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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*-hydroxyimidoil chlorides or 2-chloro-2-(hydroxyimino) acetates with benzyethynylsulfide. 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; flash-chromatography; elemental analysis; LCMS; ¹H and ¹³C 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*-hydroxyimidoil chlorides; benzyethynyl sulfide; 5-(benzylthio)-3-isoxazoles; oxidative chlorination; isoxazole-5-sulfonylchlorides

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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*-гідроксіімідойлхлоридів 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 ізоксазолного 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 ¹H та ¹³C-спектрокопії.

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

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

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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 изоксазолного цикла. Для синтеза 4-хлор-5-изоксазолилсульфонилхлоридов с удовлетворительными выходами использован вариант предварительного хлорирования ядра 5-бензилтиоизоксазолов *N*-хлоросукцинимидом с дальнейшим окислительным хлорированием.

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

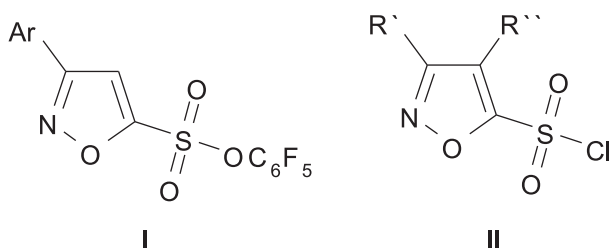
Выводы. Исследована реакция окислительного хлорирования 5-бензилтиоизоксазолов и разработан синтетический подход к ранее неизвестным представителям 5-изоксазолилсульфонилхлоридов.

Ключевые слова: *N*-гидроксиимидоилхлориды; бензилтиоацетилен; 5-бензилтиоизоксазоли; 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-substituted isoxazoles [6, 7] where isoxazole-5-sulfonamides have been found as active nematocidal sulfonamides [8], agents for the treatment of atherosclerosis [9], hydroxy steroid dehydrogenase 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



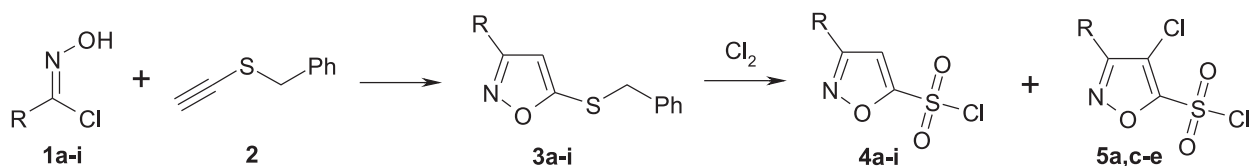
Scheme 1

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).

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 resolved by column flash-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*-chlorosuccinimide. 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**



1, 3-5, R = Me (**a**), CF₃CH₂ (**b**), cyclo-C₃H₅ (**c**), t-Bu (**d**), Ph (**e**), p-CF₃-C₆H₄ (**f**), 4-O₂N-C₆H₄ (**g**), CO₂Me (**h**), CO₂t-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 ₃ NOS	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 ₃ NOS	60.89	3.61	4.18
3g	76	127-128	313	61.66	3.94	9.06	C ₁₆ H ₁₂ N ₂ O ₃ S	61.53	3.87	8.97
3h	95	oil	250	58.00	4.40	5.54	C ₁₂ H ₁₁ NO ₃ S	57.82	4.45	5.62
3i	92	oil		61.71	5.79	4.76	C ₁₅ H ₁₇ NO ₃ S	61.83	5.88	4.81
4a	15	oil (CHCl ₃ -hexane, 35 %)		26.61	2.07	7.78	C ₄ H ₄ ClNO ₃ S	26.46	2.22	7.71
4b	45	oil (MTBE-hexane, 5 %)		24.20	1.13	5.68	C ₅ H ₃ ClF ₃ NO ₃ S	24.06	1.21	5.61
4c	5	oil (hexane)		34.64	2.99	6.71	C ₆ H ₆ ClNO ₃ S	34.71	2.91	6.75
4d	12	38-40 (CHCl ₃ -hexane, 5 %)		37.72	4.62	6.32	C ₇ H ₁₀ ClNO ₃ S	37.59	4.51	6.26
4e	20	87-88 (CHCl ₃ -hexane, 10 %)		44.52	2.59	5.86	C ₉ H ₆ ClNO ₃ S	44.36	2.48	5.75
4f	63	85-86 (MTBE-hexane, 15 %)		38.66	1.71	4.55	C ₁₀ H ₅ ClF ₃ NO ₃ S	38.54	1.62	4.49
4g	82	116-117 (CHCl ₃)		37.56	1.78	9.80	C ₉ H ₅ ClN ₂ O ₃ S	37.45	1.75	9.70
4h	41	oil (MTBE-hexane, 15 %)		26.51	1.89	6.14	C ₅ H ₄ ClNO ₅ S	26.62	1.79	6.21
4i	38	52-53 (MTBE-hexane, 5 %)		35.98	3.83	5.29	C ₈ H ₁₀ ClNO ₃ S	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 ₄ H ₃ Cl ₂ NO ₃ S	22.24	1.40	6.48
5c	16 (method a) 57 (method b)	oil (hexane)		29.86	2.13	5.88	C ₆ H ₅ Cl ₂ NO ₃ S	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 ₇ H ₉ Cl ₂ NO ₃ S	32.57	3.51	5.43
5e	22 (method a) 56 (method b)	oil (hexane)		38.74	1.87	5.09	C ₉ H ₅ Cl ₂ NO ₃ S	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).

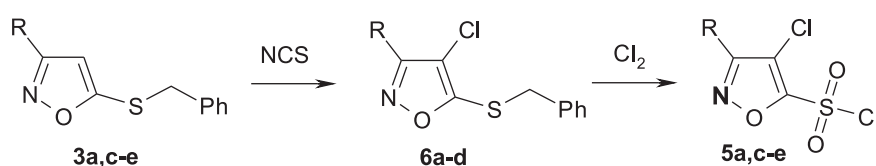
Experimental Part

All chemicals and solvents were obtained from Enamine Ltd. and used without further purification. NMR spectra were recorded on a Bruker Advance 400 spectrometer (¹H NMR at 399.98 MHz and ¹³C NMR

at 125.7 MHz) in CDCl₃ [for compounds **7a,b**, **9a,b**, **10a,b** in DMSO-*d*₆; for compounds **4a,b** in C₆D₆]. 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-



Scheme 3

Table 2

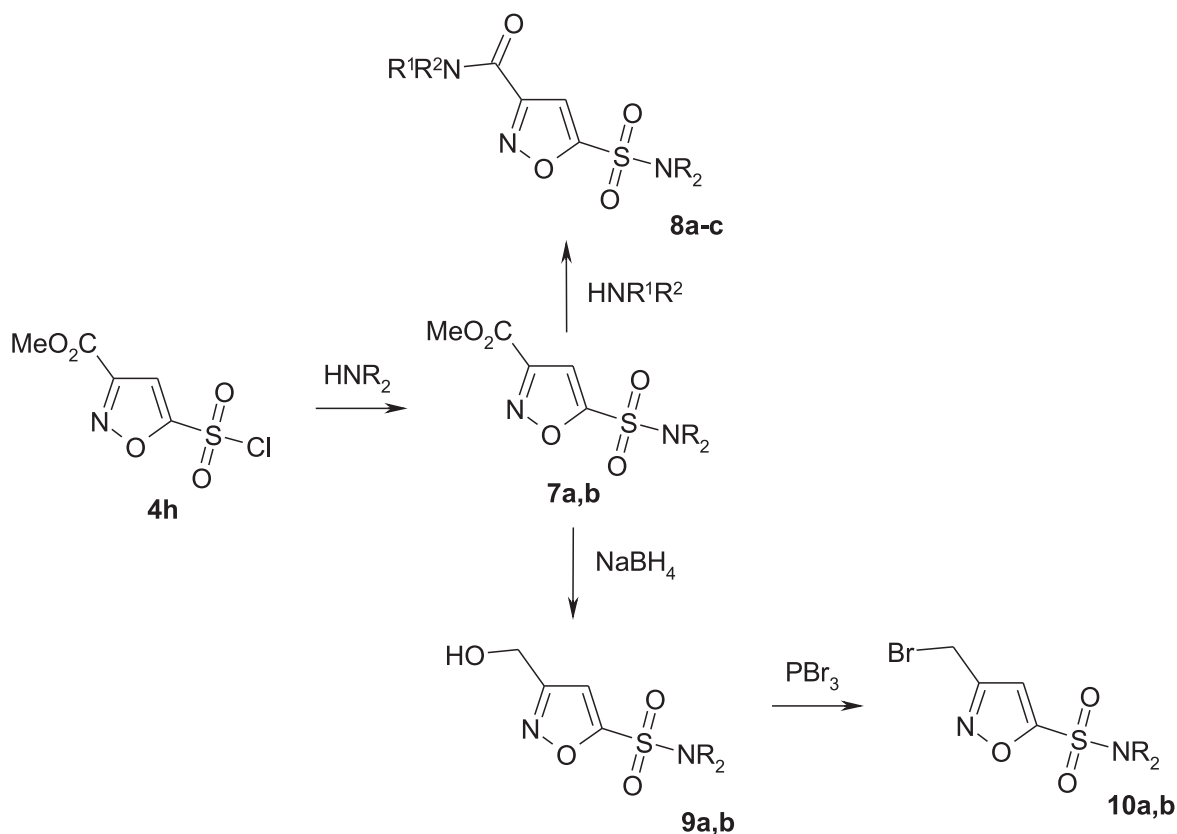
¹H and ¹³C NMR data for compounds **3a-i**, **4a-i**, **5a,c-e**

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 com-

pounds **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); R₂ = (CH₂)₂O(CH₂)₂ (b); 8, R = R¹ = R² = H (a); R₂ = (CH₂)₂O(CH₂)₂, R¹ = H, R² = PhCH₂ (b); R₂ = (CH₂)₂O(CH₂)₂, R¹R² = (CH₂)₄ (c) 9, 10, R = H (a); R₂ = (CH₂)₂O(CH₂)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 °C. Add crushed ice (500 g), then Na₂SO₃ 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.

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 (CH₃CN (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 tempe-

perature of the reaction mixture below 10 °C. Add crushed ice (500 g), then Na₂SO₃ 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 NH₄OH (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. ¹H NMR, δ, ppm: 3.93 s (3H, CH₃), 7.32 s (1H, H⁴), 8.51 br s (2H, NH₂). ¹³C NMR, δ, ppm: 53.7 (CH₃), 106.1 (C⁴), 156.8 (C³), 159.1 (C⁵), 171.1 (CO). LC-MS (APCI): *m/z* [M+H]⁺ 207.0. Anal. Calcd for C₅H₆N₂O₅S: 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. ¹H NMR, δ, ppm: 3.27-3.32 m (4H, CH₂), 3.75-3.81 m (4H, CH₂), 4.02 s (3H, CH₃), 7.16 s (1H, H⁴). ¹³C NMR, δ, ppm: 46.0 (CH₂), 53.7 (CH₃), 65.7 (CH₂), 109.7 (C⁴), 157.1 (C³), 159.0 (C⁵), 165.0 (CO). LC-MS (APCI): *m/z* [M+H]⁺ 277.0. Anal. Calcd for C₉H₁₂N₂O₆S: 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 NH₄OH (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. ¹H NMR, δ, ppm: 7.21 s (1H, H⁴), 8.03 s (1H, NH), 8.34 s (1H, NH), 8.42 br s (2H, NH₂). ¹³C NMR, δ, ppm: 105.3 (C⁴), 159.3 (C³), 159.5 (C⁵), 170.4 (CO). LC-MS (APCI): *m/z* [M-H]⁻ 190.0. Anal. Calcd for C₄H₅N₃O₄S: 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 CH₃CN (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. ¹H NMR, δ, ppm: 3.20-3.34 m (4H, CH₂), 3.66-3.83 m (4H, CH₂), 4.61-4.66 m (2H, CH₂), 7.16-7.41 m (6H, H_{Ar}). ¹³C NMR, δ, ppm: 43.7 (CH₂), 45.8 (CH₂), 66.0 (CH₂), 108.28 (C⁴), 127.9, 128.0, 128.9, 136.9 (C_{Ar}), 157.0 (C³), 158.5 (C⁵), 165.7 (CO). LC-MS (APCI): *m/z* [M+H]⁺ 352.0. Anal. Calcd for C₁₅H₁₇N₃O₅S: 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. ¹H NMR, δ, ppm: 1.92-2.02 m (4H, CH₂), 3.21-3.35 m (4H, CH₂), 3.60-3.69 m (2H, CH₂), 3.71-3.80 m (4H, CH₂), 3.81-3.89 m (2H, CH₂), 7.15 s (1H, H⁴). ¹³C NMR, δ, ppm: 23.9, 26.2, 45.8, 47.2, 48.7, 66.0 (CH₂), 109.9 (C⁴), 156.7 (C³), 159.8 (C⁵), 164.3 (CO). LC-MS

(APCI): *m/z* [M+H]⁺ 316.0. Anal. Calcd for C₁₂H₁₇N₃O₅S: 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 NaBH₄ (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. ¹H NMR, δ, ppm: 4.55 s (2H, CH₂), 5.65 br s (1H, OH), 6.9 s (1H, H⁴), 8.31 br s (2H, NH₂). ¹³C NMR, δ, ppm: 55.2 (CH₂), 105.3 (C⁴), 169.0 (C³), 165.5 (C⁵). LC-MS (APCI): *m/z* [M+H]⁺ 179.2. Anal. Calcd for C₄H₆N₂O₄S: 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. ¹H NMR, δ, ppm: 3.09-3.18 m (4H, CH₂), 3.61-3.68 m (4H, CH₂), 4.59 d (2H, CH₂, J = 5.6 Hz), 5.75 br s (1H, OH), 7.20 s (1H, H⁴). ¹³C NMR, δ, ppm: 46.1 (CH₂), 55.2 (CH₂), 65.7 (CH₂), 109.0 (C⁴), 162.8 (C³), 165.9 (C⁵). LC-MS (APCI): *m/z* [M+H]⁺ 249.2. Anal. Calcd for C₈H₁₂N₂O₅S: 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 CH₂Cl₂ (15 ml) add dropwise the solution of PBr₃ (0.16 g, 0.6 mmol, 2 equiv.) in CH₂Cl₂ (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 CH₂Cl₂ (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. ¹H NMR, δ, ppm: 4.72 s (2H, CH₂), 7.1 s (1H, H⁴), 8.40 s (2H, NH₂). ¹³C NMR, δ, ppm: 21.1 (CH₂), 106.3 (C⁴), 162.3 (C³), 169.8 (C⁵). LC-MS (APCI): *m/z* [M+H]⁺ 242.8. Anal. Calcd for C₄H₅BrN₂O₃S: 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 %). ¹H NMR, δ, ppm: 3.24-3.31 m (4H, CH₂), 3.72-3.78 m (4H, CH₂), 4.42 s (2H, CH₂), 6.86 s (1H, H⁴). ¹³C NMR, δ, ppm: 19.3 (CH₂), 45.8 (CH₂), 66.0 (CH₂), 108.6 (C⁴), 161.3 (C³), 165.0 (C⁵). LC-MS (APCI): *m/z* [M+H]⁺ 314.0. Anal. Calcd for C₄H₅BrN₂O₃S: 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.

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