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Synthesis and some transformations of 5-isoxazolylsulfonfyl 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) acetics 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; LCAMS; 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-hydroxyimidoyl chlorides; benzylethynyl sulfide; 5-(benzylthio)-3-isoxazoles; oxidative chlorination; isoxazole-5-sulfonylchlorides

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Синтез и некоторые превращения 5-изоксазолилсульфонилхлоридов

Встановлено вплив структури 5-бензилтіоізоксазолів на селективність утворення 5-ізоксазолилсульфонілхлоридів та з’ясовано хімічна поведінка останніх по відношенню до амінів.

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

Результати та їх обговорення. Циклокоndeнсацією N-гідроксіімідоклоридів або 2-хлоро-2-(гідроксііміні) ацетатів із бензилтіоімідоклоридами синтезовано низку 5-бензилтіоізоксазолів. Їх окиснювальне хлорування призводить до утворення сумішей 5-ізоксазолилсульфонілхлоридів та 4-хлоро-5-ізоксазолилсульфонілхлоридів, співвідношення яких залежить від характеру замісників у положенні 3 ізоксазольного циклу. Для синтезу 4-хлоро-5-ізоксазолилсульфонілхлоридів із задовільними виходами використано варіант попереднього окиснювального хлорування ядра 5-бензилтіоізоксазолів N-хлорсуццинідам із подальшим окиснювальним хлоруванням.

Експериментальна частина. Синтез вихідних та цільових сполук у класичних препаративних умовах; методи флеш-хроматографії, елементного аналізу, хроматомас-спектрометрії, ЯМР 1Н та 13С-спектроскопії.

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

Ключові слова: N-гідроксіімідохлориди; бензилтіоімідоклориди; 5-бензилтіоізоксазоли; окиснювальне хлорування; 5-ізоксазолилсульфонілхлориди

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Синтез та деякі перетворення 5-ізоксазолилсульфонілхлоридів

Встановлено вплив структури 5-бензилтіоізоксазолів на селективність утворення 5-ізоксазолилсульфонілхлоридів та з’ясовано хімічна поведінка останніх по відношенню до амінів.

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

Результати та їх обговорення. Циклокоndeнсацією N-гідроксіімідоклоридів або 2-хлоро-2-(гідроксііміні) ацетатів із бензилтіоімідоклоридами синтезовано низку 5-бензилтіоізоксазолів. Їх окиснювальне хлорування призводить до утворення сумішей 5-ізоксазолилсульфонілхлоридів та 4-хлоро-5-ізоксазолилсульфонілхлоридів, співвідношення яких залежить від характеру замісників у положенні 3 ізоксазольного циклу. Для синтезу 4-хлоро-5-ізоксазолилсульфонілхлоридів із задовільними виходами використано варіант попереднього окиснювального хлорування ядра 5-бензилтіоізоксазолів N-хлорсуццинідам із подальшим окиснювальним хлоруванням.

Експериментальна частина. Синтез вихідних та цільових сполук у класичних препаративних умовах; методи флеш-хроматографії, елементного аналізу, хроматомас-спектрометрії, ЯМР 1Н та 13С-спектроскопії.

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

Ключові слова: N-гідроксіімідохлориди; бензилтіоімідоклориди; 5-бензилтіоізоксазоли; окиснювальне хлорування; 5-ізоксазолилсульфонілхлориди
The heterocyclic system of isozazole is an important representative of azoles known for their wide use in modern organic synthesis [1-3] and biomedicinal chemistry [4]. The isozazole 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 isozazoles [6, 7] where isozazole-5-sulfonamides have been found as active nematicidal 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 isozazole-5-pentafluorophenyl sulfonates (I) or 5-chlorosulfonylisozazoles (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-hydroximidoyl chlorides was suggested [6], and for the synthesis of sulfonyl chlorides II the oxidative chlorination of bis(isozazole-5-yl)disulfides was proposed [12]. Thus, we have focused our attention on development of the preparative method of the synthesis of 5-isozazole-5-sulfonyl 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)isozazoles. With the above goal and considering the results of the previous work [16] the cyclocondensation of N-hydroximidoyl chlorides 1a-d [17] or 2-chloro-2-(hydroxylimino)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)-isozazoles 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 flesh-chromatography to obtain isozazole-5-sulfonyl chlorides 4a-i and 4-chloroisozazole-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 isozazole 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-chloroisozazole-5-sulfonyl chlorides 5a,c,e were 16-39 %. We suppose that the sulfonyl chloride group deactivate the mobility of position 4 of the isozazole 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 reacts 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.
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-d6; 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).**

| 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    | C11H11NOS             | 64.36 5.40    |
| 3b       | 43       | oil (MTBE-hexane, 5 %) | 274    | 52.85    | C12H10F3NOS           | 52.74 5.16    |
| 3c       | 71       | 60-62               | 232    | 67.39    | C13H13NOS             | 67.50 5.66    |
| 3d       | 71       | oil (MTBE-hexane, 5 %) | 248    | 68.11    | C14H17NOS             | 67.98 5.66    |
| 3e       | 78       | 94-96               | 268    | 71.99    | C15H17NOS             | 71.88 5.24    |
| 3f       | 76       | 118-120             | 336    | 60.76    | C16H13NOS             | 60.89 4.21    |
| 3g       | 76       | 127-128             | 313    | 61.66    | C16H12N2O3S           | 61.53 8.97    |
| 3h       | 95       | oil                 | 250    | 58.00    | C12H11NO3S            | 57.82 5.62    |
| 3i       | 92       | oil                 | 250    | 61.71    | C13H11NO3S            | 61.83 4.81    |
| 3j       | 15       | oil (CHCl3-hexane, 35 %) | 26.61  | 2.07    | C4H4ClNO3S            | 26.46 7.71    |
| 3k       | 45       | oil (MTBE-hexane, 5 %) | 24.20  | 1.13    | C5H3ClF3NO3S          | 24.06 5.61    |
| 3l       | 5        | oil (hexane)        | 34.64  | 2.99    | C6H6ClNO3S            | 34.71 6.75    |
| 3m       | 12       | 38-40 (CHCl3-hexane, 5 %) | 37.72  | 4.62    | C6H5Cl2NO3S           | 37.59 6.26    |
| 3n       | 20       | 87-88 (CHCl3-hexane, 10 %) | 44.52  | 2.59    | C7H10ClNO3S           | 44.36 5.75    |
| 3o       | 63       | 85-86 (MTBE-hexane, 15 %) | 38.66  | 1.71    | C8H6Cl2NO3S           | 38.54 4.49    |
| 3p       | 82       | 116-117 (CHCl3)    | 37.56  | 1.78    | C9H5Cl2NO3S           | 37.45 9.70    |
| 3q       | 41       | oil (MTBE-hexane, 15 %) | 26.51  | 1.89    | C10H5ClF3NO3S         | 26.62 6.21    |
| 3r       | 38       | 52-53 (MTBE-hexane, 5 %) | 35.98  | 3.83    | C11H5Cl2NO3S          | 35.90 5.23    |
| 3s       | 19 (method a) 46 (method b) | oil (CHCl3-hexane, 35 %) | 22.33  | 1.52    | C12H12ClNO3S          | 22.24 6.48    |
| 3t       | 16 (method a) 57 (method b) | oil (hexane)      | 29.86  | 2.13    | C13H12ClNO3S          | 29.77 5.79    |
| 3u       | 39 (method a) 68 (method b) | oil (CHCl3-hexane, 5 %) | 32.68  | 3.59    | C14H12ClNO3S          | 32.57 5.43    |
| 3v       | 22 (method a) 56 (method b) | oil (hexane)      | 38.74  | 1.87    | C15H12ClNO3S          | 38.87 5.04    |

Table 1 Yields, T. mp., MS spectra and elemental analysis data for compounds 3a-i, 4a-i, 5a-c,e
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-crystalize 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 the solution with ice, and pass gaseous chlorine carefully

| Compound | 1H NMR spectra, δ, ppm | 13C NMR spectra, δ, ppm |
|----------|------------------------|------------------------|
| 3a       | 2.24 s (3H, CH₃), 4.21 s (2H, CH₂), 5.90 s (1H, H⁴) | 11.5 (CH₃), 37.7 (CH₂), 105.6 (C⁴), 128.7, 128.8, 136.3 (CAr), 160.5 (C₃), 165.0 (C₅) |
| 3b       | 3.45 q (2H, CH₂, J = 10.4 Hz), 4.21 s (2H, CH₂), 6.08 s (1H, H⁴), 7.23-7.35 m (5H, H₉) | 31.8 q (CH₂, Jₓₘ = 32.0 Hz), 37.8 (CH₂), 105.0 (C⁴), 124.5 q(CF₃, Jₓₘ = 275.0 Hz), 128.8, 128.8, 135.9 (CAr), 151.5 q(CF₃) |
| 3c       | 0.66-0.83 m (2H, CH₂), 0.90-1.05 m (2H, CH₂), 1.87-1.96 m (1H, CH), 4.16 s (2H, CH₂), 5.68 s (1H, H⁴), 7.20-7.37 m (5H, H₉) | 7.4 (CH), 8.0 (CH₂), 37.8 (CH₂), 102.5 (C⁴), 127.7, 127.8, 136.3 (CAr), 164.7 (C₅), 167.1 (C₇) |
| 3d       | 1.29 s (9H, CH₃), 4.21 s (2H, CH₂), 5.95 s (1H, H⁴), 7.26-7.33 m (5H, H₉) | 29.3 (CH₃), 32.1 (CH), 37.9 (CH₂), 102.5 (C⁴), 127.7, 128.6, 136.4 (CAr), 164.3 (C₅), 172.7 (C₇) |
| 3e       | 4.29 s (2H, CH₂), 6.39 s (1H, H⁴), 7.26-7.33 m (5H, H₉) | 37.9 (CH₃), 103.2 (C⁴), 126.7, 128, 128.8, 128.9, 130.1, 136.3 (CAr), 165.0 (C₅), 165.8 (C₇) |
| 3f       | 4.28 s (2H, CH₂), 6.37 s (1H, H⁴), 7.24-7.34 m (5H, H₉), 7.68 d (2H, H₉,J = 8.4 Hz) | 37.9 (CH₃), 103.0 (C⁴), 126.7, 128, 128.8, 128.9, 130.1, 136.3 (CAr), 164.7 (C₅), 165.8 (C₇) |
| 3g       | 0.66-0.83 m (2H, CH₂), 0.90-1.05 m (2H, CH₂), 1.87-1.96 m (1H, CH), 4.16 s (2H, CH₂), 5.68 s (1H, H⁴), 7.20-7.37 m (5H, H₉) | 7.4 (CH), 8.0 (CH₂), 37.8 (CH₂), 102.5 (C⁴), 127.7, 128.6, 136.3 (CAr), 164.7 (C₅), 167.1 (C₇) |
| 3h       | 1.29 s (9H, CH₃), 4.21 s (2H, CH₂), 5.95 s (1H, H⁴), 7.26-7.33 m (5H, H₉) | 29.3 (CH₃), 32.1 (CH), 37.9 (CH₂), 102.5 (C⁴), 127.7, 128.6, 136.4 (CAr), 164.3 (C₅), 172.7 (C₇) |
| 3i       | 3.45 q (2H, CH₂, J = 10.4 Hz), 4.21 s (2H, CH₂), 6.08 s (1H, H⁴), 7.23-7.35 m (5H, H₉) | 31.8 q (CH₂, Jₓₘ = 32.0 Hz), 37.8 (CH₂), 105.0 (C⁴), 124.5 q(CF₃, Jₓₘ = 275.0 Hz), 128.8, 128.8, 135.9 (CAr), 151.5 q(CF₃) |
| 3j       | 0.66-0.83 m (2H, CH₂), 0.90-1.05 m (2H, CH₂), 1.87-1.96 m (1H, CH), 4.16 s (2H, CH₂), 5.68 s (1H, H⁴), 7.20-7.37 m (5H, H₉) | 7.4 (CH), 8.0 (CH₂), 37.8 (CH₂), 102.5 (C⁴), 127.7, 128.6, 136.3 (CAr), 164.7 (C₅), 167.1 (C₇) |
| 3k       | 1.29 s (9H, CH₃), 4.21 s (2H, CH₂), 5.95 s (1H, H⁴), 7.26-7.33 m (5H, H₉) | 29.3 (CH₃), 32.1 (CH), 37.9 (CH₂), 102.5 (C⁴), 127.7, 128.6, 136.4 (CAr), 164.3 (C₅), 172.7 (C₇) |
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$_3$CN (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 reduced pressure 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$_2$SO$_3$ 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$_4$OH (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$_2$), 13C NMR, δ, ppm: 53.7 (CH$_3$), 106.1 (C$_4$), 156.8 (C$_3$), 159.1 (C$_5$), 171.1 (C$_6$). LC-MS (APCI): $m/z$ [M+H]$^+$207.0.

**Scheme 4**
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, 9.3 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. – 175-176 °C. 1H NMR, δ, ppm: 7.21 s (1H, H2), 8.03 s (1H, NH), 8.34 s (1H, NH), 8.42 br s (2H, NH). 13C NMR, δ, ppm: 105.3 (C1), 159.3 (C5), 159.5 (C6), 170.4 (CO). LC-MS (APCI): m/z [M+H]+ 277.0. Anal. Calcd for C8H12N2O2S: C 39.13, H 4.38, N 10.14. Found: C 39.29, H 4.33, N 10.22.

5-(Aminosulfonyl)isoxazole-3-carboxamide (8a). 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). 13C NMR, δ, ppm: 55.2 (CH2), 66.0 (CH). LC-MS (APCI): m/z [M+H]+ 249.2. Anal. Calcd for C8H12N2O4S: C 30.88, H 3.56, N 9.00. Found: C 30.66, H 3.68, N 8.88.

5-Aryl-5-(morpholin-4-ylsulfonyl)isoxazole-3-carboxamides (8b,c). To the solution 7b (0.2 g, 0.72 mmol, 1 eq) in CH2CN (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). 13C NMR, δ, ppm: 43.7 (CH2), 45.8 (CH2), 66.0 (CH2). 1H NMR, δ, ppm: 127.9, 128.0, 128.9, 136.9 (C6). LC-MS (APCI): m/z [M+H]+ 316.0. Anal. Calcd for C9H12N2O4S: C 45.71, H 5.43, N 13.32. Found: C 45.59, H 5.32, N 13.24.

4-[[3-(Pyrrolidin-1-ylcarbonyl)isoxazol-5-ylsulfonyl]methyl]-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, H5). 13C NMR, δ, ppm: 23.9, 26.2, 45.8, 47.2, 48.7, 66.0 (CH2), 109.9 (C5), 156.7 (C6), 159.8 (C7), 164.3 (CO). LC-MS (APCI): m/z [M+H]+ 316.0. Anal. Calcd for C12H17N2O4S: C 47.16, H 5.43, N 13.32. Found: C 47.14, H 5.32, N 13.24.
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-sulfonoyl 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 conflict of interests to declare.

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