ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis and Physical-Chemical Properties of 5-Phenethyl-4-R-4H-1,2,4-triazole-3-thioles and Their Chemical Transformations.

Tatyana VIgnatova, Andriy GKaplaushenko, and Yuliia S Frolova*.

Department of Physical and Colloidal chemistry, Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine.

ABSTRACT

Great value for pharmacologists is the synthesis of new triazole derivatives as they have medicinal importance and are found to be used in a variety of pharmacological preparations. 1, 2, 4-triazole derivatives were reported to possess diverse biological activities, such as antimicrobial, antifungal, antitumor, anti-inflammatory, ant tuberculosis and herbicidal properties. The purpose of our research is the synthesis of new highly effective and low-toxic substances, namely of 5-phenethyl-4-R-4H-1,2,4-triazole-3-thioles and their derivatives, the establishment of physical and chemical properties of all synthesized compounds. For synthesized of 5-phenethyl-4-R-4H-1, 2, 4-triazole-3-tioles at first was esterifies butyl ester of hydrocinnamic acid, then with hydrazine hydrate was given hydrazide 3-phenylpropanoate. Further was received carbotiamids and in the last step was gotten 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles.2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles were received by adding appropriate halogen nitriles to 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles in alkaline-alcohol environment. During the experiment 11 synthetic studies of novel compounds was obtained, which have not been described previously. The structure of received compounds, namely 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles and 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles has been confirmed by elemental analyze, infrared and chromatography-mass spectrometry was confirmed by elemental analysis, infrared and chromatographic mass spectrometry, which fully confirmed their composition. The results confirmed the structure of the synthesized compounds, which indicates the possibility of their further use in biological studies.

Keywords: 1, 2, 4-triazoles, synthesis, physical-chemical properties, transformation.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

It is consider able to synthesizene we rtria zole derivatives as they have medicin a limportance and are found to be used in a variety of phar-maco logical preparations [1]. 1,2,4-triazole derivatives were reported to possess diverse biological activities, such as antimicrobial [2,3], antifungal [4], antitumor [5], anti-inflammatory [3,6], ant tuberculosis [7] and herbicidal [8] properties.

During the past decade the number of publications that contain different aspects of triazoles and tetrazoles doubled and continues to grow. Over the last few years show that compounds containing 1,2,4-triazole nucleus. It is now quite well established highly biologically active with a broad spectrum of action. This fact indicates the interest for these compounds as potential objects of modern pharmaceutical market. [9]

The purpose of our research is the synthesis of new highly effective and low-toxic substances, namely of 5-phenethyl-4-R-4H-1,2,4-triazole-3-thioles and their derivatives, the establishment of physical and chemical properties of all synthesized compounds.

MATERIALS AND METHODS

Physical-chemical properties of the synthesized compounds have been investigated according to the methods described in the State Pharmacopeia of Ukraine [10, 11]. The melting point has been determined by capillary method (2.2.14). The elemental composition of compounds has been set with the help of elemental analyzer ElementarVario L cube (CHNS) (standard – Sulfonamide). Infrared spectra have been recorded in potassium bromide tablets (1% concentration of substance) in the spectrophotometer Specord M-80 in the region of 4000–500 cm^{-1} (scanning conditions: program 3.0, time constant – τ=3s, scan time – 33 min). Tablets have been prepared by joint grinding of 200 mg of potassium bromide and 2 mg of test compound, followed by pressing.. Chromatography-mass spectrometry studies have been conducted on liquid chromatography Agilent 1260 Infinity HPLC equipped with a mass spectrometer Agilent 6120 (in electro spray ionization (ESI)) [12, 13].

RESULTS AND DISCUSSION

Steps of synthesis of 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7-9) were presented in fig. 1. The carboxyl group of hydrocinnamic acid (Compound 1, Fig. 1) was esterifies in butyl alcohol medium with presence of catalytic amount of sulphatic acid. Then butyl ester of hydrocinnamic acid (Compound 2, Fig. 1) was reacted with hydrazine hydrate to give hydrazide (Compound 3, Fig. 1) in the alcohol medium. Further 2-(3-phenylpropanoyl)hydrazine-1-carbotioamide (Compound 4, Fig. 1) was received during heating of hydrazide (Compound 3, Fig. 1) with ammonium thiocyanate in acidic medium. During hydrazide interaction (Compound 3, Fig. 1) with ethyl or phenyl isothiocyanide in the 1,4-dioxane environment N-ethil-2-(3- phenylpropanoyl)hydrazine-1-carbotioamide (Compound 5, Fig. 1) or N-phenyl-2-(3-phenylpropanoyl)hydrazine-1-carbotioamide (Compound 6, Fig. 1) were received respectively. The cyclization of carbotiamids (Compounds 4,5,6, Fig. 1) was performed in 2-mol water solution of sodium hydroxide, boiling them during two hours. Thus with high yields 5-phenethyl-4-phenyl-4H-1,2,4-triazole-3-thiol (Compounds 8, Fig. 1) was gotten. Compounds 7–9 (Table 1–2) are crystalline white (7) and gray (8, 9) substances, slightly insoluble in water, soluble in organic solvents and aqueous alkali. For the analysis 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (7-9) were recrystallized from acetic acid.

ISSN: 0975-8585

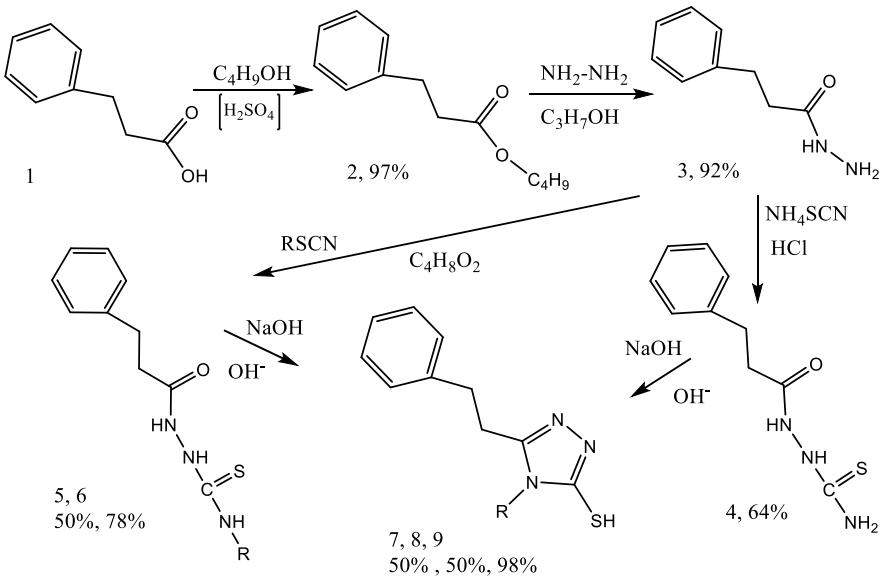


Fig 1: Scheme of synthesis of 5-phenethyl-4-R-4*H*-1, 2, 4-triazole-3-tioles

Synthesized 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7-9, Fig. 1) are white (7) and gray (8, 9) crystalline substances, soluble in organic solvents and water. For the analysis compounds 7-9 have been recrystallized from acetic acid.

On the next step compounds 10-17 (Fig. 2) were received by adding appropriate halogen nitriles (chloroacetonitrile, 3-chloropropanenitrile, 2-chlorobenzonitrile) to 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10-17, Fig. 1) in alkaline-alcohol environment.

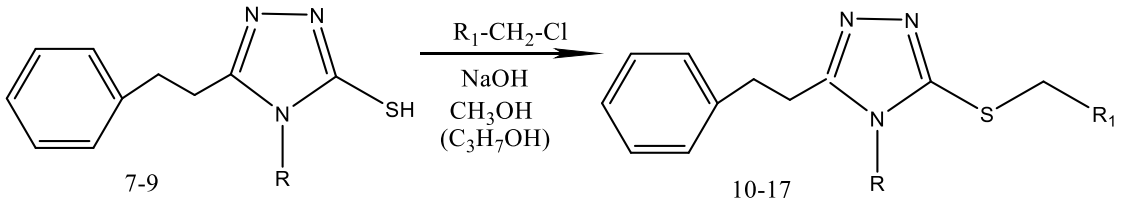


Fig 2: Scheme of synthesis of 2-((5-phenethyl-4-R-4*H*-1,2,4-triazole-3-yl)thio)nitriles

Synthesized 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10–17, Tab. 3–4) are black (10), pink (11), yellow (12, 13, 15, 17), white(14) or gray (16) crystalline substances, slightly soluble in water, soluble in organic solvents and solutions of mineral acids. For the analysis compounds 10–17 were recrystallized from ethanol.

Butyl ester of hydrocoric acid (Compound 2)

The mixture of 1.0 mol of hydrocoric acid (Compound 1, Fig. 1), 500 ml of butyl alcohol and 15 ml of concentrated sulfuric acid was boiled for 14 hours, solvent was evaporated. Residue was neutralized with sodium bicarbonate. Received compound is yellow amorphous substance not soluble in water and alkali, soluble in organic solvents.

Hydrazide3-phenylpropanoate (Compound 3)

The mixture of 0.7 molButyl ester of hydrocoric acid (Compound 2), 2 mol of hydrazine hydrate solution in 200 ml of propanol was boiled for 6 hours. The solvent was evaporated. Received compound is white crystalline substance soluble in solutions of organic solvents, insoluble in water.

ISSN: 0975-8585

2-(3-phenylpropanoyl) hydrazine-1-carbotioamide (Compound 4)

To the mixture of 0.6 mol of hydrazide 3-phenylpropanoate (Compound 3), 2 mol of hydrogen chloride and 2 mol of ammonium thiocyanate in 130 ml of water. The mixture was boiled about 6 hours. White precipitate was filtered and dried. Received 64%of 2-(3-phenylpropanoyl) hydrazine-1-carbotioamide.

N-ethil(phenyl)-2-(3- phenylpropanoyl)hydrazine-1-carbotioamide (Compounds 5, 6)

To the solution of 1 mol of hydrazide 3-phenylpropanoate (Compound 3) in 150 ml of 1,4-dioxane 1 mol of ethyl isothiocyanate or phenyl isothiocyanate was added and accordingly, the resulting mixture was left for 24 hours, the precipitate was filtered. Received 98% of N-phenyl-2-(3-phenylpropanoyl)hydrazine-1-carbotioamide (Compound 8).

5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7-9)

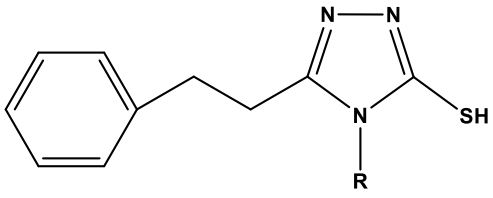
In the flask with reflux 1 mol of corresponding carbotioamides (Compounds 4–6) and 2 mol solution of sodium hydroxide in distilled water were downloaded. The mixture was boiled for 2 hours to complete dissolution of the precipitate, then the mixture was neutralized with concentrated acetic acid, cooled, precipitates of thioles (Compounds 7–9) were filtered.

2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10-17)

A mixture of 0.03 mol of 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7–9) and 0.03 mol of sodium hydroxide in 50 ml of methanol (propanol), was heated to dissolve thiol. 0.03 mol of appropriate halogen nitriles (chloroacetonitrile, 3-chloropropanenitrile, 2-chlorobenzonitrile), were added to the reaction mixture, and heated to the neutral environment. The primary precipitate of sodium chloride was filtered. After complete cooling the precipitate of 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10–17) was filtered, washed and dried with diethyl ether.

The physical data of the 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compound 7–9) were given in Table 1. The structures of the synthesized compounds were confirmed by elemental analysis (Table 1), IR spectro photometry (Table 2) and mass spectra. Thus, the infrared spectra of synthesized thioles (Compounds 7–9) shows clear oscillation bands of C=N–group between 1584-1550 cm^{-1}, C=S–group between 695–650 cm^{-1} and 1590–1568 cm^{-1}, indicating the presence of aromatic cycle. IR spectra of thioles show oscillation bands of CH– and SH– groups in 3582-3060 cm^{-1} and 675-675 cm^{-1} respectively (Table2).

Table 1: Physical-chemical properties of 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7-9)



Compound	R	M_p, °C	Empirical formula	Yield, %	Found results of elemental composition, %			
					C	H	N	S
7	H	219-220	$C_{10}H_9N_3S$	50	59,08	4,44	20,69	15,79
8	etyl	143-144	$C_{12}H_{15}N_3S$	50	68,35	5,32	17,96	11,37
9	phenyl	> 250	$C_{16}H_{15}N_3S$	98	61,75	6,45	18,05	13,75

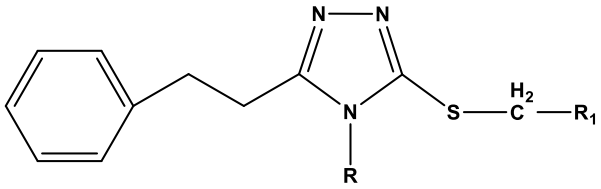
ISSN: 0975-8585

Table 2: IR-spectra of 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles (Compounds 7-9)

Compound	Adsorption rate, cm^{-1}				
	$\nu_{C=N\ cycle}$	ν_{SH}	$\nu_{C=S}$	ν_{Ar}	$\nu_{CHvalen}$
7	1570	–	695	1568	3060
8	1584	698	678	1590	3582
9	1550	675	650	1572	3106

The structure of the synthesized 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10-17)were confirmed with the integrated use of elemental analysis (Table3), IR spectrophotometric (Table4) and mass spectra. The IR spectra of final compounds showed an absorption band at 2270-2210 cm^{-1} indicative of C≡N– groups. The absorption bands in the region of 1596-1550 cm^{-1} indicative of C=N stretching in cycle and 1525-1505 cm^{-1} of aromatic cycle. The scissor bands at 2870-2840 cm^{-1} and at 2950-2915 cm^{-1} indicating the presence of methylene groups. The absorption band representing C-S stretching was appeared in the region of 705-640 cm^{-1}. [13]

Table3: Physical-chemical properties of 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10-17)



Compound	R	R_1	M_p, °C	Empirical formula	Yield, %	Found results of elemental composition, %			
						C	H	N	S
10	H	-CN	> 250	$C_{12}H_{12}N_4S$	30,2	59,03	4,90	22,97	13,10
11	H	C_6H_5CN-2	140–141	$C_{17}H_{14}N_4S$	99,0	66,67	4,58	18,32	10,43
12	ethyl	-CN	92–94	$C_{14}H_{16}N_4S$	97,0	61,76	5,87	20,59	11,78
13	ethyl	$-CH_2CN$	138–139	$C_{15}H_{18}N_4S$	84,0	62,93	6,36	19,58	11,13
14	ethyl	C_6H_5CN-2	61	$C_{19}H_{18}N_4S$	98,0	68,26	5,45	16,77	9,52
15	phenyl	-CN	77–79	$C_{18}H_{16}N_4S$	54,0	67,49	4,97	17,50	10,04
16	phenyl	$-CH_2CN$	162-163	$C_{19}H_{18}N_4S$	20,0	68,28	5,39	16,73	9,60
17	phenyl	C_6H_5CN-2	180–182	$C_{23}H_{18}N_4S$	31,4	72,25	4,72	14,67	8,36

ISSN: 0975-8585

Table4: IR-spectra of 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles (Compounds 10-17)

Compound	Adsorption rate, cm^{-1}				
	$\nu_{C=N\ cycle}$	ν_{Ar}	$\nu_{C\equiv N}$	$\nu^{s/as}_{-CH_2-}$	ν_{C-S}
10	1595	1520	2210	2870/2930	670
11	1588	1510	2260	2840/2915	650
12	1596	1505	2250	2850/2930	640
13	1575	1515	2270	2860/2950	700
14	1590	1510	2250	2840/2940	705
15	1585	1525	2220	2850/2925	680
16	1570	1515	2260	2855/2950	690
17	1550	1530	2240	2860/2935	685

CONCLUSION

The method of synthesis 5-phenethyl-4-R-4H-1,2,4-triazole-3-tioles and 2-((5-phenethyl-4-R-4H-1,2,4-triazole-3-yl)thio)nitriles, which can be used for modeling chemical molecules of new biologically active compounds has been developed.

The structure of the synthesized compounds has been confirmed by comprehensive use of modern physical-chemical methods of analysis.

REFERENCES

[1] BulutN., KocyigitU.M., Gecibesler I.H.[et al.]J.Biochem. 2017; 13: 221-231.
[2] BarbuceanuS.-F.,SarametG.,AlmajanG.L.[et al.] Eur. J. Med. Chem.2012;49:417–423.
[3] Al-OmarM.A.,Al-AbdullahE.S., ShehataI.A.[et al.]Molecules. 2010; 15: 2526–2550.
[4] ChaiX., ZhangJ., YuS.[et al.]Bioorg. Med. Chem. Lett. 2009; 19:1811–1814.
[5] BhatK.S.,PoojaryB.,PrasadD.J.[et al.]Eur. J. Med. Chem.2009; 44:5066–5070.
[6] Uzgoren-BaranA., TelB.C., SarigolD., OzturkE.I. [et al.]Eur. J. Med. Chem.2012; 57: 398–406.
[7] TatarE., KüçükgüzelŞ.G., KarakuşS., ClercqE.D.[et al.]MarmaraPharm. J.2015; 2: 88–102.
[8] LiuX.H., XuX.Y., TanC.X. [et al.]PestManag. Sci. 2015;71:292–301.
[9] HulinaYu. S.,KaplaushenkoA. G. ZaporozhyeMedicalJournal. 2017; 19(1): 100-104.
[10] TheStatePharmacopoeiaofUkraine.Kh.: PIPEH, 2001, pp. 556.
[11] TheStatePharmacopoeiaofUkraine.Kh.: PIPEH, 2004, pp. 520
[12] Sajdov T.V., Sverdlova O.V. A Practical Guide to Molecular Spectroscopy Leningrad: LGU, 1995,pp. 236
[13] Kazicyna, L. A. Application of UV, IR, NMR and mass spectroscopy in Organic Chemistry. Moscow: Mosk. un-ty, 1979, pp. 236