

An Environmentally Benign Synthesis of 1-Benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane Tribromide and Its Application as an Efficient and Selective Reagent for Oxidation of Sulfides to Sulfoxides in Solution and Solvent-free Conditions

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Stable crystalline 1-Benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane tribromide (BABOT), can be readily synthesized from the reaction of the corresponding bromide with HNO₃ and aqueous KBr. Selective Oxidation of a variety of dialkyl and alkyl Aryl sulfides to the corresponding sulfoxides in high yield was achieved by this reagent in solution (CH₃CN/H₂O) and solvent free conditions. The reaction proceeds under neutral and mild conditions and can be carried out easily at room temperature with regeneration of BABOT. In this method purification of products is straightforward and no over oxidation to sulfone was noted.

Key Words : Sulfide, Sulfoxide, Oxidation, Solvent free, 1-Benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane tribromide

Introduction

Sulfoxides are valuable synthetic intermediates for production of a range of chemically and biologically active molecules including therapeutic agents such as anti ulcer, antibacterial and antifungal.¹⁻⁹ Sulfoxides are usually prepared by the direct oxidation of sulfides. This transformation can be performed with a wide variety of reagents.¹⁰ 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.^{11,12}

Bromine derivatives offer a particularly desirable choice because they are inexpensive. However, there are disadvantages associated with molecular bromine when traditional liquid bromine is employed. To avoid toxic molecular bromine, various stable solid crystalline quaternary ammonium tribromides have been introduced as *in situ* sources of molecular bromine.¹³⁻¹⁵ Tribromides are more suitable than the liquid bromine because of their storage, transports, and maintenance of desired stoichiometry. Also, the low concentration of bromine in the reaction mixture during the oxidation of sulfide make this procedures safer and minimizes overoxidation of sulfides resulting in sulfones formation and undesired reactions of other functional groups, particularly when preparing biologically relevant sulfoxides.

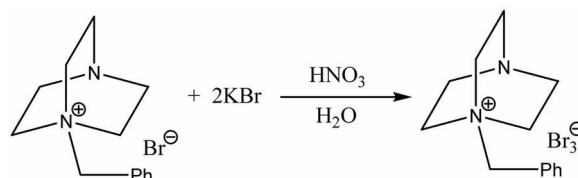
Preparations of tribromides involve organic ammonium bromide and molecular bromine in most cases, thus an indirect use of toxic molecular bromine. Recently organic ammonium tribromides have been prepared in an environmentally benign way by the reaction of V₂O₅, aqueous H₂O₂, and KBr.¹⁶ However this method generates some heavy metal as toxic waste. In continuation of our research to develop new reagents for bromination of aromatic compounds,¹⁷⁻²¹ Here we wish to report a new method for the synthesis of 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane

tribromide (BABOT) by using nitric acid and its application on selective oxidation of sulfide to sulfoxide in solution and solvent-free conditions.

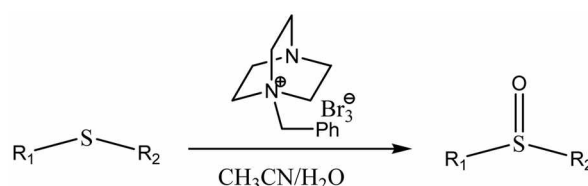
Results and Discussion

BABOT was readily obtained in almost quantitative yield by the action of 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane bromide on nitric acid in the presence of KBr as in Scheme 1. The orange crystalline bromine complex BABOT showed an intense electronic absorption at 279 nm typical of tribromide Br₃⁻.¹⁶ This reagent is easy handling compound which can be stored at room temperature for several months without any decreasing activity.

The oxidation of a variety of sulfide with BABOT in acetonitrile/water (3:1) at room temperature with the substrate/BABOT ratio 1:1 under natural conditions was optimized. This reaction gave the corresponding sulfoxide in good to excellent yields. The generality of this approach has been demonstrated by a facile and effortless oxidation of a

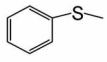
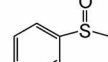
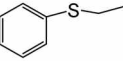
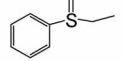
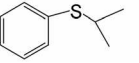
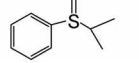
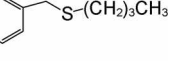
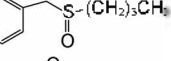
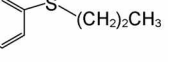
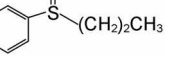

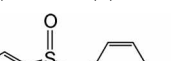

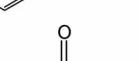
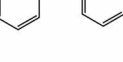
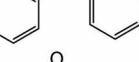
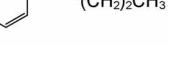
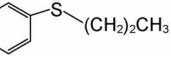
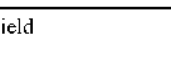
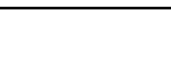


Scheme 1

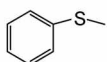
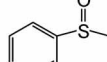
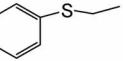
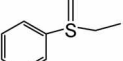
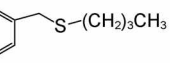
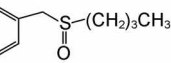
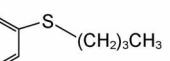
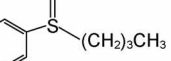
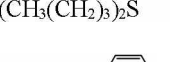
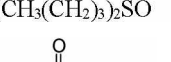

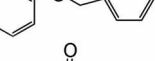
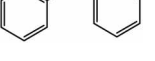
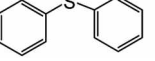


Scheme 2

Table 1. Oxidation of sulfides to corresponding sulfoxides by BABOT in CH₃CN/H₂O at room temperature

Entry	Substrate	Time (min)	Products	Yield ^a (%)
1		7		97
2		2		93
3		2		90
4		2		95
5		2		90
6		2		91
7		15		98
8		60		60
9		2		97
10		2		89

^aisolated yield**Table 2.** Oxidation of sulfides to corresponding sulfoxides by BABOT in solvent-free conditions at room temperature

Entry	Substrate	Time (min)	Products	Yield ^a (%)
1		3		95
2		2		90
3		2		93
4		3		96
5		2		95
6		5		95
7		50		65

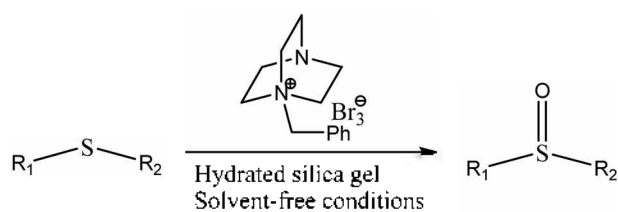
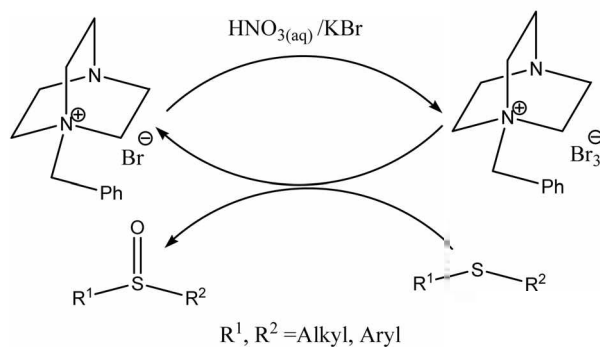
^aisolated yield

wide variety of alkyl and aryl sulfide as shown in Table 1 and Scheme 2. No evidence of sulfone formation was noted.

Reactions under solvent-free conditions have received increasing attention in recent years. The advantage of these methods over conventional homogenous reactions is that they provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulation. We examined the possibility of oxidation of sulfide to sulfoxide with BABOT on hydrated silica gel under solvent-free conditions. As indicated in Scheme 3 and Table 2, both alkyl and aryl sulfide selectively converted to corresponding sulfoxide in excellent yields. The reaction was carried out at room temperature and no evidence of further oxidation to sulfone was observed. In this reaction, hydrated silica gel plays two very important roles. (i) The water present in the hydrated silica gel affects the hydrolysis of intermediate to the sulfoxide. (ii) Silica gel minimized the evaluation of hydrogen bromide.²²

Another advantage of this method is that BABOT can be regenerated. After extraction of the sulfoxide, the aqueous layer was washed with water and then treated with a fresh bath of the aqueous HNO₃/KBr mixture to regenerate the reagent BABOT in quantitative yield (Scheme 4).

In conclusion, our methodology provides an environmentally benign method for the preparation of ammonium tribromide and its application on 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 regeneration of BABOT. In addition, in this method purification of products is straightforward.

**Scheme 3****Scheme 4**

Experimental Section

General. Yields refer to isolated pure products. The products were characterized by their spectral ($^1\text{H-NMR}$, IR) and melting and boiling points. All $^1\text{H-NMR}$ spectra were recorded at 300 MHz in CDCl_3 relative to TMS (0.00 ppm).

Preparation of BABOT by oxidation of KBr with HNO_3 . To a stirred solution of 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane bromide (9.056 g, 32 mmol) and potassium bromide (7.616 g, 64 mmol) in distilled water (30 mL) was added nitric acid solution (63% 16.0 g, 160 mmol) drop by drop. A yellow-orange precipitate was formed. Stirring of the resulting mixture was continued for 1h and then the precipitates were isolated by filtration and washed with distilled water (3×10 mL). The filtered cake was dried under vacuum and resulted in yellow crystals (10.773 g, 76% yield) which its physical data are consistent with those reported in the literature.¹⁹

Oxidation of methyl phenyl sulfide with BABOT in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$. To a stirred solution of methyl phenyl sulfide (0.124 g, 1 mmol) in CH_3CN (3 mL) and H_2O (1 mL) was added BABOT (0.443 g, 1 mmol) at room temperature. The reaction mixture was left stirring at room temperature and the progress of the reaction was monitored by TLC using Cyclohexane/Ethylacetate (7:3) as eluent. After completion of the reaction, the reaction mixture was poured into saturated NaHCO_3 solution (10 mL) and extracted with ethyl acetate (3×15 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to give almost pure methyl phenyl sulfoxide in 97% yield which its physical data are consistent with reported in literature.

Oxidation of methyl phenyl sulfide with BABOT on hydrated silicael in solvent-free conditions. Dry silica gel (1 g) was placed in a 100-mL round bottom flask containing a magnetic stirring bar. Water (0.5 g) was added to the vigorously stirred silica gel drop by drop. After complete addition of the water, stirring continued until a free flowing powder was obtained (5 min).

In a mortar was added methyl phenyl sulfide (0.124 g, 1 mmol), BABOT (0.443 g, 1 mmol) and hydrated silica gel (1.5 g) at room temperature and the mixture was grounded with a pestle. After Completion of the reaction (Monitored by TLC) the mixture was washed with ether (3×20 mL) and filtered off. The combined organic layers were dried on MgSO_4 and evaporated under vacuum to give almost pure methyl phenyl sulfoxide in 95% yield which its physical data are consistent with reported in literature.

Regeneration of BABOT. After the residue was washed with ether and filtrated, the filtered cake was washed with water (3×20 mL) to dissolve the 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane bromide. Then, to the combined aqueous solution was added KBr (0.238 g, 2 mmol) and then HNO_3 solution (0.500 g, 5 mmol) drop wise during 30 min to obtain BABOT as yellow crystals (0.287 g, 65% yield).

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