Zinc Dichromate Trihydrate ($ZnCr_2O_7{\cdot}3H_2O$) as an Efficient Reagent for the One-Pot Synthesis of Thiosulfonates from Thiols

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Abstract: $ZnCr_2O_7{\cdot}3H_2O$ is a readily available and efficient reagent for the one-pot synthesis of a variety of thiosulfonates by chemoselective oxidation of thiols.

Key words: thiosulfonates, oxidation, thiols, one pot

Thiosulfonates have properties that make them attractive in biology,[1] industry,[2] and organic chemistry.[3] They show antimicrobial and fungicidal activities by blocking the normal metabolism of the microorganism via sulfonation of the enzyme's thiol groups.[1c] Thiosulfonates have a wide industrial application both in polymer production and in photographic processes.[2] They have also been extensively utilized in organic synthesis due to their stronger sulfenylating power than disulfides and greater stability and easier handling than sulfinyl chlorides.[3]

There are several multistep approaches for the synthesis of thiosulfonates including selective reduction of sulfonyl chlorides,[4] reaction of thiosulfonates with diaryliodonium salts,[5] reaction of thiols with sulfonic acid using cyanuric chloride,[6] iodine/bromine oxidative sulfenylation of sulfinates with disulfides,[7] and oxidation of disulfides or thiosulfinates.[8] Thiosulfonates can also be prepared by one-pot oxidation of thiols. A literature survey indicates that, in contrast to the numerous methods for the oxidation of thiols to disulfides, few methods are known for the direct synthesis of thiosulfonates from thiols by oxidation.[5,8a–c,9] Moreover, the existing methods suffer from limitations such as the need for special treatment for the activation of the reagent, difficult preparation or unavailability of the reagents, and lack of general applicability to thiol substrates bearing alkyl, aryl, cyclic, and heteroaromatic moieties. Hence, there remains the need for development of new protocols for the synthesis of these important scaffolds.

Zinc dichromate trihydrate ($ZnCr_2O_7{\cdot}3H_2O$) which is easily prepared by the reaction of $ZnCO_3$ with CrO_3 in acidic solution is a stable, cheap, and easy-to-handle compound.[10] It has been used as an efficient reagent for the oxidation of alcohols, sulfides, ethers, acetals, dithioacetals, oximes, silyl and pyranyl ethers.[11] We have recently reported oxidative deamination of amines and α-aminophosphonates, oxidation of α-hydroxyphosphonates, and oxidative deprotection of dithioacetals by $ZnCr_2O_7{\cdot}3H_2O$.[12] To the best of our knowledge, there is no report on the oxidation of thiols by this reagent.

In this paper, we wish to report a facile synthesis of thiosulfonates by a one-pot oxidation of thiols in the presence of $ZnCr_2O_7{\cdot}3H_2O$ at room temperature.

At first, the oxidation reaction of thiophenol by $ZnCr_2O_7{\cdot}3H_2O$ was investigated in different solvents at room temperature (Table 1).

Table 1 Oxidation of Thiophenol by $ZnCr_2O_7{\cdot}3H_2O$ in Different Solvents at Room Temperature

Entry	Solvent	Product	Time	Yield (%)[a]
1	CH_2Cl_2	–	24 h	0
2	*n*-hexane	–	24 h	0
3	toluene	–	24 h	0
4	EtOH	**1**	5 min	98
5	MeOH	**1**	5 min	97
6	H_2O	**1**	10 min	95
7	MeCN	**2**	15 min	98

[a] Isolated yield.

No product was obtained when the reaction was carried out in solvents such as *n*-hexane, toluene, or CH_2Cl_2 (Table 1, entries 1–3). Complete conversion of thiophenol was observed in EtOH, MeOH, and H_2O as solvents, but diphenyl disulfide (**1**, Scheme 1) was isolated as the sole product (Table 1, entries 4–6). The oxidation reaction in MeCN produced the corresponding thiosulfonate (**2**, Scheme 1) in high yield (Table 1, entry 7). No byproduct was formed in this reaction, which is a good indication of excellent chemoselectively in the present method. The reaction proceeds via the disulfide intermediate since the disulfide was isolated after adding 1 equivalent of $ZnCr_2O_7{\cdot}3H_2O$ to the reaction mixture. The disulfide produced from the reaction of the thiol with $ZnCr_2O_7{\cdot}3H_2O$ then reacts with excess of the reagent to form the unstable α-disulfoxide, which undergoes subsequent oxygen transfer[13] to form the stable thiosulfonate (Scheme 2).

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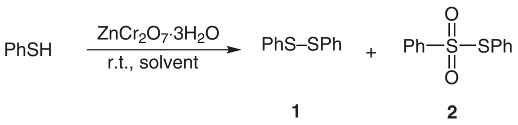
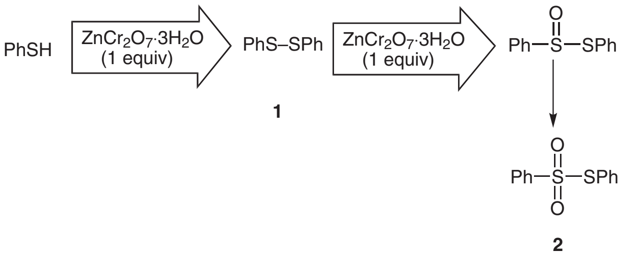


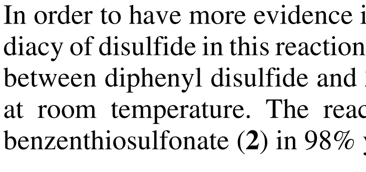
Scheme 1



Scheme 2

In order to have more evidence in support of the intermediacy of disulfide in this reaction, we performed a reaction between diphenyl disulfide and $ZnCr_2O_7{\cdot}3H_2O$ in MeCN at room temperature. The reaction furnished *S*-phenyl benzenthiosulfonate (**2**) in 98% yield after 15 minutes.

Next, the applicability of this method for the chemoselective oxidation of a variety of thiols to thiosulfonates by $ZnCr_2O_7{\cdot}3H_2O$ in MeCN at room temperature was investigated (Scheme 3). The results of these studies are summarized in Table 2.



Scheme 3

As indicated in Table 2, the oxidation reaction of thiophenols substituted with electron-donating and electron-withdrawing groups proceeded well and the corresponding thiosulfonates were obtained in high yields (entries 1–6). These results showed that existing groups on the aromatic ring had no obvious effect on the yield of the reaction products. 2-Mercaptopyridine and 2-mercaptobenzoxazole as heteroaromatic thiols underwent the oxidation reaction by $ZnCr_2O_7{\cdot}3H_2O$ and produced the corresponding thiosulfonates (**7** and **8**) in high yields (entries 7 and 8). This method was also applicable for the selective oxidation of aliphatic and cyclic thiols to thiosulfonates (entries 9–12).

We have also examined the oxidation reaction of thiophenol by some other chromium-based oxidants such as pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), nicotinium dichromate (NDC), and isonicotinium dichromate (INDC) under the present reaction conditions. Oxidation reaction in the presence of these reagents produced diphenyl disulfide as the sole product. These results showed the unique behavior of $ZnCr_2O_7{\cdot}3H_2O$ over these oxidants for the one-pot synthesis of thiosulfonates from thiols.

In conclusion, $ZnCr_2O_7{\cdot}3H_2O$ has been developed as a readily available and efficient reagent for the one-pot synthesis of a variety of thiosulfonates by chemoselective oxidation of aryl, heteroaryl, alkyl, and cyclic thiols. Simplicity of operation, high yields of the products, and short reaction times are the advantages of this method.

General Procedure for the Synthesis of Thiosulfonates

$ZnCr_2O_7{\cdot}3H_2O$ (2 mmol) was added to a stirred solution of thiol (1 mmol) in MeCN (10 mL). The resulting mixture was stirred at r.t. for the appropriate time (Table 2). The pure product was isolated from the resulting mixture by column chromatography in 90–98% yields.

S-Phenyl Benzene Thiosulfonate (1)

IR (KBr): 1134, 1313 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 7.35$ (t, 2 H, $^3J_{HH} = 6.8$ Hz), 7.37 (t, 2 H, $^3J_{HH} = 6.8$ Hz), 7.42–7.46 (m, 2 H), 7.49 (t, 1 H, $^3J_{HH} = 6.4$ Hz), 7.58 (d, 2 H, $^3J_{HH} = 8.4$ Hz), 7.48 (d, 1 H, $^3J_{HH} = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 127.5$, 127.8, 128.8, 129.4, 131.4, 133.6, 136.6, 142.9. MS (EI, 70 eV): *m/z* (%) = 250 (28.8) [M^+], 141 (33.1), 125 (80.4), 109 (47.3), 77 (100).

S-4-Fluorophenyl 4-Fluorobenzene Thiosulfonate (2)

IR (KBr): 1227, 1325 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 7.08$ (t, 2 H, $^3J_{HH} = 8.4$ Hz), 7.14 (t, 2 H, $^3J_{HH} = 8.4$ Hz), 7.38 (dd, 2 H, $^3J_{HH} = 5.2$, $^3J_{HF} = 9.0$ Hz), 7.61 (dd, 2 H, $^3J_{HH} = 4.8$, $^3J_{HF} = 9.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 116.2$ (d, $^2J_{CF} = 22.7$ Hz), 116.9 (d, $^2J_{CF} = 22.0$ Hz), 123.2, 123.3, 130.4 (d, $^4J_{CF} = 9.7$ Hz), 138.8 (d, $^4J_{CF} = 8.9$ Hz), 163.9 (d, $^1J_{CF} = 70.7$ Hz), 166.5 (d, $^1J_{CF} = 73.6$ Hz). MS (EI,70 eV): *m/z* (%) = 286 (31.1) [M^+], 159 (58.5), 143 (86.2), 127 (77.3), 95 (100).

S-4-Chlorophenyl 4-Chlorobenzene Thiosulfonate (3)

IR (KBr): 1141, 1327 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 7.33$ (d, 2 H, $^3J_{HH} = 8.4$ Hz), 7.37 (d, 2 H, $^3J_{HH} = 8.8$ Hz), 7.44 (d, 2 H, $^3J_{HH} = 9.2$ Hz), 7.54 (d, 2 H, $^3J_{HH} = 8.8$Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 128.9$, 129.2, 129.9, 130.3, 137.7, 138.6, 140.5, 141.3. MS (EI, 70 eV): *m/z* (%) = 322 [$M^+ + 4$], 320 [$M^+ + 2$], 318 [M^+], 175 (72.2), 177 (30.3), 159 (93.9), 161 (37.9), 143 (56.2), 145 (24.6), 111 (100), 113 (45.8).

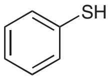
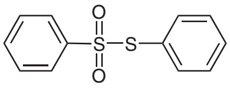
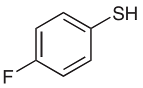
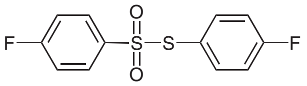
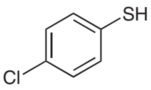
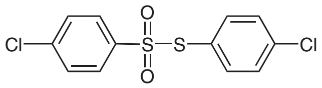
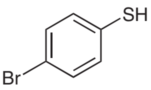
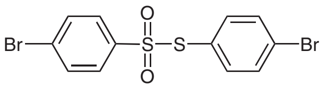
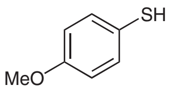
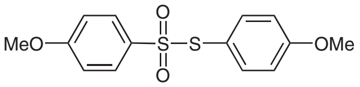
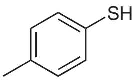
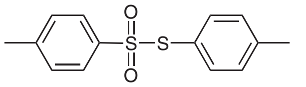
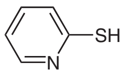
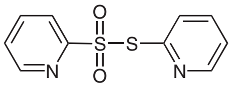
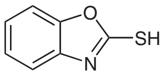
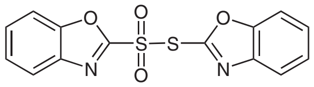
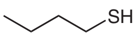
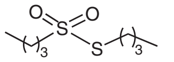
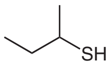
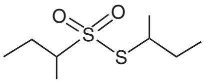
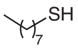
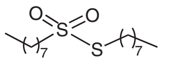
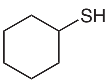
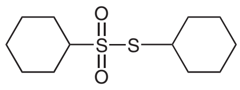
S-4-Bromophenyl 4-Bromobenzene Thiosulfonate (4)

IR (KBr): 1058, 1320 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 7.26$ (d, 2 H, $^3J_{HH} = 8.4$ Hz), 7.46 (d, 2 H, $^3J_{HH} = 8.8$ Hz), 7.53 (d, 2 H, $^3J_{HH} = 8.4$ Hz), 7.62 (d, 2 H, $^3J_{HH} = 8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 126.6$, 127.0, 128.9, 129.2, 132.3, 132.9, 137.8, 141.8. MS (EI, 70 eV): *m/z* (%) = 410 (1.7) [$M^+ + 4$], 408 (3.8) [$M^+ + 2$], 406 (2.1) [M^+], 219 (18.6), 221 (20.4), 203 (26.8), 205 (28.1), 187 (22.7), 189 (22.7), 155 (37.4), 157 (36.5), 107 (100).

Acknowledgment

We are grateful to Birjand University Research Council for their support of this work.

Table 2 Oxidation of Different Thiols by $ZnCr_2O_7 \cdot 3H_2O$ at Room Temperature

Entry	Thiols	Thiosulfonates	Time (min)	Yield (%)[a]
1		 **1**	15	98
2		 **2**	5	95[b]
3		 **3**	5	94[b]
4		 **4**	5	96[b]
5		 **5**	45	94
6		 **6**	10	92[c]
7		 **7**	5	90
8		 **8**	15	90[c]
9		 **9**	5	91
10		 **10**	5	90
11		 **11**	10	97
12		 **12**	–[d]	98

[a] Yields refer to isolated pure products characterized by spectroscopic methods and compared with authentic spectra.[8,9,14–16] *Reaction conditions*: thiol (1 mmol), $ZnCr_2O_7 \cdot 3H_2O$ (2 mmol, except for entries 2–4), MeCN (10 mL).

[b] *Reaction conditions*: thiol (1 mmol), $ZnCr_2O_7 \cdot 3H_2O$ (3 mmol), MeCN (10 mL).

[c] No solvent.

[d] Immediately.

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