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# Solvent- and metal-free selective oxidation of thiols to disulfides using $I_2$ /DMSO catalytic system

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#### ABSTRACT

We describe herein a simple, fast and inexpensive protocol for the oxidative coupling of thiols employing a stoichiometric amount of DMSO and iodine as the catalyst. Various aromatic disulfides were obtained in good to excellent yields in short reaction times at room temperature, while aliphatic disulfides were achieved in good yields when the reactions were conducted under microwave irradiation.

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#### 1. Introduction

The selective oxidation of thiols to disulfides is an important process from the synthetic, economic and biochemical points of view.<sup>1,2</sup> Although several methods and oxidizing agents have been described to accomplish this transformation,<sup>3,4</sup> the development of fast, inexpensive and less harmful protocols is still of great interest. In addition, selectivity remains a challenge in many cases, since thiols and disulfides can undergo over-oxidation leading to the production of sulfonates, sulfoxides and sulfones, among other compounds.<sup>5</sup> Taking this into account, several transition metals based catalysts have been developed and successfully applied in this transformation.<sup>6</sup> Although they offer selectivity, their high toxicity and difficulties associated with separating the catalyst from the final product are common drawbacks related to the use of metal-containing catalysts, which hampers their use in several processes.<sup>7</sup>

In this context, DMSO appears to be an interesting alternative, since it is an inexpensive and easy-to-handle reagent. Since most of the oxidizable functional groups are not affected by DMSO, it should be possible to address the issue of selectivity. The use of DMSO<sup>8</sup> and DMSO/iodine<sup>9</sup> in catalytic systems to promote the oxidation of thiols to disulfides has been previously reported, but the conditions applied to perform this conversion were harsh in comparison with our observations. For example, when DMSO was employed without iodine, an excess of DMSO, long reaction time (8 h) and high temperatures (80-90 °C) were necessary to furnish the desired disulfides.<sup>8</sup> On the other hand, when I<sub>2</sub> (or HI) was used as the catalyst, the reactions could be carried out at room temperature but, again, an excess of DMSO and long

reaction time (5 h) were required and benzene was used as the solvent.<sup>9</sup>

During our investigations on C-S coupling reactions employing aromatic thiols,<sup>10</sup> we observed that the oxidation of the latter to the corresponding disulfides was completed in a short reaction time, employing 1.0 equiv. of DMSO and 20 mol% of iodine. As part of our wider research program aimed at designing and developing eco-friendly processes,<sup>11</sup> including the use of solvent-free systems, herein we report the molecular iodine catalyzed oxidation of thiols into symmetrical diorganyl disulfides. This oxidative transformation was performed at room temperature under solvent-free conditions.

For the optimization of the reaction, thiophenol **1a** was selected as a model substrate and was evaluated under various reaction conditions (Table 1). Continuing our above-mentioned interests, the optimization reactions were conducted under solvent-free conditions. The reaction in the presence of 3.0 equiv. of DMSO at room temperature with a reaction time of 5 min without a catalyst afforded the desired product **2a** in trace yields (Table 1, entry 1). The use of 20 mol% of molecular iodine as a catalyst demonstrated a considerable improvement and **2a** was obtained in 93% yield (Table 1, entry 2). In the next step, the quantities of the additive were screened for this transformation (entries 3-7). On lowering the amount of DMSO in the reaction from 3.0 to 1.0 equiv., **2a** was obtained quantitatively (entries 2-4) while in the absence of DMSO the reaction afforded a lower yield of **2a** (entries 5).

In the subsequent step, the type of catalyst, catalytic loading and reaction time were explored for this transformation (entries 6-11). When the reaction was performed in the presence of NaI

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as the catalyst, **2a** was obtained in 12% isolated yield (entry 6). It was observed that CuI provided a slightly better yield compared to NaI (entry 6 *vs* 7); however, molecular iodine remained the best option. A constant decrease in the yield of **2a** was observed on decreasing the catalytic amount of I<sub>2</sub> (entry 2 vs 8-9). Similarly, the reaction time was also screened for this transformation (entries 4, 10) and an ideal value of 5 min was obtained.

After determining the appropriate catalyst and catalytic loading, in the next step we screened the type of additive for this reaction (entry 11-14). Surprisingly, all of the other organic additives evaluated were completely ineffective, even when the reaction time was doubled. When water was employed, the desired product **2a** was obtained in 28% yield after 10 min of reaction.

Table 1	- Optimization	for standard	reaction	parameters <sup>a</sup>
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	SH <u>c</u> ac Te	atalyst (mol%) dditive ( equiv.) mperature, time	S S 2a	
Entry	Additive (equiv.)	Cat. (mol%)	t (min)	yield (%) <sup>b</sup>
1	DMSO(3)	-	5	traces
2	DMSO(3)	I <sub>2</sub> (20)	5	93
3	DMSO (2)	I <sub>2</sub> (20)	5	Quantitative
4	DMSO (1)	I <sub>2</sub> (20)	5	Quantitative
5	-	I <sub>2</sub> (20)	5	60
6	DMSO(1)	NaI (20)	5	12
7	DMSO(1)	CuI(20)	5	37
8	DMSO(1)	I <sub>2</sub> (15)	5	85
9	DMSO(1)	I <sub>2</sub> (10)	5	76
10	DMSO(1)	I <sub>2</sub> (20)	2.5	75
11	CH <sub>3</sub> CN (1)	I <sub>2</sub> (20)	10	-
12	Hexane (1)	I <sub>2</sub> (20)	10	-
13	DMF (1)	I <sub>2</sub> (20)	10	-
14	$H_2O$	I <sub>2</sub> (20)	10	28

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol),

<sup>b</sup> Isolated yields.

After ascertaining the best conditions (Table 1, entry 4), we evaluated the generality and scope of this transformation and the reaction demonstrated wide substrate scope in terms of the thiols 1 under the optimized conditions (Table 2).

In case of structurally different organic moieties with electronwithdrawing (Cl, Br, CF<sub>3</sub>, NO<sub>2</sub> etc.), electron-donating (Me, OMe, NH<sub>2</sub>, etc.) and bulky groups (*t*-butyl) groups, the reaction was performed with success. In general, steric and electronic effects (EWG and EDG) of the substituents attached at the aryl ring of **1** afforded the desired products **2a-k** in good yields. It should be noted that thiophenols with EDG at the *para* position required longer times compared to the respective EWG. We were also delighted to find that benzylthiol afforded the desired product **2k** with 82 % yield after only 2 min of reaction.

The success in the iodine-catalyzed synthesis of symmetrical diaryl disulfides prompted us to extend this method to the preparation of dialkyl disulfides (**2l-o**). In general, aliphatic thiols were not found to be efficient substrates, since the respective

disulfides **2l-n** were isolated in low yields, even after longer reaction times. Notably, 1,2-dithiane-4,5-diol **20** was isolated in 86% yield after only 5 min of reaction.

**Table 2** Scope and generality of the reaction using arenes  $2^{a,b}$ 

$$R-SH \xrightarrow{I_2 (20 \text{ mol}\%),}_{DMSO (1 \text{ equiv})} R^{S}S^{R}$$
1
$$r.t.$$
2

	1	1.0.		2	
Entry	Product 2			t (min)	yield (%) <sup>b</sup>
1	$\bigcirc$	-S <sub>S</sub>	2a	5	98
2	MeO-	-s <sub>s</sub> -c	<sup>0Me</sup> 2b	30	77
3		-S <sub>S</sub>	2c	15	78
4	H <sub>2</sub> N	-S <sub>S</sub> -N	IH <sub>2</sub> 2d	32	95
5	YO	-s.s.	2e	42	80
6	Br	-S.S-	Br 2f	5	77
7	CI-	-s <sub>s</sub> -c	2g	8	80
8	CI	-S.S.C.	2h	12	62
9		MeO -S S OMe	2i	5	78
10		-s, s-	2j	8	73
11		S-S	2k	2	82
12	$\bigcirc$	-S <sub>s</sub> -	21	35	40
13	$\sim$	s~s	2m	23	35
14	()	S.S.M.	2n	50	68
15	10	S S OH	20	5	86

<sup>*a*</sup> Reaction conditions: **1** (0.5 mmol), in the presence of  $I_2$  (20 mol%) and DMSO (1 equiv.) at r.t.

<sup>b</sup> Isolated yields.

Considering the low yields obtained for aliphatic disulfides (**2l-n**), we decided to perform the reaction under microwave irradiation, at 23°C with 100 W of power for 10 min (Scheme 1). In all cases, better reaction yields were obtained for the corresponding disulfides, demonstrating that in the case of aliphatic disulfides the use of microwave irradiation improves the product yield.



Scheme 1. MW-assisted synthesis of disulfides 21-n.

It can be observed in Figure 1 that, in most cases, the end of the reaction could be visually identified. Initially, the brownish-red solution of DMSO/I<sub>2</sub> turns light yellow after the addition of thiophenol **1a**. The solution then returns to a brownish-red after 5 min of reaction, indicating the total consumption of thiol and regeneration of molecular iodine in the reaction medium.



**Figure 1.** Visual color changes in the reaction medium during the oxidation of thiophenol (at 10 mmole scale): (a) 20 mol% of iodine in 10 mmol of DMSO (1 molar equiv); (b) addition of 10 mmol of PhSH in the reaction medium; and (c) after 5 min of stirring at r.t.

The importance of symmetrical diorganyl disulfides in organic reactions is well established, as they are widely used as substrates and sulfenylating agents. <sup>1,2,11a-e</sup> Therefore, we further investigated the synthetic utility of this new protocol by scaling-up the reaction to 10 mmol and 100 mmol (Scheme 2). Thiophenol **1a** was selected as the reagent to be tested under optimized conditions, affording **2a** with 78% isolated yields at scale up to 100 mmol. Thus, this procedure could be used as a robust method for the synthesis on the gram scale of symmetrical diorganyl disulfides.



Scheme 2. Results for the reaction on multigram scale.

To propose a plausible mechanism for this reaction, some control experiments were carried out (Scheme 3). It was found that the presence of 3.0 equiv. of TEMPO and hydroquinone as radical inhibitor did not inhibited the reaction, and 2a was obtained in 86% and 93% yields, respectively (Scheme 2-I), which excluded the possibility of a radical pathway. Subsequently, performing the reaction under an inert atmosphere led to a slight decrease in efficacy (Scheme 3-II), while an oxygen atmosphere did not show any effect (Scheme 3-III). These results indicate that the presence of oxygen is not crucial but can contribute to obtaining high yields. Compound 2a was obtained in 87% yield when the standard reaction was performed in the presence of 1 equiv. of H<sub>2</sub>O<sub>2</sub> (Scheme 3-IV), indicating that in this system DMSO acts as an oxidant. Based on our previous research,<sup>10,11a,e</sup> with the use of HI as a catalyst instead of iodine (Scheme 3-V) 3a can be isolated with 96% yield, indicating that HI is probably one of the intermediates of this transformation.



Scheme 3. Investigation of the reaction mechanism.

Based on these results and on previous reports,<sup>10,11a,e</sup> a plausible mechanism for the transformation is proposed in Scheme 4. An electrophilic species **A** (PhSI) is most likely generated when the thiophenol **1a** undergoes reaction with the catalyst ( $I_2$ ) along with the generation of HI. Subsequently, another molecule of **1a** attacks the intermediate **A**, forming the desired product **B** with the simultaneous formation of another molecule HI. In the next step, HI reacts with DMSO affording a protonated sulfur species **C**<sup>\*</sup> (detected by HPLC-MS, ESI-S38A). This intermediate is quickly converted to **D**<sup>\*</sup> (detected by HPLC-MS, ESI-S38B), which on reaction with another HI molecule forms the iodine-dimethyl sulfide adduct **E** with the formation of water.<sup>12</sup> Lastly, the iodide species **E** eliminates dimethyl sulfide <sup>10b,11a</sup> with the regeneration of the catalyst ( $I_2$ ), completing the catalytic cycle.



Scheme 4. Proposed mechanism for the reaction.

In summary, we have developed a selective and efficient procedure for the oxidative dimerization of thiols catalyzed by iodine, using a stoichiometric amount of DMSO as a mild oxidant. This protocol afforded the desired products in good to excellent yields under solvent- and metal-free conditions and can be applied under both conventional and microwave heating conditions. Most importantly, this procedure offers significant improvements, including operational simplicity, a greener procedure and low cost, and thus represents an interesting alternative to the existing methodologies.

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#### **Supplementary Material**

Supplementary data associated with this article can be found, in the online version, at http://

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#### Highlights

- Facile access to diorganyl disulfides from thiols.
- Selective oxidation of thiols to disulfides using I<sub>2</sub>/DMSO catalytic oxidant system
- Oxidation of thiophenol to diphenyl disulfide in up to 100 mmol scale
- A greener procedure for the preparation of disulfides using conventional as well as

microwave irradiations

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