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Selective, Metal-Free Oxidation of Sulfides to Sulfoxides Using 30% Hydrogen Peroxide Catalyzed with *N*-Bromosuccinimide (NBS) under Neutral Buffered Reaction Conditions

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This paper is dedicated to Professor Habib Firouzabadi on the occasion of his 65th birthday and also his retirement

Various types of aromatic and aliphatic sulfides are selectively oxidized to the corresponding sulfoxides in good to excellent yields using 30% H_2O_2 in the presence of catalytic amounts of *N*-bromosuccinimide (NBS) in buffered aqueous acetonitrile solution (*p*H =7.00). The results showed that acid sensitive functional groups such as double bonds, and *O*,*O*-acetals remained intact under the described reaction conditions

Keywords: Sulfoxide, Oxidation, Hydrogen peroxide, *N*-Bromosuccinimide, Sulfide.

INTRODUCTION

The selective oxidation of sulfides to sulfoxides is an attractive and important transformation in organic chemistry, since sulfoxides are useful building blocks especially as chiral auxiliaries in organic synthesis [1-4] and also they play key role in activation of enzymes [5,6]. Therefore, a large number of methods and procedures have been proposed for this type of transformation [6-17]. Unfortunately, one or more equivalents of hazardous or toxic oxidizing agents are usually required to achieve this transformation [12-17]. Moreover, over-oxidation of sulfoxides to the corresponding sulfones, and also the reaction of other functional groups are common problems in many of the reported methods. However, from the standpoint of the so-called *green* and sustainable chemistry, another approach to create cleaner and more selective catalytic systems for the organic transformations has become increasingly important in recent years [18,19]. In this way, various types of metal-, and non-metal-catalyzed oxidation of sulfides using clean and cheap oxidants such as H_2O_2 [20-27], and O_2 [28-31], have been developed. Although, many of these methods are quite useful, there still remains much room for improvements especially in the case of the selectivity of the reactions. Recently, it has been shown that bromine could be an effective catalyst for oxidation of a variety of sulfides in the presence of 30 % hydrogen peroxide, through a bi-phasic system [32]. It was shown that in this process, either an electrophilic or a free radical mechanism is involved. Although this protocol showed a good selectivity and efficiency when applied to the simple arylalkyl and dialkyl sulfides, a significant amount of the corresponding benzyl bromide, benzylsulfonic acid, benzyl alcohol, and benzaldehyde were also formed in the case of sensitive benzylic sulfides. Moreover, using this method, diaryl sulfides were not oxidized and instead electrophilic bromination products were formed as sole products. On the other hand, the use of Br_2 as catalyst resulted in the formation of significant amount of HBr in the course of reaction which in turn could

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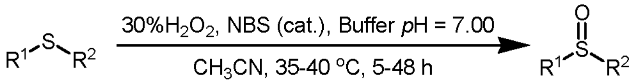
promote pummerer rearrangement of sulfoxides [33]. In our development of new methods for functional group transformations, we have been especially interested in exploring the potential use of various types of neutral catalysts [34-48]. In this way, we have introduced *N*-bromosuccinimide (NBS) as a mild and nearly neutral electrophilic catalyst for a variety of functional group transformations such as acetalization [37,41] and acylation [38] of carbonyl compounds, acetylation of alcohols [34] deoxygenation of sulfoxides [45] and deprotection of 1,3-oxatioacetals [43]. In continuation of this study, herein, we wish to explore a new chemoselective, mild and efficient protocol for the oxidation of sulfides (1 mmol) to sulfoxides using 30% aqueous H_2O_2 (3-5 equiv.) in the presence of catalytic amounts of NBS (10 mol %) under neutral buffered reaction conditions (Scheme 1).



Scheme 1. NBS-Catalyzed oxidation of sulfides to sulfoxides under neutral buffered solution

EXPERIMENTAL

General Remarks

Chemicals were either prepared in our laboratories by known methods or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. The products were characterized by comparing their physical data with those of known samples. All products are known and the isolated products gave satisfactory IR and NMR spectra.

General procedure for oxidation of sulfides using 30% H_2O_2 catalyzed with NBS under neutral reaction conditions

To a stirred solution of organic sulfide (2 mmol) in CH_3CN (10 ml) and phosphate buffer solution (Merck no. 109407, 6 ml), were successively added NBS (0.2 mmol) and 30% H_2O_2 (6-10 mmol) in two portions at 35-40 °C. After completion of the reaction (TLC or GC), the solution was extracted with ethyl ether (3 × 30 ml). The organic extracts were combined together and were washed with water (2 × 10 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was preceded by vacuum distillation or recrystalization to afford pure sulfoxide (Table).

RESULTS AND DISCUSSION

In order to control the *p*H of the reaction medium, a phosphate buffered solution (3 ml, *p*H=7.00) was added to the reaction media in all cases. We first examined the oxidation of methylphenyl sulfide (1 mmol) using 30% H_2O_2 (3 equiv.) in a solvent mixture (3 ml buffer *p*H = 7.00, 5ml CH_3CN) in the absence of NBS at temperature around 35-40 °C. It was observed that the reaction was very sluggish and only low yields of the corresponding sulfoxide was formed after 24 hours (Table 1, entry 1). However, when similar oxidation reaction was conducted in the presence of NBS (10 mol %) at 35-40 °C, methylphenyl sulfoxide was formed in excellent yields within 5 hours (Table 1, entry 2), while the *p*H of the reaction medium was strictly remained neutral. It is important to point out that the addition of buffered solution to the reaction medium does not seriously affect the rate of reaction (Table 1, entry 3). In a similar way, various types of structurally different aryl alkyl and dialkyl sulfoxides underwent smooth oxidation to selectively afford the corresponding sulfoxides, in good to excellent yields (Entries 4-12). All reactions occurred with high selectivity for sulfoxide formation; no over oxidation products such as sulfones were detected in the reaction mixture. Efficient oxidation of benzylic sulfides to the corresponding sulfoxides, without C-S bond cleavage, also showed the usefulness of the protocol (Table 1, entries 12, 13, 14). The latter result is clearly in sharp contrast to those obtained from the Br_2-catalyzed protocol [32]. Another feature of this protocol was further seen in the selective oxidation of allyl phenyl sulfide to the corresponding sulfoxide. Neither over-oxidation to sulfones nor epoxidation were observed in this case (Table 1, entry 15). On the other hand, in all of the studied oxidation reactions, no pummerer by-product was observed in any oxidation reactions. Although, formation of sulfoxides form diaryl sulfides is difficult to achieve by standard oxidation procedures using 30% H_2O_2 [20-23], under the described reaction conditions, even highly hindered sulfides furnished the corresponding sulfoxide in good yields (Table 1, entries 15, 16, 17).

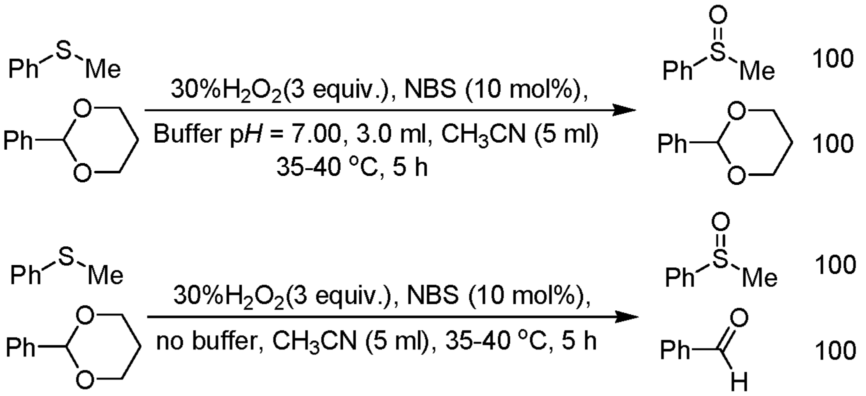
Table 1. Oxidation of Sulfides to Sulfoxide Using 30% H_2O_2 Catalyzed with NBS under Neutral Buffered Solution

Entry	Sulfide	Time (h)	Yield (%)$^{a,b)}$
1	Ph-S-Me	24	$10^{c, d}$
2	Ph-S-Me	5	93
3	Ph-S-Me	4.5	93^{e}
4	Ph-S-Et	7	96
5	Ph-S-Bu^{n}	10	95
6	Ph-S-Bu^{sec}	12	90
7	Ph-S-Pr^{iso}	10	89^{f}
8	3-(CH_3)Ph-S- Pr^{iso}	12	87^{f}
9	Ph-S- c-C_5H_9	12	93^{f}
10	Ph-S- c-C_6H_{11}	12	91^{f}
11	Ph-S-CH_2CH_2Ph	8	94
12	Bu^{n}-S-Bu^{n}	3	94
13	Ph-S-CH_2Ph	15	90
14	$PhCH_2$-S-CH_2Ph	11	90
15	Ph-S-$CH_2CH=CH_2$	15	80
16	Ph-S-Ph	48	60^{g}
17	4-(CH_3)Ph-S-Ph-(4-CH_3)	48	65^{g}

[a] Yields refer to isolated pure product unless otherwise stated. [b] The molar ratios for sulfide:H_2O_2:NBS were 1:3:0.1. [c] GC yield. [d] The reaction was conducted in the absence of NBS. [e] The reaction was conducted in the absence of buffer solution. [f] The molar ratios for sulfide:H_2O_2:NBS were 1.0 : 4.0 : 0.1. [g] The molar ratios for sulfide:H_2O_2:NBS were 1.0 : 5.0 : 0.1.

In order to further show the mildness of the method, we have also conducted competitive oxidation of methyl phenyl sulfide in the presence of acid sensitive functional groups under neutral buffered solution (scheme 2).

It is also worth mentioning that owing to the acidity of 30% H_2O_2 solution (pH ≈ 2.35), although 2-phenyl-1,3-dioxane was rapidly deprotected in the absence of any added buffer solution, in the presence of buffer solution the acetal moiety survived intact.



Scheme 2. Selective oxidation of sulfides to sulfoxides in the prsesence of acetals under neutral buffered solution

CONCLUSION

In summary, the present protocol demonstrates the potential of NBS, as a cheap and readily available reagent and effective catalyst for the oxidation of a variety of organic sulfides to sulfoxides using 30% H_2O_2 in a neutral buffered solution. Neither over-oxidation to sulfones nor epoxidation were observed in the case of allylic sulfides. Moreover, acid sensitive functional groups such as double bonds, and *O,O*-acetals remained intact under the described reaction conditions. Work in this area is currently ongoing in our laboratory.

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