Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
Tetrahedron Letters 48 (2007) 1395–1398
Tetrahedron Letters

Facile epoxidation of α,β-unsaturated ketones with cyclohexylidenebishydroperoxide

Kavitha Jakka, Jinyun Liu and Cong-Gui Zhao*

Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249-0698, United States

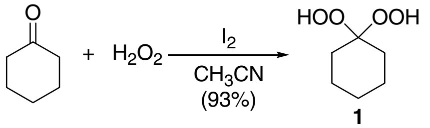
Received 10 July 2006; revised 18 December 2006; accepted 19 December 2006

Abstract—Cyclohexylidenebishydroperoxide was successfully used as the oxygen source for the oxidation of α,β-unsaturated ketones for the first time. The corresponding epoxides were obtained in excellent yields under the Weitz–Scheffer reaction conditions.

Hydrogen peroxide (H_2O_2) is an environmentally benign oxidant, as the only by-product after oxidation is water. Unfortunately, its oxidation power towards organic compound is pretty low and, therefore, for synthetic purpose, it is normally used together with a catalyst[1] or converted to hydroperoxides[2] to enhance its oxidation power. *gem*-Dihydroperoxides, which have received considerable interest in recent years because of their relevance to peroxidic antimalarial agents,[3] are structurally similar to hydroperoxides. However, to the best of our knowledge, they have never been utilized as oxidants in organic reactions. The reason was probably due to their difficult synthesis.[4]

Most recently, Iskra and co-workers reported a novel method for the preparation of *gem*-dihydroperoxides from ketones and H_2O_2 under iodine catalysis.[4] 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. Because of our continued interest in the epoxidation chemistry,[5] we became interested in using these peoxides as potential oxidants for epoxidation. Herein, we wish to report the first oxidation application of cyclohexylidenebishydroperoxide (**1**), which was prepared by following the reported procedure in a high yield (Eq. 1),[4] in the epoxidation of α,β-unsaturated ketones.

By using *trans*-chalcone (**2a**) as the model compound and 1.0 M aqueous KOH as the base, we studied the Weitz–Scheffer epoxidation reaction in various solvents at room temperature (Table 1).



(1)

It was found that nonpolar hexanes and toluene are bad solvents for this reaction, since no epoxide could be obtained in these two solvents (entries 1 and 2). Nonetheless, the reaction did happen in polar solvents, and the desired epoxide (**3a**) was obtained in 67%, 51% and 75% yields in MeOH (entry 3), CH_2Cl_2 (entry 4) and DMF (entry 5), respectively. Water-miscible polar solvent CH_3CN produced the epoxide in an even better 83% yield within 6 h (entry 6). Further screening of other water-miscible solvents revealed dimethoxyethane (DME) and 1,4-dioxane are excellent solvents for this oxidation. The reaction in DME requires 2.5 h and epoxide **3a** was generated in an 88% yield (entry 7), whereas the reaction in dioxane requires only 2 h and the formation of the product is almost quantitative (95%, entry 8). Thus, 1,4-dioxane was identified as the best solvent for this reaction, whereas DME and CH_3CN are also very good solvents. For comparison purpose, the oxidation was also carried out with hydrogen peroxide as the oxidant in dioxane and lower yields of the epoxide were obtained with either 1 (53%, entry 9) or 2 equiv (82%, entry 10) of the oxidant. It should be pointed out that cyclohexanone may be recovered in a

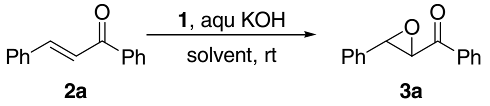
---

Keywords: Enone; Epoxide; Dihydroperoxide; Hydroperoxide; Hydrogen peroxide; Epoxidation.

* Corresponding author. Tel.: +1 210 458 5432; fax: +1 210 458 7428; e-mail: cong.zhao@utsa.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.104

Table 1. Solvent screening in the epoxidation of *trans*-chalcone (**2a**) using cyclohexylidenebishydroperoxide (**1**)[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	Hexane	24	0
2	Toluene	24	0
3	MeOH	10	67
4	CH_2Cl_2	24	51
5	DMF	3	75
6	CH_3CN	6	83
7	$MeOCH_2CH_2OMe$	2.5	88
8	1,4-Dioxane	2	95[c]
9	1,4-Dioxane[d]	2	53
10	1,4-Dioxane[e]	2	82

[a] Unless otherwise specified, all reactions were carried out with *trans*-chalcone (1.0 mmol), cyclohexylidenebishydroperoxide (**1**, 1.0 mmol), aqueous KOH (1.0 M, 1.0 mL) and the solvent (5.0 mL) at room temperature.

[b] Yield of isolated product after chromatographic purification.

[c] Cyclohexanone (91%) may be recovered and reused.

[d] With 30% H_2O_2 (1.0 mmol) as the oxidant.

[e] With 30% H_2O_2 (2.0 mmol) as the oxidant.

high yield after the reaction (91%, entry 8), which means that this is a green oxidation. (*Caution*: since compound **1** is potentially explosive, it should be handled with care. All the reactions in this study were carried out behind a safety shield inside a hood.)

To understand the scope of this reaction, we studied the reaction of various α,β-unsaturated ketones under the optimized conditions (rt, 1.0 M aqueous KOH in 1,4-dioxane),[6] and the results are summarized in Table 2.

As is evident from Table 2, besides *trans*-chalcone (entry 1), substituted *trans*-chalcones are also good substrates for this reaction. For example, *trans*-4′-methoxychalcone yielded the desired product (**3b**) in a 79% yield (entry 2). Similarly, the epoxide of *trans*-4-methoxychalcone (**3c**) was obtained in an 83% yield (entry 3). An excellent yield (93%) was also obtained for the product of *trans*-2′-chlorochalcone (**3d**, entry 4). However, the reaction of *trans*-2′-hydroxychalcone did not yield the desired epoxide. Instead, the epoxide-ring-opening product (**4**) was obtained as a minor product (28%, entry 5). The major product of this reaction was the intramolecular Michael addition product **5** (53%, entry 5). These results are not surprising, because similar results are also obtained under the Weitz–Scheffer epoxidation of this substrate by using hydrogen peroxide.[7]

Acyclic enones other than chalcones are also good substrates. *trans*-3-Penten-2-one gives the epoxide product (**3f**) in a quantitative yield according to GC analysis (entry 6).[8] Likewise, the epoxide (**3g**) of *trans*-4-phenyl-3-buten-2-one was obtained in an 86% yield (entry 7).

Table 2. Epoxidation of α,β-unsaturated ketones (**2a–l**) using cyclohexylidenebishydroperoxide (**1**) under the optimized conditions[a]

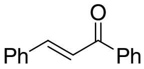
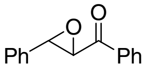
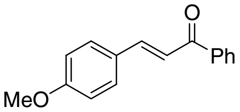
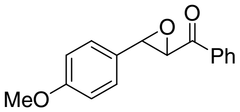
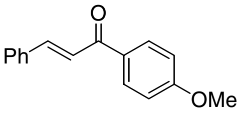
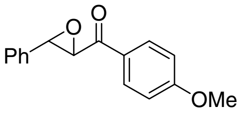
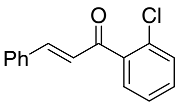
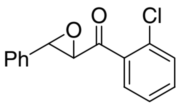
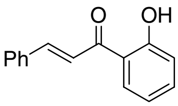
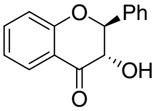
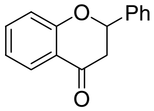
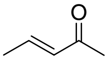
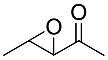
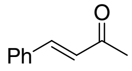
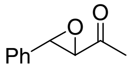
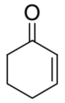
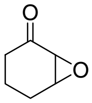
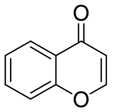
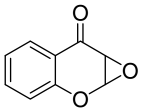
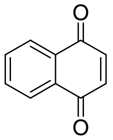
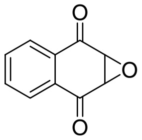
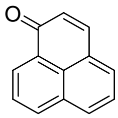
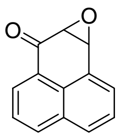
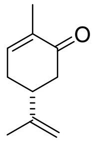
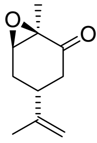
Entry	α,β-Unsaturated ketone (**2**)	Time (h)	Product	Yield[b] (%)
1	 (**2a**)	2	 (**3a**)	95
2	 (**2b**)	6	 (**3b**)	79
3	 (**2c**)	2.5	 (**3c**)	83
4	 (**2d**)	1.5	 (**3d**)	93
5	 (**2e**)	3.5	 (**4**) +  (**5**)	28 + 53
6	 (**2f**)	0.5	 (**3f**)	100[c]

Table 2 (*continued*)

Entry	α,β-Unsaturated ketone (**2**)	Time (h)	Product	Yield[b] (%)
7	 (**2g**)	3	 (**3g**)	86
8	 (**2h**)	0.5	 (**3h**)	89
9	 (**2i**)	5	 (**3i**)	86
10	 (**2j**)	1	 (**3j**)	97
11	 (**2k**)	4	 (**3k**)	81
12	 (**2l**)	2.5	 (**3l**)	91

[a] All reactions were carried out with the α,β-unsaturated ketone (1.0 mmol), cyclohexylidenebishydroperoxide (**1**, 1.0 mmol) and aqueous KOH (1.0 M, 1.0 mL) in 1,4-dioxane (5.0 mL) at room temperature.

[b] Yields of isolated products after chromatographic purification.

[c] GC yield.

Some cyclic enones were also studied. 2-Cyclohexenone produced the epoxide (**3h**) in an 89% yield (entry 8). Similarly, the epoxide of chromone (**3i**) was obtained in 86% yield (entry 9). An enedione (1,4-naphthalenedione) was also successfully epoxidized, and the product (**3j**) was obtained in an excellent yield (97%, entry 10). A good yield was also obtained for the product of perinaphthenone (**3k**) (86%, entry 11). The oxidation of (*R*)-carvone generates only the trans diastereomers (**3l**)[9] in a 91% yield (entry 12).

In summary, we have shown that *gem*-dihydroperoxide can be used as the stoichiometric oxidant for the Weitz–Scheffer epoxidation of α,β-unsaturated ketones. Excellent yields of the epoxides may be obtained under very mild reaction conditions within short reaction times. The development of an asymmetric version of this reaction is currently under way.

Acknowledgments

The generous financial support of this research from the Welch Foundation (Grant No. AX-1593; AX-0026) and the NIH-MBRS program (Grant No. S06 08194) is gratefully acknowledged.

References and notes

1. For reviews, see: (a) Nardello, V.; Aubry, J.-M.; De Vos, D. E.; Neumann, R.; Adam, W.; Zhang, R.; ten Elshof, J. E.; Witte, P. T.; Alsters, P. L. *J. Mol. Catal. A: Chem* **2006**, *251*, 185–193; (b) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457–2473.
2. For a review, see: Kratz, T.; Zeiss, W. In *Peroxide Chemistry*; Adam, W., Ed.; Wiley-VCH: Weinheim, 2000; pp 41–59.
3. For leading examples, see: (a) Iskra, J.; Bonnet-Delpon, D.; Begue, J. P. *Tetrahedron Lett.* **2003**, *44*, 6309–6312; (b) Tsuchiya, K.; Hamada, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Shibata, Y.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 4077–4080.
4. Žmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491–2494, and references cited therein.
5. (a) Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403–7406; (b) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749–2755; (c) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995–3998.

6. *General experimental procedure* (*Caution*: Although we did not encounter any problem with compound **1**, dihydroperoxides are potential explosives and should be handled with care; all reactions should be carried out behind a safety shield inside a hood): To a mixture of *trans*-chalcone (**2a**, 208 mg, 1.0 mmol) and cyclohexylidenebishydroperoxide (**1**, 148 mg, 1.0 mmol) in 1,4-dioxane (5.0 mL) was added 1.0 M aqueous KOH solution (1.0 mL). The reaction mixture was stirred at room temperature for 2 h, diluted with diethyl ether (15 mL) and washed with water (4 mL). The organic layer was dried over $MgSO_4$ and then the solvent was removed in vacuo. The crude product obtained was purified by column chromatography (95:5 hexane/ethyl acetate) to yield pure epoxide **3a** (213 mg, 95%). Cyclohexanone (89 mg, 91%) may also be recovered.
7. Loeser, R.; Chlupacova, M.; Marecek, A.; Opletalova, V.; Guetschow, M. *Helv. Chim. Acta* **2004**, *87*, 2597–2601.
8. This product is very volatile and an accurate isolated yield could not be obtained.
9. Gonzalez, M. A.; Ghosh, S.; Rivas, F.; Fischer, D.; Theodorakis, E. A. *Tetrahedron Lett.* **2004**, *45*, 5039–5041.