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# A Mild, Chemoselective Oxidation of Sulfides to Sulfoxides Using *o*-Iodoxybenzoic Acid and Tetraethylammonium Bromide as Catalyst

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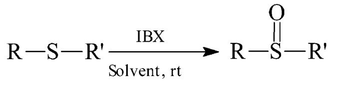
**Abstract:** A mild, selective, and high-yielding method for oxidation of sulfides to sulfoxides using IBX and tetraethylammonium bromide in a variety of solvents is described. The method offers the advantage of short reaction times, no overoxidation to sulfones, and compatibility to a wide range of functional groups.

Sulfoxides have fascinated organic chemist worldwide for a longtime, owing to their varied reactivity as a functional group for transformations into a variety of organo sulfur compounds. These transformations are useful for the synthesis of drugs and sulfur-substituted natural products.[1,2] Despite myriad of oxidants that convert sulfides to the corresponding sulfoxides, most reagents require careful control of the reaction conditions, including the quantity of oxidants, to minimize the formation of sulfones as side products.[3] Selective oxidations of sulfides to sulfoxides are reported with many hypervalent iodine(III) containing reagent systems.[4] However, insolubility and compatibility of these reagents with commonly used solvents limit their use. Kita et al. reported iodosobenzene (PhIO) in combination with CTAB and other quarternary ammonium salts to effect sulfide oxidation in variety of solvents by formation of micellar and reverse micellar systems.[5] This system was further developed for asymmetric sulfoxidation using both iodosobenzene (PhIO) and iodoxybenzene ($PhIO_2$) as oxidants.[6]

**TABLE 1. Optimization of Sulfide Oxidation**[a]



$$R{-}S{-}R' \xrightarrow[\text{Solvent, rt}]{\text{IBX}} R{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}R'$$

R, R' = $C_2H_5$

| entry | solvent | IBX (equiv) | cat. TEAB (mol %) | time | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $CHCl_3/H_2O$ | 1.1 | | 18 h | 95[c] |
| 2 | $CHCl_3/H_2O$ | 1.1 | 100 | 15 min | 98 |
| **3** | **$CHCl_3/H_2O$** | **1.1** | **5** | **20 min** | **98** |
| 4 | $CHCl_3/H_2O$ | 2.2 | 5 | 24 h | 97[d] |
| 5 | $PhCH_3/H_2O$ | 1.1 | | 36 h | 5[c] |
| 6 | $PhCH_3/H_2O$ | 1.1 | 5 | 30 min | 98 |
| 7 | DMSO/acetone | 1.1 | | 12 h | 97 |
| 8 | DMSO/acetone | 1.1 | 5 | 30 min | 97 |

[a] All reactions are run at room temperature with 5 mmol of sulfide in 10 mL of solvent (8:2 for DMSO/acetone and 100:1 for the rest of the entries). Reactions were also carried out using substrate R = Ph, R′ = $CH_3$ and similar results were obtained. [b] Yields indicate product obtained after column chromatography. [c] Reaction not gone for completion. [d] Sulfoxidation was complete in 20 min; reaction kept for 24 h to check for over-oxidation.

Though IBX finds widespread use in oxidative transformations,[7] to the best of our knowledge there are no reports on IBX-mediated selective oxidation of sulfides. In continuation of our studies on the development of newer applications of hypervalent iodine(V) compounds,[8] we wish to report the investigation leading to a new application of IBX with catalytic amounts of tetraethylammonium bromide (TEAB) for the oxidation of sulfides to sulfoxides.

In a preliminary experiment the sulfides were subjected to oxidation using IBX in chloroform. The sulfides underwent oxidation to the corresponding sulfoxides. The reaction was slow and took ~18 h to give a yield of ~95%. To expedite the process, the sulfoxidation was carried out using equivalent amounts of TEAB as an IBX activator. The oxidation was complete within 5 min in quantitative yields. By further investigation it was found that even catalytic amounts of TEAB (~5 mol %) are sufficient for facile oxidation and the reaction was complete within 30 min giving quantitative yields. In the presence of 2 equiv

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(5) Tohma, H.; Takizawa, S.; Watanabe, H.; Kita, Y. *Tetrahedron Lett.* **1998**, *39*, 4547.

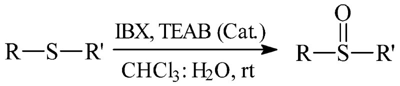
(6) (a) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519. (b) Tohma, H.; Takizawa, S.; Morioka, H.; Maegawa, T.; Kita, Y. *Chem. Pharm. Bull.* **2000**, *48* (3), 445.

(7) (a) Morales-Rojas, H.; Moss, R. A. *Chem. Rev.* **2002**, *102*, 2497. (b) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812. (c) Nicolaou, K. C.; Baran, P. S.; Zhang, Y. L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (d) Nicolaou, K. C.; Sujita, K.; Baran, P. S.; Zhang, Y. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207. (e) Nicolaou, K. C.; Zhang, Y. L.; Baran, P. S.; Sujita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145. (f) DeMunari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272.

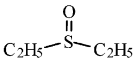
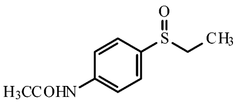
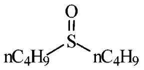
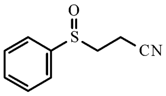
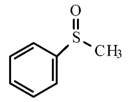
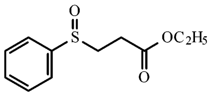
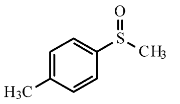
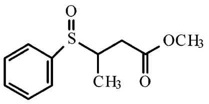
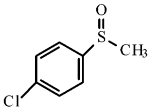
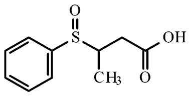
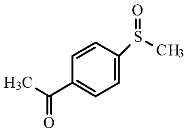
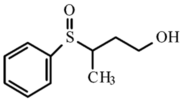
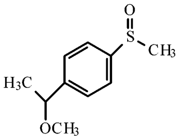
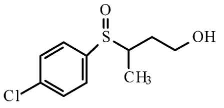
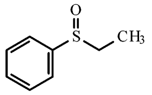
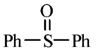
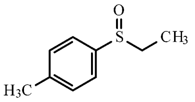
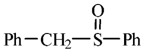
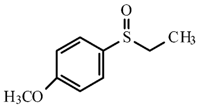
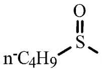
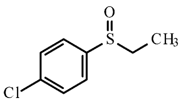
(8) (a) Ramanarayanan, G. V.; Shukla, V. G.; Akamanchi, K. G. *Synlett* **2002**, *12*, 2059. (b) Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **1999**, 760. (c) Chaudhari, S. S.; Akamanchi, K. G. *Tetrahedron Lett.* **1998**, *39*, 3209.

10.1021/jo034483b CCC: $25.00

**TABLE 2. Oxidation of Sulfides with IBX Using TEAB (Cat.) in $CHCl_3$: $H_2O$ (100: 1)**



$$R-S-R' \xrightarrow[CHCl_3:\,H_2O,\ rt]{IBX,\ TEAB\ (Cat.)} R-\overset{O}{\overset{\|}{S}}-R'$$

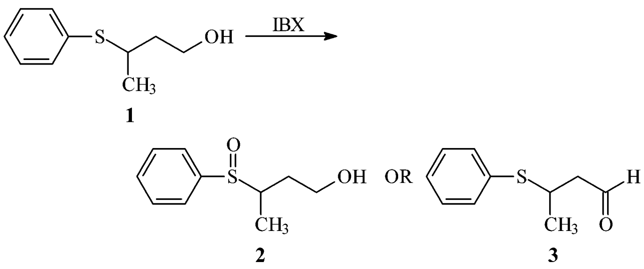
| entry | sulfoxide | time | yield (%) | entry | sulfoxide | time | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | 20 min | 98 | 12 |  | 30 min | 98 |
| 2 |  | 20 min | 98 | 13 |  | 3.5 h | 98 |
| 3 |  | 20 min | 97 | 14 |  | 4 h | 97 |
| 4 |  | 20 min | 95 | 15 |  | 4 h | 97 |
| 5 |  | 2 h | 93 | 16 |  | 8 h | 96 |
| 6 |  | 30 min | 97 | 17 |  | 30 min | 97 |
| 7 |  | 30 min | 97 | 18 |  | 1 h | 90 |
| 8 |  | 30 min | 97 | 19 |  $Ph-\overset{O}{\overset{\|}{S}}-Ph$ | 30 h | 98 |
| 9 |  | 30 min | 97 | 20 |  $Ph-CH_2-\overset{O}{\overset{\|}{S}}-Ph$ | 36 h | 96 |
| 10 |  | 30 min | 97 | 21 |  + 1-Undecene<br>(Mixed Reaction) | 30 min | 98 |
| 11 |  | 2 h | 93 | | | | |

[a] Reactions run at room temperature using 1.1 equiv of IBX and catalytic amounts of TEAB in $CHCl_3/H_2O$ (100:1). [b] Yields indicate isolated yields after column chromatography. [c] Sulfides commercially available were used as such with out further purification. Remaining sulfides were prepared using standard available literature procedures.[9] [d] All the sulfides and sulfoxides were confirmed by their physical and spectral properties (IR, NMR, and mass spectroscopy).

of IBX no over-oxidation to sulfones was observed even after 24 h. The reactions were also carried out in different solvents and were found to be equally good. The results on the optimization of sulfoxidation are recorded in Table 1.

To determine functional group compatibility and chemoselectivity of the reaction, variety of substrates were subjected to the developed and optimized method. As illustrated in Table 2, various functional groups, including acids, esters, alcohols, amide, nitriles, etc., were compatible and the sulfoxides were obtained in almost quantitative yields. In several cases, reaction was complete in 30 min to 2 h (entries 1−14). However, in case of sterically hindered and less nucleophilic sulfides such as diphenyl sulfide and benzyl phenyl sulfide (entries 19 and 20) unduly long reaction times were required. To further determine the scope of the reaction, a mixed reaction was carried out taking 1-undecene and butyl sulfide. After 30 min, complete selective sulfide oxidation occurred and 1-undecene remained unreacted (entry 21).

**TABLE 3. Chemoselectivity Studies Using 3-(Phenylthio)butan-1-ol 1**[a]



| entry | solvent | TEAB (mol %) | time | product | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | DMSO/acetone (8:2) | | 3 h | 3 | 96 |
| 2 | DMSO/acetone (8:2) | 5 | 1 h | **mixt**[c] | *c* |
| 3 | $CHCl_3/H_2O$ | | 24 h | **mixt**[c] | *c* |
| 4 | $CHCl_3/H_2O$ | 5 | 30 min | 2 | 97 |

[a] Reactions run at room temperature using 1.1 equiv of IBX. [b] Yields indicate isolated yields after removal of solvent. [c] No chemoselectivity was observed and yield not determined.

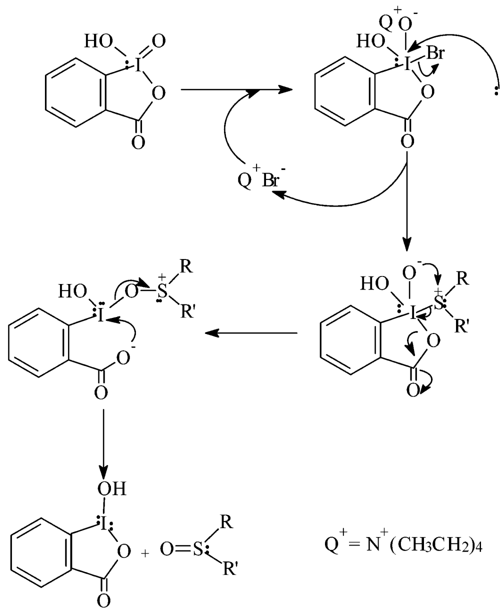
This study clearly shows that the double bond also remains unaffected.

Chemoselectivity of sulfide oxidation over alcohol is a significant observation with this system (Table 2, entries 17 and 18). Further investigation on this chemoselectivity was undertaken. Ease of alcohol oxidation by IBX is highly dependent on the solvent employed.[10] Therefore, the substrate **1** (Table 3) was subjected to oxidation in two different solvents and in the presence and absence of catalyst. The results are summarized in Table 3. It is interesting to find that by changing the solvent, selectivity can be shifted from sulfide to alcohol oxidation (Table 3, entries 1 and 4).

The following investigations were also carried out on the developed method:

(A) The residue (solid) obtained on the completion of oxidation was separated by filtration and characterized by physical and spectral properties.[11] As expected, it was hypervalent iodine(III) compound 1-hydroxy-1,2-benziodoxol-3(1H)-one (*o*-iodosylbenzoic acid). *o*-Iodosylbenzoic acid obtained from the reduction of IBX can be recycled by oxidation to IBX.[12] It is known that *o*-iodosylbenzoic acid converts sulfides to sulfoxides;[4n,6a] hence, one reaction was carried out on ethyl sulfide using 1 molar equiv of the residue in the presence of catalytic amounts of TEAB. Indeed, sulfoxidation occurred, however, the reaction was sluggish and gave 95% yield in 6 h. The residue obtained on completion of oxidation for this reaction was identified as *o*-iodobenzoic acid, which can be reused for the preparation of IBX.[13] A reaction was carried out using 0.5 molar equiv of IBX on ethyl sulfide. As expected, initially the oxidation proceeded quite rapidly but overall reaction took 6 h to give 94% yield of the sulfoxide.

**SCHEME 1**



(B) Sulfides prepared by Michael addition of thiophenol to α,*β*-unsaturated aldehydes (viz. crotonaldehyde), when subjected to oxidation, did not give the expected sulfoxide but instead the double bond got introduced to give α,*β*-unsaturated aldehydes. Further work is in progress.

We would like to suggest the mechanism as depicted in Scheme 1. The oxidation may involve the initial polarization of the I═O bond by TEAB then a nucleophilic attack of sulfur on the hypervalent iodine(V) center followed by a concerted oxygen transfer to give sulfoxides. Over-oxidation to sulfones does not occur and this could be attributed to the low nucleophilicity of sulfoxide.

In summary, we have developed an efficient, fast procedure for sulfoxidation using *o*-Iodoxybenzoic acid (IBX) in the presence of TEAB as catalyst. This method possesses increased compatibility to different functional groups, mild and neutral conditions. Further applications of this reagent combination are under investigation in our laboratory.

## Experimental Section

**General Methods.** All NMR spectra were recorded on 60 MHz. Chemical shifts are expressed in $\delta$ units relative to tetramethylsilane (TMS) signal as internal reference in $CDCl_3$. IR spectra were recorded in $CHCl_3$ or as a KBr pellet. Mass spectra were recorded by EI (70 eV) ionization. IBX was freshly prepared by standard procedure:[14] mp = 230 °C (HAZARD! Explodes) (lit.[14] mp = 232−233 °C). All the solvents were purchased from commercial sources and used with out further purification. Wherever necessary the solvents were dried by standard literature procedures.

**General Experimental Procedure.** To a stirred suspension of IBX (1.1 equiv) in $CHCl_3/H_2O$ (100:1) was added TEAB (5 mol %) followed by the addition of sulfide (1.0 equiv) in one portion. The mixture was stirred at room temperature for 20 min until complete consumption of starting material as observed by TLC. The residual solids were filtered off and washed thoroughly with $CHCl_3$. The combined filtrate was washed successively with 10% sodium bisulfite solution (2 × 15 mL), saturated sodium

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(9) (a) Gasparrini, F.; Giovannoli, M.; Misti, D. *J. Org. Chem.* **1990**, *55*, 1323 and references therein. (b) Herriott, A. W.; Picker, D. *Synthesis* **1975**, 447. (c) Baliah, V.; Uma, M. *Tetrahedron* **1963**, *19*, 455.

(10) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4* (17), 3001.

(11) Baker, G. P.; Mann, F. G.; Sheppard, N.; Tetlow, A. J. *J. Chem. Soc.* **1965**, 37721.

(12) (a) Surendra, K.; Krishnaveni, S.; Arjun Reddy M.; Nageswar, Y. V. D.; Rama Rao K. *J. Org. Chem.* **2003**, *68*, 2058. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(14) Varvoglis, A. *Hypervalent Iodine In Organic Synthesis*; Academic Press Inc.: New York, 1997; p 17.

bicarbonate solution (2 × 15 mL), water (2 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over sodium sulfate and concentrated under vacuo. Purification by silica gel column chromatography (50% EtOAc/hexane) afforded the sulfoxide.

**Acknowledgment.** We thank CSIR, New Delhi, for financial support.

**Supporting Information Available:** Experimental details. Selected IR, $^1$H NMR, and mass spectral data of intermediates and sulfoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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