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CAN/I_2-catalyzed Chemoselective Synthesis of Thiosulfonates by Oxidation of Disulfides or Thiols

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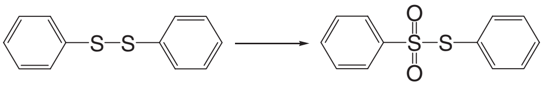
CAN/I_2 promoted synthesis of thiosulfonates by oxidation of disulfides and thiols with high chemoselectivity and excellent yields in wet poly(ethylene glycol) (PEG-400). The overall process is simple, practical, and it provides convenient access to thiosulfonates.

Thiosulfonates, with strong sulfenylating power, have found wide industrial applications both in polymer production and in photographic processes.[1] One of the most practically and widely used routes for the synthesis of thiosulfonates involve the direct oxidation of disulfides in the presence of various promoting agents, such as benzenesulfinate/bromine,[2] sodium trifluoromethanesulfinate/[bis(trifluoroacetoxy)iodo]benzene,[3] dinitrogen tetroxide/charcoal,[4] dinitrogen tetroxide supported on poly(vinylpyrrolidone),[5] tetrabutylammonium peroxymonosulfate,[6] and Re(Ph_2SO).[7] In another method, thiosulfonates have been prepared by tandem reaction of thiols under oxidative conditions.[5–8] Some other methods include selective reduction of arenesulfonyl chlorides promoted by samarium metal in DMF.[9] However, many of these processes suffer limitations, such as use of volatile organic solvents and strong oxidizing agents, drastic reaction conditions, expensive reagents, unsatisfactory yields, tedious workup procedures, and co-occurrence of several side reactions. As a consequence, the introduction of new methods and/or further work on technical improvements to overcome the limitations is still an important experimental challenge.

Ceric ammonium nitrate (CAN), as a very inexpensive and easily available oxidizing agent, has been widely used in organic reactions,[10] but it has not been carefully studied as a catalyst in the synthesis of thiosulfonates until now. CAN is a one-electron transfer reagent and has a high molecular weight, therefore, a large quantity of CAN is required for a reaction utilizing stoichiometric amounts of CAN reagent. To circumvent this limitation, several synthetic protocols have benn reported,[11] stoichiometric CAN has been replaced with a dual oxidant system consisting of a catalytic amount of CAN and another oxidant. The purpose of the co-oxidant is to regenerate Ce(IV) oxidant to continue the desired oxidation activity. I_2 as an oxidant has been used extensively due to its inherent properties of low toxicity, and easy handling. During this research, we found that CAN could catalyze synthesis of thiosulfonates in the presence of I_2. PEG is known to be inexpensive, thermally stable, recoverable, biological compatible, and nontoxic,[12] so we decided to use PEG as the reaction media for the synthesis of thiosulfonates.

In continuation of our research in developing novel synthetic routes for the formation of carbon–sulfur bonds,[13] in this study we wish to report the use of a catalytic redox cycling for the synthesis of various thiosulfonate derivatives, based on [Ce(IV)/Ce(III)]-redox-mediated oxidation of disulfides and thiols.

Table 1. Screening conditions for the oxidation of diphenyl disulfide[a]



1a **3a**

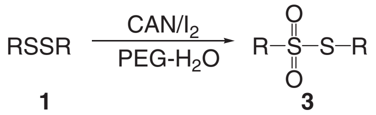
Entry	CAN/mol %	Time	Yield[b]/%
1	0	24 h	0
2	5	19 h	65
3	20	24 h	35[c]
4	20	24 h	trace[d]
5	20	75 min	99
6	20	75 min	96[e]
7	20	75 min	99[f]
8	10	16 h	97
9	15	10 h	98
10	20	24 h	80[g]
11	20	75 min	trace[h]

[a]**1a** (1 mmol), I_2 (1.5 equiv), 4 mL of PEG-400/H_2O = 3:1 (v/v), 60 °C, see Ref. 14. [b]Isolated yield. [c]PEG-400 as solvent. [d]H_2O as solvent. [e]With 1 equiv of I_2. [f]With 2 equiv of I_2. [g]Without I_2. [h]Under N_2 atmosphere.

The model oxidation reaction of 1,2-diphenyldisulfide (**1a**) was conducted to screen the optimal reaction conditions (Table 1). In our initial studies, we evaluated the feasibility of oxidation of disulfides to thiosulfonates in PEG utilizing the CAN/I_2 dual oxidant system. As expected, the reaction provided the desired product **3a** in 35% isolated yield. Encouraged by this promising result, we further optimized the reaction conditions including reaction temperature, and the amount of CAN and I_2. Recently, Firouzabadi and Iranpoor,[15] have reported the conversion of organic halides to symmetric disulfides in PEG and water solvent system. Enlightened by research, we investigated the transformation cyclocondensation reaction in the combination of PEG and water solvent system. The volume ratio of PEG and water was examined and the best results were obtained by carrying out the reaction in PEG-400/H_2O with a ratio of 3:1 (v/v). One likely reason was that water was necessary to dissolve CAN since it has limited solubility in PEG.

The role of I_2 co-oxidant utilized in this procedure is to regenerate the Ce(IV) species which oxidizes disulfides to thiosulfonates. That the actual oxidant is Ce(IV) and not I_2 was confirmed in control experiments, wherein the absence of Ce(IV) resulted in an extremely sluggish reaction insufficient for complete product formation even after 24 h. (Entry 1). The rate of oxidation reaction in the presence of 5 mol % of CAN was extremely slow (Entry 2). Increasing the amount of CAN to 20 mol % in the system increased the yield rapidly and produced a quantitative yield of **3a** (Entry 5). Although as low as 10 mol % of CAN is capable of oxidizing disulfides to thiosulfonates in

Table 2. Synthesis of thiosulfonates from disulfides[a]



Entry	R (**1**)	Time/min	Product	Yield^{b}/%
1	C_6H_5 (**1a**)	75	**3a**	99
2	*p*-$CH_3C_6H_4$ (**1b**)	60	**3b**	99
3	*p*-ClC_6H_4 (**1c**)	75	**3c**	96
4	*p*-BrC_6H_4 (**1d**)	75	**3d**	97
5	*p*-FC_6H_4 (**1e**)	30	**3e**	93
6	2,3-$Cl_2C_6H_3$ (**1f**)	75	**3f**	95
7	*n*-Bu (**1g**)	75	**3g**	98
8	*i*-Bu (**1h**)	75	**3h**	99

[a] Disulfides **1** (0.25 mmol), I_2 (0.375 mmol), CAN (20 mol %), PEG400/H_2O = 3:1 (4 mL), 60 °C. [b] Isolated yield.

16 h (Entries 8 and 9), we employed 20 mol % of CAN in these reactions to maintain short reaction times. Without I_2, the desired product **3a** was obtained in 80% (Entry 10). It was found that **3a** was not obtained under N_2 atmosphere (Entry 11). The results indicated that O_2 played an important role in the formation. However, the reaction occurred with absolute selectivity for formation of **3a** without any detectable sulfinothioate in the present protocol. This result is in sharp contrast to the fact that using CH_3CN as solvent in the system which produced a large amount of the by-product sulfinothioate.

With the optimized conditions in hand, the oxidation of various disulfides was examined to explore the scope of the reaction (Table 2). In our system, the substitution groups on the aromatic ring had no obvious effect on the yield. Oxidation of an electron-rich disulfide, such as *p*-tolyldisulfide **1b** (Entry 2) gave the corresponding product in high yields. The reaction proceeded smoothly in the presence of a variety of electron-withdrawing functional groups including fluoro, chloro, and bromo groups such as **1b**–**1f** (Entries 3–6). To our knowledge, the previous literature did not describe this function which can tolerate the electron-withdrawing functional groups in the substrates. This system is also applicable to the efficient oxidation of aliphatic disulfides such as 1,2-dibutyl disulfide **1g** and **1h** (Entries 7 and 8).

From the standpoint of methodology, the one-pot transformation of thiols to thiosulfonates has been of interest.[10–13] Using this catalytic system, a variety of thiols **2a**–**2h** were effectively oxidized to their corresponding thiosulfonates **3a**–**3h** with excellent yields and selectivities (Table 3).

A working mechanism for the preparation of thiosulfonates was proposed as outlined in Scheme 1 on the basis of an earlier proposed mechanism.[16]

In conclusion, a new methodology toward the oxidation of disulfides or thiols has been reported. Wet PEG has been found to be efficient as a reaction medium for the highly chemoselective oxidation of disulfides or thiols to thiosulfonates using the CAN/I_2 dual oxidant system. Further utilization of this procedure is in progress in our laboratory.

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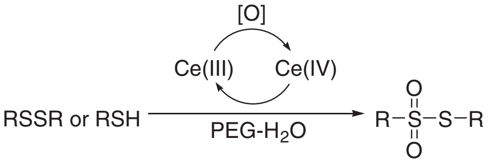
Table 3. Synthesis of thiosulfonates from thiols[a]

Entry	Thiols (**2**)	Time/min	Product	Yield^{b}/%
1	C_6H_5SH (**2a**)	70	**3a**	96
2	*p*-$CH_3C_6H_4SH$ (**2b**)	60	**3b**	98
3	*p*-ClC_6H_4SH (**2c**)	75	**3c**	95
4	*p*-BrC_6H_4SH (**2d**)	75	**3d**	97
5	*p*-FC_6H_4SH (**2e**)	35	**3e**	91
6	2,3-$Cl_2C_6H_3SH$ (**2f**)	80	**3f**	93
7	*n*-BuSH (**2g**)	75	**3g**	97
8	*i*-BuSH (**2h**)	75	**3h**	98

[a] Thiols **2** (0.25 mmol), I_2 (0.375 mmol), of CAN (20 mol %), PEG400/H_2O = 3:1 (4 mL), 60 °C. [b] Isolated yield.



Scheme 1. A working mechanism.

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