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PII: S0040-4039(15)01343-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.08.041
Reference: TETL 46625

To appear in: *Tetrahedron Letters*

Received Date: 27 July 2015
Revised Date: 15 August 2015
Accepted Date: 18 August 2015

Please cite this article as: Natarajan, P., Sharma, H., Kaur, M., Sharma, P., Haloacid/dimethyl sulfoxide-catalyzed synthesis of symmetrical disulfides by oxidation of thiols, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.08.041

Tetrahedron Letters
journal homepage: www.elsevier.com

Haloacid/dimethyl sulfoxide-catalyzed synthesis of symmetrical disulfides by oxidation of thiols

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

ABSTRACT

A novel method is developed for the oxidation of thiols to the corresponding disulfides using 20 mol % haloacid (HBr or HI) in combination with the dimethyl sulfoxide. A tentative mechanism is proposed for the oxidation. In addition to the advantages of cost-effectiveness, simple processes and broad functional group tolerance, the exclusive formation of disulfides is the principle reward of this methodology while compared to known methods that further oxidize disulfides to S-oxides and other byproducts.

Aryl- and alkyl disulfides[1] are an important class of organic compounds present in many natural products, biological compounds and pharmaceuticals. Owing to their wide range of utilities as precursors in many functional group transformations[2a] as well as in biological synthesis,[2b] a number of methods have been developed for the preparation of disulfides.[1] Among them, the most frequently used methodology is the direct oxidation of thiols in the presence of various promoting agents including benzyltriphenylphosphonium peroxymonosulfate,[3] chromate salts,[4] 1,4-diazabicyclo[2.2.2]octane-di-N-oxide-di-perhydrate,[5] 1,3-dibromo-5,5-dimethylhydantoin,[6] 2,6-dicarboxypyridinium chlorochromate,[7] dinitrogen tetroxide copper nitrate complex,[8] ferric chloride,[9] halogens,[10] hexamethyldisilazane in dimethyl sulfoxide (DMSO),[11] manganese(III)-salophen in the presence of urea hydrogen peroxide,[12] N-bromophthalimide,[13] nickel nanoparticles,[14] permanganates,[15] quinolinium tribromide,[16] rhodium(I) complexes,[17] sodium periodate,[18] sulfuryl chloride,[19] trichloronitromethane,[20] trichlorooxyvanadium,[21] trimethylchlorosilane-cyanuric chloride[22] and tungstate sulfuric acid.[23] However, many of above protocols have their own merits and demerits such as use of expensive metal-based oxidizing agents,[4,8,12,14,17] special treatment for the activation of reagents,[3,8,14] drastic reaction conditions and tedious workup procedures due to the co-occurrence of several side products (i.e., thiosulfinates, thiosulfonates and sulfonic acids) through over oxidation.[3-23] As a consequence, the development of a highly practical and mild reaction conditions is still an important challenge for exploration.[24]

The mixture of aqueous haloacid (HX = HBr, HI) and DMSO is a commercially available metal-free oxidizing agent.[25] It is

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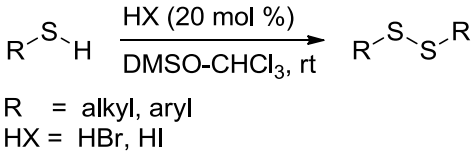
cheap, mild, selective, highly stable at ambient conditions and provides readily removable gaseous dimethyl sulfide as the sole byproduct.[25] Moreover, HX-DMSO system has been widely used for the chemoselective oxidation of 1,3-diketones to 1,2,3-trione,[26] arylmethyl ketones to aryldiketones,[26] α-bromoketones to α-ketoaldehydes[27] and epoxides to 1,2-diketones.[26] But it has not yet been employed for the synthesis of disulfides.

In continuation of our works on the oxidation of polycyclic aromatic hydrocarbons[28] and disulfides,[29] we have found that HX (HBr or HI, 20 mol %) combined with DMSO is an ideal choice for the conversion of thiols to the corresponding disulfides with no side reaction. Herein, we report a practical method (Scheme 1) for the synthesis of symmetrical disulfides from their thiols using HBr (20 mol %) or HI (20 mol %) in DMSO as an oxidizing agent. In addition, a tentative mechanism is described for the oxidation of thiols to disulfides, *vide infra*.

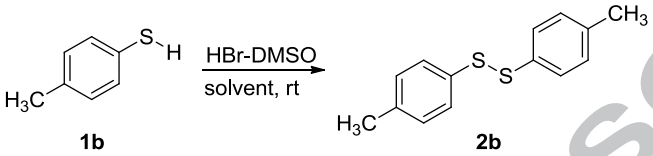
To screen the optimal reaction conditions (Table 1), initial studies were conducted using 4-methylbenzenethiol (**1b**) and HBr-DMSO, respectively, as a test substrate and an oxidizing agent. Reactions with various solvents such as DMSO and acetonitrile, chloroform ($CHCl_3$), dichloroethane, hexane, tetrahydrofuran, toluene in combination with DMSO suggested that a mixture of $CHCl_3$ and DMSO in 1:1 (v/v) ratio was the best medium for the product bis(4-methylphenyl)disulfide (**2b**) formation, cf. Table 1 and Entry 6. One likely reason is that $CHCl_3$ miscible with DMSO in all proportions to dissolve the substrates and intermediates.[30] It is worthy to

mention that the reaction did not proceed when DMSO was replaced with neat $CHCl_3$ (Table 1, Entry 16), in which case starting compound remained unreacted even after 12 h. Thus, the HBr was effective only in the presence of DMSO.



Scheme 1. HX-DMSO mediated synthesis of disulfides from thiols reported in this work.

Table 1. Solvent effect on the oxidation of 4-methylbenzene-thiol (**1b**) under identical reaction conditions[a]



1b **2b**

Entry	Solvent (v/v)[b]	Time (min)	Product yield (%)[c]
1	DMSO	15	96
2	DMSO-acetonitrile (0.8:0.2)	45	84
3	DMSO-acetonitrile (0.5:0.5)	90	86
4	DMSO-acetonitrile (0.2:0.8)	180	77
5	DMSO-$CHCl_3$ (0.8:0.2)	30	94
6	DMSO-$CHCl_3$ (0.5:0.5)	45	98
7	DMSO-$CHCl_3$ (0.2:0.8)	150	81
8	DMSO-dichloroethane (0.8:0.2)	30	93
9	DMSO-dichloroethane (0.5:0.5)	60	92
10	DMSO-hexane (0.8:0.2)	60	88
11	DMSO-hexane (0.5:0.5)	150	71
12	DMSO-tetrahydrofuran (0.8:0.2)	60	87
13	DMSO-tetrahydrofuran (0.5:0.5)	200	89
14	DMSO-toluene (0.8:0.2)	30	90
15	DMSO-toluene (0.5:0.5)	60	91
16	$CHCl_3$	720	NR[d]

[a] All reactions were run with **1b** (1.0 mmol) and HBr (1.0 mmol) in various solvents at room temperature.

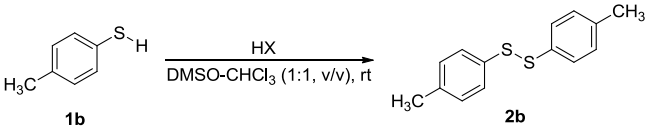
[b] Double distilled solvents were employed.

[c] Isolated yields.

[d] No reaction (NR).

Encouraged by this promising result, we further optimized the reaction conditions to arrive at an optimum stoichiometry of HBr loading to the amount of **1b** for the synthesis of **2b** in DMSO-$CHCl_3$ (1:1, v/v, Table 1, Entry 6) at room temperature. Notice that the rate of oxidation reaction in the presence of 10 mol % of HBr was extremely slow (Table 2, Entry 1). Increasing the amount of HBr to 20 mol % in the system increased the rate (Table 2, Entry 2) yielding **2b** in a quantitative yield. Further increasing the concentration of HBr (30-50 mol %, Table 2, Entries 3-5) neither increased the yield nor lowered the reaction time drastically. Although as low as 10 mol % of HBr is capable of oxidizing thiols to disulfides in 24 h (Table 2, Entry 1), we employed 20 mol % of HBr in all reactions to maintain short reaction times. Without HBr, the desired product **2b** was obtained in very poor yield (≈ 2%, Table 2, Entry 6) even after 48 h. Clearly, both HBr and DMSO are essential for the reaction, cf. Entries 16 and 6 in Tables 1 and 2, respectively. It is worth mentioning that the present protocol occurred with absolute selectivity for formation of **2b**, cf. NMR spectroscopic monitoring shown in Figure 1, under the condition employed. This result is in sharp contrast to the fact that using metal-based oxidizing agents such as permanganates,[15] chromates[4] and dichromates[7] in the reaction produced a large amount of the over oxidized byproducts.[3-23]

Table 2. The effect of molar ratio of HX on the oxidation of 4-methylbenzenethiol (**1b**) a representative compound[a]



1b 2b

Entry	HBr (mmol)	Time (h)	Product yield (%)[b]
1	0.1	24	93
2	0.2	7	96
3	0.3	7	94
4	0.4	5	96
5	0.5	5	95
6	0	48	<5
7	0.2[c]	8	97
8	0.5[c]	5	95
9	0.2[d]	10	86
10	0.5[d]	7	83
11	0.5[e]	24	11
12	1.0[e]	24	18
13	1.0[f]	24	23
14	1.0[g]	24	20
15	0.1[h]	20	96
16	0.3[h]	5	94
17	0.5[h]	4	95

[a] All reactions were run with **1b** (1.0 mmol) and HBr (0–0.5 mmol) in DMSO–$CHCl_3$ (1:1, v/v) at room temperature.

[b] Isolated yield.

[c] HI used instead of HBr.

[d] HCl used instead of HBr.

[e] NH_4Cl used instead of HBr.

[f] NH_4Br used instead of HBr.

[g] NH_4I used instead of HBr.

[h] I_2 used instead of HBr.

To generalize the optimized conditions (Tables 1 and 2), model reactions were carried out in the presence of other haloacids (HCl and HI) and their ammonium salts. Interestingly, HI afforded **2b** in quantitative yield (Table 2, Entries 7 and 8) under the optimized conditions. However, HCl, NH_4Cl, NH_4Br and NH_4I were not suitable for this transformation as the reaction was very sluggish even at elevated temperatures (60-70 °C). Thus, the optimized conditions[31] for the oxidation of thiols to disulfides can be defined as follows: 1.0 mmol of substrate, 0.2 mmol of HBr/HI, a mixture of $CHCl_3$ and DMSO in 1:1 (v/v) and 20±5 °C (Table 1, Entry 6 and Table 2, Entries 2 and 7).

With the optimized conditions in hand (Tables 1 and 2), the oxidation of various thiols was examined to explore the scope of the reaction. As can be seen from Table 3, both alkyl- and aryl thiols were readily converted to the corresponding disulfides in excellent yield. Nevertheless, sterically hindered thiols (i.e., **1c**, **1f** and **1j**) took slightly longer time to complete the reaction compared to sterically unhindered thiols (Table 3). This was not a surprise to us since influence of steric hindrance on the reaction rate is well documented in the literature.[1,2]

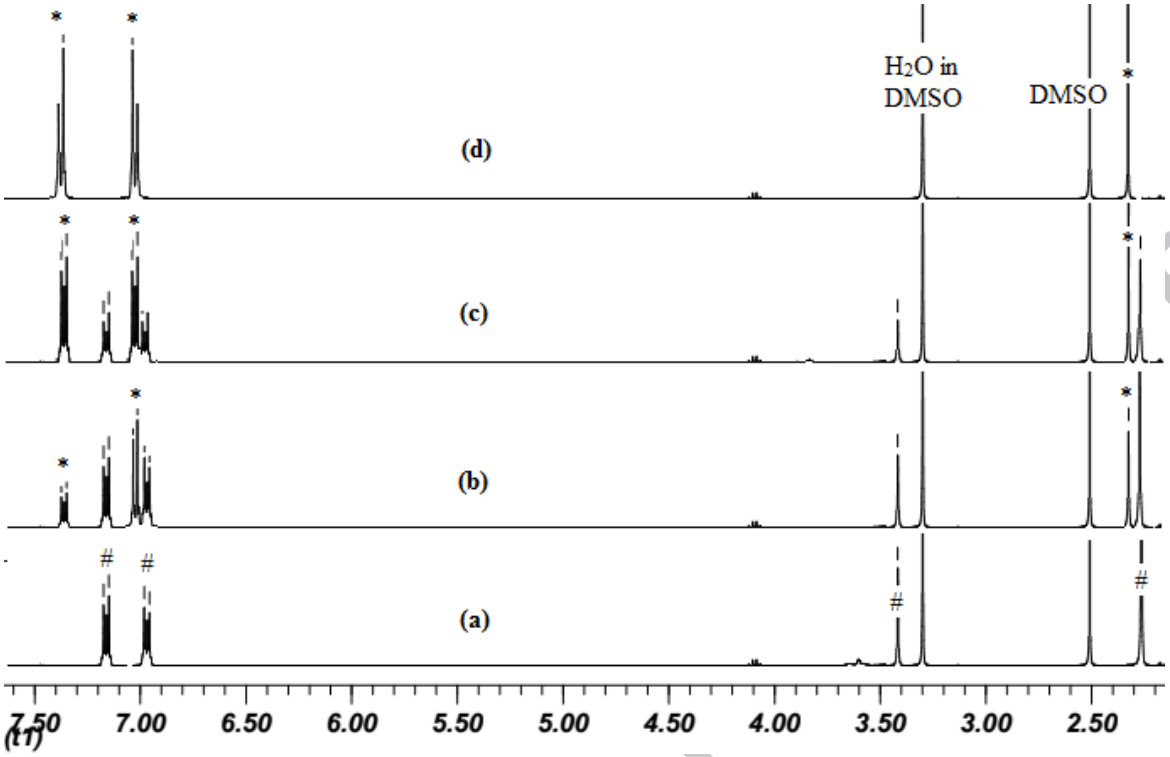
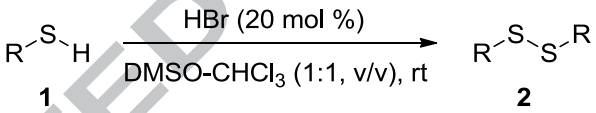
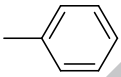
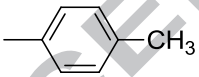
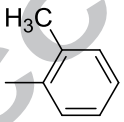
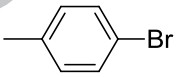
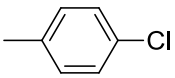
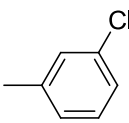
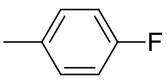
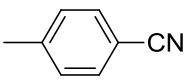
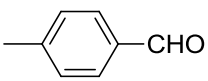
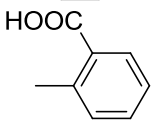
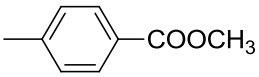
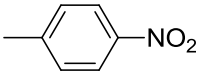
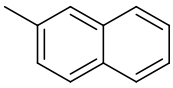
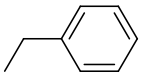
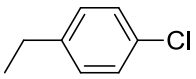
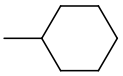
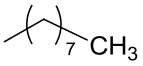
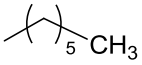
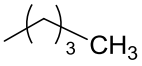
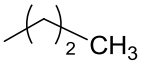
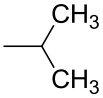
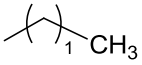


Figure 1. The ^{1}H NMR (300 MHz) spectroscopic monitoring of conversion of **1b** to **2b** at ambient conditions: (a) at beginning of the reaction, (b) after 3 h, (c) after 6 h and (d) after 8 h. Notice that new peaks (∗) corresponding to **2b** gradually appeared at 2.31, 7.08 and 7.37 ppm, while signals (#) of **1b** at 2.28, 3.41, 7.01 and 7.16 ppm have been disappeared indicating the product formation.

Table 3. Synthesis of disulfides from thiols with HBr in DMSO-$CHCl_3$ medium.[a]



Entry	R=	Substrate	Product[b]	Time (h)	Yield (%)	mp (lit. mp, °C)
1		**1a**	**2a**	7	98	57-60 (57-58)[4]
2		**1b**	**2b**	7	96	41-45 (41-43)[5]
3		**1c**	**2c**	12	88	35-39 (36-38)[4]
4		**1d**	**2d**	6	93	91-93 (94-95)[7]
5		**1e**	**2e**	7	97	72-74 (69-71)[7]
6		**1f**	**2f**	9	92	79-82 (81-82)[10]
7		**1g**	**2g**	7	89	50-53 (50-52)[4]
8		**1h**	**2h**	8	91	170-174 (171-173)[4]
9		**1i**	**2i**	8	93	99-103 (98-103)[10]
10		**1j**	**2j**	10	94	287-291 (288-290)[7]

11		**1k**	**2k**	9	92	125-127 (126-127)[4]
12		**1l**	**2l**	7	87	178-180 (180-181)[10]
13		**1m**	**2m**	6	95	136-140 (138-140)[15]
14		**1n**	**2n**	5	92	69-72 (70-71)[15]
15		**1o**	**2o**	5	93	60-63 (60-62)[15]
16		**1p**	**2p**	6	94	oil (oil)[4]
17		**1q**	**2q**	6	89	oil (oil)[4]
18		**1r**	**2r**	6	92	oil (oil)[4]
19		**1s**	**2s**	6	97	oil (oil)[4]
20		**1t**	**2t**	6	94	oil (oil)[4]
21		**1u**	**2u**	8	92	oil (oil)[4]
22		**1v**	**2v**	6	96	oil (oil)[4]

[a] All reactions were run with **1** (1.0 mmol) and HBr (0.2 mmol) in DMSO-$CHCl_3$ (1:1, v/v) at room temperature.

[b] The products were characterized by their comparison with known compounds.

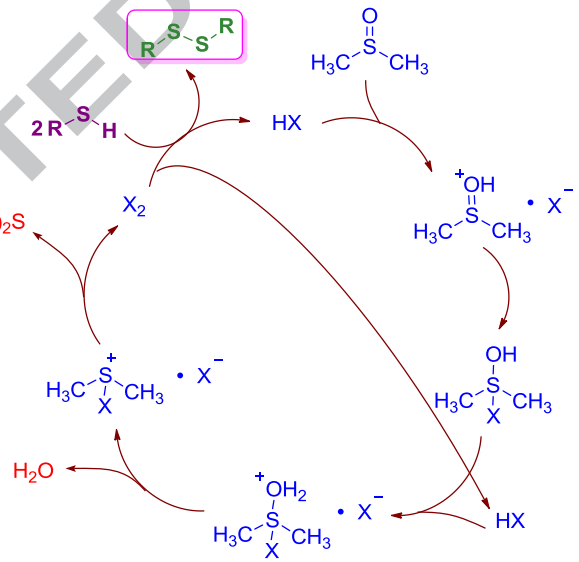


Figure 2. The proposed reaction mechanism for the synthesis of disulfides from thiols.

A working mechanism for the preparation of disulfides from thiols is outlined in Figure 2 on the basis of an earlier proposed mechanism[25,32] and the blank experiments. The blank reactions with **1b** and HX (in the absence of DMSO, Table 1, Entry 16) as well as **1b** and DMSO (in the absence of HX, Table 2, Entry 6), did not succeed indicating both HX and DMSO were played an important role in the product formation (Scheme 1). It is well-known that HX reacts with DMSO to yield halodimethylsulfonium halide,[32] which in turn afford the molecular halogen behaves as an oxidant to produce a disulfide, cf. Figure 2. The involvement of molecular halogen in the oxidation of thiols to disulfides was confirmed by performing model reactions in the presence of I_2. Indeed, expected disulfide was isolated in quantitative yield (Table 2, Entries 15-17). In addition, the formation of bromine from HBr was established by UV-Vis absorption measurements (cf. Supplementary data) as well. In the oxidation reaction (Scheme 1), simultaneously, DMSO reduced into the dimethyl sulfide. Thus, the whole process is a kind of the oxidation-reduction cycle[32] by the hydrogen halide-halogen system in DMSO leading to catalytic need of HX reagent.

In summary, a new methodology is described for the oxidation of thiols to the corresponding disulfides using 20 mol % of HBr/HI in the presence of dimethyl sulfoxide at ambient conditions. No over oxidized products were observed. A simple work-up at the end of the reaction allows product isolation in good to excellent yields. We believe that the present protocol may be employed for the synthesis of natural products and biomolecules possessing disulfides and polysulfides linkages.

Acknowledgments

P.N. gratefully acknowledges the financial support of the Department of Science & Technology (DST), India, through INSPIRE Faculty Fellowship [IFA12-CH-62]. We also thank the anonymous reviewers for their insightful comments and suggestions.

Supplementary data

Supplementary data (NMR spectral data of some selected products and UV-Vis spectra of bromine formed from hydrogen bromide) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.0000.00. 000.

References and notes

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31) *General procedure for the synthesis of symmetrical disulfides*: A mixture of thiols (1.0 mmol) and HX (0.2 mmol) in DMSO-$CHCl_3$ (5 mL, 1:1, v/v) was stirred at room temperature for respective time (Table 3). After the completion of the reaction, as monitored by TLC, the reaction mixture was diluted with 10 mL of water and extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and evaporated in a rotary evaporator under reduced pressure. A reasonably pure product obtained was further purified by recrystallization using hexane-$CHCl_3$ mixture. The purity of the compound was confirmed by melting point and NMR measurements.
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*Graphical Abstract