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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 S_NAr 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-chlorophenyldichloromethyl sulfone, sulfenyl chloride, sulfenamides, pesticides

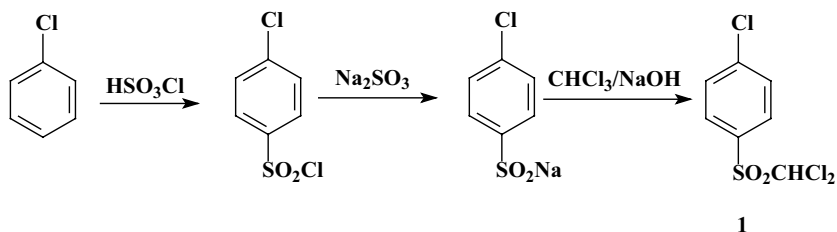
INTRODUCTION

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.

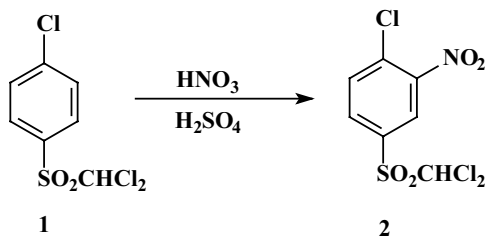
RESULTS

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

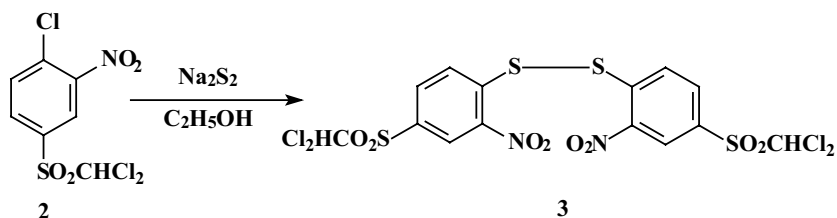


The synthesis of sulfone **1** was described in our previous paper [12].

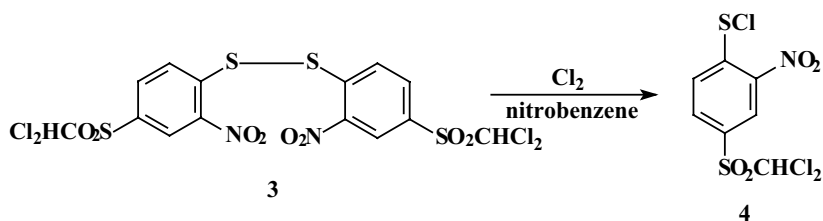
4-Chlorophenyldichloromethyl sulfone **1** was nitrated in the mixture of concentrated sulfuric acid and fuming nitric acid:



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

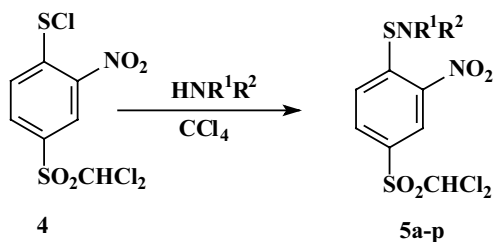


The process was carried out in refluxing ethanol and product **3** was isolated in 84% yield. Disulfide **3** was then chlorinated by gaseous dry chlorine to give sulfenyl chloride **4** according to the scheme:

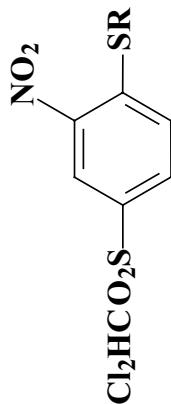


Chlorination was performed in nitrobenzene at 100°C . The product was obtained in 76% yield. Among many tested organic solvents, only the use of nitrobenzene gave a satisfactory yield. The yellow crystalline 4-dichloromethylsulfonyl-2-nitrophenylsulfenyl chloride **4** was recrystallized from an anhydrous 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.

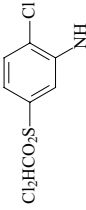
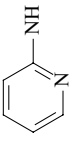
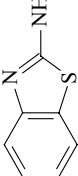
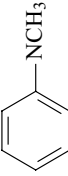

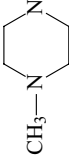
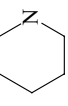
When react with amines, the obtained **4** was converted into sulfenamide derivatives:



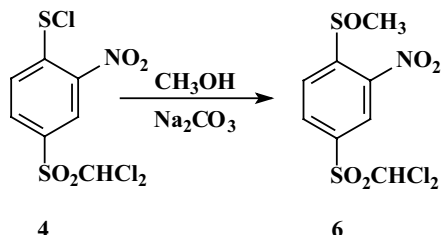
The reaction was carried out in anhydrous carbon tetrachloride at boiling point for three hours, with excess of amine as an acceptor of hydrochloride. Properties and yields of resulted sulfenamide derivatives **5a-5p** were collected in Table 1.

Table 1. Properties and yields of 4-dichloromethylsulfonyl-2-nitrophenylsulfenamide derivatives

Comp. No.	R	Mol. formula	(Mol. wt.) [g/mol]	m.p. [°C]	Yield [%]	Elemental analyses						nIR [cm ⁻¹]
						Calcd.			Found			
						% C	% H	% N	% C	% H	% N	
5a		C ₁₃ H ₁₅ Cl ₂ N ₂ O ₄ S ₂	399.31	146-147	84	39.1	4.02	7.02	39.31	4.07	6.98	NO ₂ 1360, 1525 SO ₂ 1340, 1150 NH 3350
5b		C ₁₄ H ₁₂ Cl ₂ N ₂ O ₄ S ₂	407.27	135-136	80	41.29	2.97	6.88	41.52	3.02	6.96	NO ₂ 1350, 1500 SO ₂ 1340, 1140 NH 3320
5c		C ₁₃ H ₉ BrCl ₂ N ₂ O ₄ S ₂	472.16	150-151	86	33.06	1.92	5.93	33.08	1.95	5.87	NO ₂ 1350, 1520 SO ₂ 1360, 1150 NH 3370
5d		C ₁₃ H ₈ Cl ₃ N ₂ O ₄ S ₂	427.70	114-115	76	36.51	2.12	6.55	36.51	2.04	6.21	NO ₂ 1350, 1520 SO ₂ 1340, 1180 NH 3330
5e		C ₁₂ H ₆ Cl ₂ FN ₂ O ₄ S ₂	411.25	124-125	68	37.97	2.21	6.81	37.65	2.07	6.76	NO ₂ 1330, 1500 SO ₂ 1340, 1140 NH 3340
5f		C ₁₄ H ₁₂ Cl ₂ N ₂ O ₄ S ₂	407.29	115-117	72	41.29	2.97	6.88	41.31	2.9	6.83	NO ₂ 1350, 1500 SO ₂ 1340, 1140 NH 3350
5g		C ₁₃ H ₉ Cl ₂ N ₃ O ₆ S ₂	438.26	169-171	69	35.63	2.7	9.59	35.81	2.08	9.37	NO ₂ 1350, 1500 SO ₂ 1340, 1160 NH 3270

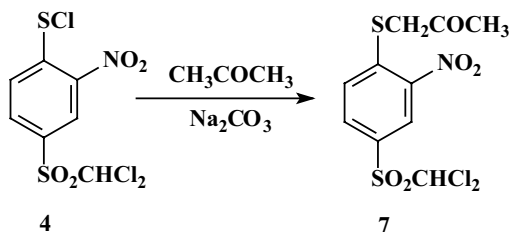
5h		$C_{14}H_9Cl_3N_3O_6S_3$	574.68	192-193	77	29.26	1.58	4.87	29.47	1.57	4.80	NO ₂ 1350, 1500 SO ₂ 1340, 1150 NH 3340
5i		$C_{12}H_9Cl_2N_3O_4S_2$	394.25	198-199	62	36.56	2.30	10.66	36.72	2.30	10.47	NO ₂ 1350, 1500 SO ₂ 1340, 1150 NH 3160
5j		$C_{14}H_9Cl_2N_3O_4S_3$	450.33	246	89	37.34	2.01	9.33	37.41	2.05	9.42	NO ₂ 1350, 1520 SO ₂ 1340, 1190 NH 3370
5k	$[(CH_3)_2CHCH_2]_2N$	$C_{15}H_{22}Cl_2N_2O_4S_2$	429.38	148-149	86	41.96	5.16	6.52	42.03	5.07	6.42	NO ₂ 1350, 1520 SO ₂ 1340, 1150
5l		$C_{14}H_{12}Cl_2N_2O_4S_2$	407.29	198-199	81	41.29	2.97	6.88	41.18	2.82	6.78	NO ₂ 1350, 1550 SO ₂ 1340, 1150
5m		$C_{16}H_{16}Cl_2N_2O_4S_2$	435.34	145-146	62	44.14	3.68	6.44	44.17	3.67	6.41	NO ₂ 1350, 1520 SO ₂ 1340, 1150
5n	$(C_6H_5)_2N$	$C_{19}H_{15}Cl_2N_2O_4S_2$	469.36	199-201	75	48.51	3.19	5.96	48.58	3.12	5.87	NO ₂ 1350, 1520 SO ₂ 1340, 1180
5o		$C_{12}H_{15}Cl_2N_3O_4S_2$	400.29	173-174	77	36.00	3.75	10.50	36.09	3.78	10.45	NO ₂ 1350, 1520 SO ₂ 1330, 1140
5p		$C_{12}H_{14}Cl_2N_2O_4S_2$	385.28	156-157	86	37.41	3.66	7.27	37.46	3.68	7.29	NO ₂ 1350, 1520 SO ₂ 1340, 1140
6	OCH ₃	$C_8H_7Cl_2NO_5S_2$	332.17	133-134	95	28.93	2.12	4.22	29.02	2.18	4.34	NO ₂ 1350, 1530 SO ₂ 1340, 1150
7	CH ₃ COCH ₂	$C_{10}H_9Cl_2NO_5S_2$	374.21	166-167	84	33.53	2.53	3.91	33.48	2.50	3.94	NO ₂ 1350, 1540 SO ₂ 1345, 1155 C=O1735

Chloride **4** was also subjected to reaction with methanol to give methyl ester **6** in high 95% of yield:



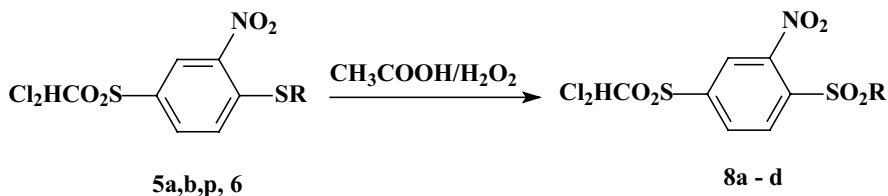
The process was carried out under reflux for one hour, in an excess of methanol, with equimolar amount of anhydrous sodium carbonate.

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

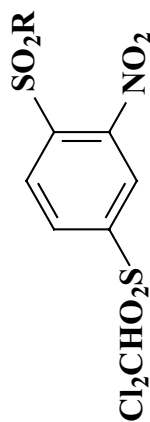


Ketosulfide **7** was obtained in 84% of yield by heating sulfenyl chloride **4** in an excess of acetone with catalytic amount of anhydrous sodium carbonate.

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



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


Comp. No.	R	Mol. formula	(Mol. wt.) [g/mol]	m.p. [°C]	Yield [%]	Elemental analyses						nIR [cm ⁻¹]
						Calcd.			Found			
						% C	% H	% N	% C	% H	% N	
8a		C ₁₄ H ₁₂ Cl ₂ N ₂ O ₆ S ₂	439.29	146-147	81	38.28	2.75	6.38	38.32	2.78	6.11	NO ₂ 1350, 1520 SO ₂ 1340, 1150 NH 3090
8b		C ₁₂ H ₁₄ Cl ₂ N ₂ O ₆ S ₂	417.28	199-200	72	34.54	3.38	6.71	34.37	3.39	6.68	NO ₂ 1350, 1500 SO ₂ 1340, 1140
8c		C ₁₃ H ₁₆ Cl ₂ N ₂ O ₆ S ₂	431.31	228-230	83	36.20	3.74	6.50	36.28	3.36	6.51	NO ₂ 1350, 1520 SO ₂ 1360, 1150 NH 3240
8d	CH ₃ O	C ₈ H ₇ Cl ₂ NO ₇ S ₂	364.17	276-278	79	26.39	1.94	3.85	26.49	1.88	3.87	NO ₂ 1350, 1520 SO ₂ 1340, 1180

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. $^1\text{H-NMR}$ spectra were recorded in CDCl_3 solution at $20\text{ }^\circ\text{C}$ 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 $60\text{ }^\circ\text{C}$ and concentrated nitric acid (18 mL, 0.49 mol) was then slowly added, at such a rate lest the temperature exceed over $70\text{ }^\circ\text{C}$. The mixture was stirred and heated at $90\text{ }^\circ\text{C}$ 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. $92\text{-}93\text{ }^\circ\text{C}$.

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. = $276\text{ }^\circ\text{C}$ 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 $100\text{ }^\circ\text{C}$ 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. = $129\text{-}130\text{ }^\circ\text{C}$. 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 sodium 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), sodium 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

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