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Synthesis of cetyltrimethylammonium tribromide (CTMATB) and its application in the selective oxidation of sulfides to sulfoxides

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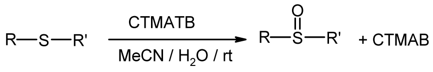
Abstract—The bright yellow crystalline cetyltrimethylammonium tribromide (CTMATB) reagent has been synthesized from the reaction of CTMAB and KBr with $H_2MoO_4 \cdot H_2O$, H_2O_2 and H_2SO_4 in the molar ratio 1:2:0.01:4:0.93. CTMATB selectively oxidizes a variety of dialkyl and alkyl aryl sulfides to the corresponding sulfoxides in high yields under mild conditions. © 2003 Elsevier Science Ltd. All rights reserved.

Owing to their importance as intermediates in organic synthesis[1] and their key role in enzyme activation,[2] sulfoxides are much sought after. Consequently, selective oxidation of sulfides to sulfoxides has been a challenge for many years. Since the first reported synthesis of sulfoxides by Maercker in 1865, a number of methods have been developed for the transformation of sulfides to sulfoxides.[3] Unfortunately, most of the methods use hazardous, toxic reagents[4] or complex reaction procedures[5] accompanied by overoxidation to the sulfone or other unwanted side products.[6] Molecular bromine might serve as a good alternative but its use has been restricted because of it being expensive, toxic and environmentally unfriendly, and also because it contaminates the main product with the formation of side products such as sulfonic acids, sulfinic acids, bromo substituted sulfides and sulfoxides.[7] Extension of the Br_2 oxidation methodology to aromatic sulfides resulted in the competitive aromatic electrophilic substitution of bromine along with electrophilic attack on sulfur, thereby affording unwanted products along with low yields of the target molecules. Sodium metaperiodate, $NaIO_4$, might be a good choice for the oxidation of sulfides to sulfoxides[8] but for it being prohibitively expensive. Furthermore, the preparation and recycling of the reagent are both very difficult. In view of the above a protocol is required for the selective oxidation of sulfides to sulfoxides in a clean and cost effective manner under mild conditions. Most relevantly, recent work has demonstrated that vanadium bromoperoxidase (VBrPO)[9] oxidizes sulfides to sulfoxides in the presence of hydrogen peroxide wherein the tribromide (Br_3^-) formed in situ has been suggested to be responsible for the sulfide oxidation. Taking cues from this and being inspired by positive results of the reactivity of a newly developed tribromide reagent, cetyltrimethylammonium tribromide (CTMATB),[10,11] it was envisaged that CTMATB might be suitable for sulfide oxidation (Scheme 1). In this paper the first clean synthesis of CTMATB is disclosed and its efficacy for the selective oxidation of sulfides to sulfoxides in very good yields under mild conditions is reported.

The synthesis[12] of the reagent is based on the peroxomolybdenum-catalyzed oxidation of bromide to tribromide (Br_3^-) followed by precipitation with the cetyltrimethylammonium cation. A peroxomolybdenum intermediate is generated in situ from the interaction of MoO_4^{2-} with H_2O_2. CTMATB has a very long shelf life and is environmentally acceptable as a reagent. The reagent so prepared has been found to oxidize a variety of sulfides to sulfoxides.[13] The reaction is generalized through entries 1–10 as shown in Table 1.



where R =R'= alkyl, aryl

Scheme 1.

Keywords: cetyltrimethylammonium tribromide; new reagents; selective oxidation; sulfoxide.

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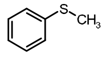
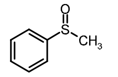
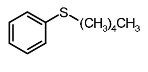
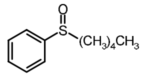
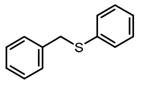
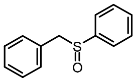
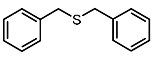
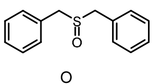
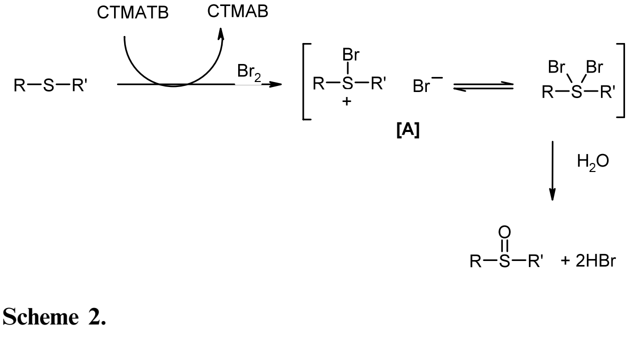
Table 1. Oxidation of sulfides to sulfoxides using CTMATB

Entry	Substrates	Time (h)	Products	% Yield*
1		12		93
2		12		95
3		20		94
4		2		92
5	$C_{18}H_{37}SC_2H_5$	2	$C_{18}H_{37}\overset{\overset{O}{\|}}{S}C_2H_5$	90
6	$HOC_2H_4SC_5H_{11}$	6	$HOC_2H_4\overset{\overset{O}{\|}}{S}C_5H_{11}$	85
7	$AcOC_2H_4SC_2H_5$	2	$AcOC_2H_4\overset{\overset{O}{\|}}{S}C_2H_5$	89
8	CH_3SCH_3	2	$CH_3\overset{\overset{O}{\|}}{S}CH_3$	78
9	$C_{16}H_{33}SC_2H_5$	2	$C_{16}H_{33}\overset{\overset{O}{\|}}{S}C_2H_5$	95
10	$C_8H_{17}SC_5H_{11}$	2	$C_8H_{17}\overset{\overset{O}{\|}}{S}C_5H_{11}$	87

* Yields refer to isolated yields. The compounds were characterized by ^{1}H NMR, ESMS and IR spectroscopy and by comparison with the literature.

Against the backdrop of the reagent acting as a brominating agent[10b] for aromatics and olefins as well as a deprotecting agent[11a] for dithioacetals and as a protecting/deprotecting agent for carbonyl-1,3-oxathiolane interconversion, it is believed that the active species in these reactions is molecular bromine generated in situ which in turn acts as an electrophile. Importantly, the amount of the active species can be tuned by regulating the amount of reagent, an operation that is rather difficult in the direct use of liquid bromine or a bromine solution. An electrophilic attack of bromine on sulfur then leads to the intermediate [**A**], which is then hydrolyzed by water to give the corresponding sulfoxide as shown in Scheme 2.

It is evident from the results summarized in Table 1 that the oxidation of dialkyl sulfides is easier than alkyl aryl sulfides, which can be understood in terms of the +I and −I effects of the alkyl and aryl groups, respectively. The +I effect of an alkyl group makes the sulfur atom more nucleophilic and hence comparatively more reactive under the present experimental conditions.



Scheme 2.

In conclusion, we have provided a cleaner synthesis of a newly developed reagent cetyltrimethylammonium tribromide, CTMATB, based on the oxidation of bromide by a peroxometal intermediate, and developed a selective, mild and high yielding method for the oxidation of sulfides to sulfoxides using CTMATB as the oxidizing agent. Under these conditions functional groups such as hydroxyl and acetate remain unaffected.[14] The by-product cetyltrimethylammonium bromide (CTMAB) can be recycled to give CTMATB thereby rendering the protocol economic. The results obtained so far suggest that the new reagent is highly suitable for the selective transformation of sulfides to sulfoxides, which is otherwise rather difficult to achieve, and also that the protocol might serve as a method for similar types of oxidations.

Acknowledgements

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12. Synthesis of cetyltrimethylammonium tribromide: A solution of 5.2 g (43.7 mmol) of KBr in 20 mL (20 mmol) of 1 M H_2SO_4 was added to a clear light yellow solution of 0.04 g (0.22 mmol) of $H_2MoO_4 \cdot H_2O$ in 10 mL (88.2 mmol) of 30% H_2O_2. The resulting solution was then added to a solution of 7.9 g (21.7 mmol) of CTMAB in 75 mL of water in portions with stirring to afford a deep yellow solution. This was stirred for ca. 2 h in an ice bath and then the bright yellow colored crystalline CTMATB which had precipitated was separated by suction filtration, washed three or four times with ice cold water (12 mL) and finally dried in vacuo over fused $CaCl_2$. The yield was 9.9 g (87%) and the compound analyzed; mp 87–88°C (DSC onset 87°C); UV–vis: 269, 385 nm; IR: 203s (νas, Br-Br), 152s (νs, Br-Br); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J=6.8$ Hz, 3H, -CH_3), 1.27 (m, 28H, -CH_2-), 1.67 (m, 2H, -CH_2-), 3.36 (s, 9H, 3 -N-CH_3), 3.49 (t, $J=8.4$ Hz, 2H, -N-CH_2-). Anal. calcd for $C_{19}H_{42}Br_3N$: C, 43.53; H, 8.08; N, 2.67. Found: C, 43.09; H, 7.99; N, 2.74.
13. General procedure for the oxidation of sulfides to sulfoxides: Methyl phenyl sulfide (0.21 g, 1.69 mmol) in a mixed acetonitrile (2 mL)–water (1 mL) solvent was reacted with CTMATB (1.06 g, 2.02 mmol) under stirring at room temperature for 12 h. The reaction was monitored by TLC and GC and no overoxidation was detected. On completion of the reaction, acetonitrile was removed under reduced pressure and 7 mL of water added. The product was extracted with ethyl acetate, dried over Na_2SO_4 and then evaporated to dryness, while the aqueous layer was retained for recovery of CTMAB. In order to remove any traces of CTMAB, the product was transferred to a silica gel (60–120 mesh) column and eluted with ethyl acetate: hexane (1:8). Methyl phenyl sulfoxide was isolated as a liquid in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (s, 3H, -CH_3), 7.55 (m, 3H, aromatic), 7.64 (m, 2H, aromatic). IR: 2989, 1091, 1051 cm^{-1}; ESMS: (M^++1) 141. The aqueous layer containing CTMAB was concentrated by evaporation until a white crystalline compound was obtained. The CTMAB thus recovered was recycled to CTMATB following the described procedure.[12]
14. (a) *n*-Pentyl-2-hydroxyethyl sulfoxide: ^{1}H NMR (300 MHz): δ 0.92 (t, $J=6.9$ Hz, 3H, -CH_3), 1.41 (m, 4H, 2-CH_2-), 1.77 (m, 2H, -CH_2-), 2.89 (m, 4H, -CH_2SOCH_2-), 4.10 (m, 2H, -CH_2-O-); IR: 3370, 2965, 2924, 2868, 1475, 1024, 1034, 748 cm^{-1}; ESMS: (M^++1) 165.
    (b) 2-Ethylsulfinylethyl acetate: ^{1}H NMR (300 MHz): δ 1.38 (t, $J=7.38$ Hz, 3H, -CH_3), 2.10 (s, 3H, CH_3CO-), 2.78 (m, 2H, -CH_2SO-), 2.95 (m, 2H, -CH_2SO-), 4.51 (m, 2H, -CH_2-OAc); IR: 3370, 2965, 2924, 2868, 1475, 1024, 1034, 748 cm^{-1}; ESMS: (M^++1) 165.