Selective Oxidation of Sulfides to Sulfoxides Using IBX-Esters

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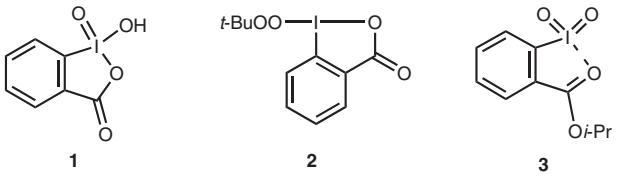
Abstract: IBX-esters (esters of 2-iodoxybenzoic acid) are convenient hypervalent iodine reagents for the clean and selective oxidation of organic sulfides to sulfoxides. This reaction proceeds without over-oxidation to sulfones and is compatible with the presence of the hydroxy group, double bond, phenol ether, benzylic carbon, and various substituted phenyl rings in the molecule of the substrate.

Key words: hypervalent iodine, IBX-esters, sulfides, sulfoxides

The chemistry of sulfoxides has been attractive to organic chemists for a long time. The interest to the chemistry and preparation of sulfoxides is due to the fact that sulfoxides are often a part of natural products and drugs and also have unique reactivity as a functional group for various transformations into organosulfur compounds.[1] The selective preparation of sulfoxides from corresponding sulfides was performed with a variety of reagents. However, many of these reagents need a careful control of the reaction conditions such as temperature and quantity of the reagent in order to avoid the formation of sulfones as side products.[2] Moreover, the majority of oxidizing reagents are incompatible with other sensitive functionalities (e.g., hydroxy group, aldehyde, phenol ether, double bond, etc.) present in the molecule of organic substrate. Hypervalent iodine reagents were found to be the most useful oxidizing reagents toward organic sulfides.[3,4] In particular, PhIO, $PhIO_2$ or IBX (**1**) can oxidize sulfides to sulfoxides in the presence of bromide anion as a catalyst.[4a–e] However, the same reagents can oxidize alcohols to carbonyl compounds and therefore they are incompatible with the hydroxy group.[3d] Likewise, peroxybenziodoxole **2** is an efficient oxidizing reagent toward sulfides,[4f] as well as many other functional groups,[3d] and therefore its reactions lack chemoselectivity. [Hydroxy(tosyloxy)iodo]benzene (HTIB) and its analogs can also oxidize sulfides,[4g–i] but at the same time, these reagents are powerful oxidizers toward alkenes and ketones.[3] Finally, iodobenzene dicarboxylates and their polymer-supported analogs usually oxidize sulfides non-selectively to a mixture of sulfoxides and sulfones and, in addition, are incompatible with numerous functional groups, including phenol ethers and double bonds.[3,4j–m]

Recently we reported the preparation and structure of the novel pentavalent iodine reagents with pseudo-benziodoxole structure, IBX-esters.[5] The most readily available representative of IBX-esters, isopropyl ester of 2-iodoxybenzoic acid **3**, has excellent solubility in organic solvents (up to 2.86 M in CH_2Cl_2), which is explained by a partial disruption of the polymeric nature of IBX due to the presence of the intramolecular I···O bonding interaction in the pseudo-benziodoxole ring.[5] We have also found that IBX-ester **3** has lower oxidizing reactivity compared to IBX. In particular, in the absence of acid catalysis, compound **3** does not react with primary or secondary alcohols even at high temperatures.[5] In the present paper we report the use of reagent **3** for chemoselective oxidation of sulfides to sulfoxides with IXB-ester **3** in acetonitrile under mild conditions. This procedure is applicable toward alkyl or aryl sulfides and it is completely compatible with other sensitive functionalities present in the molecule of organic substrate.



1 2 3

Figure 1

In order to find the best conditions for the oxidation of sulfides to sulfoxides, we investigated the reaction of phenylmethyl sulfide with IBX-ester **3** in various solvents at different temperatures. We have found that no oxidation occurs in methylene chloride or chloroform even under reflux conditions. This low reactivity of **3** in non-polar solvents can be explained by the partially oligomeric nature of reagent **3** due to the relatively weak intermolecular I···O interactions that were observed in the X-ray structure of this compound.[5] The presence of intermolecular I···O interactions can significantly decrease electrophilicity of the iodine center and thus reduce its reactivity toward sulfide. A more polar solvent is required to facilitate dissociation of this oligomeric reagent and to give access of the sulfur atom to the iodine center. Indeed, we have found that the oxidation of phenylmethyl sulfide with IBX-ester **3** in acetonitrile proceeds at room temperature; however, the reaction is slow and takes about two days for full conversion. The same reaction under reflux is complete after one hour and no over-oxidation with the formation of sulfones was observed. All reactions with other sulfides were carried out under these optimized conditions; the substrates and the yields of products are listed in Table 1.

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Table 1 Oxidation of Sulfides to Sulfoxides with IBX-Ester **3**[a]

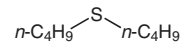
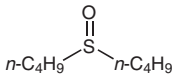
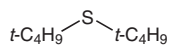
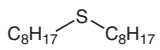
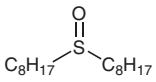
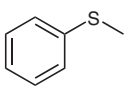
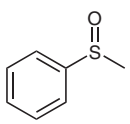
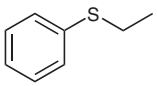
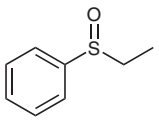
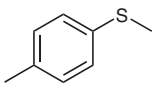
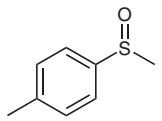
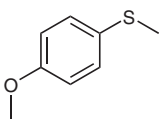
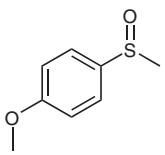
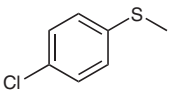
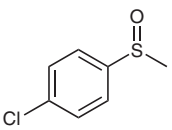
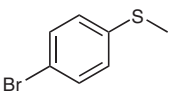
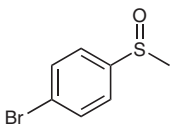
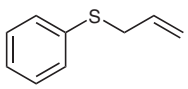
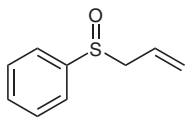
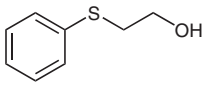
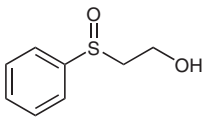
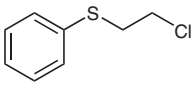
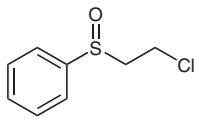
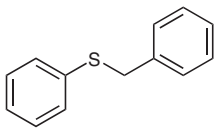
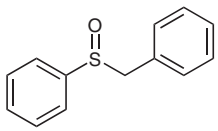
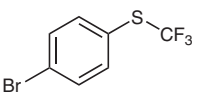
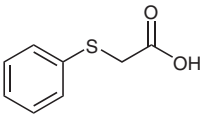
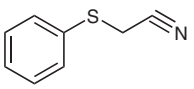
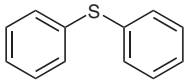
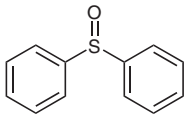
Entry	Substrate	Product[b]	Yield (%)[c,d]
1			100
2		No reaction[e]	0
3			91
4			91
5			84
6			79
7			87
8			89
9			81
10			92
11			71
12			86
13			91

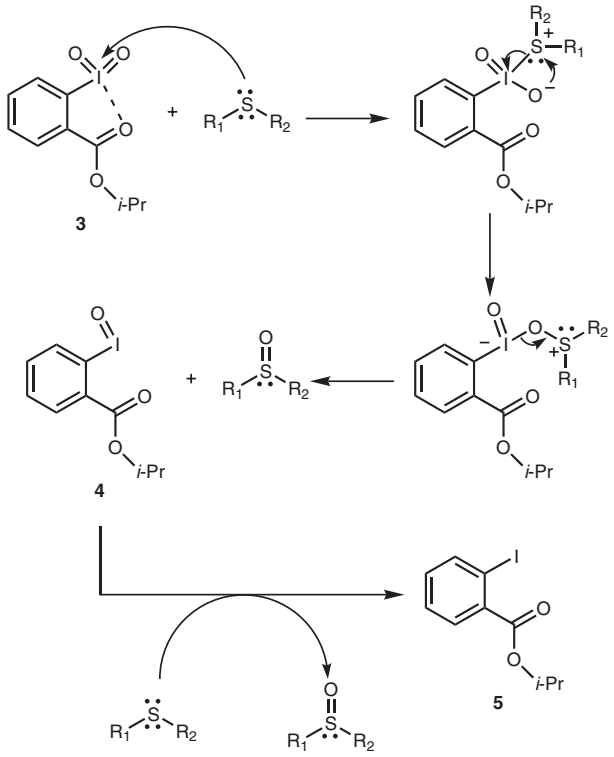
Table 1 Oxidation of Sulfides to Sulfoxides with IBX-Ester **3**[a] (continued)

Entry	Substrate	Product[b]	Yield (%)[c,d]
14		No reaction[e]	0
15		No reaction[e]	0
16		No reaction[e]	0
17			97

[a] All reactions were performed in acetonitrile under reflux using 0.6 equivalents of IBX-ester.
[b] Isopropyl ester of 2-iodobenzoic acid (**5**) was isolated as a by-product in all oxidations.
[c] All yields listed in the table are yields of products isolated after column chromatography.
[d] All products were identified using comparison of their physical and spectral data (IR, NMR, and MS) with those reported in the literature.[4,6]
[e] No oxidation was observed even after 10 hours of reflux.

In order to determine the scope and limitations of this procedure, a variety of functionalized sulfides were oxidized as listed in Table 1. Most notably, in the presence of the hydroxy group in the molecule (Entry 11) no oxidation to aldehyde was observed. Likewise, this oxidation is compatible with the presence of the double bond (Entry 10), phenol ether (Entry 7), benzylic carbon (Entry 13), and various substituted phenyl rings. The oxidation is limited to the sterically non-hindered sulfides, as illustrated by the absence of any oxidized products from *tert*-butyl sulfide even after 10 hours of reflux (Entry 2). Likewise, the oxidation does not occur when strong electron-withdrawing groups are present in the molecule of sulfide (Entries 14–16).

A plausible mechanism of this oxidation is shown in Scheme 1. The initial step of oxidation involves a nucleophilic attack of sulfur on the hypervalent iodine center, followed by concerted oxygen transfer to give sulfoxides after elimination of the iodine(III) fragment. Over-oxidation to sulfones does not occur probably due to the low nucleophilicity of sulfur in sulfoxides. The trivalent iodine compound **4** formed in situ can oxidize the second molecule of sulfide with the formation of monovalent derivative **5** by a similar mechanism. An alternative pathway may involve the disproportionation of intermediate **4** to compounds **3** and **5**.



Scheme 1

In conclusion, we have found that IBX-esters are convenient hypervalent iodine reagents for clean and selective oxidation of organic sulfides to sulfoxides. The reaction proceeds without over-oxidation to sulfones and is compatible with the presence of the hydroxy group, double bond, phenol ether, benzylic carbon, and various substituted phenyl rings in the molecule of sulfide.

Preparation of Reagent 3

To a rigorously stirred suspension of the isopropyl ester of 2-iodobenzoic acid (1.45 g, 5 mmol) and sodium hypochlorite solution ('bleach', 5% NaOCl, 15 mL), CH_2Cl_2 (20 mL) was added, followed by an excess of dry ice in the course of 10 min. The reaction mixture was stirred overnight and then the organic layer was separated while the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over anhyd $MgSO_4$, the solvent was evaporated in vacuo to afford 1.43 g (89%) of product **3**.

Mp 156 °C (decomp.).

IR (KBr): 1673, 789, 743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.34 (d, *J* = 7.8 Hz, 1 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 7.84 (t, *J* = 7.5 Hz, 1 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 5.31 (m, 1 H) 1.35 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 167.5, 149.6, 134.9, 131.8, 130.2, 126.8, 124.8, 71.9, 21.8.

Anal. Calcd for $C_{10}H_{11}IO_4$: C, 37.29; H, 3.44; I, 39.40. Found: C, 37.21; H, 3.49; I, 39.36.

Oxidation of Sulfides to Sulfoxides with Reagent 3 in MeCN; General Procedure

To a stirred mixture of reagent **3** (88.5 mg, 0.275 mmol) in MeCN (6 mL) the appropriate sulfide (0.5 mmol) was added. The mixture was refluxed until full consumption of the reagent (monitored by TLC) was observed. Then the reaction mixture was concentrated in vacuo and separated by column chromatography (EtOAc–hexanes, 1:2 followed by EtOAc) to afford analytically pure sulfoxide.

Acknowledgment

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