SYNTHESIS OF SOME S-DERIVATIVES OF 1,2,4-TRIAZOLES

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The reactions of 5-mercapto-3,4-disubstituted-1,2,4-triazoles with ethyl chloroacetate have been investigated. It has been shown that mercapto group reacted and S-substituted derivatives were formed. On the next step hydrazinolysis by 85% hydrazine hydrate was carried out and on the base of obtained hydrazides thiosemicarbazides were synthesized. Further by means of intermolecular cyclization bis-1,2,4-triazoles were obtained, structure of heterocyclic rings were connected by thio-methyl bridge.

Keywords: 1,2,4-triazoles, hydrazinoles, thiosemicarbazides, bis-triazoles.

Introduction. It’s known that heterocyclic compounds play a very important role in our lives: by their utility in the form of medicinal compounds and in the form of modern materials. In series of heterocyclic compounds of particular interest are derivatives of 1,2,4-triazoles with a broad spectrum of biological action and this is applied especially for heteryl condensing derivatives-1,2,4-triazoles substituted by benz-thiazole, benz-oxazole, thiazole fragments which exhibit a pronounced anti-inflammatory [1], antibacterial [2], anti-tuberculosis, analgesic [3] and other properties.

We have previously shown that 5-mercapto-3,4-disubstituted-1,2,4-triazoles are antioxidants and anti-radiation agents [4], and also good as starting materials for the synthesis of non-protein β-amino acid (BAA), derivatives of which are the nutritional supplements [5].

The foregoing confirms the relevance and expediency of studies in the field of azoles. It can be assumed from these data that S-substituted derivatives of 1,2,4-triazoles also represent pharmacological value.

Materials and Methods. In order to expand assortment of 1,2,4-triazoles, the number of reactions according to the following Scheme leads to new heteryl substituted compounds, which have not been described in the literature yet, were carried out.

The alkylation reaction of compounds Ia, Ib chem-selectively takes place with the formation of only S-derivatives. It was established, that type of substituent at 3-position of triazole ring does not influence on the course of the reactions (Ia, Ib).

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The functionalization of the starting 1,2,4-triazoles opens up opportunities for the use of II a, II b compounds in fine organic synthesis. In particular, it has been shown, that the reaction of hydrazinolysis was advantageously realized with 85% hydrazine hydrate solution in ethanol. This process was completed in a short time, providing high yields of the desired products – hydrazides of 2-(4-phenyl-5-sulfanyl-4H-1,2,4-triazole-3-ylthio)acetic acids (III a, III b). On the next step, obtained hydrazides have been transformed into the corresponding 1,4-disubstituted thiosemicarbazides (IV a, IV b). By the method of intermolecular cyclization triazole-triazoles (V a, V b) were synthesized. The synthesis of compounds IV a, IV b, V a, V b were performed by the known method [6, 7].

**Experimental Part.** ¹H and ¹³C NMR spectra were registered on spectrometer Varian Mercury-300 from solution in DMSO : CDCl₃ = 1 : 3. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (development in iodine vapor). Melting points were determined on “Boetius” micro-heating stage.

Methods of synthesis of the starting compounds I a, I b were described in [6, 7].

**Compounds II a, II b (General Procedure).** On mixture of 0.01 mol of corresponding 1,2,4-triazole (I a, I b) in the 15 mL abs. acetone 0.006 mol of potassium carbonate and 0.01 mol chloro acetate were added, and stirred for 1 h at room temperature and 10 h at 50–60°C. The mixture was cooled and the solvent was removed. The resulting crystals were treated with aqueous ammonia to pH 8–9, washed with water and recrystallized.

**Ethyl-2-(5-(bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)acetate (II a).** Yield 90%, mp 158°C (water : ethanol = 3 : 2). Rf 0.51 (C₆H₆OH : C₆H₅O₆ = 1 : 5). ¹H NMR (300 MHz) spectrum, δ, ppm: 1.29 t (3H, J=7.1 Hz, CH₃CH₂O); 4.03 s (2H, CH₂S); 4.17 q (2H, J=7.1 Hz, CH₃CH₂O); 7.22–7.31 m (2H, Ar); 7.32–7.40 m (2H, Ar); 7.40–7.48 m (2H, Ar); 7.49–7.61 m (3H, Ar). ¹³C NMR (75 MHz) 13.7; 33.6; 60.8; 123.2; 125.4; 127.0; 129.1; 129.6; 131.0; 133.4; 153.0; 167.0. IR-spectrum, ν, cm⁻¹: 1570, 1586 (C=N); 1600 (C=O); 1743 (C=O); 3041; 3055; 3060; 3099; 3181 (=CH). Found, %: C 51.42; H 3.55; N 10.96; Br 19.25; S 7.99. C₁₈H₁₄N₃O₃BrS. Calculated, %: C 51.68; H 3.86; Br 19.10; N 10.05; S 7.67.
Ethyl-2-(5-(pyridyl-3-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)acetate (II b).

Yield 88%, mp 138°C (water : ethanol = 2 : 1). δ (30 MHz; CDCl3) ppm: 2.26 (a, t, 3H, J = 7.9 Hz, CH3); 4.06 t (5H, J = 7.9 Hz, CH2); 4.18 q (2H, J = 7.9 Hz, CH2); 7.37–7.44 m (2H, Ar); 7.53–7.60 m (4H, Ar); 7.68–7.73 m (2H, Ar); 8.50–8.59 m (2H, Ar). 

Compounds III a, III b (General Procedure). Hydrazinolysis of Esters.

A mixture of 10 mmol of corresponding esters in the 20 mL ethanol was added to 15 mmol 85% solution of hydrazine hydrate. The mixture was stirred 2 h at room temperature and heated for 4 h at 50–60°C. The mixture was cooled and the solvent was removed. The resulting crystals were washed with water and recrystallized.

2-(5-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetohydrazide (III a). Yield 81%, mp 230–232°C (ethanol). δ (30 MHz; CDCl3) ppm: 2.25 (a, t, 3H, J = 7.9 Hz, CH3); 4.05 t (5H, J = 7.9 Hz, CH2); 7.23–7.31 m (2H, Ar); 7.33–7.40 m (2H, Ar); 7.40–7.47 m (2H, Ar); 7.49–7.60 m (3H, Ar); 9.29 br. s (1H, NH). C (75 MHz) ppm: 13.2; 125.2; 129.2; 129.5; 131.0; 133.5; 151.6; 152.7; 152.9. IR-spectrum, ν, cm⁻¹: 1572; 1584 (C=N); 1601 (C=O); 1741 (C=O); 3041; 3054; 3062; 3095; 3183 (=CH). Found, %: C 59.52; H 4.75; N 16.46; S 9.37. C15H15BrN3O2S. Calculated, %: C 59.78; H 4.74; N 16.46; S 9.42.

2-(5-(4-Phenyl-5-(pyridyl-3-yl))-4H-1,2,4-triazole-3-ylthio)acetohydrazide (III b). Yield 90 %, mp 225°C (water : ethanol = 1 : 5). δ (30 MHz; CDCl3) ppm: 2.26 (a, t, 3H, J = 7.9 Hz, CH3); 4.04 t (5H, J = 7.9 Hz, CH2); 7.27 dd (1H, J = 7.8, 4.8 Hz, Pyr); 7.38–7.43 m (2H, Ar); 7.53–7.60 m (3H, Ar); 7.66 dd (1H, J = 7.8; 2.1; 1.8 Hz, Pyr); 8.51 dd (1H, J = 4.8; 1.8 Hz, Pyr); 8.53 d (1H, J = 2.1 Hz Pyr) 9.29 br. s (1H, NH). C (75 MHz) ppm: 13.2; 125.2; 129.5; 129.6; 129.9; 131.0; 133.5; 151.6; 152.9; 165.8. IR-spectrum, ν, cm⁻¹: 1561; 1584; 1602 (C≡N); 1649 (C=O); 3021; 3054; 3080; 3110 (=CH); 3205; 3298; 3324; 3519 (NHNH2). Found, %: C 55.52; H 4.45; N 25.80; S 9.89. C15H15BrN3O2S. Calculated, %: C 55.20; H 4.32; N 25.75; S 9.82.

General Procedure for Synthesis of Thiosemicarbazides (IV a, IV b). On the mixture of 7.9 mmol III a (III b) in 10 mL ethanol 7.79 mmol phenylthiocarbamide were added and stirred at room temperature for 1 h and at 75–80°C for 2 h. The mixture was cooled. The resulting crystals were washed with ethanol and recrystallized.

2-(5-(4-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetetyl)-N-phenyl-hydrazine-1-carbothioamide (IV a). Yield 95%, mp 222°C (water : ethanol = 1 : 3). δ (30 MHz; CDCl3) ppm: 2.27 (a, t, 3H, J = 7.9 Hz, CH3); 4.04 t (5H, J = 7.9 Hz, CH2); 7.17–7.20 m (1H, Ar); 7.21–7.34 m (4H, Ar); 7.35–7.48 m (4H, Ar); 7.51–7.60 m (3H, Ar); 8.61–8.71 m (2H, Ar); 9.57 br. s (2H, NH); 10.31 br. s (1H, NH). C (75 MHz) ppm: 123.3; 124.2; 125.3; 127.1; 127.3; 129.1; 129.5; 129.6; 131.1; 133.4; 138.7; 151.7; 153.0; 180.4. IR-spectrum, ν, cm⁻¹:
1550, 1577 (C=N); 1601 (C=C); 1677 (C=O); 3021; 3036; 3051; 3062; 3085; 3138 (C=CH); 3250; 3398; 3459 (NH). Found, %: C 51.22; H 3.45; Br 14.88; N 15.80; S 9.89. C_{23}H_{18}BrN_2O_2. Calculated, %: C 51.21; H 3.55; Br 14.81; N 15.58; S 11.89.

**N-Phenyl-2-((4-phenyl-5-pyridin-3-yl)-4H-1,2,4-triazole-3-thiol)acetyl)-hydrazine carbothioamido (4V b).** Yield 80%, mp 180°C (water : ethanol = 1 : 3). R_f 0.65 (C_5H_12O : C_6H_6 : n-C_6H_{14} = 4 : 1 : 1). ^1H NMR (300 MHz) spectrum, δ, ppm: 3.95 s (2H, CH_2S); 7.08–7.14 m (1 H, Ar); 7.24–7.32 m (3H, Ar); 7.41–7.46 m (2H, Ar); 7.54–7.68 m (6H, Ar); 8.50–8.53 m (2H, Ar); 9.57 br.s. (1H, NH); 9.59 br.s. (1H, NH); 10.33 br.s. (1H, NH). ^13C NMR (75 MHz) 18.2; 34.0; 56.0; 122.5; 122.7; 124.3; 127.3; 127.4; 129.7; 129.8; 133.2; 134.5; 138.8; 147.9; 149.8; 151.7; 152.1; 180.4. IR-spectrum, ν, cm\(^{-1}\): 1552; 1580 (C=N); 1598 (C=C); 1675 (C=O); 1691; 1705; 3087; 3104 (=CH); 3251; 3395; 3460 (NH). Found, %: C 57.22; H 4.15; N 21.40; S 13.92. C_{22}H_{19}N_2O_2S. Calculated, %: C 57.25; H 4.15; N 21.24; O 3.47; S 13.89

**General Procedure for Synthesis of Bis-triazoles (Va, Vb).** On a water solution of NaOH (5ml 10%) 7.5 mmol of corresponding thiosemicarbazide was added, stirred at room tempure for 1 h and refluxed 4 h. After cooling, the mixture was diluted with water and acidified with hydrochloric acid (pH 2–3). The resulting crystals were washed with water and recrystallized.

5-((5-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (V a). Yield 90%, mp 236°C (ethanol). R_f 0.65 (C_5H_12O : C_6H_6 = 2.5 : 6). ^1H NMR (300 MHz) spectrum, δ, ppm: 4.18 s (2H, CH_2S); 7.11–7.36 m (6H, Ar); 7.39–7.60 m (8H, Ar); 13.71 s (0.2H, NH). ^13C NMR (75 MHz) 44.9; 123.3; 124.2; 125.3; 127.1; 127.3; 129.1; 129.6; 131.1; 133.4; 138.7; 151.7; 153.0; 180.4. IR-spectrum, ν, cm\(^{-1}\): 1571; 1595 (C=N); 1618 (C=C); 3030; 3055; 3071 (=CH); 3425 (SH). Found, %: C 52.92; H 3.15; Br 15.35; N 16.30; S 13.92. C_{25}H_{17}BrN_2S_2C_2. Calculated, %: C 52.98; H 3.29; Br 15.32; N 16.12; S 12.30.

4-Phenyl-5-((4-phenyl-5-pyridin-3-yl)-4H-1,2,4-triazole-3-thio)methyl)-4H-1,2,4-triazole-3-thiol (V b). Yield 90%, mp 159–160°C (water : ethanol = 2 : 3). R_f 0.65 (C_5H_12O : n-C_6H_{14} = 2 : 1). ^1H NMR (300 MHz) spectrum, δ, ppm: 4.18 s (2H, CH_2S); 7.07–7.14 m (1 H, Ar); 7.22–7.30 m (3H, Ar); 7.40–7.48 m (2H, Ar); 7.54–7.70 m (6H, Ar); 8.50–8.54 m (2H, Ar); 13.79 s (1H, SH). ^13C NMR (75 MHz) 18.0; 34.2; 56.9; 122.6; 122.7; 124.3; 127.2; 127.3; 129.7; 129.8; 133.2; 133.5; 138.8; 147.9; 149.8; 151.7; 152.1; 180.0. IR-spectrum, ν, cm\(^{-1}\): 1575; 1592 (C=N); 1599; 1615 (C=C); 3030; 3065; 3108 (=CH); 3426 (SH). Found, %: C 59.52; H 3.85; N 22.30; S 14.92. C_{22}H_{17}N_2S_2. Calculated, %: C 59.57; H 3.86; N 22.11; S 14.46.

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