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Cu(II)-catalyzed oxidation of sulfides

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ABSTRACT

A variety of sulfides and disulfides were converted into the corresponding sulfoxide derivatives with 70% *t*-BuOOH (water) as the oxidant in the presence of catalytic quantity of $CuBr_2$. The method described does not involve cumbersome work-up, has wide range of applicabilities, exhibits chemoselectivity, and proceeds under mild reaction conditions, and the resulting products are obtained in good yields within reasonable time.

Catalytic oxidation processes play a key role in the manufacture of bulk and fine chemicals.[1] Sulfides may be considered as important intermediates in organic chemistry owing to their versatile usage in fundamental research;[2] especially the chiral sulfoxides serve as important intermediates in the synthesis of biologically and medicinally important compounds.[3] They are also employed in the large scale separation of radioactive and less-common metals.[4] They often play an important role as antiulcer,[5] antiatherosclerotic,[6] antihelmintic,[7] antihypertensive,[8] and cardiotonic agents,[9] as well as psycotonics[10] and vasodilators.[11] The most popular and widely used method for the preparation of sulfoxides is the oxidation of the corresponding sulfides. Literature cites several important methods for this transformation.[12] The use of traditional oxidants such as trifluoroperacetic acid,[13] HNO_3/H_2SO_4 solution in nitromethane,[14] iodic acid,[15] and other hypervalent iodides[16] are well established for such transformation. However, most of these reagents show unsatisfactory performance in medium- to large-scale because of low and effective oxygen content and have to be used in larger amounts. In addition, these methods bear high cost and often lead to the generation of environmentally unfavorable byproducts.

Some interesting transition-metal catalyzed transformations have been reported which include the use of vanadium,[17] rhenium,[18] iron,[19] manganese,[20] and titanium[21] for the selective oxidation of sulfides to sulfoxides in the presence of a suitable oxidant. A recent efficient methodology for the transformation of sulfides into sulfoxides employs a vanadium based catalytic process along with H_2O_2 in the presence of ionic liquids as solvent.[22] However, the high cost and the viscosity associated with ionic liquids hampered the commercialization of this process. Recently, self-catalyzed sulfoxidation reaction at high temperature (i.e., 70 °C) with H_2O_2 has been reported.[23] It is highly desirable to find simple, less expensive, safe, and high efficiency sulfoxidation methods that will selectively oxidize sulfides to sulfoxides but not sulfones. Our recent success in oxidation reactions with environmentally benign salts further inspired us to examine the capability of Cu(II) for the conversion of sulfides into sulfoxides/sulfones, in the presence of a suitable oxidant.[24] The preference of Cu(II) is obvious because of its stability under ambient conditions, inexpensive nature, and ease of availability.

Initial attempts to optimize the reaction conditions for the oxidation of sulfides were performed with methyl phenyl sulfide as a suitable substrate in the presence of different solvents, oxidants and 5 mol % of different Cu(II) salts (Table 1). The conversion of methyl phenyl sulfide into methylsulfinylbenzene is extremely facile in the presence of 5 mol % $CuBr_2$ and 5 equiv 70% *t*-BuOOH (water) as the oxidant in MeCN under reflux condition. This conversion is almost negligible (<10%) in the absence of $CuBr_2$. Lower stoichiometric amounts of *t*-BuOOH (water) resulted in lower isolated yield of product. The reaction took 1.5 h for completion with 5 mol % $CuBr_2$ and 5 equiv 5 M *t*-BuOOH (decane) with 85% isolated yield of the product under these conditions. With 30% H_2O_2 as the oxidant, the reaction yielded 60% of the product after 24 h. Among the different solvents used in this study (Table 1, entries 1–7), MeCN yielded best results. The other Cu(II) salts (Table 1, entries 8–12) were not as good with respect to $CuBr_2$. It is pertinent to highlight herein that the mass spectra of the crude product did not reveal the presence of sulfone during this entire optimization,

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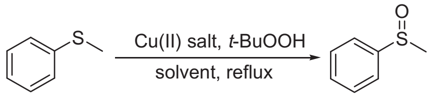
Table 1

Optimization of reaction conditions for the conversion of methyl phenyl sulfide to methylsulfinylbenzene with different solvents, 5 equiv 70% *t*-BuOOH (water) and 5 mol % Cu(II) salts



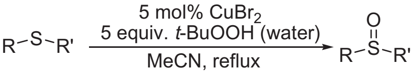
Entry	Catalyst	Solvent	Time[a] (h)	Yield[b] (%)
1	$CuBr_2$	MeCN	0.75	94
2	$CuBr_2$	EtOAc	4.5	88
3	$CuBr_2$	Toluene	20	90
4	$CuBr_2$	DMF	24	60
5	$CuBr_2$	DMSO	24	70
6	$CuBr_2$	EtOH	12	89
7	$CuBr_2$	CH_3NO_2	2	91
8	$CuCl_2{\cdot}2H_2O$	MeCN	8	90
9	$Cu(OAc)_2{\cdot}H_2O$	MeCN	24	60
10	$CuSO_4{\cdot}5H_2O$	MeCN	10	89
11	$Cu(NO_3)_2{\cdot}3H_2O$	MeCN	12	90
12	$Cu(acac)_2$	MeCN	9	88

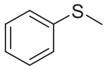
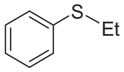
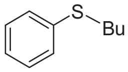
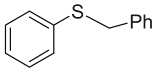
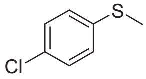
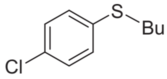
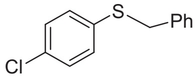
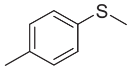
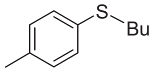
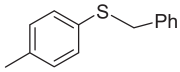
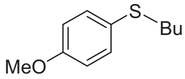
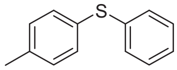
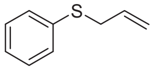
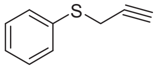
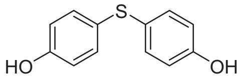
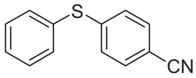
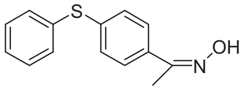
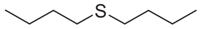
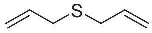
[a] Monitored using TLC until all the sulfide was found consumed.

[b] Isolated yield after column chromatography of the crude product.

Table 2

$CuBr_2$ catalyzed selective oxidation of sulfides to sulfoxides[a]



Entry	Sulfide	Time[b] (h)	Yield[c] (%)
1		0.75	94
2		2.25	93
3		2.50	94
4		2	93
5		4	89
6		5.50	88
7		3.50	90
8		1.50	93
9		1.30	94
10		1.50	91
11		1.60	93
12		12	87
13		22	85
14		2.30	86
15		3	92
16		2.75	85
17		24	80
18		2.25	89
19		1.60	88

[a] Reactions performed in MeCN with 5 mol % $CuBr_2$ and 5 equiv 70% *t*-BuOOH under reflux conditions.

[b] Monitored using TLC until all the sulfide was found consumed.

[c] Isolated yield after column chromatography of the crude.

even in the presence of 10 mol % $CuBr_2$ and 20 equiv *t*-BuOOH (water), making this conversion 100% selective.

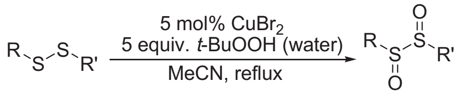
Having optimized the right conditions for sulfoxidation, we continued our quest with a variety of aromatic and aliphatic substrates (Table 2). A variety of substituted and unsubstituted aryl–alkyl (Table 2, entries 1–11), diaryl (Table 2, entry 12), benzyl–aryl (Table 2, entries 4, 7 and 10), and dialkyl sulfide (Table 2, entry 18) were successfully and selectively oxidized to the corresponding sulfoxides in high yields and purity. Sulfides with additional functionalities susceptible to oxidation or deprotection such as alkenes (Table 2, entries 13 and 19), alkynes (Table 2, entry 14), phenol (Table 2, entry 15), nitrile (Table 2, entry 16), and oxime (Table 2, entry 17) were found to yield sulfoxides without affecting the sensitive functional groups. It is interesting to note that no epoxidation was observed during the oxidation of allyl phenyl sulfide (Table 2, entry 13). Phenyl propargyl sulfide was oxidized to the sulfoxide in good yields (Table 2, entry 14) without any dimerization. Again, it is very important to note that not a trace of sulfone was ever seen in the mass spectra of the various crude reaction mixtures.

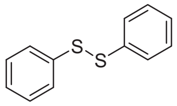
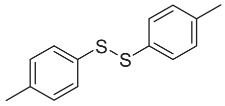
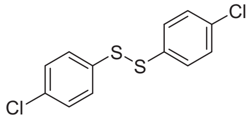
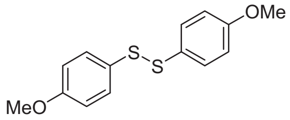
Our catalytic system has the capability of transforming disulfides to disulfoxides under similar reaction conditions. The results are depicted in Table 3.

This reaction reveals the same general trends as seen for sulfides (Table 2). It is noteworthy that neither mono sulfoxide nor sulfone was realized in this reaction.

The kinetic studies of the sulfoxidation with methyl phenyl sulfide, *bis*(4-hydroxy)phenylsulfide and 4-methoxydilsulfide were explored next. High-pressure liquid chromatography (HPLC) was used to determine the various starting materials and products present as a function of time. The concentration of reactant and product for the oxidation of methyl phenyl sulfide is shown in Figure 1. The concentration of the sulfide decreases steadily while that of the sulfoxide increases. We have calculated the rate of such reactions. As an example let us consider the conversion of methyl phenyl sulfide into methylsulfinylbenzene. Van't Hoff differential method was used to determine the order (n) and rate constant (k) (Fig. 2). From Figure 1, the rate of the reaction at different concentrations can be estimated by evaluating the slope of the tangent at each point on the curve corresponding to that of methyl phenyl sulfide. With these data, $\log_{10}$ (rate) versus $\log_{10}$ (concentration) is plotted. The order (n) and rate constant (k) are given by the slope of the line and its intercept on the $\log_{10}$ (rate) axis. From Figure 2, it is clear that this reaction proceeds with second-order kinetics ($n = 2.03$) and the rate constant $k = 1.32 \times 10^{-2}\ \mathrm{L\,mol^{-1}\,s^{-1}}$. For the other substrates namely *bis*(4-hydroxy)phenylsulfide and

Table 3
$CuBr_2$ catalyzed selective oxidation of disulfides to disulfoxides[a]



Entry	Disulfide	Time[b] (h)	Yield[c] (%)
1		18	87
2		10	85
3		21	86
4		1.50	92

[a] Reactions performed in MeCN with 5 mol % $CuBr_2$ and 5 equiv 70% *t*-BuOOH under reflux conditions.
[b] Monitored using TLC until all the disulfide was found consumed.
[c] Isolated yield after column chromatography of the crude.

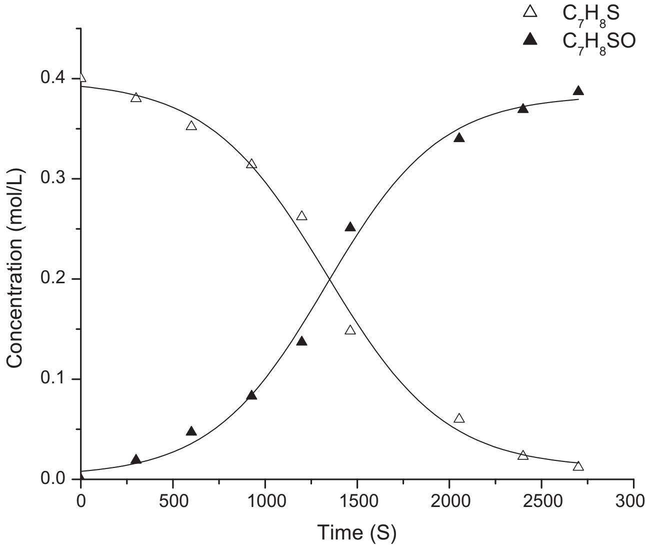


Figure 1. Concentration versus time in the oxidation of methylphenylsulfide with 5 mol % $CuBr_2$ and 5 equiv ^{t}BuOOH in acetonitrile under reflux condition.

4-methoxydilsulfide, the order of the reaction $n \approx 2$ with rate constants (k) $4.30 \times 10^{-4}\ \mathrm{L\ mol^{-1}\ s^{-1}}$ and $5.62 \times 10^{-3}\ \mathrm{L\ mol^{-1}\ s^{-1}}$, respectively (see Supplementary data for details).

On the basis of the literature available for sulfoxidation with iron compounds,[25] we propose the following mechanism as shown in Scheme 1.

The role of $CuBr_2$ is to form the active oxidant–substrate complex. Thereafter, transfer of oxygen to sulfur leads to the formation of product.

In summary, we have developed a simple, efficient, chemoselective, and inexpensive catalytic method for the oxidation of sulfides to sulfoxides with a table top reagent such as $CuBr_2$.[26] It is noteworthy that this method does not use ligands and other additives.

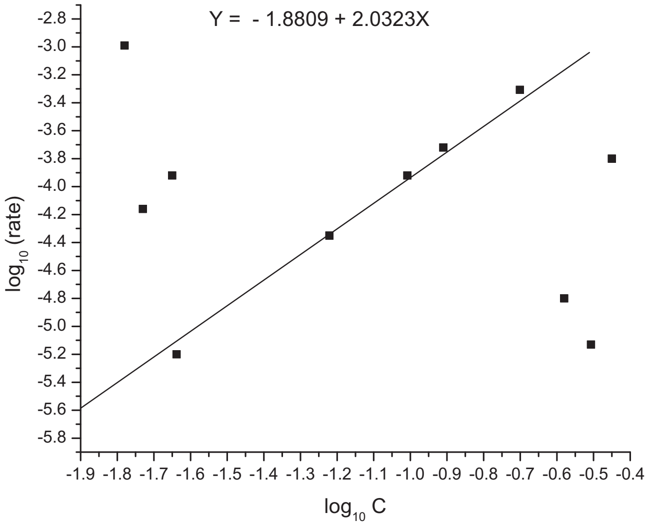
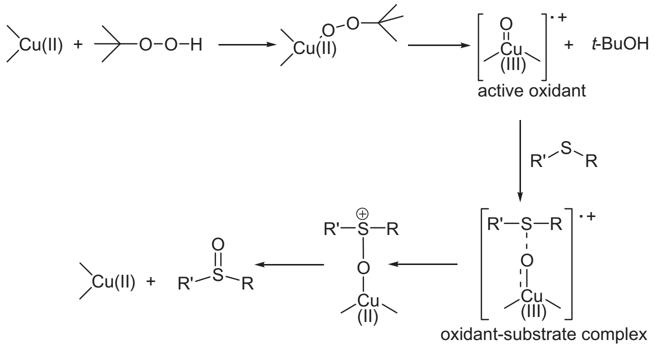


Figure 2. Van't Hoff differential plot for the oxidation of methylphenylsulfide with 5 mol % $CuBr_2$ and 5 equiv ^{t}BuOOH in acetonitrile under reflux condition.



Scheme 1. Proposed mechanism for sulfoxidation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.081.

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26. *Typical experimental procedure*: To a stirred solution of CuBr$_2$ (11.2 mg, 0.05 mmol) and sulfide/disulfide (1 mmol) in 2.5 mL MeCN was added 70% *t*-BuOOH (water) (0.64 mL, 5 mmol). The reaction mixture was heated to reflux and the progress was monitored by TLC until all sulfide/disulfide was found consumed. After completion, MeCN was evaporated and the crude mixture was washed with NaHCO$_3$ and extracted with ethyl acetate. The ethyl acetate was evaporated followed by flash column purification to obtain the pure sulfoxides. The product was characterized using ^{1}H, ^{13}C NMR spectroscopy and ESI-MS. The data were found to be in accordance with the literature (see Supplementary data).