

Self-Catalyzed Oxidation of Sulfides with Hydrogen Peroxide: A Green and Practical Process for the Synthesis of Sulfoxides

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Abstract: A self-catalyzed selective oxidation of sulfides to sulfoxides has been developed. The scope of the protocol is demonstrated in the selective oxidation of 17 different substrates. High yields and chemoselectivity (in general >90%) are achieved in most cases.

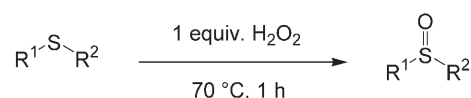
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For the sustainable development of our economy, the further use of green chemistry is an important issue. In this respect preventing waste, but not treating or cleaning it up, is a basic requirement.^[1] In a given chemical process, reducing the use of toxic chemicals and waste remitting with high atom-efficiency are key points. One of the major challenges of organic synthesis is undoubtedly to develop more environmentally friendly oxidation processes.^[2] As an example, herein we report an efficient oxidation of sulfides to sulfoxides.

The selective oxidation to give sulfoxides has attracted much attention over the years since sulfoxides constitute useful building blocks in organic synthesis for the preparation of biologically active compounds and activation of enzymes.^[3] Traditionally, the synthesis is performed with a stoichiometric amount of organic or inorganic oxidant and a large amount of toxic waste is produced.^[4] In order to run this transformation in a “greener” manner, there are three factors that can be improved: use of (i) environmentally benign oxidants, (ii) less or even no organic solvent and (iii) non-toxic catalysts. Hence, aqueous hydrogen peroxide has been used as the terminal oxidant since the beginning of the last century,^[5] because it is cheap, environmentally benign, readily available, of high atom-efficiency (47%), and theoretically only generates water as the by-product.^[6] Different kinds of catalysts including acids,^[7] iron,^[8] vanadium,^[9] tung-

sten,^[10] manganese,^[11] copper,^[12] titanium,^[13] platinum,^[14] and magnesium^[15] based systems were used to obtain good yields.

During our continuous investigation for selective oxidation reactions using aqueous hydrogen peroxide as the terminal oxidant,^[16] we found serendipitously that the sulfoxides themselves, produced during the reaction, can be very effective catalysts for the selective oxidation of sulfide to sulfoxide (Scheme 1). This



Scheme 1. Selective oxidation of sulfides to sulfoxides.

is one of the relatively few cases of self-catalyzed reactions.^[17] This process needs no additional catalysts, solvents and proceeds highly selectively.

In our initial exploratory experiments applying thioanisole in the presence of different transition metal catalysts under solvent-free conditions, all reactions gave good yields of methylsulfinylbenzene after 12 h at room temperature. To our surprise, the control experiment without catalyst also showed high yield of the corresponding sulfoxide (>98%, GC yield). At 70°C, the oxidation of thioanisole to methylsulfinylbenzene with 1 equiv. 30 wt % H₂O₂ gave even full conversion within 1 h! When the reaction was carried out at room temperature, the yield to methylsulfinylbenzene was only 63% (GC yield) after 6 h. As shown in Figure 1 the reaction started at a very low rate. However, when a small amount of methylsulfinylbenzene is produced, the reaction is accelerated and became faster and faster. After the formation of 4.7% sulfoxide in the mixture (5 min), ~90% of thioanisole could be further converted into methylsulfinylbenzene in the next 15 min. It is clear that the concentration of methylsulfinylbenzene, but not the concentration of thioanisole or hydrogen peroxide determined the initial reaction rate. In order to clarify this

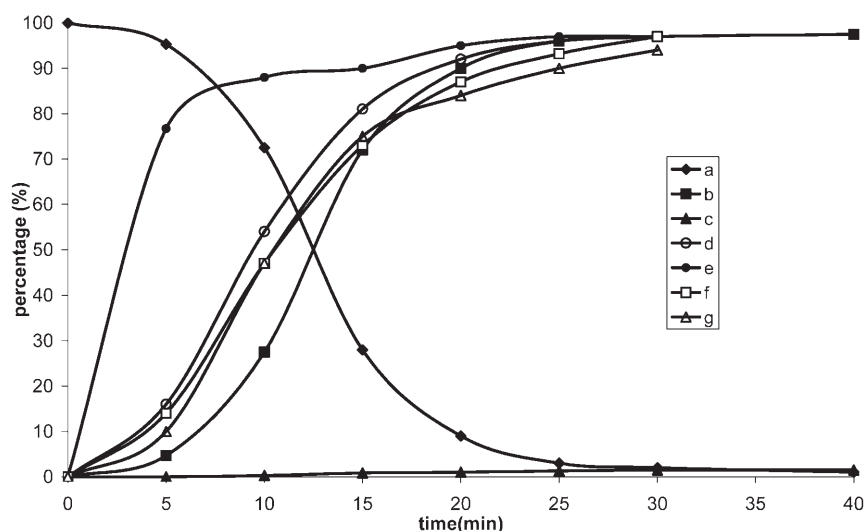


Figure 1. Typical reaction conditions: 5.0 mmol (620 mg) thioanisole and 5.0 mmol (0.50 mL) 30 wt % H₂O₂ and the appropriate catalyst [no sulfoxide or sulfone was added for (a)–(c), 5 mol % methylsulfinylbenzene, 20 mol % methylsulfinylbenzene, 20 mol % methylsulfonylbenzene, or 20 mol % dimethyl sulfoxide were initially present in (d), (e), (f) and (g) respectively] were heated at 68–70 °C. (a) thioanisole (%) vs. reaction time; (b) methylsulfinylbenzene (%) vs. reaction time; (c) methylsulfonylbenzene (%) vs. reaction time; (d), (e), (f) and (g) methylsulfonylbenzene (%) vs. reaction time.^[18]

effect, methylsulfinylbenzene was further added to the reaction mixture. 16 % or 76 % of thioanisole are converted in 5 min with 5 or 20 mol % of added methylsulfinylbenzene. The reaction rates became similar after 20 min, because much more sulfoxide than the pre-added amount was produced. This is a direct evidence for the acceleration of the sulfide oxidation by the self-generating sulfoxide. Interestingly, both phosphine oxides and nitroxyl radicals decrease the rate of the sulfide oxidation. Hence, the addition of 20 mol % of trioctylphosphine oxide and 20 mol % TEMPO gave a significantly lower yields (50–60 % after 30 min) compared with the blank experiment (90 % after 30 min). Also the corresponding sulfone is not the catalyst in the reaction system because up to 60 min, only ~1 % of methylsulfonylbenzene is observed by GC-FID and GC-MS. In fact, the reaction in the presence of 20 mol % sulfone is much slower

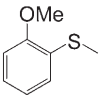
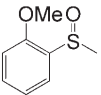
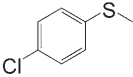
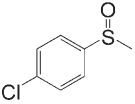
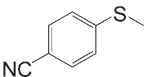
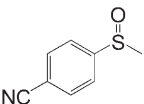
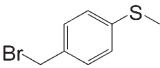
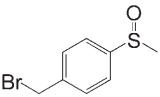
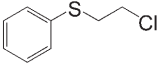
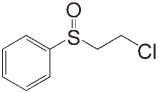
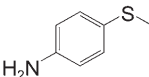
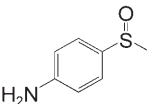
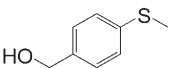
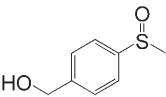
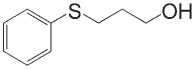
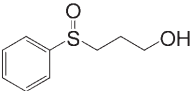
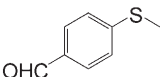
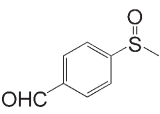
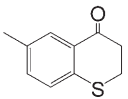
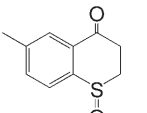
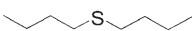
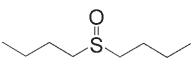
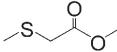
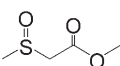
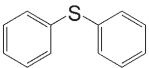
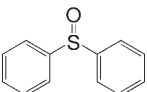
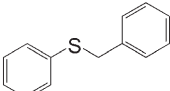
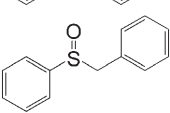
than that with sulfoxide. The addition of dimethyl sulfoxide exhibited comparable activity to methylsulfonylbenzene but it was much lower than with methylsulfinylbenzene, Figure 1 (h). Therefore, the structure of sulfoxide but not only the functional group itself has a great effect on its activity.

In order to explore the generality for this protocol, we further tested this selective oxidation with various sulfides (Table 1). Typical sulfides, such as thioanisole, methyl *p*-tolyl sulfide and ethyl phenyl sulfide gave the corresponding sulfoxides in excellent yields, 92–97 % (Table 1, entries 1–3). It is noteworthy that only 1 % sulfones formed in the oxidation of thioanisole and methyl *p*-tolyl sulfide. This indicates that the present protocol is very selective and easily controllable. Functional groups are also tolerated in this procedure. Methyl phenyl sulfide derivatives with –OMe, –Cl, –CN, –CH₂Br and –CH₂CH₂Cl substituents re-

Table 1. Selective oxidation of sulfides to sulfoxides with hydrogen peroxide.^[a]

Entry	Substrate	Product	Sulfoxide:Sulfone ^[b]	Yield ^[c] [%]
1			99:1	97
2			99:1	94
3			94:6	92

Table 1. (Continued)

Entry	Substrate	Product	Sulfoxide:Sulfone ^[b]	Yield ^[c] [%]
4			99:1	98
5			97:3	91
6			98:2	88
7			91:9	52
8			94:6	90
9			91:1	90
10			99:1	90
11			99:1	87
12			88:12	69
13			99:1	93
14			96:4	87
15			96:4	81
16 ^[d]			83:17	80
17 ^[e]			86:14	84

^[a] 2.0 mmol sulfide, 2.0 mmol H₂O₂ (30 wt % in water, 1 equiv., VWR), 70 °C (oil bath temperature), 1 h.

^[b] Determined by GC-MS.

^[c] Isolated yield for sulfoxide.

^[d] 24.0 mmol H₂O₂, 12 h.

^[e] 16.0 mmol H₂O₂, 2 h.

sulted in excellent yields (Table 1, entries 4–8). With 2-(methoxyphenyl)methylsulfane, the isolated yield reached 98 % (Table 1, entry 4). However, a lower yield (52 %) is obtained with 4-(methylthio)benzyl bromide. Here, GC-MS analysis showed that hydrolysis of the bromomethyl group to the corresponding 4-methylthiobenzyl alcohol and oxidation of the benzyl bromide group to 4-methylthiobenzylaldehyde are the major side reactions.

The selective oxidation of compounds with two functional groups within one molecule is always an interesting topic in oxidation chemistry. Hence, sulfides containing oxidizable $-\text{NH}_2$, $-\text{CH}_2\text{OH}$, $-\text{CHO}$ and $-\text{C}(\text{O})-$ groups were tested (Table 1, entries 9–13). To our delight, for compounds containing amine and alcohol groups, the oxidation occurred selectively on the sulfur atom. Even with 4-methylthiobenzaldehyde, a good isolated yield of 69 %, was obtained.

Moreover, for the selective oxidation of aliphatic sulfides, good yields are also achieved (Table 1, entries 14 and 15). Methyl (methylthio)acetate was easily oxidized into methyl methylacetate sulfoxide, a synthetically useful reagent, in 81 % yield.^[19] Notably, this protocol can be easily scaled up. As a demonstration of a 200-mmol scale reaction, 29.2 g of di-*n*-butyl sulfide were oxidized to di-*n*-butyl sulfoxide. Merely by extracting the reaction mixture was a quantitative yield of product obtained with > 93 % purity.

The formation of sulfoxides from diphenyl sulfide and benzyl phenyl sulfide are more difficult to achieve under the known standard oxidation procedures. Even in the presence of highly active catalysts, much more hydrogen peroxide and longer reaction times were necessary in order to accomplish satisfactory results.^[10b] In the presence of an excess of hydrogen peroxide, the yield for diphenyl sulfoxide reached 80 % (Table 1, entry 16) and the yield of benzyl phenyl sulfoxide reached 84 % (Table 1, entry 17).

In conclusion, a self-catalyzed selective oxidation of sulfides to sulfoxides has been developed for the first time. The scope of the protocol is demonstrated in the selective oxidation of 17 different substrates. High yield and chemoselectivity (in general > 90 %) are achieved in most cases. Compared with the previous protocols, this system has the advantage that no organic solvents or any additional catalyst is necessary. This makes the reaction environmentally benign, more practical and easily manageable. The study of the reaction mechanism and the development of a stereoselective version of this reaction are now undergoing in our laboratory.^[20]

Experimental Section

General Procedure for the Self-Catalyzed Selective Oxidation of Sulfide to Sulfoxide

All reactions were carried out in an oil bath (69–70 °C, oil bath temperature). To a glass reactor (40 mL), 2.0 mmol (0.292 g) di-*n*-butyl sulfide and 2.0 mmol H_2O_2 (30 wt % in water, from VWR, 0.20 mL) were added, respectively. The reaction was vigorously stirred (500–750 rpm) at 70 °C for 1 h. The mixture was then cooled to room temperature and extracted by CH_2Cl_2 (20 mL $\times$ 3). After drying with anhydrous Na_2SO_4 , the organic mixture was removed in vacuum and a colorless liquid (0.301 g) was obtained. The sample was analyzed by GC-MS, which indicated that the ratio between sulfoxide and sulfone was 96:4. ^1H NMR analysis showed that the ratio between sulfoxide and sulfone was 95:5.

Analytically pure dibutyl sulfoxide was obtained by column chromatography (silica gel 60, 70–230 mesh) using CH_2Cl_2 to ethyl acetate as the gradient eluent. After removal of the solvent and drying under high vacuum for 2 h, a white solid was obtained; yield: 282 mg (87 %).

Example of a Scaling-Up for the Selective Oxidation of Dibutyl Sulfide

To a round-bottom flask (250 mL), 200 mmol (29.2 g) of di-*n*-butyl sulfide and 200 mmol H_2O_2 (30 wt % in water, from VWR, 20 mL) were added respectively. The reaction mixture was vigorously stirred (500–750 rpm) at 70 °C for 1 h. During the reaction, the system should be open to air and well cooled with a condenser.^[21] The mixture was then cooled to room temperature and extracted by ethyl acetate (200 mL $\times$ 4). After drying with anhydrous Na_2SO_4 , the organic mixture was removed in vacuum and a colorless liquid (34.6 g) was obtained. The sample was analyzed by GC-MS, which indicated that the ratio between sulfoxide and sulfone was 93:7. ^1H NMR analysis showed that the ratio between sulfoxide and sulfone was 93:7. *1-(Butylsulfinyl)butane*: R_f = 0.84 (ethyl acetate); colorless semi-solid; ^1H NMR (300.1 MHz, CDCl_3): δ = 0.93 (6H, t, J = 7.3 Hz), 1.35–1.54 (4H, m), 1.66–1.76 (4H, m), 2.54–2.70 (4H, m); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 13.7, 22.1, 24.6, 52.1; GC-MS (E.I., 70 eV): m/z (rel. int.) = 162 (M^+ , 1), 106 (12), 89 (32), 63 (16), 57 (35), 56 (12), 55 (22), 41 (100), 39 (36).

Acknowledgements

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- [18] Typical reaction conditions: 5.0 mmol (620 mg) thioanisole and 5.0 mmol (0.50 mL) 30 wt % H₂O₂ and the appropriate catalyst [no sulfoxide or sulfone was added for (a)–(c), 5 mol % methylsulfinylbenzene, 20 mol % methylsulfinylbenzene, 20 mol % methylsulfonylbenzene, or 20 mol % dimethyl sulfoxide were initially present in (d), (e), (f) and (g).] were heated at 68–70 °C. A small aliquot (~20 µL) was taken out during the reaction and quenched with CH₂Cl₂ (~1.5 mL) and the reaction was monitored by GC-FID. All the reactions were performed in a multi-reactor in parallel (Carousel 12 station, RADLEYS). The methylsulfinylbenzene added at beginning was subtracted by analyzing the sample before addition of hydrogen peroxide. Thioanisole does not react with 30 wt % H₂O₂ in CH₂Cl₂ at room temperature. In a control experiment, thioanisole (12.4 mg, 0.10 mmol) and 30 wt % H₂O₂ (10.0 µL) were dissolved in 2 mL CH₂Cl₂ and monitored by GC-MS. After 6 h, only < 0.1 % of thioanisole was converted to methylsulfinyl benzene.
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- [21] Even on this scale, we did not observe any explosion during the reaction. For safety reason, the system should be open to air and well cooled with a condenser.