UDC 547.792.3 https://doi.org/10.26577/2218-7979-2017-10-1-57-61

[1]Zhaimukhambetova L.N., [1]Dyusebaeva M.A.,
[2,3]Aisa H., [1*] Jenis J.

[1]Faculty of Chemistry and Chemical Technology, Al-Farabi Kazakh National University, Almaty, Kazakhstan
[2]Xinjiang Technical Institutes of Physics and Chemistry, Central Asian of Drug Discovery and Development
[3]Xinjiang Key Laboratory of Plant Resources and Natural Product Chemistry, XTIPC CAS, R. P. China
[*]e-mail: janarjenis@mail.ru

Synthesis of New, Potentially Biologically Active Derivatives of 1,3,4-Oxadiazole-2-yl carbothioates

Abstract. It is well known that the derivatives of nitrogenous heterocycles have a wide range of biological activity (antituberculosis, antimicrobial, antitumor, antimalarial, anti-inflammatory, etc.), and oxadiazole derivatives also play same important role. In the current work, in order to synthesize the initial synthons we were carried out the esterification of benzoic (**1**) and isonicotinic (**2**) acids were obtained the corresponding ethers (**3**, **4**). Further, interaction with hydrazine hydrate, the corresponding acid hydrazides were synthesized (**5**, **6**). As a result of the cyclization reaction with carbon disulfide were obtained substituted 1,3,4-oxadiazole-2-thiols (**7**, **8**). Finally compounds **7**, **8** undergo the alkylation reaction lead to yield two new compounds *S*-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) and *S*-5- (pyridin-4-yl) -1,3,4-oxadiazol-2-yl carbonothioate (**10**). The structures of synthesized compounds were confirmed by NMR spectra. The physico-chemical characteristic data of synthesized compounds were in full agreement with corresponded compounds in reference. The synthesized new compounds have an interest for further investigation of biological activities.

Key words: biologicaly active derivatives, oxadiazole derivatives, esterification of benzoic and isonicotinic acids.

Introduction

Chemistry of nitrogen heterocycles belongs to a broad section of organic chemistry. Nitrogen heterocycles – pyridine, oxadiazole, triazole, thiadiazole and their derivatives – are highly reactive and biologically active at relatively low toxicity, and can functionally transformed to obtain analogs of bioactive compounds.

At present, the search for chemical compounds possessing biological activity, conduct according to certain scientific principles and quantitative approaches that allow predicting the structure of compounds, essentially lead and their purposeful synthesis. There are several trends in the development of scientific research in this field, one of them is the introduction of pharmacophore fragments into the molecule, increase the activity of the preparation, for example: the addition of phenyl, pyridine and dichlorophenyl radicals increases the water solubility, and the introduction of the alkyl group increases the lipophilicity, the complex and ether groups increase the pharmacological activity and the sulfur atom reduces toxicity.

In organic chemistry, the synthesis of cyclic oxygen-containing compounds attach great importance in view of their valuable biological properties. Oxadiazoles and their derivatives are an integral part of many natural biologically active compounds, which have a wide spectrum of biological activity [1-5]. Continuing research on the synthesis of target bioactive compounds including nitrogen heterocycles, we carried out synthesis of two new oxadiazole derivatives.

Experimental

***General experimental procedures*:** Thin layer chromatography of the synthesized compounds were carried out on Silufol UV-254 plates, were exhibited by a UV lamp. The melting points of the new synthesized compounds were tested on a Buchi Melting Point B-540, Germany.

The NMR spectra of the new synthesized compounds were recorded on a Bruker WM 250 spectrometer and a Bruker DRX 500 spectrometer operating at 250.500 MHz in a DMSO solution.

***The general procedure for the synthesis of ethyl esters of cyclic carboxylic acids (3, 4)*:** A mixture

 Printed in Kazakhstan

(0.1 mol) of cyclic carboxylic acid, 54.6 g of absolute ethanol, 7.36 g of conc. H_2SO_4 with stirring is heated for 3 hours at a temperature of 80-850C. At the end of the reaction, ethanol is distilled off. Extracted with diethyl ether, the final product accelerated in an oil pump vacuum.

Ethyl benzoate (3) was obtained in 12 g (80%) yield, and isonicotinic acid ethyl ester (4) was obtained with 13.7 g (90.7%). All physico-chemical parameters were corresponded to the reference data.

***The general procedure for the synthesis of hydrazides (5, 6)*:** A mixture of (0.15 mol) cyclic carboxylic acid ethyl ester and (0.2 mol) hydrazine hydrate heated in a water bath for 6 hours. The resulting crystals washed with cold ethanol.

Benzoic acid hydrazide (**5**) was obtained in a yield of 17.2 g (84.3%).The isonicotinic acid hydrazide (**6**) was obtained in 10.9 g (86.5%) yield. All the physical and chemical parameters are also consistent with the reference data.

***The general procedure for the synthesis of substituted 1,3,4-oxadiazol-2-thiol (7, 8)*:** To hydrazide (0.01 mol) in ethanol at 0^oC is added 0.76 g of carbon disulphide and 0.46 g of potassium hydroxide, the reaction mixture is heated until the evolution of the carbon disulfide ceased (about 12 hours).

Excess ethanol is distilled off, and the residue is dissolved with water and acidified with HCl (10%) till pH = 5. The precipitate is filtered off, dried and recrystallized from C_2H_5OH. 5-Phenyl-1,3,4-oxadiazole-2-thiol (**7**) was obtained in 1.53 g (85.4%) yield, and 5-(pyridin-4-yl) -1,3,4-oxadiazol-2-thiol (**8**) was obtained in a yield of 1.47 g (82.1%).

While identifying the synthesized compounds, the physico-chemical data fully corresponded to the reference data. A fairly high yield of compounds allowed further modification of the compounds.

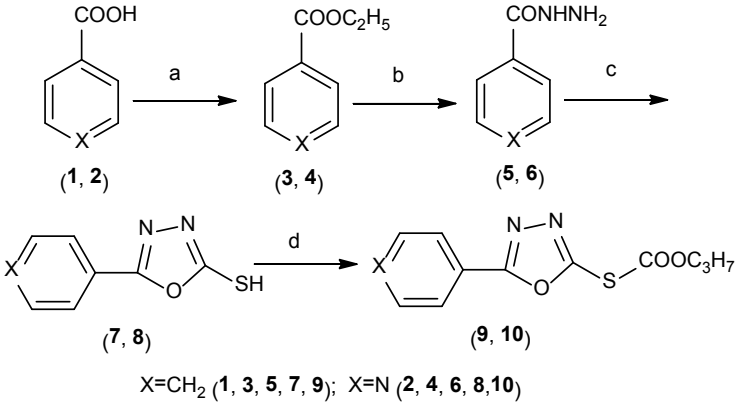
***The general procedure for the synthesis of substituted 1,3,4-oxadiazol-2-yl O-propyl carbonothioates (9, 10)*:** To a solution (2 mmol) of substituted 1,3,4-oxadiazole-2-thiol and (2 mmol) NaOH in 50 ml of acetonitrile is added dropwise (2 mmol) of propyl carbonobromidate. The mixture is heated, the reaction is monitored by TLC. After completion of the reaction, the acetonitrile is distilled off under vacuum. The resulting crystals are recrystallized from a suitable solvent.

S-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) was obtained with T = 87-88 ° C (recrystallized from ethyl acetate), and yielded 0.47 g (90%).

O-propyl S-5- (pyridin-4-yl) -1, 3, 4-oxadiazol-2-yl carbonothioate (**10**) was obtained with $T_{mel.}$ = 287-288 ° C (recrystallized from acetonitrile), and yielded 0.46 g (87%).

Results and discussion

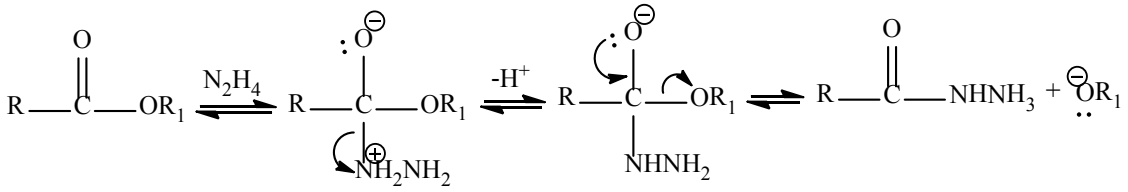
Based on biological activities of oxadiazole derivatives as well as continuation of purposeful synthesis, the structure of the synthesized compounds have been introduced various pharmacophore groups [6, 7]. The synthesized two new compounds *S*-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) and *O*-propyl *S*-5- (pyridin-4-yl) -1,3,4-oxadiazol-2-yl carbonothioate (**10**) have not been reported before. Intermediate compounds in the synthesis of the final compounds are esters of cyclic carboxylic acids (**3**, **4**) their hydrazide (**5**, **6**) and substituted oxadiazoline (**7**, **8**), and the reaction procedure please see the Scheme 1.



Scheme 1 – Synthesis of compounds (**9**) and (**10**). Reagents and solvents:
(a) C_2H_5OH, H_2SO_4, 80-85^{0}C, 3 hours; (b) N_2H_4*H_2O, 90^{0}C, 6 hours; (c) CS_2, KOH, C_2H_5OH, 90^{0}C, 12 hours; (d) $BrCOOC_3H_7$, NaOH, MeCN, 80-85^{0}C, 8-12 hours.

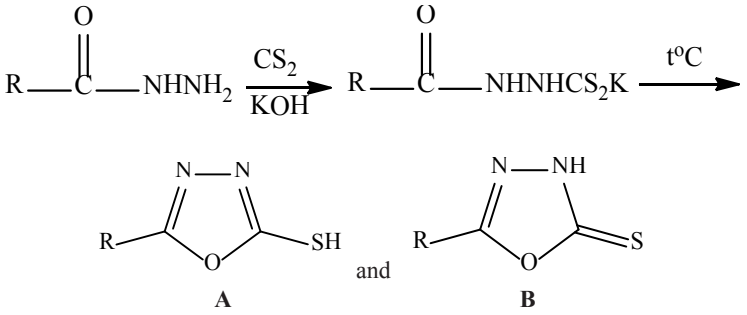
The starting synthons in the synthesis of potentially biologically active compounds are the ethyl esters of benzoic acid (**3**) and isonicotinic acid (**4**). These esters were synthesized by esterification of benzoic and isonicotinic acid by the interaction with ethanol in sulfuric acid.

From the research there is evidence that the reactions, obtaining the hydrazides are extremely numerous. One of the main ways of obtaining hydrazides is the interaction of esters of carboxylic acids with hydrazine hydrate. Hydrazide is nucleophilic agents with good reactivity, which can easily interact with electrophile.



Thus, in the reaction of ethyl ester of benzoic acid (**3**) and ethyl ester of isonicotinic acid (**4**) with aqueous hydrazine hydrate synthesized benzohydrazide (**5**) and hydrazide of isonicotinic acid (**6**), respectively. Physicochemical constants of the synthesized compounds were in complete agreement with the reference data, and the reaction with high yield of compounds can be used as a synthon in further syntheses study.

At next step, we carried out the reaction of cyclization of hydrazides (**5**, **6**) with carbon disulfide in presence of alkali. The reaction of cyclization were obtained 5-phenyl-1,3,4-oxadiazole-2-thiol (**7**) and 5- (pyridine-4-yl) – 1,3,4-oxadiazole-2-thiol (**8**). The intermediate compound can be potassium salt of 3-aroyldithiocarbazate. Below shown a diagram of cyclization:

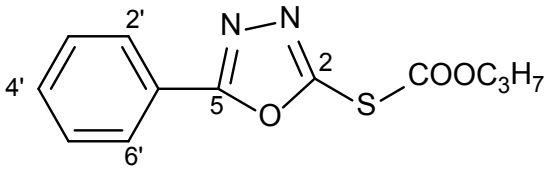


As a result of the cyclization process, it is possible to form two isomeric products, namely 1,3,4-oxadiazole-2-thiol (A) and 2-mercapto-1,3,4-oxadiazole (B) derivatives or in a thionic form, respectively. In the alkaline medium, there is predominantly a thiol form (A), and in acidic and neutral media, the thionic form (B). The physico-chemical parameters of the thions obtained and fully confirmed the structure of the compounds, which allow us to make further modification to them.

With the aim of producing compounds containing a large number of pharmacophore groups, we synthesized *S*-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) and *O*-propyl *S*-5- (pyridin-4-yl)-1,3,4-oxadiazol-2-yl carbonothioate (**10**) by reacting substituted 1,3,4-oxadiazol-2-thiols (**7**, **8**) with propyl carbonobromidate in acetonitrile under heating during the 8-12 hour. The course of the reaction controlled by thin layer chromatography.

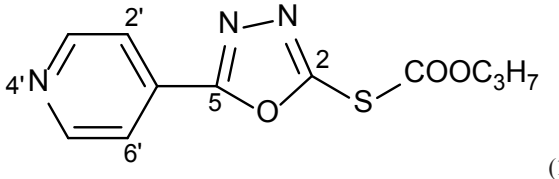
In this study, we were synthesized two new compounds, the derivatives of 1,3,4-oxadiazol-2-yl O-propyl carbonothioate (**9**, **10**) that previously not been described in the literature. Structures of *S*-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) and *O*-propyl *S*-5- (pyridin-4-yl) -1,3,4-oxadiazol-2-yl carbonothioate (**10**) were exactly proved by the basis of the spectra of ^{1}H and ^{13}C NMR. The NMR data are shown in Table 1.

Table 1 – ^{1}H and ^{13}C NMR data of new substituted oxadiazole carbonothioates (**9**, **10**)



(**9**)

^{1}H NMR (400 MHz, DMSO)			^{13}C NMR (101 MHz, DMSO)	
Protons	δ_H	*J*, Hz	Carbon	δ_C
2H, H = 2`, 6`	7.93(d)	7.8	1C, -COO	174.2
1H, H = 4`	7.70(t)	7.3	2C, oxad	157.6, 147.4
2H, H = 3`, 5`	7.62(dd)	13.6, 6.8	6C, Ph	133.1, 129.5, 129.4,
2H, H = OCH_2	4.38 (t)	6.5		126.7, 126.1, 121.6
2H, H = CH_2	1.81- 1.71(m)		1C, -O-CH_2	70.3
3H, H = CH_3	1.00(t)	7.4	Alk. CH_2, CH_3	21.4, 10.1



(**10**)

^{1}H NMR (400 MHz, DMSO)			^{13}C NMR (101 MHz, DMSO)	
Protons	δ_H	*J*, Hz	Carbon	δ_C
2H, H = 2`, 6`	8.81(d)	5.8	1C, -COO	178.17
2H, H = 3`, 5`	7.81(d)	6.0	2C, oxad	159.23
2H, H = OCH_2	4.20-4.15 (t)	14.2, 6.8	5C, Ph	151.26
2H, H = CH_2	1.80 (dt)	7.4		130.21,
3H, H = CH_3	1.01			120.43, 120.05
			1C, -O-CH_2	75.41
			Alk. CH_2, CH_3	22.82, 13.01

Conclusion

In summary, we have synthesized 10 compounds by using different reactions methods and in which two compounds (*S*-5-phenyl-1,3,4-oxadiazol-2-yl *O*-propyl carbonothioate (**9**) and *S*-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl carbonothioate (**10**) are novel compounds. Meanwhile, they are potentially biologically active compounds. The research work is continued and biological activities of two new compounds (**9**, **10**) are being tested.

References

1. Gobec M., Tomasic T., Markovic T., Mlinaric-Rascan I., Sollner Dolenc

2. M., Jakopin Z. Antioxidant and anti-inflammatory properties of 1, 2, 4-oxadiazole analogs of resveratrol // Chem.-Biol. Interactions 2015, № 240. – P. 200-207.

3. Janardhanan J., Chang M., Mobashery Sh. The oxadiazole antibacterials // Current Opinion in Microbiology 2016, № 33, P. 13–17.

4. Leemans E., Boudreau M.A., Yamaguchi T., Schroeder V.A., Wolter W.R., Llarrull L.I., Song W., Lastochkin E., Kumarasiri M., Antunes N.T., Espahbodi M., Lichtenwalter K., Suckow M.A., Vakulenko S., Mobashery S., Chang M. Discovery of a new class of non-beta-lactam inhibitors of penicillin-binding proteins with Gram-positive antibacterial activity // J. Am. Chem. Soc. 2014. – №136. – P. 3664.

5. Jain P.P., Degani M.S., Raju A., Anantram A., Seervi M., Sathaye S., Ray M., Rajan M.R. Identification of a novel class of quinoline-oxadiazole hybrids as anti-tuberculosis agents // Bioorg. Med. Chem. Lett 2016, Vol 26(2). P. 645-649.

6. Krolenko K.Yu., Vlasov S.V., Zhuravel I.A. Synthesis and antimicrobial activity of 5-(1H-1, 2, 3-triazo l-4-yl)-1, 2, 4-oxadiazole derivatives // Chemistry of Heterocyclic Compounds 2016. – Vol. 52 (10). – P. 823-830.

7. Jenis J., Nugroho A.E., Akiyo H., Jun D., Yusuke H., Wong Ch. P., Toshio K., Osamu Sh., Morita H. A New Benzylisoquinoline Alkaloid from Leontice altaica // Natural product communications, 2015, Vol 10(2), 291-292.

8. Dyusebaeva M.A., Kalugin S. N. Thiosemicarbazides of piperidylacetic acid in the synthesis of bisheterocyclic compounds // Russian Journal of General Chemistry, 2015. – Vol. 85. – № 7. – P. 1775-1778.