Tetrahedron Letters 51 (2010) 6939–6941

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

TMSCl-promoted selective oxidation of sulfides to sulfoxides with hydrogen peroxide

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ARTICLE INFO

Article history:
Received 1 August 2010
Revised 18 October 2010
Accepted 29 October 2010
Available online 4 November 2010

ABSTRACT

Selective oxidation of sulfides to sulfoxides is achieved using H_2O_2 and TMSCl as the promotor. Aromatic and aliphatic sulfides are oxidized to sulfoxides in excellent yields and in short reaction times. Different functional groups including ketone, alkene, ester, and alcohol are tolerated.

1. Introduction

Selective oxidation of sulfides to sulfoxides is a very important reaction in organic synthesis, since they are useful synthetic intermediates for the construction of various chemically and biologically significant molecules,[1] especially drugs and natural products.[2] The direct oxidation of sulfides is an important and widely studied reaction for the preparation of sulfoxides. Although a number of methods are available for the conversion of sulfides into sulfoxides,[3–9] there are various limitations such as the use of strong acidic or basic conditions, elevated temperatures, long reaction times, hazardous organic solvents and reagents, transition metal catalysts, the formation of sulfones as side products from over-oxidation and undesired side reactions occurring on other functional groups. Hence, there is still a need for the development of new, efficient, highly selective, and widely applicable methods for this transformation under mild reaction conditions.

The use of H_2O_2 as an oxidant has been studied extensively. Aqueous H_2O_2 has the advantage that it is a cheap, environmentally benign, and a readily available reagent.[10] Since water is the only expected side product, catalytic oxidation methods using this reagent are appealing, provided efficient catalysis is accomplished. This feature has stimulated the development of useful procedures for H_2O_2 oxidation, especially with various types of catalyst systems.[11]

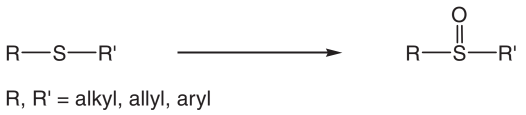
Trimethylsilyl chloride (TMSCl) is an efficient Lewis acid which has found widespread use as a catalyst in organic transformations.[12–14] To the best of our knowledge, there are no reports on TMSCl-mediated selective oxidation of sulfides.

In continuation of our recent work on the oxidation of sulfides,[15] herein we report an efficient protocol in which H_2O_2 has been used in the presence of TMSCl for the chemoselective oxidation of sulfides to sulfoxides in excellent yields and in short reaction times (Scheme 1).

In order to check the feasibility of the H_2O_2–TMSCl system in an organic medium, we performed the oxidation in acetonitrile, toluene, chloroform, and THF. The best results based on yields and times were achieved using acetonitrile.

We next performed a set of preliminary experiments on benzyl phenyl sulfide to examine the effects of different amounts of aqueous 30% H_2O_2 and TMSCl in acetonitrile at 25 °C (Table 1).

It is noteworthy that in a blank experiment (Table 1, entry 1), no significant oxidation was observed in the absence of TMSCl, and



Scheme 1. Reagents and conditions: H_2O_2 (2 equiv), TMSCl (1 equiv), CH_3CN, 25 °C.

Table 1
Optimization of the reaction conditions for the oxidation of benzyl phenyl sulfide using H_2O_2 and TMSCl[a]

Entry	30% H_2O_2 (mmol)	TMSCl (mmol)	Yield[b] (%)
1	2	0	35[c]
2	2	0.75	75
3	1	1	40
4	2	1	98

[a] Reaction conditions: benzyl phenyl sulfide (1 mmol), 2 min, 25 °C.
[b] Isolated yield.
[c] Reaction not complete after 6 h.

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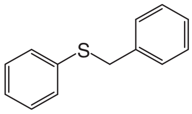
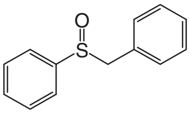
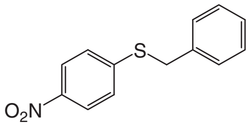
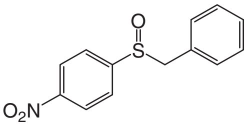
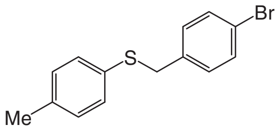
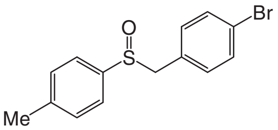
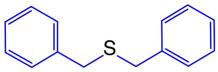
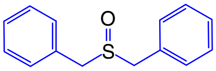
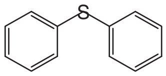
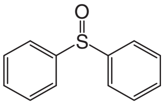
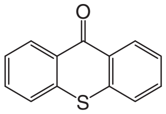
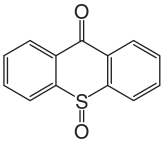
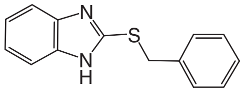
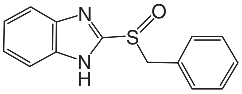
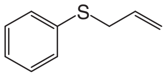
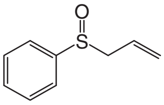
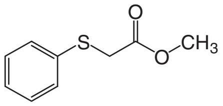
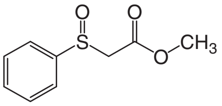
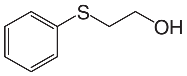
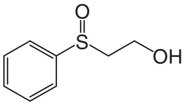
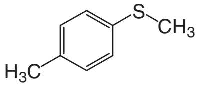
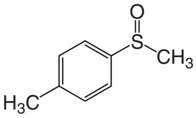
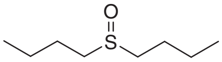
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.171

only a low yield of sulfoxide was obtained in the presence of 2 equiv of H_2O_2 after 6 h.

Increasing the temperature to 50 °C reduced the reaction time, however, 15% of the corresponding sulfone was formed along with the sulfoxide. Control experiments showed that oxidation with less 30% H_2O_2 (1 equiv) took longer (40 min) while the use of excess 30% H_2O_2 (3 equiv) increased sulfone contamination, thereby reducing the selectivity of the oxidation.

Several functionalized sulfides were selected to examine the scope and limitations of this procedure (Table 2). Aryl alkyl, aryl allyl, diaryl, dialkyl, cyclic and heterocyclic sulfides could be oxidized to the corresponding sulfoxides in excellent yields. Sulfides carrying either electron-withdrawing (entry 2) or electron-donating (entries 3 and 11) substituents gave the corresponding sulfoxides in excellent yields with high purity. Importantly, this method was compatible with other functional groups such as ketone (entry 6), alkene (entry 8), ester (entry 9), and alcohol (entry 10). Typically, these oxidations could usually be stopped at the sulfoxide stage without over-oxidation to the sulfone.

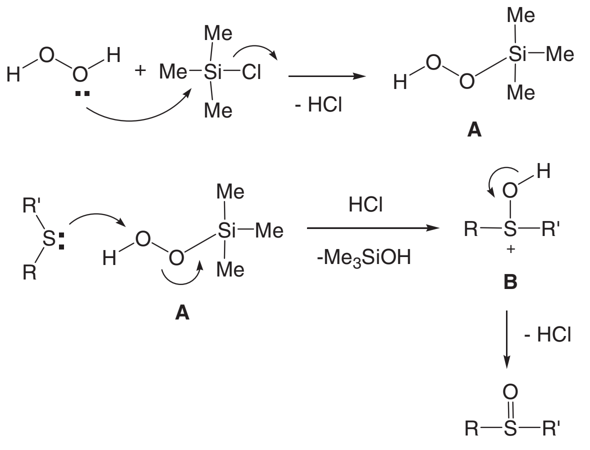
Table 2
Selective oxidation of sulfides to sulfoxides using the H_2O_2–TMSCl system in CH_3CN[a]

Entry	Sulfide	Sulfoxide	Yield[b] (%)/time (min)	Mp (°C)
1			98 (2)	120–122[16a]
2			99 (20)	163–164[16b]
3			94 (15)	158[16c]
4			95 (2)	132[16d]
5			96 (3)	68[16d]
6[c]			94 (10)	199–201[16e]
7			96 (10)	172[15e]
8			94 (3)	Oil[16f]
9			93 (35)	Oil[16g]
10			98 (3)	151–153[16h]
11			98 (10)	39–40[16d]
12			92 (3)	29–30[15c]
13	$(CH_3)_2S$	$(CH_3)_2S{=}O$	95 (3)	Oil[16i]

[a] The purified products were characterized by mp and ^1H and ^{13}C NMR spectroscopy.

[b] Yield refers to pure isolated product.

[c] 1,4-Dioxane was used as the solvent.



Scheme 2. Proposed mechanism for the oxidation of sulfides.

To demonstrate the feasibility of applying this method on a preparative scale, the oxidation of diphenyl sulfide was carried out on 20 mmol scale. The reaction proceeded smoothly and the desired product was obtained in 95% isolated yield.

A plausible reaction mechanism is shown in Scheme 2. Nucleophilic attack of H_2O_2 on TMSCl leads to the intermediate **A** in which the oxygen atom is more electrophilic. Next, nucleophilic attack of the sulfide on this intermediate gives cation **B** which undergoes hydrogen abstraction to yield the corresponding sulfoxide. It is significant that the by-product, trimethylsilyl alcohol, is soluble in water and as a result, does not contaminate the product. Simple extraction or recrystallization of the product from a mixture of ethanol and water afforded pure product.

In conclusion, TMSCl promotes the chemoselective and efficient oxidation of sulfides to sulfoxides using environmentally friendly 30% H_2O_2. In all cases, the reaction proceeded cleanly and afforded the desired sulfoxides as the only products. Advantages of this method are the easy work-up, mild reaction conditions, high selectivity, and excellent conversion of substrates.

2. General procedure for the oxidation of sulfides

In a round-bottomed flask (50 mL) equipped with a stir bar, a solution of sulfide (2 mmol) in CH_3CN (10 mL) was prepared. Aqueous 30% H_2O_2 (4 mmol, 0.4 mL) and TMSCl (2 mmol) were added and the mixture was stirred at 25 °C for the time period specified in Table 2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/EtOAc, 7:3). After disappearance of the sulfide, the reaction mixture was quenched by adding H_2O (10 mL), extracted with EtOAc (4×5 mL), and the extract dried with anhydrous $MgSO_4$. Evaporation gave the corresponding sulfoxide as the only product. Spectral and physical data for selected compounds can be found in the Supplementary data.

Acknowledgment

We are thankful to the Razi University Research Council for partial support of this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.171.

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