

Communication

Effective Oxidation of Sulfides to Sulfoxides with Hydrogen Peroxide under Transition-Metal-Free Conditions

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Abstract: A “green” highly selective oxidation of organic sulfides to the corresponding sulfoxides was developed using hydrogen peroxide and glacial acetic acid under transition metal-free and mild conditions. The oxidation procedure is very simple and the products are easily isolated in excellent yields (90-99%).

Keywords: Sulfide, glacial acetic acid, hydrogen peroxide, selective oxidation, sulfoxide.

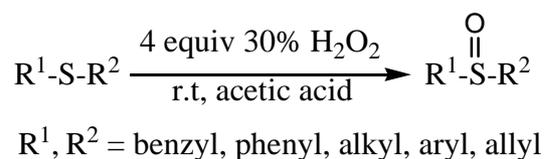
Introduction

The growth in the chemistry of organic sulfoxides during last decade was due to their importance as synthetic intermediates for the production of a wide range of chemically and biologically active molecules. They often perform a major function as therapeutic agents such as anti-ulcer (proton pump inhibitor) [1], antibacterial, antifungal, anti-atherosclerotic [2], antihypertensive [3] and cardiogenic agents [4], as well as psychotonics [5] and vasodilators [6].

The oxidation of sulfides to sulfoxides is the most straightforward synthetic route to the latter, and numerous reagents and oxidative procedures are available for this transformation. However, many of them cause overoxidation to the corresponding sulfones. Therefore, control of the reaction conditions, that is, time, temperature and the relative amount of oxidants, plays an important role in avoiding the formation of oxidation side products, but this is often hard to achieve and therefore there is still considerable interest in the development of selective oxidants for this transformation [7-12].

Much of the current work in this area focuses on the use of transition-metal catalyzed processes [7-22]. However, a large number of such oxidation reactions often require the use of toxic metal reagents or catalysts. Consequently, from a Green Chemistry standpoint it is very important to develop a “green” oxidation system for chemical manufacturing. Hydrogen peroxide is considered as an ideal “green” oxidant due to its strength and lack of toxic by-products. Among the research on the oxidation of sulfides to the corresponding sulfoxides under transition metal-free conditions [23-33] some most promising results were reported by Ravikumar *et al.* [34], in which hydrogen peroxide in solvent of hexafluoro-2-propanol was used for the selective oxidation of sulfides to sulfoxides. Although the yields of these reactions were quite high, hexafluoro-2-propanol is poisonous, expensive and volatile, which severely restrict its practical use in organic synthesis. In continuation of our current studies on the selective oxidation of hydrocarbons [35-40] we wish to report herein a very efficient and simple method for the oxidation of sulfides to the corresponding sulfoxides using H₂O₂ under mild conditions, as shown in Scheme 1.

Scheme 1. Oxidation of sulfides to the corresponding sulfoxides.



Results and Discussion

Methyl phenyl sulfide was selected as a model substrate for optimization, and the oxidation of this substrate in various solvents was studied. Among the solvents examined, glacial acetic acid was the most effective (Table 1, entries 1-5). The reaction was also carried out at different temperatures under the same conditions. As the results indicate (Table 1, entries 6-9), the oxidation proceeded to completion faster at elevated temperatures. Further, when the oxidation of methyl phenyl sulfide was carried out using different concentrations of hydrogen peroxide, the reaction did not reach completion using less than 8 mmol of H₂O₂. However, when a large concentration was employed neither the conversion nor selectivity of the reaction was improved (Table 1, entries 10-13). The large excess of hydrogen peroxide required was a result of its decomposition in acetic media. The oxygen released in the decomposition played little role in the oxidation of the sulfides, as proven by the fact that the oxidation occurred in poor yield when carried out in the absence of hydrogen peroxide by bubbling molecular oxygen through the reaction mixture under similar reaction conditions (Table 1, entry 14). In an independent experiment the oxidation of methyl phenyl sulfoxide to the corresponding sulfones was investigated under the same reaction conditions; no oxidation took place during 120 min and the starting material was recovered.

Table 1. Oxidations of methyl phenyl sulfide ^a.

Entry	H ₂ O ₂ (mmol)	Solvent (2 mL)	Time (min)	Temp. (°C)	Conversion (%) ^b	Sulfoxide Selectivity (%) ^b
1	8	CH ₃ COOH	80	25	100	>99
2	8	CH ₂ Cl ₂	90	25	0	0
3	8	CH ₃ CN	90	25	<5	>99
4	8	CH ₃ NO ₂	90	25	<5	>99
5	8	CH ₃ OH	240	25	20	>99
6	8	CH ₃ COOH	440	0	93	>99
7	8	CH ₃ COOH	35	45	100	>99
8	8	CH ₃ COOH	20	60	100	>99
9	8	CH ₃ COOH	8	80	100	>99
10	1	CH ₃ COOH	80	25	8	>99
11	2	CH ₃ COOH	80	25	13	>99
12	5	CH ₃ COOH	80	25	23	>99
13	8	CH ₃ COOH	80	25	100	>99
13	10	CH ₃ COOH	75	25	100	>99
14 ^c	-	CH ₃ COOH	600	25	7	>99

^a In all experiments 2 mmol of substrate were used.

^b Isolated yield on the basis of the weight of the pure product obtained.

^c The reaction was carried out under an atmosphere of O₂ instead of in the presence of 30% H₂O₂.

The oxidations of other sulfides such as diaryl, dibenzyl, dialkyl, diallyl, arylbenzyl, arylalkyl, benzyl -alkyl, allylphenyl and cyclic sulfides were then examined using the optimized reaction conditions (Table 2). In all cases, the reactions resulted in 100% conversion of the sulfides. In the case of benzyl sulfides (Table 2, entries 2 and 6), no oxidation was observed at the benzylic C-H bond. Similarly, the carbon-carbon double bonds in allyl sulfides remained intact during the oxidation (Table 2, entries 5 and 8). This procedure can also be applied to the oxidation of cyclic sulfides (Table 2, entry 10).

Table 2. Oxidation of sulfides to sulfoxides with hydrogen peroxide ^a.

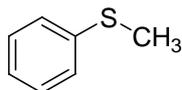
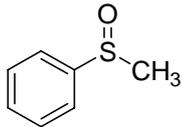
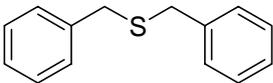
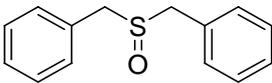
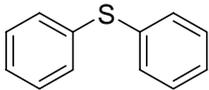
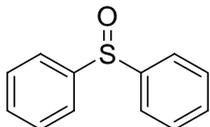
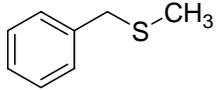
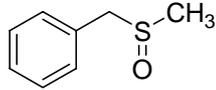
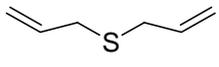
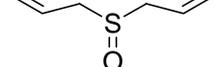
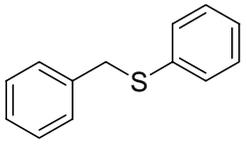
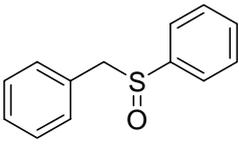
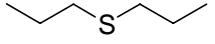
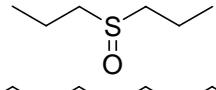
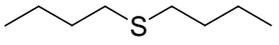
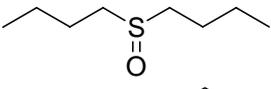
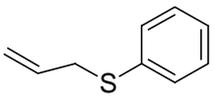
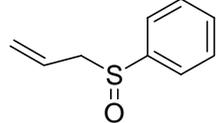
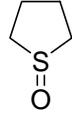
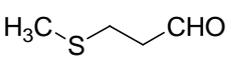
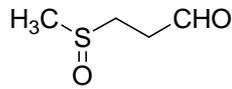
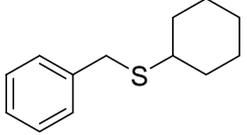
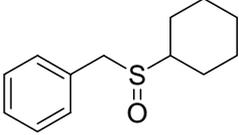
Entry	Substrate	Time (min)	Conversion (%)	Sulfoxide ^b	Yield (%) ^c
1		80	100		99
2		120	100		93
3		75	100		94

Table 2. Cont.

Entry	Substrate	Time (min)	Conversion (%)	Sulfoxide ^b	Yield (%) ^c
4		50	100		92
5		35	100		90
6		70	100		93
7		50	100		91
8		60	100		92
9		48	100		90
10		30	100		96
11		26	100		93
12		45	100		91

^a 2 mmol of substrate at room temperature and 8 mmol of 30% aqueous H₂O₂, in glacial acetic acid (2 mL) at room temperature.

^b The products were identified by comparison of physical and spectroscopic properties with authentic compounds.

^c Isolated yields on the basis of the weight of the pure product obtained.

Large scale oxidation of methyl phenyl sulfoxide (2 mol) was also investigated and the results demonstrated that oxidation took place in good yield (typically less than 2% yield was lost). The kinetic studies show that the oxidation of sulfide is a second order reaction and is not acid catalyzed, so the reaction times remained constant as a result of increasing the acidities of the medium by the addition of trichloroacetic acid at fixed content of acetic acid. However, experiments demonstrate that dry hydrogen peroxide (percarbonate) in glacial acetic acid does not generate peracetic acid on standing. Further, kinetic study with peracetic acid under identical reaction conditions reveal that the oxidation of sulfides is very fast; too fast to follow by titrimetry. Although the exact mechanism of this transformation is still unclear, the oxidation probably involves the electrophilic attack of the peroxide oxygen on sulfur. Despite the fact that, protonated hydrogen peroxide is a powerful oxidizing

agent the oxidation of sulfides is ruled out by this oxidizing mediator as the reaction is not acid catalyzed; acetic acid and trichloroacetic acid fail to protonate hydrogen peroxide.

Conclusions

As shown, the proposed system was found to be a selective method for the hydrogen peroxide oxidation at room temperature of a variety of sulfides to the corresponding sulfoxides. Although the precise mechanism of this transformation is still uncertain, the oxidation probably involves the electrophilic attack of the peroxide oxygen on the sulfide sulfur atom. Moreover, this oxidation system is clean, safe and operationally simple and the yields of the products are high, so the oxidation method meets the needs of contemporary “green chemistry” and is suitable for practical synthesis.

Acknowledgements

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Experimental

General

All chemicals were used without further purification as received from different commercial sources (Merck, Aldrich, Fluka). All the isolated sulfoxide compounds were identified through comparison of their GLC (retention time) IR, NMR and melting points with literature data.

General method for the oxidation of sulfides to sulfoxides

Hydrogen peroxide (8 mmol, 30%) was slowly added to the sulfide (2 mmol) in glacial acetic acid (2 mL). The reaction mixture was then stirred at room temperature until thin layer chromatography indicated the reaction was complete. The resulting solution was neutralized with aqueous NaOH (4 M) and the product was extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to yield analytically pure product. Rate measurements were made in glacial acetic acid under second order conditions at constant temperature. For each kinetic run a fresh solution of the oxidant in glacial acetic acid was prepared and standardized iodometrically. The progress of the oxidation, with the sulfides present in excess over the oxidant, was followed by iodometric estimation of the unconsumed oxidizing agent.

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Sample Availability: Available from authors.