Synthesis and transformation of 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride into new compounds with potential pesticidal activity

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Abstract: The synthesis of 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride and its transformation into new compounds with promising pesticidal activity is reported. The title compounds were obtained by a three-step synthesis, starting from 4-dichloromethylchlorophenyl sulfone. It was nitrated and then subjected to the SNAr reaction with sodium disulfide to give proper diphenyl disulfide, which was next chlorinated by chlorine. The obtained phenylsulfenyl chloride was transformed into sulfenamide derivatives by reactions with amines.

Keywords: 4-chlorophenyl dichloromethyl sulfone, sulfenyl chloride, sulfenamides, pesticides

INTRODUCTION

Some sulfenamide derivatives are known as the non-systemic fungicides widely used to control foliage and fruit diseases of tomatoes, coffee berry, potato and many other fruits and vegetables [1, 2]. Galactofuranosyl-N,N-dialkyl sulfenamides displayed an antimycobacterial activity [3]. Some N-sulfenyl heterocycles are effective sulfenylating agents of aromatic amines [4]. In addition, they are the important intermediates in many reactions, promising in the prodrug technologies [5, 6]. On the other hand, it is well known that chemical compounds with chloromethyl groups show an interesting biological activity [1]. We have proved in our previous investigations that chloro- and dichloromethylsulfonyl...
groups in aromatic compounds were favorable to pesticidal activities [7-11]. It was interesting to synthesize some new sulfenamide derivatives bearing dichloromethylsulfonyl group in a benzene ring, in order to test their pesticidal activity and determine the relationship between their structure and biological activity.

RESULTS

4-Chlorophenyldichloromethyl sulfone was obtained by three-step synthesis, according to the following scheme:

\[
\begin{align*}
\text{Cl} & \quad \text{HSO}_3\text{Cl} \quad \text{Cl} \\
\text{SO}_2\text{Cl} & \quad \text{Na}_2\text{SO}_3 \quad \text{CHCl}_3/\text{NaOH} \\
\text{SO}_2\text{Na} & \quad \text{SO}_2\text{CHCl}_2
\end{align*}
\]

The synthesis of sulfone 1 was described in our previous paper [12]. 4-Chlorophenyldichloromethyl sulfone 1 was nitrated in the mixture of concentrated sulfuric acid and fuming nitric acid:

\[
\begin{align*}
\text{Cl} & \quad \text{SO}_2\text{CHCl}_2 \quad \text{HNO}_3 \quad \text{H}_2\text{SO}_4 \\
\text{Cl} & \quad \text{NO}_2 \quad \text{SO}_2\text{CHCl}_2
\end{align*}
\]

Nitrosulfone 2 was isolated in 94% yield, and next transformed into biphenyl disulfide 3 by nucleofilic substitution of chlorine atom with disodium disulfide. The last was freshly-prepared from sodium sulfide and sulfur [13]:

The process was carried out in refluxing ethanol and product 3 was isolated in 84% yield. Disulfide 3 was then chlorinated by gaseous dry chlorine to give sulfenyl chloride 4 according to the scheme:

Chlorination was performed in nitrobenzene at 100 °C. The product was obtained in 76% yield. Among many tested organic solvents, only the use of nitrobenzene gave a satisfactory yield. The yellow crystalline 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride 4 was recrystallized from an anhydrous carbon tetrachloride. Chloride 4 appeared to be not stable and after few days of storage at room temperature it transformed into diphenyldisulfide. For this reason, it should be stored in the anhydrous conditions, under an inert atmosphere of dry nitrogen, in a cool place, or used immediately to the further transformation.

When react with amines, the obtained 4 was converted into sulfenamide derivatives:

The reaction was carried out in anhydrous carbon tetrachloride at boiling point for three hours, with excess of amine as an acceptor of hydrochloride. Properties and yields of resulted sulfenamide derivatives 5a-5p were collected in Table 1.
Table 1. Properties and yields of 4-dichloromethylsulfonyl-2-nitrophenylsulfenamide derivatives

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>Mol. formula</th>
<th>(Mol. wt.) [g/mol]</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Elemental analyses</th>
<th>nIR [cm⁻¹]</th>
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<td>Calcd. [C %] % H % N</td>
<td>Found [C %] % H % N</td>
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<td>NH</td>
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<td>146-147</td>
<td>84</td>
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<td>135-136</td>
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<td>Formula</td>
<td>MW (g/mol)</td>
<td>mp (°C)</td>
<td>ξ (°C)</td>
<td>Δξ (°C)</td>
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<td>C_{10}H_{9}Cl_{2}NO_{5}S_{2}</td>
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<td>166-167</td>
<td>84</td>
<td>33.53</td>
<td>2.53</td>
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Synthesis and transformation of 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl...
Chloride 4 was also subjected to reaction with methanol to give methyl ester 6 in high 95% of yield:

\[
\begin{align*}
\text{SClNO}_2\text{SO}_2\text{CHCl}_2 \quad \xrightarrow{\text{CH}_3\text{OH}} \quad \text{SOCH}_3\text{NO}_2\text{SO}_2\text{CHCl}_2
\end{align*}
\]

The process was carried out under reflux for one hour, in an excess of methanol, with equimolar amount of anhydrous natrium carbonate.

Sulfenyl chloride 4 undertaken the reaction with acetone, gave product of substitution 7:

\[
\begin{align*}
\text{SClNO}_2\text{SO}_2\text{CHCl}_2 \quad \xrightarrow{\text{CH}_3\text{COCH}_3} \quad \text{SCH}_2\text{COCH}_3\text{NO}_2\text{SO}_2\text{CHCl}_2
\end{align*}
\]

Ketosulfide 7 was obtained in 84% of yield by heating sulfenyl chloride 4 in an excess of acetone with catalytic amount of anhydrous natrium carbonate.

Some of the obtained sulfenamides were easily oxidized by peroxyacetic acid to the proper sulfonamides, according to the scheme:

\[
\begin{align*}
\text{Cl}_2\text{HCO}_2\text{SR} \quad \xrightarrow{\text{CH}_3\text{COOH/H}_2\text{O}_2} \quad \text{Cl}_2\text{HCO}_2\text{SO}_2\text{R}
\end{align*}
\]

The process was done by keeping substrate in refluxing solution of glacial acetic acid and hydrogen peroxide for two hours. Properties and yields of sulfonamide derivatives 8a-c and ester 8d were collected in Table 2.
Table 2. Properties and yields of 4-dichloromethylsulfonyl-2-nitrophenylsulfonamide derivatives

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>Mol. formula</th>
<th>(Mol. wt.) [g/mol]</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Elemental analyses</th>
<th>nIR [cm⁻¹]</th>
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<tr>
<td>8a</td>
<td>CH₂NH</td>
<td>C₁₄H₁₂Cl₂N₂O₆S₂</td>
<td>439.29</td>
<td>146-147</td>
<td>81</td>
<td>38.28  2.75  6.38</td>
<td>38.32  2.78  6.11</td>
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<tr>
<td>8b</td>
<td>N</td>
<td>C₁₂H₁₄Cl₂N₂O₆S₂</td>
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<td>199-200</td>
<td>72</td>
<td>34.54  3.38  6.71</td>
<td>34.37  3.39  6.68</td>
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<tr>
<td>8c</td>
<td>NH</td>
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<td>431.31</td>
<td>228-230</td>
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<td>36.20  3.74  6.50</td>
<td>36.28  3.36  6.51</td>
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<td>8d</td>
<td>CH₃O</td>
<td>C₈H₇Cl₂NO₇S₂</td>
<td>364.17</td>
<td>276-278</td>
<td>79</td>
<td>26.39  1.94  3.85</td>
<td>26.49  1.88  3.87</td>
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</table>
EXPERIMENTAL

All melting points were not corrected. Elemental microanalyses were obtained by means of a Perkin Elmer 2400 apparatus. IR spectra were recorded in paraffin oil on a Specord M80 Zeiss Jena spectrophotometer. ¹H-NMR spectra were recorded in CDCl₃ solution at 20 °C on a Varian Mercury 400 MHz spectrometer. Chemical shifts (δ) are given in parts per million, relative to TMS.

4-Chloro-3-nitrophenyldichloromethyl sulfone 2
Sulfone 1 (75.26 g, 0.29 mol) was dissolved in concentrated sulfuric acid (300 mL). The mixture was heated to 60 °C and concentrated nitric acid (18 mL, 0.49 mol) was then slowly added, at such a rate lest the temperature exceed over 70 °C. The mixture was stirred and heated at 90 °C for 2 hours. After cooling it was poured into ice (500 mL). The precipitated crude 2 was filtered, washed with water and air dried. Product 2 was recrystallized from ethanol. Yield: 94%, m.p. 92-93 °C.

Bis(4-dichloromethylsulfonyl-2-nitrophenyl) disulfide 3
First, sodium sulfide (6 g, 0.075 mol) and sulfur (2.4 g, 0.075 mol) were refluxed in ethanol (50 mL) for 15 min, following by the resulted disulfide filtration. 4-Chloro-3-nitrophenyl-dichloromethyl sulfone 2 (0.05 mol) was dissolved in ethanol (40 mL) and freshly prepared sodium disulfide was then slowly added. The mixture was heated under reflux for 4 hours. After cooling, the precipitate was filtered off and air dried. Product was recrystallized from acetic acid. Yield – 85%, m.p. = 276 °C with decomposition.

4-Dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride 4
To the suspension of disulfide 3 (18.07 g, 0.03 mol) in nitrobenzene (75 mL), iodine (0.15 g, 0.004 mol) was added. The mixture was stirred and heated at 100 °C and dry gaseous chlorine was put to bubble through until the precipitate of disulfide was dissolved. After cooling the solution to the room temperature, the nitrogen was blow through by 15 min. The nitrobenzene was then distilled off and obtained precipitate was recrystallized from dry carbon tetrachloride. A yellow crystalline sulfenyl chloride 4 was obtained in 78% of yield, m.p. = 129-130 °C. It should be stored in hermetic bottle under nitrogen in cool and dark conditions.

Sulfenamide derivatives 5a-5p
To the solution of 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride 4
(3.36 g, 0.01 mol) in carbon tetrachloride (10 mL), appropriate amine (0.022 mol) in carbon tetrachloride (10 mL) was dropped. The mixture was stirred and refluxed for 3 hours. After cooling the precipitate was filtered off, washed by three portions (30 mL) of diluted solution of hydrochloric acid and water (1:10). The precipitate was dried and recrystallized from 2-propanol.

4-Dichloromethylsulfonyl-2-nitrophenylsulfenic acid methyl ester 6
4-Dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride 4 (3.36 g, 0.01 mol), and natrium carbonate (1.06 g, 0.01 mol) were refluxed in methanol (15 mL) for 3 hours. After cooling, the inorganic salts were filtered off. The solvent was evaporated and resulted precipitate was recrystallized from 2-propanol. The expected ester was obtained in 95% of yield, m.p. = 132-133 °C. 1H-NMR; 8.82-7.96 (m, 3H), 6.24 (s, 1H), 1.65 (s, 3H).

4-Dichloromethylsulfonyl-2-nitrophenylthioacetone 7
4-Dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride 4 (3.36 g, 0.01 mol), natrium carbonate (1.06 g, 0.01 mol) were refluxed in acetone (25 mL) for 2 hours. After cooling, the inorganic salts were filtered off. The solvent was evaporated and residue was recrystallized from 2-propanol. Thioketone 11 was obtained in 84% of yield, m.p. = 166-167 °C. 1H-NMR; 8.84-8.02 (m, 3H), 6.28 (s, 1H), 3.85 (s, 2H), 2.35 (s, 3H).

4-Dichloromethylsulfonyl-2-nitrophenylsulfonamide 8a-c and ester 8d
Sulfenamide 5a,b,p or ester 6 (0.12 mol) was dissolved in glacial acetic acid (95 mL). When the mixture was refluxed, 30% solution of hydrogen peroxide (40 mL) was slowly added. The mixture was refluxed for 2 hours. After cooling, the solution was poured into water with ice (1000 mL). The precipitate was filtered off, washed with water and dried. Products 8a-c were recrystallized from 2-propanol, and ester 8d – from ethanol.

Acknowledgment
This work was financially supported by Warsaw Technical University.

REFERENCES