

Chemistry

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

T. V. GHOCHIKYAN*, M. A. SAMVELYAN**, A. S. GALSTYAN, S. V. GRIGORYAN

Chair of Organic Chemistry YSU, Armenia

The reactions of 5-merkapto-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].

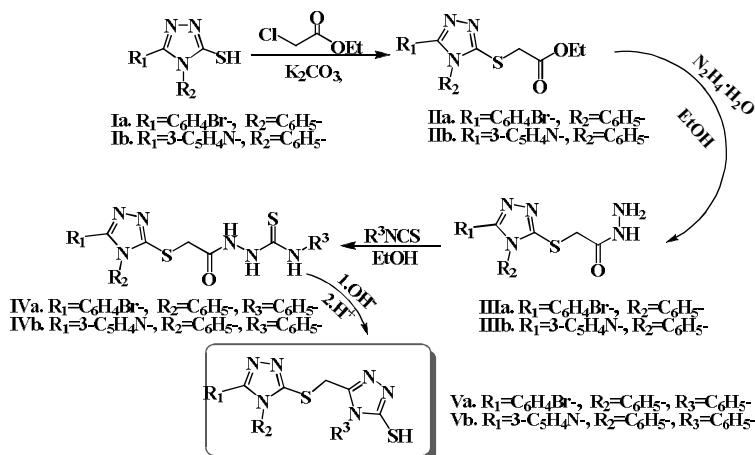
The foregoing confirms the relevance and expediency of studies in the field of azoles. It can be assumed from these data that S-substituted derivatives of 1,2,4-triazoles also represent pharmacological value.

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 **I a**, **I b** 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 (**I a**, **I b**).

* E-mail: ghochikyan@ysu.am

** E-mail: msamvelyan@ysu.am



Scheme.

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-(substituted)-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 triazolo-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 ^{13}C NMR spectra were registered on spectrometer Varian Mercury-300 from solution in DMSO : $CCl_4 = 1 : 3$. 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). R_f 0.51 ($C_2H_5OH : C_6H_6 = 1 : 5$). 1H NMR (300 MHz) spectrum, δ , ppm: 1.29 t (3H, $J=7.1$ Hz, $\underline{CH_3}CH_2O$); 4.03 s (2H, $\underline{CH_2}S$); 4.17 q (2H, $J=7.1$ Hz, $\underline{CH_3}CH_2O$); 7.22–7.31 m (2 H, Ar); 7.32–7.40 m (2H, Ar); 7.40–7.48 m (2H, Ar); 7.49–7.61 m (3H, Ar). ^{13}C 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=C); 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. $C_{18}H_{16}N_3O_2BrS$. 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). R_f 0.48 (C₂H₅OH : C₆H₆ = 1 : 5). ¹H NMR (300 MHz) spectrum, δ , ppm: 1.30 t (3H, $J=7.1$ Hz, $\underline{\text{CH}_3\text{CH}_2\text{O}}$); 4.06 s (2H, $\underline{\text{CH}_2\text{S}}$); 4.18 q (2H, $J=7.1$ Hz, $\text{CH}_3\underline{\text{CH}_2\text{O}}$); 7.27 dd (1H, $J=7.9$; 4.8 Hz, Pyr); 7.37–7.44 m (2H, Ar); 7.53–7.60 m (4H, Ar); 7.68 dt (1H, $J=7.9$; 1.9 Hz, Pyr); 8.49–8.54 m (2H, Ar). ¹³C NMR (75 MHz) 13.7; 33.7; 60.8; 122.5; 122.6; 127.0; 129.6; 129.8; 133.2; 134.4; 147.9; 149.7; 151.1; 151.7; 167.0. IR-spectrum, ν , cm^{-1} : 1572; 1584 (C=N); 1601 (C=C); 1741 (C=O); 3041; 3054; 3062; 3095; 3183 (=CH). Found, %: C 59.52; H 4.75; N 16.96; S 9.99. C₁₇H₁₆N₄O₂S. Calculated, %: C 59.98; H 4.74; N 16.46; S 9.42.

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

A mixture of 10 mmol of corresponding esters in the 20 mL ethanol were added to 15 mmol 85% solution of hydrazin 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-Bromo)phenyl-4-phenyl-4H-1,2,4-triazole-3-ylthio)acetohydrazide (III a).

Yield 81%, mp 230–232°C (ethanol). R_f 0.48 (C₂H₅OH : C₆H₆ = 2 : 5). ¹H NMR (300 MHz) spectrum, δ , ppm: 3.86 s (2H, $\underline{\text{CH}_2\text{S}}$); 4.08 br s (2H, NH₂); 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). ¹³C NMR (75 MHz) 33.8; 123.2; 125.5; 127.1; 129.2; 129.5; 131.0; 133.5; 151.6; 152.9; 165.8. IR-spectrum, ν , cm^{-1} : 1563; 1584 (C=N); 1597 (C=C); 1645 (C=O); 3028; 3056; 3085; 3106 (=CH); 3209; 3295; 3328; 3517 (NHNH₂). Found, %: C 47.52; H 3.45; Br 19.80, N 14.46; S 7.99. C₁₆H₁₄BrN₅OS. Calculated, %: C 47.53; H 3.49; Br 19.76; N 17.32; S 7.93.

2-(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). R_f 0.50 (C₂H₅OH : C₆H₆ : *n*-C₆H₁₄ = 3 : 3 : 1). ¹H NMR (300 MHz) spectrum, δ , ppm: 3.87 s (2H, $\underline{\text{CH}_2\text{S}}$); 4.12 br. s. (2H, NH₂); 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 ddd (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). ¹³C NMR (75 MHz) 33.8; 123.2; 125.5; 127.1; 129.2; 129.5; 131.0; 133.5; 151.6; 152.9; 165.8. IR-spectrum, ν , cm^{-1} : 1561, 1580 (C=N); 1602 (C=C); 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. C₁₅H₁₄N₆OS. Calculated, %: C 55.20; H 4.32; N 25.75; S 9.82.

General Procedure for Synthesis of Thiosemicarmazides (IV a, IV b).

On the mixture of 7.9 mmol III a (III b) in 10 mL ethanol 7.79 mmol phenylisothiocyanate 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-(2-(5-(4-Bromophenyl)-4-phenyl-4-H-1,2,4-triazole-3-ylthio)acetyl)-N-phenyl-hydrazine-1-carbothioamid (IV a). Yield 95%, mp 222°C (water : ethanol = 1 : 3). R_f 0.54 (C₂H₅OH : C₆H₆ = 2.5 : 5). ¹H NMR (300 MHz) spectrum, δ , ppm: 3.93 s (2H, $\underline{\text{CH}_2\text{S}}$); 7.07–7.16 m (1H, Ar); 7.21–7.34 m (4H, Ar); 7.35–7.48 m (4H, Ar); 7.51–7.60 m (3H, Ar); 7.61–7.71 m (2H, Ar); 9.57 br.s. (2H, NH); 10.31 br.s. (1H, NH). ¹³C NMR (75 MHz) 34.0; 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 (=CH); 3250; 3398; 3459 (NH). Found, %: C 51.22; H 3.45; Br 14.88; N 15.80; S 9.89. C₂₃H₁₉BrN₆OS₂. Calculated, %: C 51.21; H 3.55; Br 14.81; N 15.58; S 11.89.

N-Phenyl-2-(2-(4-phenyl-5-pyridin-3-yl)-4H-1,2,4-triazole-3-ylthio)acetyl-hydrazine carbothioamide (**IV b**). Yield 80%, mp 180°C (water : ethanol = 1 : 3). *R*_f 0.65 (C₂H₅OH : C₆H₆ : *n*-C₆H₁₄ = 4 : 1 : 1). ¹H NMR (300 MHz) spectrum, δ, ppm: 3.95 s (2H, CH₂S); 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; 127.2; 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); 3021; 3035; 3051; 3061; 3087; 3140 (=CH); 3251; 3395; 3460 (NH). Found, %: C 57.22; H 4.15; N 21.40; S 13.92. C₂₂H₁₉N₇OS₂. 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 temperature 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-ylthio)methyl-4-phenyl-4H-1,2,4-triazole-3-thiol (**V a**). Yield 90%, mp 236°C (ethanol). *R*_f 0.65 (C₂H₅OH : C₆H₆ = 2.5 : 6). ¹H NMR (300 MHz) spectrum, δ, ppm: 4.18 s (2H, CH₂S); 7.11–7.36 m (6H, Ar); 7.39–7.60 m (8H, Ar); 13.71 s (0.8H, SH); 14.03 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); 1595; 1618 (C=C); 3030; 3055; 3107 (=CH); 3425 (SH). Found, %: C 52.92; H 3.15; Br 15.35; N 16.30; S 13.92. C₂₃H₁₇BrN₆S₂C₂₂. 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-ylthio)methyl-4H-1,2,4-triazole-3-thiol (**V b**). Yield 90%, mp 159–160°C (water : ethanol = 2 : 3). *R*_f 0.65 (C₂H₅OH : *n*-C₆H₁₄ = 2 : 1). ¹H NMR (300 MHz) spectrum, δ, ppm: 4.18 s (2H, CH₂S); 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; 127.4; 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; 3056; 3108 (=CH); 3426 (SH). Found, %: C 59.52; H 3.85; N 22.30; S 14.92. C₂₂H₁₇N₇S₂. Calculated, %: C 59.57; H 3.86; N 22.11; S 14.46.

Received 28.04.2016

REFERENCES

1. Siddiqui N., Ashan W., Shamsher Alam M., Jain S., Akhtar J. Triazoles: As Potential Bioactive Agents. // International Journal of Pharmaceutical Review and Research, 2011, v. 8, № 1, p. 161–169.

2. **Khan S.I., Badshah A., Aslam M., Akhtar M.S.** Synthesis and Antibacterial Activities of Substituted 4-Amino-1,2,4-triazole-3-thiols. // *Medical Chemistry & Drug Discovery*, 2012, v. 3, № 2, p. 116–121.
3. **Saad H.A., Osman N.A., Moustafa A.H.** Synthesis and Analgesic Activity of Same Triazoles and Pyrazoles. // *Molecules*, 2011, v. 16, p. 10187–10201; doi: 10.3390/molecules 161210187.
4. **Ghochikyan T.V., Samvelyan M.A., Arutyunyan E.V., Arutyunyan V.S., Avetisyan A.A., Malakyan M.G.** Search for New Drugs: Synthesis and Antioxidant Activity of New 1,2,4-Triazole Derivatives. // *Pharmaceutical Chemistry Journal*, 2011, v. 44, № 10, p. 525–527.
5. **Saghyan A.S., Simonyan H.M., Petrosyan S.G., Mkrtchyan A.F., Khachatryan L.V., Geolchanyan A.V., Ghochikyan T.V., Samvelyan M.A., Kelzhanova N., Saginayev A.T., Langer P.** Asymmetric Synthesis of Enantiomerically Enriched α -Amino Acids Containing 2-Furyl- and 2-Thienyl-1,2,4-Triazoles in the Side-Chain. // *Z. Naturforsch.*, 2014, v. 69b, p. 451–460.
6. **Ghochikyan T.V., Arutyunyan V.S., Samvelyan M.A., Arutyunyan E.V., Avetisyan A.A.** Method of Synthesis 1,4-Disubstituted Thiosemicarbazides. Patent RA 2039 A2, 2007, № 4, p. 11.
7. **Ghochikyan T.V., Arutyunyan V.S., Samvelyan M.A., Arutyunyan E.V., Avetisyan A.A.** Method of Synthesis 3,4-Disubstituted-5-mercapto-1,2,4-triazoles. Patent RA, 2040 A2, 2007, № 4, p. 12.