1,3-Dibromo-5,5-Dimethylhydantoin [DBDMH] as an Efficient and Selective Agent for the Oxidation of Thiols to Disulfides in Solution or under Solvent-Free Conditions

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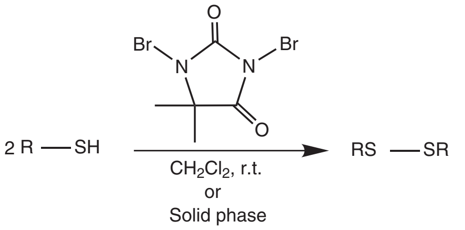
Abstract: A useful method for oxidation of various thiols to their corresponding disulfides with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in very short reaction times and mild conditions under both solution and solvent-free conditions is described.

Keyword: 1,3-dibromo-5,5-dimethylhydantoin, oxidation, thiol, disulfide

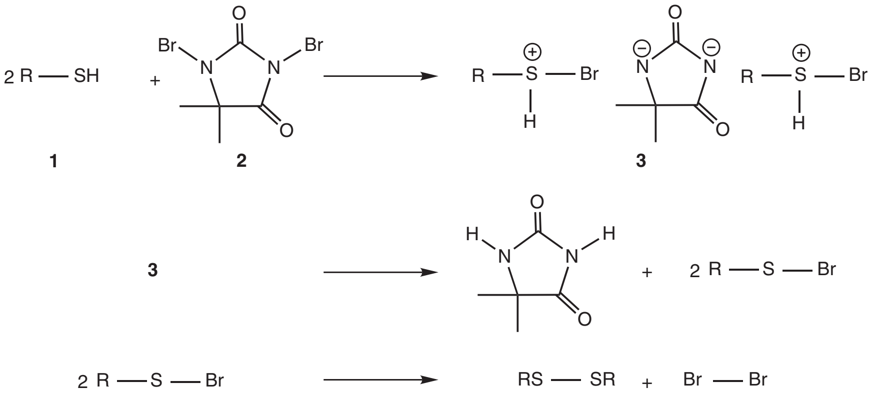
The controlled oxidative coupling of thiols to disulfides under neutral and mild conditions is of practical importance both in synthetic chemistry[1] and biochemistry (sulfur-sulfur bonds between cysteine residues stabilize three-dimensional structures of many peptides, hormones and toxins).[2] Industrially, these compounds have found wide applications as vulcanizing agents[3] for rubber and elastomers, importing them excellent tensile strength. Also, disulfides are important intermediates with many applications in organic synthesis.[4] Various oxidants, metal-assisted methods,[5] and nonmetal-containing oxidants[6] have been employed for this conversion. Most of these reagents involve toxic metal ions and solvents in protocols that lack the general applicability to thiols substrates bearing alkyl, aryl and heterocyclic moieties and are not eco-friendly. Other disadvantages of these methods are long reaction times, expensive and unstable reagents, and cumbersome work-up procedures. Thus, there is still a need for an eco-friendly methodology to synthesize aliphatic, aromatic and heterocyclic disulfides from the corresponding thiols under mild reaction conditions in a short time, using readily available, safe, stable, and cheap reagents.

During the course of our systematic study on oxidation of organic compounds with N-halo reagents,[7] we found that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is a cheap, commercially available reagent that has been used for aromatic bromination and oxidation reactions as an alternative to bromine or NBS. Therefore, we wish to report a convenient method for the effective conversion of thiols to their corresponding disulfides by using DBDMH both in solution and under solvent-free conditions, as depicted in Scheme 1.



Scheme 1

On the basis of previously reported mechanisms for the application of NCS/Me_2S[8] or NBS/Ph_3P[9] and our observation of the color of generated bromine and 5,5-dimethylhydantoin during the course of the reaction, the mechanism shown in Scheme 2 is proposed.



Scheme 2

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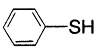
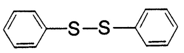
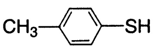
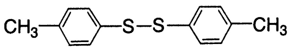
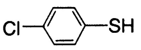
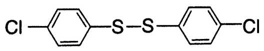
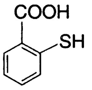
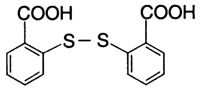
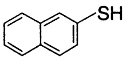
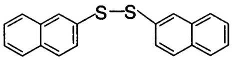
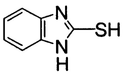
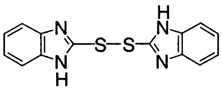
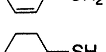
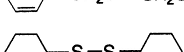
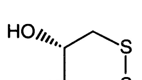
Table 1 Oxidation of Thiols to Disulfides with 1,3-Dibromo-5,5-Dimethylhydantoin (DBDMH) both in CH_2Cl_2 (**I**) and under Solvent-Free Conditions (**II**) at Room Temperature

Entry	Substrate	Product[a]	Time		Molar ratio Oxid/Sub		Yield (%)		Mp	Lit.Mp
			I (h)	**II** (min)	I	II	I	II	(°C)	(°C)
1			1	1	1	1.5	93	90	60–61	58–60[6h]
2			0.8	1	1	1.5	94	90	44–45	45–46[6h]
3			1.2	1	1	1.5	93	91	69–71	72–74[5h]
4			5	10	1	1.5	94	90	287–289	286[6h]
5			1.5	1	1	1.5	90	90	143–145	144–145[5e]
6			4	8	1	1.5	92	89	198–200	200–201[6h]
7			2.2	2	1	1.5	93	88	70–72	69–70[6f]
8			2.4	3.5	1	1.5	94	90	126–128	124–129[5e]
9	$CH_3(CH_2)_6CH_2SH$	$CH_3(CH_2)_6CH_2SSCH_2(CH_2)_6CH_3$	3	2.5	1	1.5	88	87	Oil	Oil[5h]
10	$CH_3(CH_2)_2CH_2SH$	$CH_3(CH_2)_2CH_2SSCH_2(CH_2)_2CH_3$	3	3	1	1.5	89	87	Oil	Oil[5h]
11	$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2SSCH_2CH_2COOH$	3.5	5	1	1.5	90	87	156–158	157–15[10]
12	$HOCH_2CH_2SH$	$OHCH_2CH_2SSCH_2CH_2OH$	3.2	4	1	1.5	87	87	Oil	Oil[5h]
13			2.8	3	1	1.5	90	88	131–133	130–132[6i]

[a] All products were characterized by comparison of their spectral data (^1H NMR and IR spectroscopies) and physical properties with those of authentic samples.

The results of this study are summarized in Table 1. As shown in the Table 1, aliphatic (cyclic and acyclic), aromatic (with electron-withdrawing and electron-releasing groups), benzylic, and the heterocyclic thiols were oxidized to the corresponding disulfides with high yield in the presence of DBDMH in CH_2Cl_2 or solvent-free conditions. Also, oxidations of some of the substrates were carried out in very short times under solvent-free conditions. The oxidation of thiols to disulfides without over-oxidation of disulfides, oxidation of the SH functional group in the presence of a hydroxy group (entries 12 and 13) and the oxidation of aromatic thiols to their corresponding disulfides without bromination of aromatic rings (entries 1–7) demonstrate the chemoselectivity of this method.

In conclusion, the advantages of DBDMH for oxidation of thiols are as follows:

i) The use of DBDMH provides a remarkably simple, mild, very rapid, selective, general and practical procedure for the high-yielding preparation of a variety of disulfides.

ii) DBDMH is an excellent, cheap and conveniently handled reagent, so it is better than NBS for the oxidation of organic compounds.

Oxidation of Thiol in Solution; General Procedure

To a solution of thiol (1 mmol) in CH_2Cl_2 (10 mL) was added DBDMH (1 mmol), after 30 s the mixture turned red. The mixture was stirred vigorously at r.t. for the time indicated in Table 1. The reaction was monitored by TLC (hexane–EtOAc, 4:1). After completion of the reaction, CH_2Cl_2 (20 mL) was added and the reaction mixture was extracted with sat. $NaHCO_3$ (2 × 20 mL) and dried over anhyd $CaCl_2$ (1 g). Evaporation of the solvent, followed by recrystallization or chromatography on silica gel, afforded pure disulfide in 87–94% yield.

Oxidation of Thiols to Disulfides under Solvent-Free Conditions; General Procedure

The oxidizing agent (1.5 mmol) was added to thiols (1 mmol) slowly in a mortar at r.t. The mixture turned deep red and the reaction was completed after very short time (Table 1). To the resulting solid mixture, CH_2Cl_2 was added and the mixture was extracted with sat. $NaHCO_3$ (2 × 20 mL) and dried over anhyd $CaCl_2$ (1 g). Evaporation of the solvent, followed by recrystallization or chromatography on silica gel, afforded pure disulfide in 87–90% yield.

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