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-sulfon chloride and 4-chloroisoxazole-5-sulfon chloride. 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; LC/MS; 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-sulfon chloride has been developed.

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

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The heterocyclic system of isoxazole is an important representative of azoles known for their wide use in modern organic synthesis [1-3] and biomedicine [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 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 isoxazol-5-yl or 5-chlorosulfonylisoxazoles (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 sulfonyl with aryl N-hydroxymidoyl 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 chlorination benzylaryl- or benzylheteroaryl sulfides based on oxidative reagents for sulfonylation.

The method of the synthesis of isoxazole-5-sulfonyl chlorides that are universal reagents for sulfonylation was solved by advanced chlorination of compounds 3a-c with N-chlorosuccinimide. This allowed obtaining 4-chloroisoxazole-5-sulfonyl chlorides 5a-c,e with the yield of 46-68 % (method b, Tab. 1, Scheme 3). 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 advanced 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, 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.

![Scheme 1](image1)

![Scheme 2](image2)
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 ZorbaxSB 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.

## Table 1

<table>
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<tr>
<th>Compound</th>
<th>Yield, %</th>
<th>T. mp., °C (eluent)</th>
<th>[M+1]+</th>
<th>Found, %</th>
<th>The empirical formula</th>
<th>Calculated, %</th>
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<td>74</td>
<td>oil (hexane)</td>
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<td>64.55</td>
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<td>oil (MTBE-hexane, 5 %)</td>
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<tr>
<td>3c</td>
<td>71</td>
<td>60-62</td>
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<td>67.39</td>
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<td>3d</td>
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<td>oil (MTBE-hexane, 5 %)</td>
<td>248</td>
<td>68.11</td>
<td>C₁₀H₁₀N₂OS</td>
<td>67.98 6.93 5.66</td>
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<tr>
<td>3e</td>
<td>78</td>
<td>94-96</td>
<td>268</td>
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<tr>
<td>3f</td>
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<td>118-120</td>
<td>336</td>
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<td>76</td>
<td>127-128</td>
<td>313</td>
<td>61.66</td>
<td>C₁₁H₁₁N₂O₅S</td>
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<tr>
<td>3h</td>
<td>95</td>
<td>oil</td>
<td>250</td>
<td>58.00</td>
<td>C₁₁H₁₁N₂OS</td>
<td>57.82 4.45 5.62</td>
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<td>3i</td>
<td>92</td>
<td>oil</td>
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<tr>
<td>4a</td>
<td>15</td>
<td>oil (CHCl₃-hexane, 35 %)</td>
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<td>2.07</td>
<td>C₄H₄ClNO₃S</td>
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<td>4b</td>
<td>45</td>
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<td>24.06 1.21 5.61</td>
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<tr>
<td>4c</td>
<td>5</td>
<td>oil (hexane)</td>
<td>34.64</td>
<td>2.99</td>
<td>C₆H₆ClNO₃S</td>
<td>34.71 2.91 6.75</td>
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<tr>
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<td>12</td>
<td>85-86 (CHCl₃-hexane, 5 %)</td>
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<td>4.62</td>
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<td>37.59 4.51 6.26</td>
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<tr>
<td>4e</td>
<td>20</td>
<td>85-86 (CHCl₃-hexane, 10 %)</td>
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<td>2.59</td>
<td>C₆H₆ClNO₃S</td>
<td>44.36 2.48 5.75</td>
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<td>4f</td>
<td>63</td>
<td>85-86 (MTBE-hexane, 15 %)</td>
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<td>1.71</td>
<td>C₆H₅ClNO₃S</td>
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<tr>
<td>4g</td>
<td>82</td>
<td>116-117 (CHCl₃)</td>
<td>37.56</td>
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<tr>
<td>4h</td>
<td>41</td>
<td>oil (MTBE-hexane, 15 %)</td>
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<td>1.89</td>
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<tr>
<td>4i</td>
<td>38</td>
<td>52-53 (MTBE-hexane, 5 %)</td>
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<td>3.83</td>
<td>C₇H₇ClNO₃S</td>
<td>35.90 3.77 5.23</td>
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<tr>
<td>5a</td>
<td>19 (method a)</td>
<td>46 (method b) (CHCl₃-hexane, 35 %)</td>
<td>22.33</td>
<td>1.52</td>
<td>C₄H₃Cl₂NO₃S</td>
<td>22.24 1.40 6.48</td>
</tr>
<tr>
<td>5c</td>
<td>16 (method a)</td>
<td>57 (method b) (oil (hexane))</td>
<td>29.86</td>
<td>2.13</td>
<td>C₆H₅Cl₂NO₃S</td>
<td>29.77 2.08 5.79</td>
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<tr>
<td>5d</td>
<td>39 (method a)</td>
<td>68 (method b) (oil (CHCl₃-hexane, 5 %)</td>
<td>32.68</td>
<td>3.59</td>
<td>C₇H₇Cl₂NO₃S</td>
<td>32.57 3.51 5.43</td>
</tr>
<tr>
<td>5e</td>
<td>22 (method a)</td>
<td>56 (method b) (oil (hexane))</td>
<td>38.74</td>
<td>1.87</td>
<td>C₇H₇Cl₂NO₃S</td>
<td>38.87 1.81 5.04</td>
</tr>
</tbody>
</table>

### Scheme 3

**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-cristalize compounds 3c,e,f,g from 2-propanol, purify compounds 3a,b,d by flash chromatography, and obtain compounds 3b,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
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.

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, H₅). 13C NMR, δ, ppm: 46.0 (CH₂), 53.7 (CH₂), 65.7 (CH₃), 109.7 (Cᵢ), 157.1 (C₅), 159.0 (C₆), 165.0 (CO). LC-MS (APCI): m/z [M+H]+ 314.0. Anal. Calcd for C₇H₁₂N₂O₅S: 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 s br s (1H, OH), 6.9 s (1H, H₅), 8.31 br s (2H, NH₂). 13C NMR, δ, ppm: 55.2 (CH₂), 105.3 (Cᵢ), 169.0 (C₅), 165.5 (C₆). LC-MS (APCI): m/z [M+H]+ 179.2. Anal. Calcd for C₇H₁₀N₂O₅S: 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 (2H, CH₂), 3.61-3.68 m (4H, CH₂), 4.59 d (2H, CH₂) = 5.6 Hz, 7.57 br s (1H, OH), 7.20 s (1H, H₅). 13C NMR, δ, ppm: 46.1 (CH₂), 55.2 (CH₂), 65.7 (CH₂), 107.9 (Cᵢ), 162.8 (C₅), 165.9 (C₆). LC-MS (APCI): m/z [M+H]+ 249.2. Anal. Calcd for C₇H₁₂N₂O₅S: 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: 7.14 s (2H, CH₂), 7.14 s (1H, H₅), 8.42 s (2H, NH₂). 13C NMR, δ, ppm: 21.1 (CH₂), 106.3 (Cᵢ), 162.3 (C₅), 169.8 (C₆). LC-MS (APCI): m/z [M+H]+ 242.8. Anal. Calcd for C₇H₁₂BrN₂O₅S: 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, H₅). 13C NMR, δ, ppm: 19.3 (CH₃), 45.8 (CH₂), 66.0 (CH₂), 108.6 (Cᵢ), 161.3 (C₅), 165.0 (C₆). LC-MS (APCI): m/z [M+H]+ 314.0. Anal. Calcd for C₇H₁₂BrN₂O₅S: 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 conflict of interests to declare.

References


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