethylamino-6-methyl-2-pyrimidin-yl)sulfanylmethyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 s). This compound was obtained in 2.32 g (39%) yield, mp 225-227°C (butylacetate); ir: 3284, 3073, 2928 (NH_2, NH), 1658 (NH_2), 1597 (C=N), 1506 (C=S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 3.04 (s, 6H, (CH_3)$_2$N), 4.40 (s, 2H, SCH_2), 5.61 (s, 2H, NH_2), 6.28 (s, 1H, CH), 13.57 (s, 1H, NH) ppm. *Anal.* Calcd for $C_{10}H_{15}N_7S_2$ (297.40): C, 40.39; H, 5.08; N, 32.97. Found: C, 40.60; H, 5.08; N, 33.00.

4-Amino-5-(6-methyl-4-oxo-3,4-dihydro-2-pyrimidinyl)-sulfanylmethyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 t).

This compound was obtained in 3.03 g (56%) yield, mp 257-260°C (water); ir: 3304, 3147, 2923 (NH_2, NH), 1655(CO, NH_2), 1576 (C=N), 1476 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 4.47 (s, 2H, SCH_2), 5.63 (s, 2H, NH_2), 6.07 (s, 1H, CH), 12.27 (s, 1H, NH), 13.65 (s, 1H, NH) ppm. *Anal.* Calcd for $C_8H_{10}N_6OS_2$ (270.33): C, 35.55; H, 3.73; N, 31.09. Found: C, 35.69; H, 3.61; N, 31.10.

4-Amino-5-(2,6-dioxo-1,2,3,4-tetrahydro-4-pyrimidinyl)-methyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 u). This compound was obtained in 2.56 g (53%), mp 290-291°C (water); ir: 3258, 3159, 2940 (NH_2, NH), 1724 (CO), 1665(CO, NH_2), 1570 (C=N), 1509 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.82 (s, 2H, CH_2), 5.27 (s, 1H, CH), 5.57 (s, 2H, NH_2), 11.07 (s, 2H, 2xNH), 13.68 (s, 1H, NH) ppm. *Anal.* Calcd for $C_7H_8N_6O_2S$ (240.24): C, 35.00; H, 3.36; N, 34.98. Found: C, 34.89; H, 3.20; N, 35.15.

5-Substituted 4-amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thiones 2 j-n from acids. 4-Amino-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (**2 j**) was synthesized according to the procedure described in Ref. [20] with some modifications. The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 2 ml formic acid was refluxed for 5 min. After cooling, 30 ml of diethylether was added. The precipitate was collected by filtration, washed with diethylether and dried. Crystallization of product, which are the mixture of compounds **2 j** and **4** (**2j:4** = 2:1, according ^1H-NMR spectra), from methanol gave 1.09 g of compound **2 j** (47% yield). The filtrate after crystallization was evaporated to dryness, the residue was dissolved in 10 ml water with a few drops of conc. HCl, and the reaction mixture was refluxed for 2 h, evaporated to dryness and dried. Crystallization from methanol yielded 0.7 g of compound **2 j** (30% yield). Compound **2 j** was obtained in 1.79 g (77%) overall yield, mp 169-171°C; (yield: 79%, mp 167-168°C (ethanol), Ref. [20]).

4-Amino-5-methyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 k) was synthesized according to the procedure described in Ref. [20]. The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 10 ml acetic acid was refluxed for 15 min., then cooled. The precipitate was filtered off, dried and recrystallized from water to yield 1.97 g (76%), mp 203.5–205°C; (yield: 75%, mp 201-202°C (water), Ref. [20]).

4-Amino-5-propyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 l). The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 10 ml butyric acid was heated at 145-150°C for 1.5 h, then cooled, 50 ml of hexane was added, the precipitate was collected by filtration, washed with hexane and dried. The product was dissolved in 25 ml 10% NaOH water solution and the mixture was refluxed for 1 h. After cooling the solution was acidified with conc. HCl to pH ~ 4-5 and left in +5°C for 2 h. The precipitate was collected by filtration, washed with a small amount of cold water, dried and recrystallized from toluene to yield 1.93 g (61%), mp 108-109.5°C.

4-Amino-5-hexyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 m). The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 6 ml heptanoic acid was heated at 145-150°C for 1.5 h, then cooled, 50 ml of hexane was added, the precipitate was collected by filtration, washed with hexane and dried. The product was dissolved in 25 ml 10% NaOH water solution and the mixture was refluxed for 1 h. Then cooled, acidified with conc. HCl to pH ~ 4-5. The precipitate was collected by filtration, washed with water, dried and recrystallized from toluene to yield 3.01 g (75%), mp 111-113°C.

4-Amino-5-benzyl-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (2 n) was synthesized according to the procedure described in Ref. [21] with some modifications. The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 2.72 g (0.02 mol) phenylacetic acid was heated at 145-150°C for 1.5 h, then cooled, 30 ml of diethylether was added, the precipitate was collected by filtration, washed with diethylether and dried. The product was dissolved in 50 ml 10% NaOH water solution and the mixture was refluxed for 1 h. After cooling the solution was acidified with conc. HCl to pH ~ 4-5. The precipitate was collected by filtration, washed with water, dried and recrystallized from butylacetate to yield 2.31 g (56%), mp 181-183°C; (yield: 88%, m.p.: 179-180°C (ethanol), Ref. [21]).

4-Formylamino-2,3-dihydro-4*H*-1,2,4-triazole-3-thione (4). The mixture of 2.12 g (0.02 mol) thiocarbohydrazide and 4 ml formic acid was refluxed for 6 h. After cooling 50 ml of diethylether was added. The precipitate was collected by filtration, washed with diethylether, dried and recrystallized from butylacetate-methanol to yield 2.25 g (78%), mp 189-191°C; ir: 3256, 3123, 2943 (NH), 1690 (C=O), 1553 (C=N), 1473 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.40 (s, 1H, CH), 8.62 (s, 1H, CHO), 11.49 (s, 1H, NH(CHO)), 13.95 (s, 1H, NH) ppm. *Anal.* Calcd for $C_3H_4N_4OS$ (144.15): C, 25.00; H, 2.80; N, 38.87. Found: C, 25.27; H, 3.04; N, 39.02.

REFERENCES

[1] Eweis, N. F.; Bahajaj, A. A.; Elsherbini, E. A. *J. Heterocycl. Chem.* **1986**, *23*, 1451.

[2] Eweis, N. F.; Bahajaj, A. A. *J. Heterocycl. Chem.* **1987**, *24*, 1173.

[3] El-Khawass, S. M.; Habib, N. S. *J. Heterocycl. Chem.* **1989**, *26*, 177.

[4] Wang Z.; Shi, H.; Shi, H. *J. Heterocycl. Chem.* **2001**, *38*, 355.

[5] Chande, M. S.; Karnik, B. M. *Indian J. Heterocycl. Chem.* **1991**, *1*, 117; *Chem. Abstr.* **1992**, *116*, 151731.

[6] Kudari, S. M.; Beede, S. M.; Munera, W. *Asian J. Chem.* **1997**, *9*, 20; *Chem. Abstr.* **1997**, *126*, 186026.

[7] Holla, B. S.; Sarojini, B. K.; Rao, B. S.; Akberali, P. M.; Kumari, N. S.; Shetty, V. *Farmaco* **2001**, *56*, 565.

[8] Ghorab, M. M.; El-Sharief, A. M. Sh.; Ammar, Y. A.; Mohamed, Sh. I. *Farmaco* **2000**, *55*, 354.

[9] Husain, M. I.; Kumar, V. *Indian J. Chem.* **1992**, *31B*, 673; *Chem. Abstr.* **1993**, *118*, 22179.

[10] El-Samii, Z. K. A.; El-Feky, S. A. H.; Moustafa, M. A. A. *Zhonghua Yaoxue Zazhi* **1993**, *45*, 379; *Chem. Abstr.* **1994**, *121*, 35463.

[11] Sudan, S.; Gupta, R.; Kachroo, P. L. *J. Indian Chem. Soc.* **1996**, *73*, 625; *Chem. Abstr.* **1997**, *126*, 186030.

[12] Sarhan, E. Z.; Mohammed, S. R.; Mikhael, A. N.; El-Banna, H. A. *Alexandria J. Pharm. Sci.* **1993**, *7*, 41; *Chem. Abstr.* **1993**, *122*, 81233.

[13] Heindel, N. D.; Laskin, J. D.; Heck, D. E.; Rapp, R. D.; Guillon, C.; Mendel, A. M. *WO 0,010,564*, **2000**; *Chem. Abstr.* **2000**, *132*, 180604.

[14] Ghorab, M. M.; Abdel-Hamide, S. G.; El-Gaby, M. S. A.; El-Sayed, S. M. *Acta Pharm.* **1999**, *49*, 1.

[15] Sarva, M. C.; Romeo, G.; Guerrera, F.; Siracusa, M.; Salerno, L.; Russo, F.; Cagnotto, A.; Goegan, M.; Mennini, T. *Bioorg. Med. Chem.* **2002**, *10*, 313.

[16] Menzies, C. M.; Squattrito, P. J. *Inorg. Chim. Acta* **2001**, *314*, 194.

[17] Hoggart, E. *J. Chem. Soc.* **1952**, 4811.

[18] Reid, J. R.; Heindel, N. D. *J. Heterocycl. Chem.* **1976**, *13*, 925.

[19] Armenov, V. N.; Shvaika, O. P. *Khim. Geterotsikl. Soed.* **1971**, 905.

[20] Beyer, H.; Kroger, C. F. *Liebigs Ann. Chem.* **1960**, *637*, 135.

[21] Invidiata, F. P.; Furno, G.; Lampronti, I.; Simoni, D. *J. Heterocycl. Chem.* **1997**, *34*, 1255.

[22] Audrieth, L. F.; Scott, E. S.; Kippur, P. S. *J. Org. Chem.* **1954**, *19*, 733.

[23] Awad, L. F.; El Ashry, E. S. H. *Carbohydr. Res.* **1998**, *312*, 9.

[24] Vainilavicius, P.; Smicius, R.; Jakubkiene, V.; Tumkevicius, S. *Monatsh. Chem.* **2001**, *132*, 825.

[25] Demirbas, N.; Demirbas, A.; Karaoglu, S. A.; Celik, E. *Arkivoc* **2005**, 75.

[26] Smicius, R.; Jakubkiene, V.; Burbuliene, M. M.; Vainilavicius, P. *Monatsh. Chem.* **2002**, *133*, 173.

[27] Smicius, R.; Jakubkiene, V.; Burbuliene, M. M.; Mikalainyte A., Vainilavicius P. *J. Chem. Res. (S)* **2002**, 170.

[28] Burbuliene, M. M.; Jakubkiene, V.; Mekuskiene, G.; Udrenaite, E.; Smicius, R.; Vainilavicius, P. *Farmaco* **2004**, *59*, 767.

[29] Voight, H.; Heydenhauss, D.; Hofmann, F.; Jaenecke, G. *Z. Chem.* **1974**, *14*, 436.

[30] Santilli, A. A.; Scotese, A. C.; Tomarelli, R. M. *US 3,901,887*, **1975**; *Chem. Abstr.* **1976**, *84*, 17410.

[31] Vainilavicius, P.; Burbuliene, M.; Rocka, N.; Lauciuviene, N. *Khim.-Farm.Zh.* **1982**, *16*, 931; *Chem. Abstr.* **1983**, *98*, 16638.

[32] Jasinskas, L.; Vainilavicius, P.; Urbonas, A. *Liet. TSR Aukst. Mokyklu Mokslo Darb., Chem. Chem. Technol.* **1967**, *8*, 75; *Chem. Abstr.* **1969**, *70*, 68299.

[33] Shvachkin, Yu. P.; Berestenko, M. K.; Mishin, G. P. *Biol. Aktivn. Soedin., Akad Nauk SSSR* **1965**, 72; *Chem. Abstr.* **1966**, *64*, 9720.