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Oxidation of thiols to disulfides with molecular bromine on hydrated silica gel support

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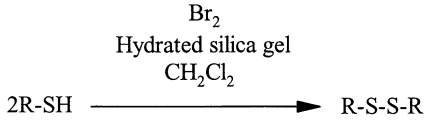
Abstract—Results of oxidation of thiols to disulfides with molecular bromine on silica gel solid support are reported. The procedure utilizes organic media and does not require a base to neutralize HBr by-products to suppress acid promoted side reactions. Utilization of silica gel support simplifies work up and product isolation. © 2002 Elsevier Science Ltd. All rights reserved.

Disulfides play important roles in 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) salts,[2] permanganates,[3] transition metal oxides,[4] air in combination with transition metal catalysts,[5] sodium perborate,[6] ferric chloride,[7] sodium chlorite,[8] nitric oxide,[9] hydrogen peroxide[10] and halogens,[11] among others have been utilized for oxidation of thiols to disulfides.

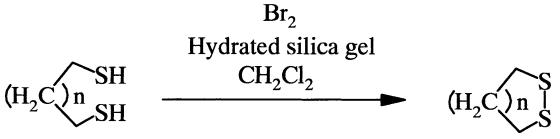
Halogens offer a particularly desirable choice because they are inexpensive. However, there are disadvantages associated with halogen reagents when traditional aqueous–organic biphasic reaction media is employed. The reported halogen oxidations of thiols to disulfides are cumbersome, non-selective, and are not safe from practical point of view. Potential exposure to the toxic hydrogen halides or the halogens themselves limits utility of these oxidants. The most significant disadvantage results from hydrogen halide by-products formed in the reaction. If the hydrogen halides are not removed as they are formed, acid promoted side reactions complicate the oxidation reaction.

Various procedures have been reported to avoid acid-promoted side reactions and potential hazards involved in this reactions.[11] The later procedures include phase transfer conditions employing a base to neutralize hydrogen halides produced in the reactions[11b,c] and oxidation of thiols in the absence of a solvent.[11a] In the solvent less reaction conditions, HBr is neutralized by passing it through an alkaline solution. The potential leak of toxic HBr gas and the highly exothermic nature of this reaction make this procedure unsafe. Phase transfer procedure requires cumbersome extraction of the product from water. A number of amine complexes of bromine reported in the literature revealed some success in suppressing undesired acid promoted side reaction.[11d,12] However, preparation of these complexes is tedious. We have developed a simpler as well as safer procedure for oxidation of thiols to disulfides utilizing inexpensive halogens that will benefit synthetic organic chemists.

We have reported elsewhere a method for oxidation of sulfides to sulfoxides with molecular bromine on hydrated silica gel support.[13] This procedure does not require the presence of a base in the reaction mixture to neutralize the hydrogen bromides produced as a



Scheme 1.



Scheme 2.

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Table 1. Oxidation of thiols **1** to disulfides **2**

	Thiols (**1**)	Disulfide (**2**)	Yield (%)[a]
a	Ethanethiol	Diethyldisulfide	92
b	*sec*-Butylthiol	Di-*sec*-butyldisulfide	99
c	Isopropylthiol	Diisopropyldisulfide	98
d	*tert*-Butylthiol	Di-*tert*-butyldisulfide	97
e	Butylthiol	Dibutyldisulfide	99
f	Cyclohexylthiol	Dicyclohexyldisulfide	95
g	Octyllthiol	Dioctyldisulfide	99
h	2-Hydroxyethylthiol	Bis[2-hydroxyethyl] disulfide	98
i	3-Phenylpropylthiol	Bis-3-phenylpropyldisulfide	92
j	Benzylthiol	Dibenzyldisulfide	97
k	Phenylthiol	Diphenyldisulfide	93
l	Furanylthiol	Difuranyldisulfide	87
m	*p*-Methoxyphenylthiol	Bis[*p*-methoxyphenyl]disulfide	98
n	*p*-Chlorophenylthiol	Bis[*p*-chlorophenyl]disulfide	97
o	*p*-Tolylthiol	Di-*p*-ditolyldisulfide	98
p	2-Pyridylthiol	Mixture of products	
q	Allylthiol	Mixture of products	
r	1,3-Propanedithiol	1,2-Dithiolane	87
s	1,4-Butanedithiol	1,2-Dithiane	96
t	Dithiothreitol	*trans*-1,2-Dithiane-4,5-diol	94
u	1,5-Pentanedithiol	1,2-Dithiepane	86
v	1,6-Hexanedithiol	1,2-Dithiacyclooctane	91
w	1,8-Octanedithiol	1,2-Dithiacyclodecane	86

[a] Isolated yields.

byproduct. We postulated that the silica gel removes the hydrogen bromides formed in the reaction, and makes it unavailable for side reactions. We have found that this procedure is suitable for rapid and efficient oxidation of thiols to the disulfides (Scheme 1), and dithiols to the disulfides (Scheme 2).

This paper reports the results of the oxidation of thiols to disulfides utilizing molecular bromine on hydrated silica gel. The greatest advantages of this procedure arise from its employment of non-aqueous media. The silica gel acts as both a heat sink and as HBr scavenger. No significant amounts of acid-catalyzed side reaction products are found. No rise in reaction temperature is observed. A simple filtration at the end of the reaction followed by removal of the solvent from the filtrate allows product isolation. High yields and high purity in most cases indicated by both the NMR and TLC analysis.

We have been able to oxidize a wide variety of thiols to the corresponding disulfides in excellent yields. The results of attempted oxidation reactions of these thiols are presented in Table 1. Both alkyl and aryl thiols gave similar results. As expected, sterically hindered thiols took slightly longer time to complete the reaction compared to sterically unhindered thiols. Impure products were purified utilizing radial chromatography. Hydroxyl, methoxy, benzylic and halogen functionalities do not interfere with the oxidation of thiol group (**1h–j**, **1l–o**, **1t**). This procedure produced good yields of dithiols from the furfural thiol. 2-Pyridylthiol **1p** gave us a mixture of products that contained up to 45% of dipyridyldisulfide. Allylthiol **1q** failed to produce acceptable yield of diallyldisulfide. Addition of bromine across the double bond of allylthiol complicated the oxidation reaction. This was not a surprise to us since addition of bromine across carbon–carbon double bond is well documented in the literature. The most notable feature is that we have been able to apply this procedure successfully in the oxidation of dithiols to cyclic disulfides. Large ring disulfides are difficult to synthesize due to competing inter molecular reaction. The intramolecular reaction produces cyclic disulfides whereas the intermolecular reactions yield oligomers.

Previously reported procedures for large ring disulfides synthesis from dithiols produced poor to moderate yield.[12b,15] Also, most of these methods employed high dilution techniques to avoid intermolecular reaction. In contrast, our procedure produces excellent yields of large ring disulfides without requiring any extra precautions. We believe dispersion of dithiols over the large surface area provided by the silica gel avoids intermolecular reactions. Our procedure produced excellent yields of cyclic disulfides **2r–2w**.[14]

In conclusion, the method for oxidizing thiols with molecular bromine on hydrated silica gel support reported in this paper is a simple, efficient, and mild procedure for the conversion of thiols to the disulfides and dithiols to cyclic disulfides.

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14. The following oxidation procedure for ethylthiol is representative of all thiols presented in Table 1. Water (2.5 mL) was added drop-by-drop using a syringe to a stirred 5.0 g of flash chromatography grade silica gel in a 100 mL round-bottomed flask fitted with a septum. Stirring continued until a free flowing powder was obtained (takes only a few minutes). Methylene chloride (25 mL) was added to the flask followed by the addition of a solution of ethanethiol **1a** (250 mg, 4.02 mmol) in methylene chloride (5 mL). A solution of bromine in methylene chloride (1.16 M, 3.50 mL, 4.06 mmol) was added drop wise from a syringe to the reaction mixture. The characteristic brown color of the bromine disappeared as soon as the bromine solution came in contact with the reaction mixture in the flask. However, when a faint brown color persisted (indication that the reaction was over) addition of bromine solution ceased and the reaction mixture was filtered through a sintered glass funnel. The solid residue was washed with methylene chloride (60 mL). Methylene chloride was removed under vacuum to recover the product **2a**. NMR and IR analysis indicated this clear oil (240 mg, 92% yield) as pure diethyl disulfide.
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