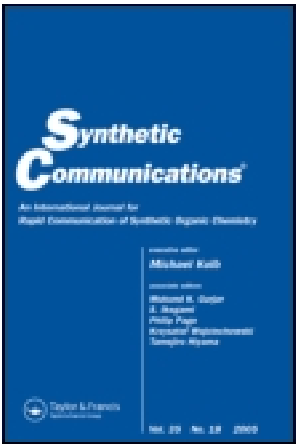

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Simple, Extremely Fast, and High-Yielding Oxidation of Thiols to Disulfides

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Simple, Extremely Fast, and High-Yielding Oxidation of Thiols to Disulfides

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Abstract: Results of oxidation of thiols to disulfides with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) are described. A simple addition of 0.20–0.25 mol equivalent of solid DBDMH to thiol in chloroform at room temperature yielded the disulfides in excellent yield. The reaction is extremely fast and gave no other oxidized side products.

Keywords: 1,3-Dibromo-5,5-dimethylhydantoin, disulfides, oxidation of thiols

Disulfides play important roles in the biological and chemical processes.[1] Oxidation of thiols is the most exploited method for disulfide synthesis mainly because a large number of thiols are commercially available and/or are easily synthesized. Reagents such as cerium(IV) salt,[2] permanganates,[3] transition metal oxides,[4] air in combination with transition-metal catalyst,[5] sodium perborate,[6] ferric chloride,[7] sodium chlorite,[8] nitric oxide,[9] halogen peroxide,[10] halogens,[11] and bromine supported on hydrated silica gel,[12] among others, have been utilized for oxidation of thiols to disulfides.

Here we wish to report an extremely fast and high-yielding method for the preparation of disulfides by oxidation of thiols. We found 1,3-dibromo-5,5-dimethylhydantoin particularly suitable for oxidation of thiols

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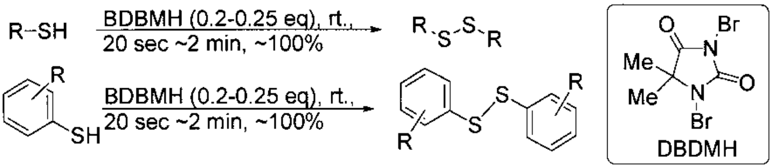
to disulfide as compared with other oxidants such as halogen oxidants, Br_2, I_2 (Scheme 1).

Although DBDMH is mainly used for the bromination of aromatics, we found that it oxidized thiols to disulfides nicely and only 0.20–0.25 mol equiv. of DBDMH is sufficient for the oxidation. Commercially available, cheap, and stable, solid DBDMH is very easy to handle and calculative amounts of it can be used particularly for small-scale reactions. In this method, no other oxidized side products have been detected by gas chromatograph-mass spectroscopy (GC-MS) analysis even when excess DBDMH is used. For other oxidizing agents, sometimes oxidized side products are formed.

Table 1 summarizes the results of the oxidation of various thiols to disulfides. It is noted that for most of the thiols, the yield was 100% or nearly 100% (lowest yield is 96.6%, entry 4). For comparison, we carried out a similar oxidation reaction by molecular iodine (entries 3, 4). Although the yield of disulfide **3b** from 2-methyl thiophenol **3a** (entry 3) looked good, GC-MS analysis showed that the product was a mixture of the desired disulfide, unconverted thiol, and an unknown compound at the ratio of 5.6:1:0.85, which was difficult to separate over silica-gel column chromatography. So, the net yield of **3b** is 77%. Similarly, 2-trifloromethyl thiophenol **4a** (entry 4) gave the disulfide **4b** in 69% yield that was found to be the 1:1 mixture of thiol and disulfide, that is, the net yield of **4b** is only 34.5%.

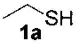
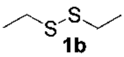
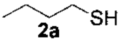
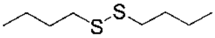
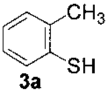
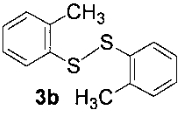
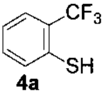
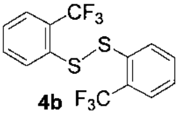
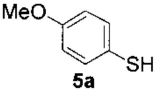
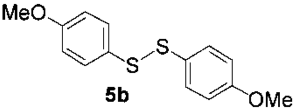
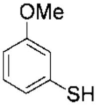
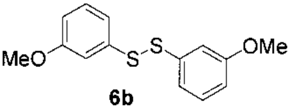
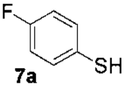
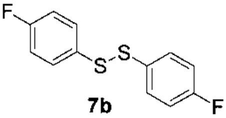
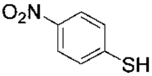
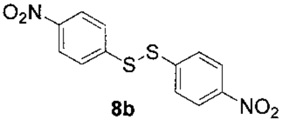
We also checked the oxidation of thiols using the similar N-halogenated compound, N-bromosuccinamide (NBS). For NBS, the result was somewhat irregular. Although with NBS, thiol **3a**, for example, gave 93% yield of disulfide **3b** in 10 min, but thiol **7a** took 3 h to give disulfide **3b** in 95%. In the case of DBDMH, besides the higher yield, all reactions were completed within 1–3 min. On the other hand, although 0.50 equiv. of NBS was used for **7a**, for thiol **3a** oxidation was incomplete even after several hours with 0.50 equiv. of NBS, and 1.00 equiv. of NBS was necessary for completion of the reaction. In the case of DBDMH, only 0.20–0.25 equiv. was sufficient for all the thiols.

Usually thiols are oxidized to corresponding disulfides in higher yields. The efficiency of a method can be judged by its simplicity, reaction time, purity of product, easy access and stability of the reagents, and of course the yield. If these results are compared to the reported literature, it is found that this method offered the oxidized product in higher yields or equal to



Scheme 1.

Table 1. Oxidation of thiols to disulfides

Entry	R-SH	Product, R-S-S-R	Reaction condition	Yield
1	 **1a**	 **1b**	DBDMH (0.20 eq.), <1 min	100%
2	 **2a**	 **2b**	DBDMH (0.20 eq.), <1 min	98%
3	 **3a**	 **3b**	DBDMH (0.24 eq.), 1 min I_2, (0.50 eq.), 4 h NBS (1.00 eq.[b]), 2h	100% 96%[a] 93%
4	 **4a**	 **4b**	DBDMH (0.24 eq.), 3 min I_2, (0.50 eq.), 4 h	96% 69%[c]
5	 **5a**	 **5b**	DBDMH (0.25 eq.), 5 min	100%
6	 **6a**	 **6b**	DBDMH (0.24 eq.), 1 min	99.6%
7	 **7a**	 **7b**	DBDMH (0.25 eq.), 1 min NBS (0.50 eq.), 10 min	100% 95%
8	 **8a**	 **8b**	DBDMH (0.25 eq.), 1 min	100%

[a] GC-MS indicated the mixture of thiol, disulfide, and an unknown at a ratio of 1:5.6:0.85

[b] With 0.50 equiv. of NBS, the reaction was incomplete even after several hours.

[c] GC-MS indicated the mixture of thiol, disulfide, and unknown at a ratio of 1:1:0.1

the one of the highest reported yields. For instance, the reported yield is 41%[13]–92%[12] for the disulfide **1b**, 22–53%[13] for **2b**, and 26%[14]–88%[15] or 95%[16] for **3b.** Similarly, for disulfide **5b** lower yield is 14%[17]–73%[18] and higher is 97%.[16] So, we can say, besides the simplicity of our method, it provided a higher yield than (or at least equal to) that of the reported highest yields. On the other hand, all the higher yields mentioned involved the use of complicated methods, catalysts, complex oxidizing agents, or long reaction times.

In conclusion, we can say that it is an excellent method because of the excellent yield of disulfides from a wide variety of thiols, mild reaction conditions, simplicity of the procedure, very fast reaction time, and the formation of a single desired product.

EXPERIMENTAL

General

All reactions were carried out in ordinary chloroform at room temperature. The progress of the reactions was monitored by the color change and GC-MS. Flash chromatography was performed on silica gel (Merck, 60N, spherical, neutral, 40–50 mesh). IR was recorded on a Thermo Nicolet Avatar 360T2 instrument using attenuated total reflection (ATR). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded by JEOL AL 300 instrument. GC-MS was studied in a SHIMADZU GCMS-QP5000 instrument.

A typical procedure is as follows: Solid DBDMH (0.20–0.25 mol equiv.) was added to thiol in chloroform (ordinary, not dry) with stirring at room temperature. Upon addition of DBDMH, the color of the reaction mixture became brown or light yellow. The completion of the reaction was marked by the disappearance of the yellow color and was confirmed by GC-MS measurement. For most cases the reaction was completed instantaneously, whereas for other thiols it took 1–3 min. GC-MS analysis indicated the presence of no other side product except the solid side product derived from DBDMH. This solid substance can be separated easily by simple filtration or by passing it through a short silica-gel column to yield the pure disulfide. ^{1}H NMR and GC-MS indicated the high purity of all disulfides.

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