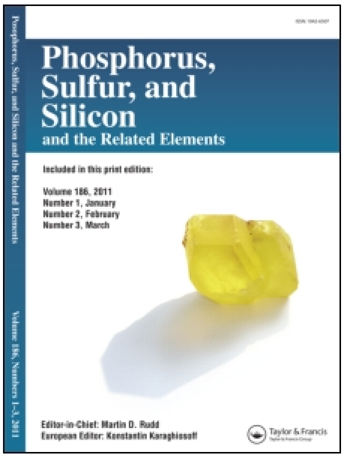

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Conversion of Thiols to Disulfides Using a Hexamethylenetetramine-Bromine Complex

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Conversion of Thiols to Disulfides Using a Hexamethylenetetramine-Bromine Complex

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Hexamethylenetetramine-bromine complex, a yellow-orange, very stable homogeneous solid, affects a mild and fairly general conversion of thiols to disulfides.

Keywords Disulfide; hexamethylenetetramine-bromine complex; oxidation; thiol

INTRODUCTION

The conversion of thiols to the corresponding disulfides (oxidative S–S coupling) is an important reaction and many stoichiometric reagents such as dichromates,[1] chlorochromates,[2] manganese dioxide,[3] diethyl azodicarboxylate,[4] halosilane-chromium trioxide,[5] nickel peroxide,[6] chromium peroxide,[7] tetrabutylammonium cerium(IV) nitrate,[8] sodium perborate,[9] and silver trifluoromethanesulfonate,[10] which have been reported to be effective oxidants for it. However, the susceptibility of the disulfide bond to further oxidation narrows the choice of the reagent for the oxidation of thiols to disulfides in good yields. The discovery of oxidants that are able to achieve the thiol-to-disulfide conversion in a high yield with a variety of substrates has a key importance for the development of the synthesis of complex organic compounds. The oxidation of alcohols by *N*-halogenoamines[11–14] and *N*-halogenoamides[15] has been

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reported, and these reagents are important as practical, stable sources of active halogen, which can oxidize thiols to disulfide systems.

RESULTS AND DISCUSSION

In this article, we report the oxidation of thiols by a hexamethylenetetramine-bromine complex. Our results are shown in Table I. This solid, an easily handled and storable reagent, allows for the conversion of thiols to disulfides. These reactions share the virtues of ease of operation; simplicity of product isolation; formation of products in high yields; and absence of side reactions, including over-oxidation and halogenation of the products. The conditions are adaptable to both small- and fairly large-scale operation.

The hexamethylenetetramine-bromine complex can be readily prepared by adding bromine to a chloroform solution of the amine. This homogeneous, non-hygroscopic solid is very stable at r.t., is not affected by ordinary exposure to light, air, or water; and has no offensive odor of bromine or amine. The reagent is transformed during the reaction to easily removable products and presents a convenient alternative to other *N*-halogenoamines.

All reaction products were analyzed by IR and ^{1}H NMR spectroscopy and gas chromatography and were found to be identical with pure authentic samples.

In conclusion, a hexamethylenetetramine-bromine complex is an oxidant, which promises to be economical, convenient, and efficient for a wide variety of cases.

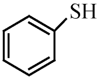
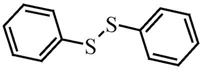
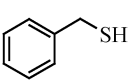
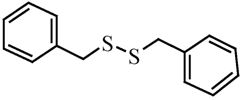
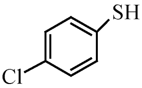
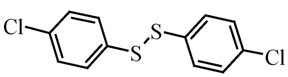
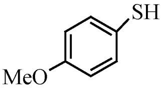
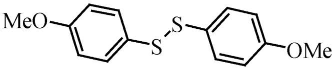
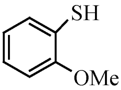
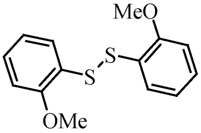
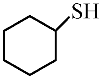
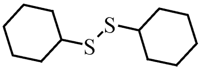
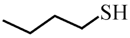
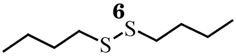
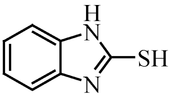
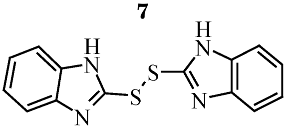
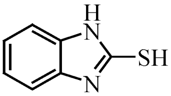
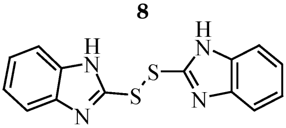
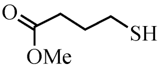
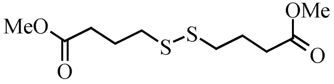
EXPERIMENTAL

All products are known compounds and were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were recorded as films, or as KBr pellets on a Shimadzo 460 IR spectrometer. Proton NMR spectra were recorded at 300 MHz with a Bruker 300-AVANCE FT-NMR instrument with $CDCl_3$ as a solvent and Me_4Si as an internal standard. A hexamethylenetetramine-bromine complex was prepared as previously described.[14] The reagents and solvents used in this work were obtained from Fluka and used without further purification.

The Oxidation of Methyl 4-Sulfanylbutanoate to Methyl 4-[4-(Methyloxy)-4-oxobutyl] Disulfanyl-Butanoate (10): Typical Procedure

To a mixture of hexamethylenetetramine-$2Br_2$ (4.6 g, 10 mmol, 15 mmol active Br_2), water (30 mL), and dichloromethane (30 mL) in a 250-cm^3

TABLE I The Oxidation of Thiols to Disulfides by a Hexamethylentetramine-Bromine Complex in Dichloromethane-Water (1:1) at 30°C

Substrate	Product	Reaction Time (min)	Yield (%)[a]
	 **1**	8	96
	 **2**	5	96
	 **3**	10	94
	 **4**	8	94
	 **5**	10	94
	 **6**	15	92
	 **7**	12	92
	 **8**	2	98
	 **9**	5	96
	 **10**	14	96

[a] Yields refer to the isolated product: All products were identified by comparing their IR, ^{1}H NMR, and TLC with those of authentic samples.

round-bottomed flask was added with stirring a mixture of methyl 4-sulfanylbutanoate (20 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at r.t. until the yellow color of the complex disappeared. The organic layer (Solution A) was separated, the remaining aqueous layer was washed twice with 20-mL portions of CH_2Cl_2, and the washings were added to the organic layer. The CH_2Cl_2 solution was washed successively with diluted (1%) aqueous HCl, water, diluted (3%) aqueous sodium carbonate, and water. The dried ($MgSO_4$) solution was concentrated to afford **10**, which was of good purity without further purification needed. IR (KBr) $\upsilon_{\max}$ (cm^{-1}): 1730 (C=O), 1428, 1354, 1011. ^1H NMR ($CDCl_3$) $\delta = 1.35$–1.39 (4 H, m, CH_2), 2.81–3.00 (8 H, m, OCH_2 and SCH_2), 4.03 (6 H, s, OMe). - ^{13}C NMR ($CDCl_3$): $\delta = 29.3$ (CH_2), 32.8 (OCH_2), 33.6 (SCH_2), 51.6 (OMe), 172.4 (C=O) ppm.

Accordingly, compounds **1–9** were prepared in 92–98% yields (see Table I). ^1H and ^{13}C NMR spectra of the crude reaction mixtures clearly indicated the formation of the disulfides. Any product other than disulfides could not be detected by NMR spectroscopy.

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