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# Selective and efficient oxidation of sulfides to sulfoxides with *N*-bromosuccinimide in the presence of β-cyclodextrin in water☆

K. Surendra, N. Srilakshmi Krishnaveni, V. Pavan Kumar, R. Sridhar and K. Rama Rao*

*Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

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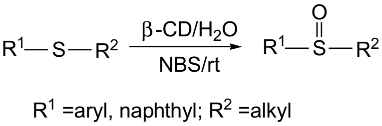
**Abstract**—A simple and highly selective oxidation of sulfides to sulfoxides with *N*-bromosuccinimide (NBS) catalyzed by β-cyclodextrin in water has been developed. A series of sulfides were oxidized selectively at room temperature in excellent yields. This reaction proceeds without over-oxidation to sulfones under mild conditions using water as a solvent and has many advantages over the existing methodologies.

Organic sulfoxides are versatile synthons for C–C bond formation, molecular rearrangements, functional group transformations and are also utilized as precursors for biologically active and chemically important compounds.[1] The selective and catalytic oxyfunctionalization of sulfur is a pivotal reaction in organic synthesis.[2] Hence, selective oxidation of organic sulfides is very important from both industrial and green chemistry points of view as organosulfur compounds are a major source of environmental pollution.[3] In view of the importance of sulfoxides, several reagents have been used for this key transformation such as hypervalent iodine compounds,[4] $H_2O_2$ and its derivatives,[5] CAN,[6] $MnO_2$–$H_2SO_4$/silica gel,[7a] $MnO_2$–HCl[7b] and metal salts,[8] photochemical oxidations,[9] etc. Though different approaches have been reported, there are various limitations such as the use of strong acidic or basic conditions, elevated temperatures, long reaction times, hazardous organic solvents and reagents, transition metal catalysts, promoters for the activation of catalysts and low yields.

The previously reported use of *N*-bromosuccinimide for the oxidation of sulfides has usually been carried out using anhydrous solvents at various temperatures.[10] It had been shown earlier that certain aromatic sulfides could be oxidized to sulfoxides in 70% dioxane–water with NBS but substrates like *p*Me-$C_6H_4$SMe, etc., gave no sulfoxide, but instead underwent C–S bond cleavage under these conditions.[11]

Cyclodextrins are cyclic oligosaccharides, which catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes. In continuation of our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins in water,[12] we report herein an efficient, simple and practical method for the oxidation of sulfides with NBS catalyzed by β-cyclodextrin in water under neutral conditions (Scheme 1).

In general, the reaction was carried out by the in situ formation of the β-cyclodextrin complex of the substrate in water followed by the addition of NBS and stirring at room temperature to give the corresponding sulfoxides in high yields (Table 1).[13] The reaction goes smoothly at room temperature without the formation of any side products. No over-oxidation to sulfones was observed. No stringent conditions were required for these selective oxidations. Hydrogen bonding may also assist in controlling the chemoselectivity, since cyclodextrin can bind the product sulfoxide by hydrogen bonding with the



**Scheme 1.**

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*Keywords*: Sulfides; Sulfoxides; Oxidation; *N*-bromosuccinimide; β-Cyclodextrin; Biomimetic; Water.

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* Corresponding author. Tel.: +91 4027193164; fax: +91 4027160757; e-mail: drkrrao@yahoo.com

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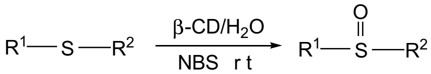
**Table 1.** Oxidation of sulfides to sulfoxides with NBS in the presence of β-CD in water



$$R^1\text{—S—}R^2 \xrightarrow[\text{NBS rt}]{\beta\text{-CD/H}_2\text{O}} R^1\text{—}\overset{\text{O}}{\overset{\|}{\text{S}}}\text{—}R^2$$

| Entry | $R^1$ | $R^2$ | β-CD (1.0 mmol) | | β-CD (0.1 mmol) | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%)[a,b] | Time (h) | Yield (%)[a,b] |
| 1 | Ph | $CH_3$ | 2.0 | 95 | 6.0 | 94 |
| 2 | Ph | $(CH_2)_2CH_3$ | 2.5 | 93 | 8.0 | 90 |
| 3 | Ph | $CH(CH_3)_2$ | 2.5 | 92 | 8.0 | 90 |
| 4 | $p$-$BrC_6H_4$ | $CH_3$ | 2.0 | 96 | 6.0 | 96 |
| 5 | $p$-$ClC_6H_4$ | $CH_3$ | 2.0 | 95 | 6.0 | 94 |
| 6 | $p$-$ClC_6H_4$ | $CH_2CH_3$ | 2.0 | 94 | 7.0 | 94 |
| 7 | $p$-$MeC_6H_4$ | $CH_3$ | 2.5 | 95 | 7.0 | 92 |
| 8 | $p$-$MeC_6H_4$ | $CH_2CH_3$ | 2.5 | 94 | 8.0 | 94 |
| 9 | $p$-$MeC_6H_4$ | $CH(CH_3)_2$ | 2.5 | 92 | 8.0 | 90 |
| 10 | $o$-$MeC_6H_4$ | $CH_3$ | 2.6 | 93 | 8.0 | 90 |
| 11 | $p$-$MeOC_6H_4$ | $CH_3$ | 2.2 | 94 | 6.5 | 92 |
| 12 | $PhCH_2$ | $CH_3$ | 2.5 | 92 | 7.0 | 90 |
| 13 | $PhCH_2$ | $CH_2CH_3$ | 2.5 | 90 | 8.0 | 90 |
| 14 | $PhCH_2$ | $CH(CH_3)_2$ | 2.5 | 90 | 8.0 | 88 |
| 15 | $C_{10}H_7$ | $CH_3$ | 3.0 | 92 | 8.0 | 90 |

[a] All the products were characterized by $^1H$ NMR, IR and mass spectroscopy.

[b] Isolated yields.

oxygen of the sulfoxides, thereby decreasing the nucleophilicity of the sulfur and preventing further oxidation of the sulfoxide to the sulfone.

This methodology is also compatible in the presence of other functionalities such as chloro, bromo, methoxy and isopropoxy. These cyclodextrin mediated water based reactions proceed under mild conditions and are also useful from the view point of not having to handle flammable and anhydrous organic solvents. Though inclusion complexation of sulfides with β-CD takes place in situ during the reaction, these inclusion complexes have been isolated separately and characterized by powder X-ray diffraction[14] and $^1H$ NMR studies.[15] All the sulfoxides were characterized by mass, $^1H$ NMR, IR and by comparison with known compounds.[4,5] In these reactions, succinimide was obtained as the by-products and can be recycled to NBS as described in the experimental section. Cyclodextrin was also recovered and reused. It was also observed that though these reactions do take place with catalytic amounts of CD (0.1 mmol) the reaction times were much longer (6–8 h). The fact that these reactions do not take place in the absence of cyclodextrin indicates the essential role of CD. The CD may be forming an inclusion complex with the thioether from the secondary side with attack of NBS from the primary side enabling the reaction to proceed as observed in our earlier studies.[12a] Though asymmetric induction was seen to some extent in these reactions, the ee's observed were not encouraging (<10%).

In conclusion, our methodology provides a method for the selective oxidation of sulfides to sulfoxides without any over-oxidation to sulfones. Moreover, the reaction proceeds under neutral and mild conditions and can be carried out easily at room temperature with recycling of cyclodextrin and regeneration of NBS.

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13. β-Cyclodextrin (1 mmol) was dissolved in water (15 ml) at 60 °C, then the substrate (1 mmol) in acetone (1 ml) was added slowly with stirring and the mixture cooled to room temperature. NBS (1 mmol) was added and stirring at room temperature was continued until the reaction was complete (Table 1). The mixture was extracted with ethyl acetate and the filtrate was cooled to 5 °C to recover CD by filtration. The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was removed under vacuum to give the products, seen as single compounds by TLC, which were further purified by passing through a column of silica gel using ethyl acetate–hexane (1:1) as eluent. To the filtrate, which contained succinimide and HBr was added $NaBrO_3$ and conc. $H_2SO_4$ as already reported[16] and the mixture stirred for 30 min, extraction with ethyl acetate giving NBS in an isolated yield of 75–80%.
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