ISSN 2308-8303 (Print) Žurnal organìčnoï ta farmacevtičnoï hìmìï. – 2017. – Vol. 15, Iss. 3 (59) ISSN 2518-1548 (Online)

UDC 547.786 + 547.269.3 https://doi.org/10.24959/ophcj.17.922

P. S. Lebed[1, 2], A. O. Tolmachov[1, 2], Yu. O. Zubchuk[3], O. M. Boyko[2], M. V. Vovk[4]

[1] Enamine Ltd., 78 Chervonotkatska Street, Kyiv, 02094, Ukraine
[2] Chem Bio Center, Kyiv National Taras Shevchenko University
[3] Ukr Org Syntez Ltd. (UORSY)
[4] Institute of Organic Chemistry National Academy of Sciences of Ukraine

Synthesis and some transformations of 5-isoxazolylsulfonyl chlorides

The effect of the structure of 5-(benzylthio)isoxazoles on selectivity of the synthesis of 5-(chlorosulfonyl) isoxazoles has been determined. The chemical behavior in relation to amines has been described.

Aim. To develop the methods for the synthesis of 5-(chlorosulfonyl)- isoxazoles and 4-chloro-5-(chlorosulfonyl) isoxazoles as promising reagents for construction of prospective bioactive compounds.

Results and discussion. The number of 5-(benzylthio)isoxazoles was obtained by cyclocondensation of *N*-hydroxyimidoyl chlorides or 2-chloro-2-(hydroxyimino) acetates with benzylethynylsulfide. Their oxidative chlorination with gaseous chlorine led to formation of the mixture of isoxazole-5-sulfonyl chlorides and 4-chloroisoxazole-5-sulfonyl chlorides. The ratio between these products in the mixture depended on the nature of the substitution group in position 3 of the isoxazole ring. For the synthesis of 4-chloro-5-(chlorosulfonyl)isoxazoles with acceptable yields the approach of an advance chlorination of 5-benzylthioisoxazoles by N-chlorosuccinimide with further oxidative chlorination was used.

Experimental part. The synthesis of the starting and target compounds was performed in classic preparative conditions; flesh-chromatography; elemental analysis; LCMS; ^{1}H and ^{13}C NMR-spectroscopy were used.

Conclusions. The reaction of oxidative chlorination of 5-(benzylthio)-3-isoxazoles has been studied. The synthetic approach for the previously unknown representatives of isoxazole-5-sulfonylchlorides has been developed.

Key words: *N*-hydroxyimidoyl chlorides; benzylethynyl sulfide; 5-(benzylthio)-3-isoxazoles; oxidative chlorination; isoxazole-5-sulfonylchlorides

П. С. Лебедь, А. О. Толмачов, Ю. О. Зубчук, О. М. Бойко, М. В. Вовк

Синтез та деякі перетворення 5-ізоксазолілсульфонілхлоридів

Встановлено вплив структури 5-бензилтіоізоксазолів на селективність утворення 5-ізоксазолілсульфонілхлоридів та з'ясована хімічна поведінка останніх по відношенню до амінів.

Мета роботи – створення методів синтезу 5-ізоксазоліл- та 4-хлоро-5-ізоксазолілсульфонілхлоридів як перспективних реагентів для конструювання потенційно біоактивних речовин.

Результати та їх обговорення. Циклоконденсацією N-гідроксіімідоїлхлоридів або 2-хлоро-2-(гідроксііміно) ацетатів із бензилтіоацетиленом синтезовано низку 5-бензилтіоізоксазолів. Їх окиснювальне хлорування приводить до утворення суміші 5-ізоксазолілсульфонілхлоридів та 4-хлоро-5-ізоксазолілсульфонілхлоридів, співвідношення між якими залежить від характеру замісників у положенні 3 ізоксазольного циклу. Для синтезу 4-хлоро-5-ізоксазолілсульфонілхлоридів із задовільними виходами використано варіант попереднього хлорування ядра 5-бензилтіоізоксазолів N-хлоросукцинімідом із подальшим окиснювальним хлоруванням.

Експериментальна частина. Синтез вихідних та цільових сполук у класичних препаративних умовах; методи флеш-хроматографії, елементного аналізу, хроматомас-спектрометрії, ЯМР ^{1}H та ^{13}C-спектроскопії.

Висновки. Досліджена реакція окиснювального хлорування 5-бензилтіоізоксазолів та розроблено синтетичний підхід до раніше невідомих представників 5-ізоксазолілсульфонілхлоридів.

Ключові слова: N-гідроксіімідоїлхлориди; бензилтіоацетилен; 5-бензилтіоізоксазоли; окиснювальне хлорування; 5-ізоксазолілсульфоніл-хлориди

П. С. Лебедь, А. А. Толмачов, Ю. А. Зубчук, А. Н. Бойко, М. В. Вовк

Синтез и некоторые превращения 5-изоксазолилсульфохлоридов

Определено влияние структуры 5-бензилтиоизоксазолов на селективность образования 5-изоксазолилсульфонилхлоридов и выявлено химическое поведение последних по отношению к аминам.

Цель работы – создание методов синтеза 5-изоксазолил- и 4-хлор-5-изоксазолилсульфонилхлоридов как перспективных реагентов для конструирования потенциально биоактивных веществ.

Результаты и их обсуждение. Циклоконденсацией N-гидроксиимидоилхлоридов или 2-хлоро-2-(гидроксиимино)ацетатов из бензилтиоацетиленом синтезировано ряд 5-бензилтиоизоксазолов. Их окислительное хлорирование приводит к образованию смеси 5-изоксазолилсульфонилхлоридов и 4-хлор-5-изоксазолилсульфонилхлоридов, соотношение между которыми зависит от характера заместителей в положении 3 изоксазольного цикла. Для синтеза 4-хлор-5-изоксазолилсульфонилхлоридов с удовлетворительными выходами использован вариант предварительного хлорирования ядра 5-бензилтиоизоксазолов N-хлорсукцинимидом с дальнейшим окислительным хлорированием.

Экспериментальная часть. Синтез исходных и целевых соединений в классических препаративных условиях; методы флеш-хроматографии, элементного анализа, хроматомасс-спектрометрии, ЯМР ^{1}H и ^{13}C-спектроскопии.

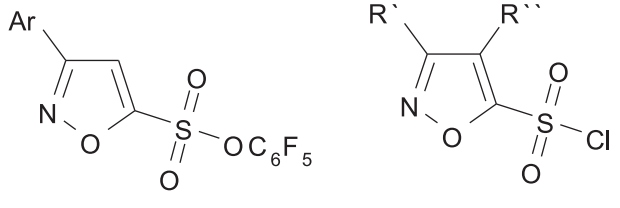
Выводы. Исследована реакция окислительного хлорирования 5-бензилтиоизоксазолов и разработан синтетический подход к ранее неизвестным представителям 5-изоксазолилсульфонилхлоридов.

Ключевые слова: N-гидроксиимидоилхлориды; бензилтиоацетилен; 5-бензилтиоизоксазолы; окислительное хлорирование; 5-изоксазолил-сульфонилхлориды

The heterocyclic system of isoxazole is an important representative of azoles known for their wide use in modern organic synthesis [1-3] and biomedical chemistry [4]. The isoxazole core is the key pharmacophore in a number of biologically active compounds: oxygenase inhibitor 2-Parecoxib, antagonist of GABA Sulfamethoxazole, antibiotic Oxacillin, herbicide Isoxaflutole, and the drug for rheumatoid arthritis Leflunomide [5]. The most recent investigations are focused on 5-subtitued isoxazoles [6, 7] where isoxazole-5-sulfonamides have been found as active nematocidal sulfonamides [8], agents for the treatment of atherosclerosis [9], hydroxy steroid dehydrogenaze inhibitors [10], and protein kinase inhibitors [11]. Such sulfonamides are usually synthesized by the modification of basic amino compounds of isoxazolyl-5-pentafluorophenyl sulfonates (**I**) or 5-chlorosulfonylisoxazoles (**II**) (Scheme 1).

The diversity of the titled reagents is limited, while methods of synthesis are not perfect. For example, for the synthesis of sulfonates **I** the cyclocondensation of α-bromopentafluorophenylvinyl sulfonate with aryl *N*-hydroxyimidoyl chlorides was suggested [6], and for the synthesis of sulfonyl chlorides **II** the oxidative chlorination of bis(isoxazol-5-yl)disulfides was proposed [12]. Thus, we have focused our attention on development of the preparative method of the synthesis of 5-isoxazolylsulfonyl chlorides that are universal reagents for sulfonylation.

The method of the synthesis of aromatic and heteroaromatic sulfonyl chlorides based on oxidative chlorination benzylaryl- or benzylheteroaryl sulfides was published [13-15]. We used such approach for synthesis of a number of 5-(chlorosulfonyl)isoxazoles. With the above goal and considering the results of the previous work [16] the cyclocondensation of *N*-hydroxyimidoyl chlorides **1a-d** [17] or 2-chloro-2-(hydroxyimino)acetates **1h,i** [18] with benzylethynylsulfide **2** [19] was performed. It was found that compounds **1a-i** after treatment with triethylamine gave the corresponding nitrile oxides which in mild conditions had inclination to [3+2]-cycloaddition with acetylene derivative **2** with formation of 5-(benzylthio)- isoxazoles **3a-i** with the yield of 71-95 %. The abovementioned had an exception with compound **3b** with 2,2,2-trifluoroethyl substitution group for which yield was not more than 43 % (Tab. 1, 2).



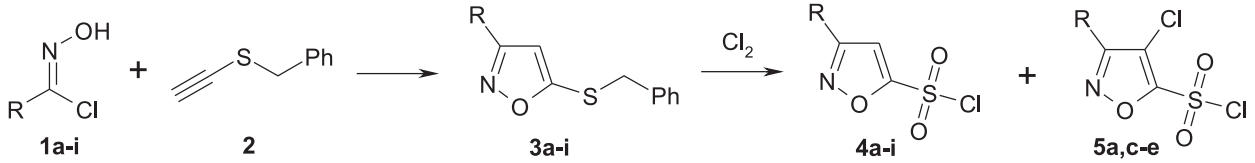
I **II**

Scheme 1

Solutions of **3a-i** in the mixture of water and chloroform were chlorinated with gaseous chlorine at 5-10 °C. The conversion of these mixtures finished in 3 h. The resulting mixtures were resoluted by column flesh-chromatography to obtain isoxazole-5-sulfonyl chlorides **4a-i** and 4-chloroisoxazole-5-sulfonyl chlorides **5a,c-e** (method *a*, Tab. 1, 2). The ratio between these products in the mixture depended on the nature of the substitution group in position 3 of the isoxazole ring. Compounds with electron donating alkyl and phenyl groups in **3** formed the corresponding products **4a,c-e** with the yield of 5-20 %, while compounds with electron withdrawing groups formed the corresponding products **4b,f-i** with the yield of 38-63 %. At the same time, the isolated yields of 4-chloroisoxazole-5-sulfonyl chlorides **5a,c-e** were 16-39 %. We suppose that the sulfonyl chloride group deactivate the mobility of position 4 of the isoxazole ring. Thus, the increase of the chlorination period from 3 h up to 5 h did not affect the overall yield of products **5** (Scheme 2).

The problem of a direct process towards formation of sulfonyl chlorides **5a,c-e** was solved by advance chlorination of compounds **3a,c-e** with N-chloro succinimide. This allowed obtaining 4-chloro substituted derivatives **6a-d** used for further oxidative chlorination with gaseous chlorine without additional purification. Such approach allowed obtaining the target compounds **5a,c-e** with the yield of 46-68 % (method *b*, Tab. 1, 2, Scheme 3).

To display the synthetic potential of the derivatives obtained the bifunctional derivative **4h** was selected as a convenient representative. Compound **4h** is an interesting scaffold for design of new promising bioactive structures. It reacted with aqueous ammonia at -40 °C with formation of sulfonamide **7a.** The same transformation with the ammonia excess at 0 °C finalized with carboxamide **8a**. The reaction of **4h** with morpholine at 0 °C led to compound **7b**. Compounds **7a,b** could be easily transformed into diamides **8a-c**



1a-i **2** **3a-i** **4a-i** **5a,c-e**

1, 3-5, R = Me (**a**), CF_3CH_2 (**b**), cyclo-C_3H_5 (**c**), t-Bu (**d**), Ph (**e**), p-CF_3-C_6H_4 (**f**), 4-O_2N-C_6H_4 (**g**), CO_2Me (**h**), CO_2t-Bu (**i**)

Scheme 2

Table 1

Yields, T. mp., MS spectra and elemental analysis data for compounds **3a-i, 4a-i, 5a,c-e**

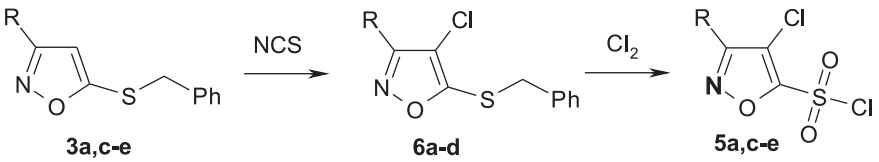
Compound	Yield, %	T. mp., °C (eluent)	$[M+1]^+$	Found, %			The empirical formula	Calculated, %		
				C	H	N		C	H	N
3a	74	oil (hexane)	206	64.55	5.51	6.90	$C_{11}H_{11}NOS$	64.36	5.40	6.82
3b	43	oil (MTBE-hexane, 5 %)	274	52.85	3.76	5.16	$C_{12}H_{10}F_3NOS$	52.74	3.69	5.13
3c	71	60-62	232	67.39	5.78	6.00	$C_{13}H_{13}NOS$	67.50	5.66	6.06
3d	71	oil (MTBE-hexane, 5 %)	248	68.11	7.04	5.69	$C_{14}H_{17}NOS$	67.98	6.93	5.66
3e	78	94-96	268	71.99	4.98	5.17	$C_{16}H_{13}NOS$	71.88	4.90	5.24
3f	76	118-120	336	60.76	3.69	4.22	$C_{17}H_{12}F_3NOS$	60.89	3.61	4.18
3g	76	127-128	313	61.66	3.94	9.06	$C_{16}H_{12}N_2O_3S$	61.53	3.87	8.97
3h	95	oil	250	58.00	4.40	5.54	$C_{12}H_{11}NO_3S$	57.82	4.45	5.62
3i	92	oil		61.71	5.79	4.76	$C_{15}H_{17}NO_3S$	61.83	5.88	4.81
4a	15	oil ($CHCl_3$-hexane, 35 %)		26.61	2.07	7.78	$C_4H_4ClNO_3S$	26.46	2.22	7.71
4b	45	oil (MTBE-hexane, 5 %)		24.20	1.13	5.68	$C_5H_3ClF_3NO_3S$	24.06	1.21	5.61
4c	5	oil (hexane)		34.64	2.99	6.71	$C_6H_6ClNO_3S$	34.71	2.91	6.75
4d	12	38-40 ($CHCl_3$-hexane, 5 %)		37.72	4.62	6.32	$C_7H_{10}ClNO_3S$	37.59	4.51	6.26
4e	20	87-88 ($CHCl_3$-hexane, 10 %)		44.52	2.59	5.86	$C_9H_6ClNO_3S$	44.36	2.48	5.75
4f	63	85-86 (MTBE-hexane, 15 %)		38.66	1.71	4.55	$C_{10}H_5ClF_3NO_3S$	38.54	1.62	4.49
4g	82	116-117 ($CHCl_3$)		37.56	1.78	9.80	$C_9H_5ClN_2O_5S$	37.45	1.75	9.70
4h	41	oil (MTBE-hexane, 15 %)		26.51	1.89	6.14	$C_5H_4ClNO_5S$	26.62	1.79	6.21
4i	38	52-53 (MTBE-hexane, 5 %)		35.98	3.83	5.29	$C_8H_{10}ClNO_5S$	35.90	3.77	5.23
5a	19 (method *a)* 46 (method *b*)	oil ($CHCl_3$-hexane, 35 %)		22.33	1.52	6.60	$C_4H_3Cl_2NO_3S$	22.24	1.40	6.48
5c	16 (method *a*) 57 (method *b*)	oil (hexane)		29.86	2.13	5.88	$C_6H_5Cl_2NO_3S$	29.77	2.08	5.79
5d	39 (method *a*) 68 (method *b*)	oil ($CHCl_3$-hexane, 5 %)		32.68	3.59	5.50	$C_7H_9Cl_2NO_3S$	32.57	3.51	5.43
5e	22 (method *a*) 56 (method *b*)	oil (hexane)		38.74	1.87	5.09	$C_9H_5Cl_2NO_3S$	38.87	1.81	5.04

by the reaction with amines or ammonia. The carboxylic function in **7a,b** could be transformed into synthetic promising derivatives with hydroxymethyl (compounds **9a,b**) or bromomethyl (compounds **10a,b**) group (Scheme 4).

Experimental Part

All chemicals and solvents were obtained from Enamine Ltd. and used without further purification. NMR spectra were recorded on a Bruker Advance 400 spectrometer (^{1}H NMR at 399.98 MHz and ^{13}C NMR at 125.7 MHz) in $CDCl_3$ [for compounds **7a,b**, **9a,b**, **10a,b** in DMSO-d_6; for compounds **4a,b** in C_6D_6]. LC/MS spectra were recorded on an Agilent 1100 LCMSD SL instrument, column Zorbax SB C18 1.8 μm 4.6 × 15 mm, solvent DMSO, ionization at atmospheric pressure (70 eV). The melting points were measured with a Kohler melting point apparatus and were not corrected.

5-(Benzylthio)-3-substitutedisoxazoles(3a-i). To the mixture of *N*-hydroxyimidoyl chlorides **1a-i** (40 mmol, 1 equiv) and benzylethynyl sulfide **2** (5.92 g, 40 mmol, 1 equiv) in ethyl acetate (150 mL) add drop-



3a,c-e **6a-d** **5a,c-e**

Scheme 3

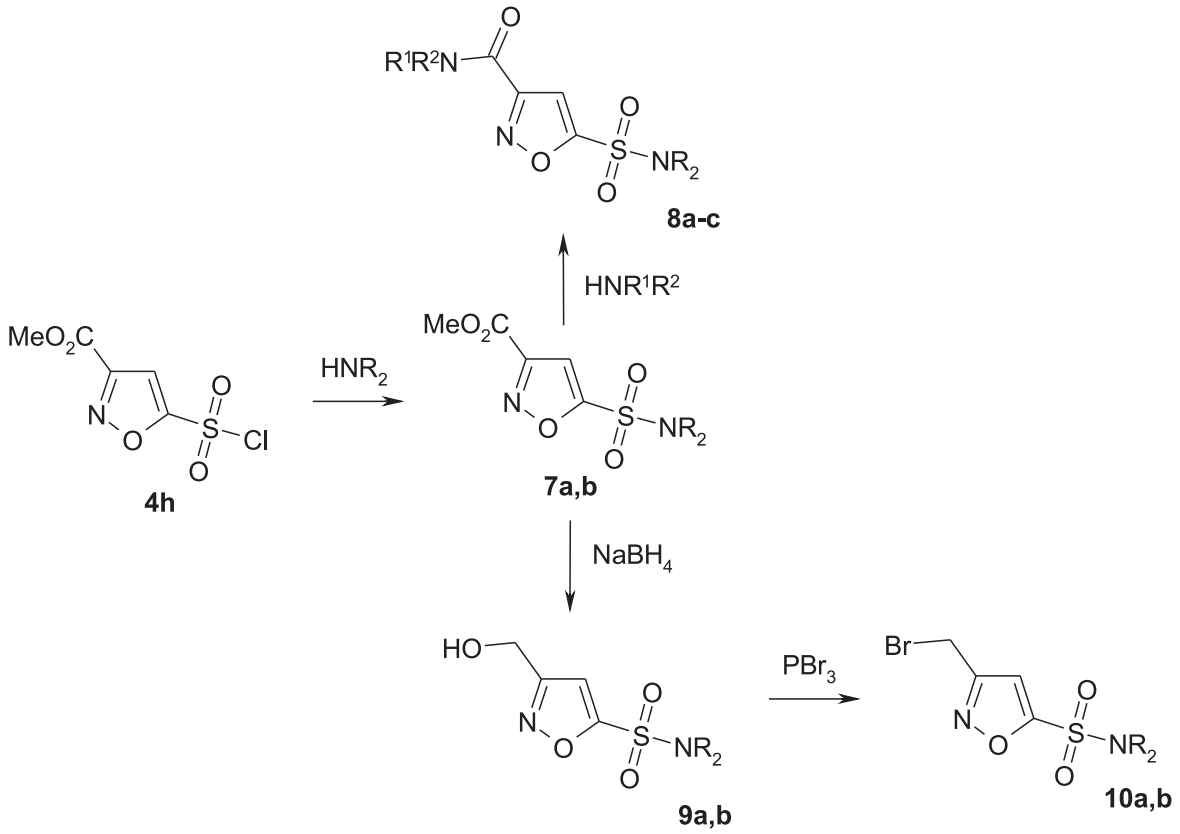
Table 2

^{1}H and ^{13}C NMR data for compounds **3a-i, 4a-i, 5a,c-e**

Compound	^{1}H NMR spectra, δ, ppm	^{13}C NMR spectra, δ, ppm
3a	2.24 s (3H, CH_3), 4.21 s (2H, CH_2), 5.90 s (1H, H^4), 7.22-7.35 m (5H, H_{Ar})	11.5 (CH_3), 37.7 (CH_2), 105.6 (C^4), 127.7, 128.7, 128.8, 136.3 (C_{Ar}), 160.5 (C^3), 165.0 (C^5)
3b	3.45 q (2H, CH_2, J = 10.4 Hz), 4.21 s (2H, CH_2), 6.08 s (1H, H^4), 7.23-7.35 m (5H, H_{Ar})	31.8 q (CH_2, J_{C-F} = 32.0 Hz), 37.8 (CH_2), 105.0 (C^4), 124.5 q(CF_3, J_{C-F} = 275.0 Hz), 128.8, 128.8, 135.9 (C_{Ar}), 155.1 q(C^3, J_{C-F} = 4.0 Hz), 167.0(C^5)
3c	0.66-0.83 m (2H, CH_2), 0.90-1.05 m (2H, CH_2), 1.87-1.96 m (1H, CH), 4.16 s (2H, CH_2), 5.68 s (1H, H^4), 7.20-7.37 m (5H, H_{Ar})	7.4 (CH), 8.0 (CH_2), 37.8 (CH_2), 102.5 (C^4), 127.7, 128.7, 128.9, 136.3 (C_{Ar}), 164.7 (C^3), 167.1(C^5)
3d	1.29 s (9H, CH_3), 4.21 s (2H, CH_2), 5.95 s (1H, H^4), 7.26-7.33 m (5H, H_{Ar})	29.3 (CH_3), 32.1 (CH), 37.9 (CH_2), 103.4 (C^4), 127.7, 128.6, 128.9,136.4 (C_{Ar}), 164.3 (C^3), 172.7 (C^5)
3e	4.29 s (2H, CH_2), 6.39 s (1H, H^4), 7.26-7.37 m (5H, H_{Ar}), 7.43-7.48 m (3H, H_{Ar}), 7.73-7.78 m (2H, H_{Ar})	37.9 (CH_2), 103.2 (C^4), 126.7, 127.85, 128.7, 128.8, 128.9, 128.9, 130.1, 136.3 (C_{Ar}), 163.0 (C^3), 165.8(C^5)
3f	4.28 s (2H, CH_2), 6.37 s (1H, H^4), 7.24-7.34 m (5H, H_{Ar}), 7.68 d (2H, H_{Ar},J = 8.4 Hz), 7.83 d(2H, H_{Ar},J = 8.4 Hz)	37.9 (CH_2), 103.0 (C^4), 123.8 q(CF_3, J_{C-F} = 271.0 Hz), 125.9 (C_{Ar}, J_{C-F} = 4.0 Hz), 127.1, 127.9, 128.8, 128.8, 131.8, 132.1, 136.1 (C_{Ar}), 161.9 (C^3), 166.8(C^5)
3g	4.32 s (2H, CH_2), 6.43 s (1H, H^4), 7.26-7.39 m (5H, H_{Ar}), 7.92 d (2H, H_{Ar}, J = 8.5 Hz), 8.31 d (2H, H_{Ar}, J = 8.5 Hz)	37.9 (CH_2), 102.9 (C^4), 124.2, 127.6, 128.0, 128.8, 128.8, 134.8, 135.9, 148.7 (C_{Ar}), 161.2 (C^3), 167.4(C^5)
3h	3.93 s (3H, CH_3), 4.24 s (2H, CH_2), 6.45 s (1H, H^4), 7.24-7.32 m (5H, H_{Ar})	38.0 (CH_2), 52.9 (CH_3), 105.3 (C^4), 128.0, 128.8, 128.8, 135.6, 156.6 (C_{Ar}), 160.0 (C^3), 168.2(C^5)
3i	1.56 s (9H, CH_3), 4.22 s (2H, CH_2), 6.38 s (1H, H^4), 7.15-7.34 m (5H, H_{Ar})	28.0 (CH_3), 37.9 (CH_2), 83.8 (CH), 105.3 (C^4), 127.9, 128.8, 135.8, 158.1 (C_{Ar}), 158.6 (C^3), 167.5 (C^5)
4a	1.46 s (3H, CH_3), 5.57 s (1H, H^4)	10.4 (CH_3), 109.2 (C^4), 160.2 (C^3), 164.7 (C^5)
4b	2.62 q (2H, CH_2, J = 10.0 Hz), 6.09 s (1H, H^4)	30.8 q(CH_2, J_{C-F} = 33.0 Hz), 108.5(C^4), 123.9 q(CF_3, J_{C-F} = 277.0 Hz), 155.2 (C^3), 166.2 (C^5)
4c	0.82-0.98 m (2H, CH_2), 1.07-1.29 m (2H, CH_2), 1.97-2.11 m (1H, CH), 6.72 s (1H, H^4)	7.5 (CH), 9.0 (CH_2), 107.0 (C^4), 165.0 (C^3), 167.4 (C^5)
4d	1.36 s(9H, CH_3), 6.94 s (1H, H^4)	29.2 (CH_3), 32.9 (CH), 107.3(C^4), 165.1(C^3), 172.8(C^5)
4e	7.24 s (1H, H^4), 7.44-7.56 m (3H, H_{Ar}), 7.74-7.85 m (2H, H_{Ar})	107.2 (C^4), 126.4, 129.4, 131.6 (C_{Ar}), 163.1(C^3), 165.9 (C^5)
4f	7.39 s (1H, H^4), 7.78 d (2H, H_{Ar},J = 8.4 Hz), 7.95 d (2H, H_{Ar}, J = 8.4 Hz)	107.0 (C^4), 123.5 q (CF_3, J_{C-F} = 270.0 Hz), 126.4 q (J_{C-F} = 4.0 Hz), 127.4,129.8,133.3 q(C_{Ar}, J_{C-F} = 33.0 Hz), 161.9(C^3), 166.5 (C^5)
4g	7.44 s (1H, H^4), 8.03 d (2H, J = 8.4 Hz), 8.37 d (J = 8.4 Hz)	107.1 (C^4),124.6, 128.1, 132.3, 149.6(C_{Ar}), 161.3(C^3), 166.8 (C^5)
4h	4.00 s (3H, CH_3), 7.41 s (1H, H^4)	53.7 (CH_3), 109.4 (C^4), 156.6 (C^3), 157.9 (CO), 166.8 (C^5)
4i	1.59 s (9H, CH_3), 7.33 s (1H, H^4)	27.9 (CH_3), 85.6 (CH), 109.4 (C^4), 156.5 (C^3), 157.9 (CO), 166.5 (C^5)
5a	2.40 s (3H, CH_3)	10.0 (CH_3), 115.0 (C^4), 159.7 (C^3), 160.7 (C^5)
5c	1.13-1.20 m (4H, CH_2), 1.87-1.95 m (1H, CH)	5.8 (CH), 8.8 (CH_2), 115.0 (C^4), 159.6 (C^3), 165.5 (C^5)
5d	1.46 s (9H, CH_3)	27.4 (CH_3),34.2 (CH), 113.3 (C^4), 160.8 (C^3), 168.9 (C^5)
5e	7.51-7.65 m (3H, H_{Ar}), 7.87 d (2H, H_{Ar}J = 7.0 Hz)	113.4 (C^4), 124.7, 128.1, 129.1, 131.5 (C_{Ar}), 160.8 (C^3), 161.3 (C^5)

wise the solution of TEA (4.45 g, 44 mmol, 1.1 equiv) in ethyl acetate (100 mL) within subsequent 10-12 h at 0 °C. When addition is completed, stir the resulting reaction mixture for 15 h at room temperature. Then dilute it with water (150 mL), wash with brine (100 mL). Dry the organic layer separated over sodium sulfate and concentrate under reduced pressure. Re-crystallize compounds **3c,e,f,g** from 2-propanol, purify compounds **3a,b,d** by flash chromatography, and obtain compounds **3h,i** without purification.

3-Substituted isoxazole-5-sulfonyl chlorides (4a-i) and 4-chloro-3-substituted isoxazole-5-sulfonyl chlorides (5a,c-e) (method *a*). Place the mixture of compounds **3a-i** (75 mmol) in dichloromethane (800 mL) and water (300 mL) in a glass flask. Then cool it with ice, and pass gaseous chlorine carefully



7, R = H (**a**); R_2 = $(CH_2)_2O(CH_2)_2$ (**b**); **8,** R = R^1 = R^2 = H (**a**); R_2 = $(CH_2)_2O(CH_2)_2$, R^1 = H, R^2 = $PhCH_2$ (**b**); R_2 = $(CH_2)_2O(CH_2)_2$, R^1R^2 = $(CH_2)_4$ (**c**) **9, 10,** R = H (**a**); R2 = $(CH_2)_2O(CH_2)_2$ (**b**)

Scheme 4

through the mixture while stirring vigorously for over the next 3 h, keeping the temperature of the reaction mixture below 10 ºC. Add crushed ice (500 g), then Na_2SO_3 till discoloration of the organic layer keeping the temperature of the reaction below 10 ºC. Separate the organic layer, and wash the aqueous layer with dichloromethane (1 × 200 mL). Dry the combined organic layers over sodium sulfate and concentrate under reduced pressure on a water bath at the temperature of not more than 35 °C. Purify the residue by flash chromatography.

4-Chloro-3-substituted isoxazole-5-sulfonyl chlorides (5a,c-e) (method *b*). To the solution of compounds **3a,c-e** (16 mmol, 1 equiv.) in the appropriate solvent (CH_3CN (30 ml) for **3a,c,e** or DMF (30 ml) for **3d** add *N*-chlorosuccinimide (2.38 g, 18 mmol, 1.1 equiv), and stir the resulting mixture overnight at room temperature. Then dilute it with water (120 mL) and extract with ethyl acetate (2 × 70 ml). Wash the combined organic phases with brine (100 ml), dry over sodium sulfate, and concentrate under vacuum to obtain compounds **6a-d** used without purification. Place the mixture of compounds **6a-d** (75 mmol) in dichloromethane (800 mL) and water (300 mL) in a glass flask. Then cool it with ice, and pass gaseous chlorine carefully through the mixture while stirring vigorously for over the next 3 h, keeping the temperature of the reaction mixture below 10 °C. Add crushed ice (500 g), then Na_2SO_3 till discoloration of the organic layer keeping the temperature of the reaction below 10 °C. Separate the organic layer, and wash the aqueous layer with dichloromethane (1 × 200 mL). Dry the combined organic layers over sodium sulfate and concentrate under reduced pressure on a water bath at the temperature of not more than 35 °C. Purify the residue by flash chromatography.

Methyl 5-(aminosulfonyl)isoxazole-3-carboxylate (7a). To the solution of NH_4OH (25 % 0.41 g, 2.6 mmol, 2.2 equiv.) in THF (15 ml) add dropwise the solution of compound **4h** (0.3 g, 1.2 mmol, 1 equiv.) in THF (10 ml) while stirring at – 40 °C. When addition is completed, stir the resulting mixture for 10 min, and add hydrochloric acid (10 M) to the mixture to adjust pH 2. Then concentrate it, and dissolve the residue in water (30 ml). Extract the resulting solution with ethyl acetate (2 × 30 ml). Dry the combined organic layers over sodium sulfate, and concentrate under reduced pressure to obtain the target compound. Yield – 0.2 g (72 %). M. p. – 133-136 °C. ^{1}H NMR, δ, ppm: 3.93 s (3H, CH_3), 7.32 s (1H, H^4), 8.51 br s (2H, NH_2). ^{13}C NMR, δ, ppm: 53.7 (CH_3), 106.1 (C^4),156.8 (C^3), 159.1 (C^5), 171.1 (CO). LC-MS (APCI): *m/z* $[M+H]^+$207.0. Anal. Calcd for $C_5H_6N_2O_5S$: C 29.13, H 2.93, N 13.59. Found: C 29.31, H 3.01, N 13.65.

Methyl 5-(morpholin-4-ylsulfonyl)isoxazole-3-carboxylate (7b). To the solution of morpholine (0.63 g, 7.2 mmol, 2 equiv.) in THF (20 ml) add dropwise the solution of compound **4h** (0.81 g, 3.6 mmol, 1 equiv.) in THF (10 ml) while stirring at 0 °C. When addition is completed, stir the resulting mixture for 30 min. After that concentrate it, and dissolve the residue in water (30 ml). Extract the resulting solution with ethyl acetate (2 × 30 ml). Dry the combined organic layers over sodium sulfate, and concentrate under reduced pressure to obtain the target compound. Yield – 0.88 g (89 %). M. p. – 115-117 °C. ^{1}H NMR, δ, ppm: 3.27-3.32 m (4H, CH_2), 3.75-3.81 m (4H, CH_2), 4.02 s (3H, CH_3), 7.16 s (1H, H^4). ^{13}C NMR, δ, ppm: 46.0 (CH_2), 53.7 (CH_3), 65.7 (CH_2), 109.7 (C^4), 157.1 (C^3), 159.0 (C^5), 165.0 (CO). LC-MS (APCI): *m/z* $[M+H]^+$ 277.0. Anal. Calcd for $C_9H_{12}N_2O_6S$: C 39.13, H 4.38, N 10.14. Found: C 39.29, H 4.43, N 10.22.

5-(Aminosulfonyl)isoxazole-3-carboxamide (8a). To the solution of NH_4OH (25 %, 0.66 g, 9.7 mmol, 4 equiv.) in THF (15 ml) add dropwise the solution of compound **7a** (1.09 g, 4.85 mmol, 1 equiv.) in THF (15 ml) while stirring at 0 °C. In 30 min concentrate the solvent under vacuum and add water (10 ml) to the residue. Extract the water solution with ethyl acetate (3 × 20 ml). Combine organic layers, dry with sodium sulfate and concentrate under vacuum providing a pure product. Yield – 0.73 g (79 %). M. p. – 175-176 °C.^{1}H NMR, δ, ppm: 7.21 s (1H, H^4), 8.03 s (1H, NH), 8.34 s (1H, NH), 8.42 br s (2H, NH_2). ^{13}C NMR, δ, ppm: 105.3 (C^4), 159.3 (C^3), 159.5 (C^5), 170.4 (CO). LC-MS (APCI): *m/z* $[M-H]^-$ 190.0. Anal. Calcd for $C_4H_5N_3O_4S$: C 25.13, H 2.64, N 21.98. Found: C 24.98, H 2.73, N 22.07.

N-Alkyl-5-(morpholin-4-ylsulfonyl)isoxazole-3-carboxamides (8b,c). To the solution **7b** (0.2 g, 0.72 mmol, 1 eq) in CH_3CN (10 ml) add the corresponding amine (0.79 mmol, 1.1 eq), and reflux the resulting mixture for over 8 h. Then concentrate it, and re-crystallize the residue from 2-propanol to obtain a target compound.

N-Benzyl-5-(morpholin-4-ylsulfonyl)isoxazole-3-carboxamide(8b). Yield – 0.17 g (68 %). M. p. – 138-141 °C.^{1}H NMR,δ, ppm: 3.20-3.34 m (4H, CH_2), 3.66-3.83 m (4H, CH_2), 4.61-4.66 m (2H, CH_2), 7.16-7.41 m (6H, H_{Ar}). ^{13}C NMR, δ, ppm: 43.7 (CH_2), 45.8 (CH_2), 66.0 (CH_2), 108.28 (C^4), 127.9, 128.0, 128.9, 136.9 (C_{Ar}), 157.0 (C^3), 158.5 (C^5), 165.7 (CO). LC-MS(APCI): *m/z* $[M+H]^+$ 352.0. Anal. Calcd for $C_{15}H_{17}N_3O_5S$: C 51.27, H 4.88, N 11.96. Found: C 51.42, H 4.97, N 12.06.

4-{[3-(Pyrrolidin-1-ylcarbonyl)isoxazol-5-yl] sulfonyl}morpholine (8c). Yield – 0.18 g (79 %). M. p. – 131-134 °C. ^{1}H NMR, δ, ppm: 1.92-2.02 m (4H, CH_2), 3.21-3.35 m (4H, CH_2), 3.60-3.69 m (2H, CH_2), 3.71-3.80 m (4H, CH_2), 3.81-3.89 m (2H, CH_2), 7.15 s (1H, H^4). ^{13}C NMR, δ, ppm: 23.9, 26.2, 45.8, 47.2, 48.7, 66.0 (CH_2), 109.9 (C^4), 156.7 (C^3), 159.8 (C^5), 164.3 (CO). LC-MS (APCI): *m/z* $[M+H]^+$ 316.0. Anal. Calcd for $C_{12}H_{17}N_3O_5S$: C 45.71, H 5.43, N 13.32. Found: C 45.59, H 5.32, N 13.24.

3-(Hydroxymethyl)isoxazole-5-sulfonamides (9a,b). To the solution of compounds **7a,b** (1.8 mmol, 1 equiv.) in ethanol (25 ml) add the powdered $NaBH_4$ (0.14 g, 3.6 mmol, 2 equiv.) in several portions while stirring and cooling with an ice bath. When addition is completed, stir the resulting mixture overnight at room temperature, then concentrate it under reduced pressure on a water bath at a temperature of not more than 35 °C. Suspend the residue in water (4 ml), and then extract with EtOAc (3 × 10 ml). Dry the combined organic layers over sodium sulfate and concentrate under vacuum. Re-crystallize the residue from 2-propanol to obtain a target compound.

3-(Hydroxymethyl)isoxazole-5-sulfonamide (9a). Yield – 0.24 g (76 %). M. p. – 89-91 °C. ^{1}H NMR, δ, ppm: 4.55 s (2H, CH_2), 5.65 br s (1H, OH), 6.9 s (1H, H^4), 8.31 br s (2H, NH_2). ^{13}C NMR, δ, ppm: 55.2 (CH_2), 105.3 (C^4), 169.0 (C^3), 165.5 (C^5). LC-MS (APCI): *m/z* $[M+H]^+$ 179.2. Anal. Calcd for $C_4H_6N_2O_4S$: C 26.97, H 3.39, N 15.72. Found: C 27.11, H 3.49, N 15.63.

[5-(Morpholin-4-ylsulfonyl)isoxazol-3-yl]methanol (9b). Yield – 0.23 g (51 %). M. p. – 98-100 °C. ^{1}H NMR, δ, ppm: 3.09-3.18 m (4H, CH_2), 3.61-3.68 m (4H, CH_2), 4.59 d (2H,CH_2, J = 5.6 Hz), 5.75 br s (1H, OH), 7.20 s (1H, H^4). ^{13}C NMR, δ, ppm: 46.1 (CH_2), 55.2 (CH_2), 65.7 (CH_2), 109.0 (C^4), 162.8 (C^3), 165.9 (C^5). LC-MS (APCI): *m/z* $[M+H]^+$ 249.2. Anal. Calcd for $C_8H_{12}N_2O_5S$: C 38.71, H 4.87, N 11.28. Found: C 38.54, H 4.99, N 11.37.

3-(Bromomethyl)isoxazole-5-sulfonamide (10a,b). To the solution of the corresponding compounds **9a,b** (1.2 mmol, 1 equiv.) in CH_2Cl_2 (15 ml) add dropwise the solution of PBr_3 (0.16 g, 0.6 mmol, 2 equiv.) in CH_2Cl_2 (5 ml) while stirring at 0 °C. When addition is completed, stir the resulting mixture overnight. Then dilute it with crushed ice (40 g), and add sodium bicarbonate to adjust pH 7. Extract the resulting mixture with CH_2Cl_2 (2 × 30 ml). Dry the combined organic layers over sodium sulfate and concentrate under vacuum.

3-(Bromomethyl)isoxazole-5-sulfonamide (10a). Yield – 0.13 g (46 %). M. p. – 92-93 °C. ^{1}H NMR, δ, ppm: 4.72 s (2H, CH_2), 7.1 s (1H, H^4), 8.40 s (2H, NH_2). ^{13}C NMR, δ, ppm: 21.1 (CH_2), 106.3 (C^4), 162.3 (C^3), 169.8 (C^5). LC-MS (APCI): *m/z* $[M+H]^+$ 242.8. Anal. Calcd for $C_4H_5BrN_2O_3S$: C 19.93, H 2.09, N 11.62. Found: C 20.09, H 2.21, N 11.72.

4-{[3-(Bromomethyl)isoxazol-5-yl]sulfonyl} morpholine (10b). Yield – 0.25 g (68 %). ^{1}H NMR, δ, ppm: 3.24-3.31 m (4H,CH_2), 3.72-3.78 m (4H, CH_2), 4.42 s (2H, CH_2), 6.86 s (1H, H^4). ^{13}C NMR, δ, ppm: 19.3 (CH_2), 45.8 (CH_2), 66.0 (CH_2), 108.6 (C^4), 161.3 (C^3), 165.0 (C^5). LC-MS (APCI): *m/z* $[M+H]^+$ 314.0. Anal. Calcd for $C_4H_5BrN_2O_3S$: C 30.88, H 3.56, N 9.00. Found: C 30.66, H 3.68, N 8.88.

Conclusions

1. The reaction of oxidative chlorination of 5-(benzylthio)-3-isoxazoles has been studied. The data obtained has been efficiently used for the synthesis of the previously unknown isoxazole-5-sulfonyl chlorides.

2. The synthetic potential of the resulting compounds has been demonstrated by the examples of the interaction of 5-(chlorosulfonyl)isoxazole-3-carboxylate with amines. The above products are reduced and brominated with formation of sulfonamides.

Conflicts of Interests: authors have no coflict of interests to declare.

References

1. Pinho e Melo, T. Recent advances on the synthesis and reactivity ofisoxazoles / T. Pinho e Melo // Curr. Org. Chem. – 2005. – Vol. 9, Issue 10. – P. 925–958. doi: 10.2174/1385272054368420
2. Recent advances in isoxazole chemistry / A. V. Galenko, A. F. Khlebnikov, M. S. Novikov et al. // Russ. Chem. Rev. – 2015. – Vol. 84, Issue 4. – P. 335–377. doi: 10.1070/rcr4503
3. Hu, F. Recent developments in the synthesis and reactivity of isoxazoles : method catalysis and beyond / F. Hu, M. Szostak // Adv. Synth. Catal. – 2015. – Vol. 357, Issue 12. – P. 2583–2614. doi: 10.1002/adsc.201500319
4. A review on synthesis and reactivity of isoxazoles and pyrazolines / K. Manna, U. Banik, P. S. Grosh, M. Dos // Nirma University J. Pharm. Sci. – 2014. – Vol. 1, Issue 1. – P. 37–49.
5. Goodman and Gilman`s the pharmacological basis of therapeutics / eds. L. Brunton, B. A. Chabner, B. Knollman. – McGrow–Hill, 2011.
6. Lee, C. C. 3,5–Isoxazoles from α–bromopentafluorophenylvinyl sulfonates : synthesis of sulfonates and sulfonamides / C. C. Lee, R. J. Fitzmaurice, S. Caddik // Org. Biomol. Chem. – 2009. – Vol. 7, Issue 21. – P. 4349–4351. doi: 10.1039/b911098d
7. Unexpected heterocyclization of electrophilic alkenes by tetranitromethane in the presence of triethylamine. Synthesis of 3–nitroisoxazoles / Y. A. Volkova, E. B. Averina, Y. K. Grishin et al. // J. Org. Chem. – 2010. – Vol. 75, Issue 9. – P. 3047–3052. doi: 10.1021/jo100319p
8. Nematocidal sulfonamides. Pat. WO 2010129500(A2) / Lahm G. P., Lett R. M., Smith B. T., Smith B. K., Tyler C. A. – declared 04.05.2009; published 11.10.2010.
9. Benzofuryl pyrone derivatives. Pat. US 6589984(B1) / Nanyva Y., Ymai H., Ida T., Muratoni E., Kitaki K., Sugimoto Y., Kosugi T., Takeuchi A., Watanabe K., Tokuyama T., Takeuchi T., Hamada M. – declared 11.09.2000; published 08.07.2003.
10. Hydroxy steroid dehydrogenaze inhibitors. Pat. US 20060223829(A1) / Aertgeerts K., Breennan N., Cao S., Chang E., Kiryanova A., Liu X. – declared 31.03.2005; published 05.10.2006.
11. 3,4–Diarylpyrazoles as proteinkinase inhibitors. Pat. WO 2010010154(A1) / Pulici M., Zuccoto F., Badari A., Nuvoloni S., Cervi G., Traqeandi G., Bionrado S., Trifiro P., Marchionni C., Moduguo M. – declared 24.07.2008; published 28.01.2010.
12. Adembri, G. Oxidation products of 5–isoxazolthiolsand 5–ethylisoxazoles : sulfoxides, sulfones, sulfonicacids and derivatives / C. Ademri, R. Nesi // J. Heterocycl. Chem. – 1972. – Vol. 9, Issue 3. – P. 695–697. doi: 10.1002/jhet.5570090336
13. Synthesis of isomeric fluorobenzene–sulfonylchlorides / S. Zhersh, O. Lukin, V. Matvienko, A. Tolmachev // Tetrahedron. – 2010. – Vol. 66, Issue 32. – P. 5982–5986. doi: 10.1016/j.tet.2010.06.036
14. Baker, R. H. The cleavage of organic sulfides with chlorine / R. H. Baker, R. M. Dodson, B. Riegel // J. Am. Chem. Soc. – 1946. – Vol. 68, Issue 12. – P. 2636–2639.doi: 10.1021/ja01216a063
15. Barry, W. J. Derivatives of 5–o–merkaptophenyl–3–methyl–1–phenylpyrazole / W. J. Barry, J. L. Finar // J. Chem. Soc. – 1954. – P. 138–140. doi: 10.1039/jr9540000138
16. Preparation of novel antibacterial agents. Replacement of the central aromatic ring with heterocycles / J. Li, B. D. Wakefild, J. C. Ruble et al. // Bioorg. Med. Chem. Lett. – 2007. – Vol. 17, Issue 8. – P. 2347–2350. doi:10.1016/j.bmcl.2006.12.055
17. Liu, K–C. A particularly convenient preparation of benzohydroximinoil chlorides (nitrile oxide precursors) / K–C. Liu, B. R. Shelton, R. K. Howe // J. Org. Chem. – 1980. – Vol. 45, Issue 19. – P. 3916–3918. doi: 10.1021/jo01307a039
18. Kozikowski, A. P. Methods for stereoselective cis–cyanohydroxylation and carboxyhydroxylation of olefins / A. P. Kozikowski, M. Adamczyk // J. Org. Chem. – 1983. – Vol. 48, Issue 3. – P. 366–372. doi: 10.1021/jo00151a017
19. In pursuit of an acetylen dithiolate synthesis / W. W. Seidel, M. J. Meel, M. Schaffrath, T. Pape // Eur. J. Org. Chem. – 2007. – Vol. 2007, Issue 21. – P. 3526–3532. doi: 10.1002/ejoc.200601107

References

1. Pinho e Melo, T. (2005). Recent advances on the synthesis and reactivity ofisoxazoles. *Current Organic Chemistry, 9 (10)*, 925–958. doi: 10.2174/13852720543684200
2. Galenko, A. V., Khlebnikov, A. F., Novikov, M. S.et al. (2015). Recent advances in isoxazolechemistry. *Russian Chemical Review*, *84 (4)*, 335–377. doi: 10.1070/rcr4503
3. Hu, F., Szostak, M. (2015). Recent developments in the synthesis and reactivity of isoxazoles: method catalysis and beyond. *Advanced Synthesis and Catalysis*, *357 (12)*, 2583–2614. doi: 10.1002/absc.201500319
4. Manna, K., Banik, U., Grosh, P. S., Dos, M. (2014). A review on synthesis and reactivity of isoxazoles and yrazolines *Nirma University Journal of Pharmaceutical Sciences*, *1(1)*, 37–49.
5. Brunton, L., Chabner, B. A., Knollman, B. (2011). Goodmanand Gilman`s the pharmacological basis of therapeutics. *McGrow–Hill*.
6. Lee, C. C., Fitzmaurice, R. J., Caddik, S. (2009). 3,5–Isoxazoles from α–bromopentafluorophenylvinyl sulfonates: synthesis of sulfonates and sulfonamides. *Organic and Biomolecular Chemistry, 7 (21),* 4349–4351. doi: 10.1039/b911098d
7. Volkova, Y. A., Averina, E. B., Grishin, Y. K. et al. (2010). Unexpected heterocyclization of electrophilic alkenes by tetranitromethane in the presence of triethylamine. Synthesis of 3–nitroisoxazoles. *Journal of Organic Chemistry, 75 (9),* 3047–3052. doi: 10.1021/j0100319p
8. Lahm, G. P., Lett, R. M., Smith, B. T., Smith, B. K. et al. (2010). *Nematocidal sulfonamides*. Pat. WO 2010129500 (A2); declared 04.05.2009; published 11.10.2010.
9. Nanyva, Y., Ymai, H., Ida, T., Muratoni, E. et al.(2003). *Benzofurylpyrone derivatives.* Pat. US 6589984(B1); declared 11.09.2000; published 08.07.2003.
10. Aertgeerts, K., Breennan, N., Cao, S., Chang, E.et al. (2006). *Hydroxysteroid dehydrogenaze inhibitors*. Pat. US 20060223829(A1); declared 31.03.2005; published 05.10.2006.
11. Pulici, M., Zuccoto, F., Badari, A., Nuvoloni, S. et al. (2010). *3,4–Diarylpyrazoles as protein kinase inhibitors*. Pat. WO 2010010154(A1); declared 24.07.2008; published 28.01.2010.
12. Ademri, C., Nesi, R. (1972). Oxidation products of 5–isoxazolthiolsand 5–ethylisoxazoles: sulfoxides, sulfones, sulfonic acids and derivatives. *Journal of Heterocyclic Chemistry, 9 (3),* 695–697. doi: 10.1002/jhet.5570090336

13. Zhersh, S., Lukin, O., Matvienko, V., Tolmachev, A. (2010). Synthesis of isomeric fluorobenzene–sulfonyl chlorides. *Tetrahedron, 66 (32),* 5982–5986. doi: 10.1016/j.tet.2010.06.036
14. Baker, R. H., Dodson, R. M., Riegel, B. (1946). The cleavage of organic sulfides with chlorine .*Journal of the American Chemical Society, 68 (12),* 2636–2639.doi: 10.1021/ja01216a063
15. Barry, W. J., Finar, J. L. (1954). Derivatives of 5–*o*–merkaptophenyl–3–methyl–1–phenylpyrazole.*Journal of the ChemicalSociety*, 138–140. doi: 10.1039/jr9540000138
16. Li, J., Wakefild, B. D., Ruble, J. C. et al. (2007). Preparation of novel antibacterial agents. Replacement of the central aromatic ring with heterocycles. *Bioorganic and Medicinal Chemistry Letters, 17 (8),* 2347–2350. doi: 10.1016/j.bmcl.2006.12.055
17. Liu, K–C., Shelton, B. R., Howe, R. K. (1980). A particularly convenient preparation of benzohydroximinoil chlorides (nitrile oxide precursors). *Journal of Organic* Chemistry, *45 (19)*, 3916–3918.doi: 10.1021/jo01307a039
18. Kozikowski, A. P., Adamczyk, M. (1983). Methods for stereoselective cis–cyanohydroxylation and carboxyhydroxylation of olefins. *Journal of Organic Chemistry,48 (3)*, 366–372. doi: 10.1021/jo00151a017
19. Seidel, W. W., Meel, M. J., Schaffrath, M., Pape, T. (2007). In pursuit of an acetylendithiolate synthesis. *European Journal of Organic Chemistry, 2007 (21),* 3526–3532. doi: 10.1002/ejoc.200601107

Надійшла до редакції 04.07.2017 р.

Acknoledgments
The authors are grateful to Enamine Ltd. for providing financial and technical support.