Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 49 (2008) 3463–3465

Tetrahedron Letters

A novel rapid sulfoxidation of sulfides with cyclohexylidenebishydroperoxide

J. Jon Paul Selvam, V. Suresh, K. Rajesh, D. Chanti Babu, N. Suryakiran, Y. Venkateswarlu *

Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 29 November 2007; revised 17 March 2008; accepted 21 March 2008
Available online 28 March 2008

Abstract

Cyclohexylidenebishydroperoxide was successfully used as the oxygen source for the oxidation of sulfides to sulfoxides for the first time. The sulfoxides were obtained in good to high yields without any detectable over-oxidation to sulfones under normal conditions.

Keywords: Oxidation; Peroxides; Sulfides; Sulfoxides; Cyclohexylidenebishydroperoxide

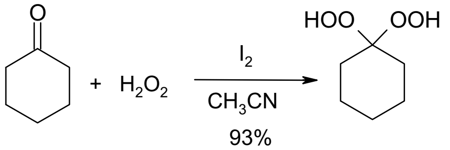
1. Introduction

Increasing interest and applications of sulfoxides have stimulated investigations on new methods of sulfoxide synthesis. Organic sulfoxides are useful synthetic intermediates for the construction of various chemically and biologically active molecules. These often play an important role as therapeutic agents such as antiulcer (proton pump inhibitor),[1–3] antibacterial, antifungal, antiatherosclerotic,[4–6] anthelmintic,[7] antihypertensive,[8] and cardiotonic agents,[9] as well as psycotonics[10,11] and vasodilators.[12]

The oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides. Racemic sulfoxidation has been studied in solution and on solid phase using several types of oxidizing agents. For example, in solution, H_2O_2 is one of the most used,[13] but classical oxygen transfer reagents, such as *m*-CPBA,[14] or ozone[15] have also been examined. On solid phase, there are some references to sulfide oxidation using H_2O_2 with a catalytic amount of AcOH,[16] or $Sc(OTf)_3$,[17] TBHP with *p*-TSA[18] as catalyst or using 4,8-dihydro-3*H*-[1,2]oxazineno-[3,2-*a*]isoquinoline.[19] Many of these reagents will result in over-oxidation to sulfones. Therefore, the reaction conditions time, temperature and the relative amount of oxidants have to be controlled to avoid the formation of side product.

Recently, Iskra and co-workers reported a novel method for the preparation of *gem*-dihydroperoxides from ketones and H_2O_2 under iodine catalysis.[20] This method uses readily available starting materials and is easy to operate, which paves the way for the synthetic applications of these interesting peroxides as stoichiometric oxidants. As a result of our continued interest in the development of new methodologies,[21–25] we became interested in using these peroxides as potential oxidizing agents for sulfoxidation. Herein, we report the application of cyclohexylidenebishydroperoxide, which was prepared following the reported procedure in a high yield (Scheme 1), in the sulfoxidation of sulfides.

Initially, we used methyltolyl sulfide (Table 1, entry 2) as the model compound for the sulfoxidation using cyclohexylidenebishydroperoxide in dichloromethane as the solvent at room temperature (Scheme 2). The reaction was



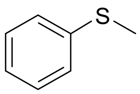
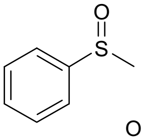
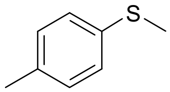
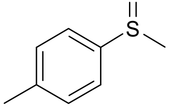
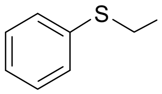
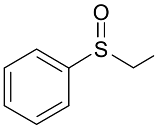
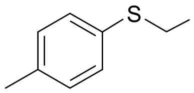
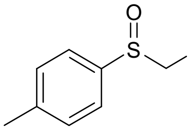
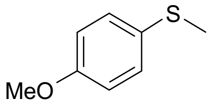
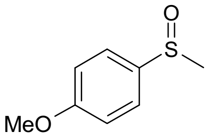
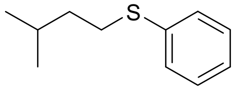
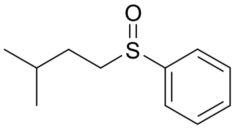
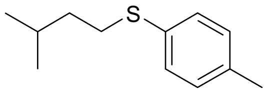
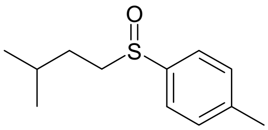
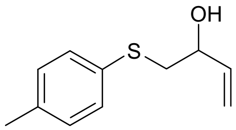
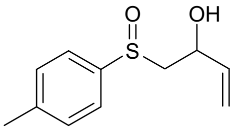
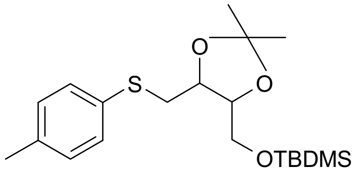
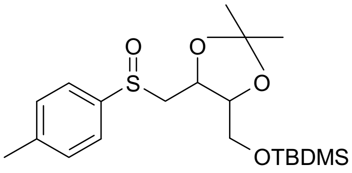
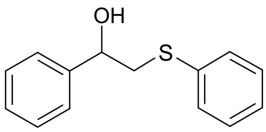
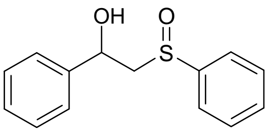
Scheme 1. Preparation of cyclohexylidenebishydroperoxide.

---

[*] Corresponding author. Tel.: +91 40 27193167; fax: +91 40 27160512.
E-mail address: luchem@iict.res.in (Y. Venkateswarlu).

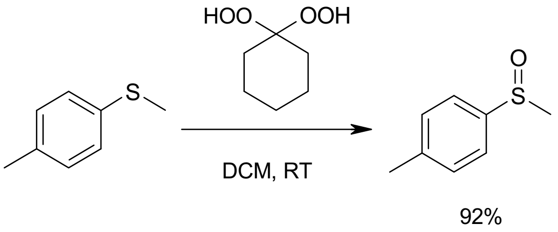
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.03.122

Table 1
Sulfoxidation of various sulfides using cyclohexylidenebishydroperoxide (**1**)

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1			30	89
2			30	92
3			50	90
4			50	87
5			60	91
6			120	93
7			120	92
8			120	81
9			120	83
10			60	79

[a] Isolated yields after chromatographic purification.

complete in 30 min to give the corresponding sulfoxide in good yield. To understand the scope of this reaction, we studied the reaction of various sulfides under optimized conditions (room temperature) and the results are summarized in Table 1. The formation of products was established from downfield chemical shift of the vicinal protons of the sulfoxide compared to the sulfide in the ^{1}H NMR spectra. For example, the methyl group attached to sulfoxide appeared at δ 2.61 (s, 3H) (Table 1, entry 1), as compared to the sulfide methyl at δ 2.46 (s, 3H) in the ^{1}H NMR spec-



Scheme 2. Preparation of sulfoxides using cyclohexylidenebishydroperoxide.

trum of the starting material. Further, the downfield chemical shift of the aromatic *ortho* protons of the sulfoxide from δ 7.27 to 7.62 in the ^{1}H NMR spectra of sulfoxides was further proof of successful oxidation. It is evident from Table 1 that the conversions are very good within reaction times at room temperature.

In contrast to other oxidizing reagents, cyclohexylidenebishydroperoxide is a good oxidizing reagent to oxidize sulfides to the corresponding sulfoxides without producing over-oxidation products. The reagent is compatible with sensitive groups such as TBDMS, and acetonide (entry 9), alcohol (entries 8 and 10) and double bonds (entry 8).

We have demonstrated cyclohexylidenebishydroperoxide as a very good oxidizing reagent for the preparation of sulfoxides under mild reaction conditions within short reaction times. Further, the reagent can be prepared easily and can be stored for several weeks in a refrigerator without the loss of its activity.

2. Procedure for the preparation of cyclohexylidenebishydroperoxide 1

To a solution of I_2 (25.4 mg, 0.1 mmol) in CH_3CN (10 mL) were added cyclohexanone (98 mg, 1 mmol) and 30% aq H_2O_2 (0.45 mL, 4 mmol), and the reaction mixture was stirred at room temperature for 24 h. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure, water (10 mL) was added and the product was extracted into dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified through a small column of silica gel using ethyl acetate/hexane (1:9) as eluent to give pure cyclohexylidenebishydroperoxide **1**, in 93% yield (0.93 mmol, 137.6 mg).

3. General experimental procedure for the preparation of sulfoxides

To a solution of sulfide (1 mmol) in DCM (10 mL) was added cyclohexylidenebishydroperoxide (1 mmol) and the reaction mixture was allowed to stir for the appropriate amount of time (see Table 1) at room temperature. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure and pure products were obtained after silica gel column chromatography.

Acknowledgements

The authors thank the CSIR, MoES and DBT, New Delhi, India, respectively, for the financial support and the Director of the Indian Institute of Chemical Technology, for his encouragement.

References and notes

1. Spencer, C. M.; Faulds, D. *Drugs* **2000**, *60*, 321–329.
2. Salas, M.; Ward, A.; Caro, J. *BMC Gastroenterol.* **2002**, *2*, 17.
3. Lai, K. C.; Lam, S. K.; Chu, K. M.; Wong, B. C.; Hui, W. M.; Hu, W. H.; Lau, G. K.; Wong, W. M.; Yuen, M. F.; Chan, A. O.; Lai, C. L.; Wong, J. *New Engl. J. Med.* **2002**, *346*, 2033–2038.
4. Focke, M.; Feld, A.; Lichtenthaler, K. *FEBS Lett.* **1990**, *12*, 106–108.
5. Agarwal, K. C. *Med. Res.* **1996**, *16*, 111–124.
6. Perez-Giraldo, C.; Cruz-Villalon, G.; Sanchez-Silos, R.; Martinez-Rubio, R.; Blanco, M. T.; Gomez-Garcia, A. C. *J. Appl. Microbiol.* **2003**, *95*, 709–711.
7. Merino, G.; Molina, A. J.; Garcia, J. L.; Pulido, M. M.; Prieto, J. G.; Alverez, A. I. *J. Pharm. Pharmacol.* **2003**, *55*, 757–764.
8. Kotelanski, B.; Grozmann, R. J.; Cohn, J. N. *Clin. Pharmacol. Ther.* **1973**, *14*, 427–433.
9. Scimied, R.; Wang, G. X.; Korth, M. *Circ. Res.* **1991**, *68*, 597–604.
10. Lechin, F.; Van der Dijis, B.; Pardey-Maldonado, B.; John, E.; Jimenez, V.; Orozco, B.; Baez, S.; Lechin, M. E. *J. Med.* **2000**, *31*, 333–361.
11. Zifko, U. A.; Rupp, M.; Schwarz, S.; Zipco, H. T.; Maida, E. M. *J. Neurol.* **2002**, *249*, 983–987.
12. Padmanaban, S.; Lavin, R. C.; Durant, G. J. *Tedrahedron: Asymmetry* **2000**, *11*, 3455–3457.
13. Kaczorowska, K.; Kolaraska, Z.; Mitka, K.; Kowalski, P. *Tetrahedron* **2005**, *61*, 8315–8327.
14. Patek, M.; Drake, B.; Lebel, M. *Tetrahedron Lett.* **1995**, *36*, 2227–2230.
15. Sylvian, S.; Wanger, A.; Mioskowosky, C. *Tetrahedron Lett.* **1997**, *38*, 1043–1044.
16. Miranda, Les P.; Lubell, D. W.; Halkes, M. K.; Groth, T.; Grotli, M.; Rademann, J.; Gotferdsen, C. H.; Meldal, M. *J. Comb. Chem.* **2002**, *4*, 523–529.
17. Matteucci, M.; Bhalay, G.; Bradley, M. *Org. Lett.* **2003**, *5*, 235–237.
18. Cole, D. C.; Stock, J. R.; Kapple, J. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1791–1793.
19. Rolland, C.; Hanquet, G.; Ducep, J. B.; Solladie, G. *Tetrahedron Lett.* **2001**, *42*, 7563–7566.
20. Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491–2494. and references cited therein.
21. Jon Paul Selvam, J.; Suresh, V.; Rajesh, K.; Ravinder Reddy, S.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 2507–2509.
22. Suryakiran, N.; Rajesh, K.; Prabhakar, P.; Jon Paul Selvam, J.; Venkateswarlu, Y. *Catal. Commun.* **2007**, *8*, 1635–1640.
23. Suryakiran, N.; Prabhakar, P.; Srikanth Reddy, T.; Chinni Mahesh, K.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 877–881.
24. Chinni Mahesh, K.; Narasimhulu, M.; Srikanth Reddy, T.; Suryakiran, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 55–59.
25. Srikanth Reddy, T.; Narasimhulu, M.; Suryakiran, N.; Chinni Mahesh, K.; Ashalatha, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *46*, 6825–6829.