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

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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 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

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