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A Convenient Synthesis of Substituted 1,2,4-Trioxepanes *via* Co(II) Catalyzed Oxygenation of Cinnamyl Alcohol

Chang Ho Oh*[†] and Ji Hye Kang[‡]

[†] Department of Chemistry, Hanyang University, Haengdang-17 Sungdong-Gu, Seoul 133-791, Korea
[‡]Department of Chemistry, Inje University, Kimhae Aubang-607, Kyungnam 621-749, Korea

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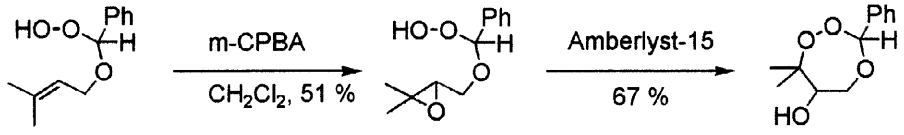
Abstract: *Co (II) catalyzed oxygenation of three alkenes in the presence of triethylsilane was carried out according to the Mukaiyama's procedure in two solvents. One product, 3-phenyl-3-triethylsilylperoxy-1-propanol derived from cinnamyl alcohol, was simultaneously desilylated and cyclized with aldehydes or ketones to give the corresponding 1,2,4-trioxepanes in high yields under mild condition. While aldehyde gave some selectivity when forming 1,2,4-trioxepane, unsymmetrical ketone did not give good selectivity.*

Since the isolation and the structural determination of artemisinin[1] and the elucidation of its biological activity as a potent antimalarial drug,[2] new and convenient syntheses of the structurally diverse cyclic peroxides have been attracted attention to synthetic organic chemists. For the past two decades, numerous peroxide-containing natural products and their analogs possessing important biological activities have been isolated and synthesized by organic chemists.[3] In spite of these efforts, there is still a prompt need to develop new and convenient synthetic methodologies for the diverse types of natural and unnatural peroxides. In the line of our continuing work on synthesis of 1,2,4-trioxanes as for searching potent antimalarial drugs,[4] we have initiated a research to develop new synthetic methods of 1,2,4-trioxepanes and now wish to report here our preliminary results. Although many synthetic methods of 1,2,4-trioxanes have been known such as copper (II) catalyzed cyclization of vicinal hydroxy hydroperoxide,[5] acid-catalyzed cyclization of hydroperoxy acetals with olefins[6] or epoxides,[7] 1,2-dioxetane with ketones or aldehydes,[8] peroxyaldehyde with ketones or aldehydes,[9] and cationic ring expansion of ozonides,[10] only a few synthetic methods of 1,2,4-trioxepanes, as far as we are aware, has been recently reported shown in eq 1.[11]



(1)

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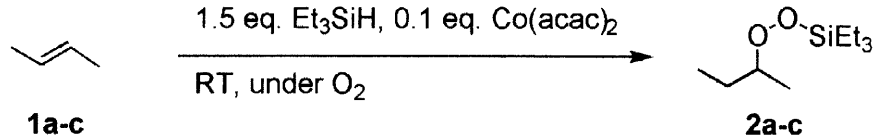
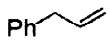
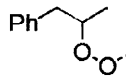
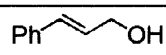
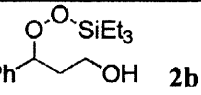
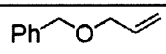
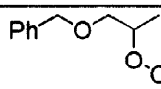
This method is indeed an extension of the cyclization of hydroperoxiacetals with a pendant epoxide or a double bond.[6,7] Dealing with hydroperoxiacetals requires much care due to their instability during reaction. Our approach was based on the triplet oxygenation of a double bond followed by cyclization with a carbonyl group of aldehydes or ketones. This exhibited to be very efficient and mild enough to be experimentally carried out. Basic idea was an extension of Mukaiyama work combined with choice of our substrate. Mukaiyama and his coworkers have studied cobalt(II)-catalyzed trialkylsilylperoxidation of olefins with molecular oxygen and trialkylsilanes.[12] We have adopted their method to prepare the triethylsilylperoxides as shown in Table 1.

Table 1. Triethylsilylperoxidation of Alkenes in Two Different Solvents.



1a-c **2a-c**

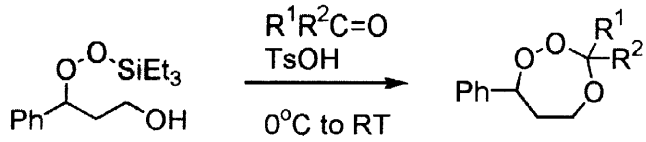
Substrates	Products	Solvent,	Rxn Time	Yield (%)
 **1a**	 **2a**	CH_2ClCH_2Cl	12	68
		CH_3CH_2OH	2	74
 **1b**	 **2b**	CH_2ClCH_2Cl	12	63
		CH_3CH_2OH	2	64
 **1c**	 **2c**	CH_2ClCH_2Cl	16	22
		CH_3CH_2OH	2	61

We have found that the reactions were generally slow or incomplete for some alkenes. Allylbenzene, cinnamyl alcohol, and allyl benzyl ether required, in fact, 12 to 16 hrs for completion. After fine-tuning the reaction conditions, we could conclude that the solvent effect was important. Among various solvents such as 1,2-dichloroethane, dichloromethane, THF, acetonitrile, DMF, and ethanol, ethanol could complete the desired reactions both in isolated yields and in shorter reaction times. The present oxygenations were highly selective, that the slight difference in the substituents of the double bonds exhibited the great reactivity difference to give the Markovnikov-typed products. A typical experimental procedure is as follows. In a oven-dried 50 ml two-necked flask were charged cinnamyl alcohol (106.5 mg, 0.7 mmol), cobalt(II) acetylacetonate (18.0 mg, 0.07 mmol) and dry ethanol (5.0 ml), and then triethylsilane (0.22 ml, 1.4 mmol) *via* 1.0 ml gas-tight syringe. The resulting solution was stirred at room temperature under slightly positive oxygen atmosphere (about 1.1 atmosphere). After the reaction was complete, the solvent was carefully rotary-evaporated for flash chromatography. Silica gel chromatography of the resulting residue afforded the corresponding peroxide (127.4 mg) in 64 % yield.[13]

Having these results, we ought to find a possibility that 3-phenyl-3-triethylsilylperoxi-1-propanol (**2b**) could be cyclized to the corresponding seven-membered rings with ketones or aldehydes. The peroxide **2b** was treated with several ketones and aldehydes in the presence of a catalytic amount of *p*-toluenesulfonic acid. Thus, to a 2.0 ml chloroform solution of the above peroxide **2b** (135.3 mg, 0.48 mmol) were added acetone (0.1 ml, 1.36 mmol), and then *p*-toluenesulfonic acid (5.0 mg, mmol) under argon atmosphere. After 1 h stirring at room temperature, concentration and flash chromatography of the reaction mixture gave the

corresponding 1,2,4-trioxepane **3e** (71.5 mg) as a colorless oil in 71 % yield. These results were summarized in Table 2.

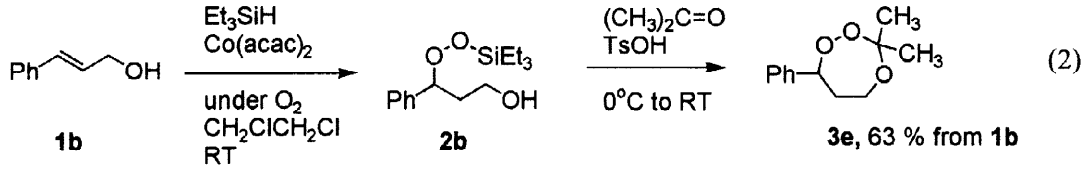
Table 2. Cyclization of 3-Phenyl-3-triethylsilylperoxi-1-propanol (2b) with Aldehydes or Ketones



2b **3a-g**

No	R^1, R^2	Time /h	**Product**	Yield /%	Isomer Ratio
1	-H, -Me	0.5	**3a**	75	
2	-H, -Ph	2.0	**3b**	67	8:2
3	-H, $-CH(CH_3)_2$	1.0	**3c**	63	
4	-H, $-CH_2CH_2CH_3$	1.0	**3d**	70	
5	-Me, -Me	0.2	**3e**	71	
6	-Me, -Ph	6.0	**3f**	58	~1:1
7	$-CH_2(CH_2)_4CH_2-$	2.0	**3g**	75	

It should be noted that most of synthetic procedures leading to peroxides have been harmful from many unwanted side reactions. Surprisingly, cyclization of the peroxide **2b** with structurally simple aldehydes or ketones occurred to give the desired products in high yields. While benzaldehyde gave *cis/trans* selectivity in 2:8 ratio when forming 1,2,4-trioxepane **3b**, the other aldehydes and unsymmetrical ketone, acetophenone, did not give any promising *cis/trans* selectivity. Even with only a few examples, the results described in this paper clearly opened a new field for constructing 1,2,4-trioxepane rings with varied side chain and even varied functional groups since the reactions can provide the desired product in high yield under mild and convenient conditions. Furthermore, this whole sequence could be carried out in one pot reaction (eq. 2).



(2)

After triethylsilylperoxidation was complete in 1,2-dichloroethane solution, treatment of acetone with a catalytic amount of *p*-toluenesulfonic acid gave the clean desired product in 63 % yield. This result is even much better in practical sense, since combining two separate steps could save tedious workup procedure and time. In conclusion, 1,2,4-trioxepane syntheses were accomplished by acid catalyzed cyclizations of 3-phenyl-3-triethylsilylperoxy-1-propanol prepared from triplet oxygenation of cinnamyl alcohol. Starting this excellent work, we now plan to expand this methodology for general use and for applications to natural products or unnatural products which could have good biological activities.

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References and Notes

1. (a) Klayman, D. L. *Science* **1985**, *228*, 1049-1055. (b) Zaman, S. S.; Sharma, R. P. *Heterocycles* **1991**, *32*, 1593. (c) Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211. (d) Butler, A. R.; Wu, Y.-L. *Chem. Soc. Rev.* **1992**, 85-90.
2. (a) Abourashed, E. A.; Hufford, C. D. *J. Nat. Prod.* **1996**, *59*, 251-253. (b) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301-315. (c) Duc, D. D.; DeVries, P. J.; Khanh, N. X.; Binh, L. N.; Kager, D. A.; Van Boxtel, C. J. *Am. J. Trop. Med. Hyg.* **1994**, *51*, 785.
3. (a) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624. (b) Xu, X.-X.; Zhu, J.; Huang, D. Z.; Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819. (c) Avery, M. A.; Gao, F.; Chong, W. K. M.; Hendrickson, T. F.; Inman, W. D.; Crews, P. *Tetrahedron* **1994**, *50*, 957. (d) Keper, J. A.; Philip, A.; Lee, Y. W.; Morey, M. C.; Carrol, F. I. *J. Med. Chem.* **1988**, *31*, 713. (e) Zeng, M.-Y.; Li, L.-N.; Chen, S.-F.; Li, G.-Y.; Liang, X.-T.; Chen, M.; Clardy, J. *Tetrahedron* **1983**, *39*, 2941. (f) Jefford, C. W.; Rossier, J. C.; Boukouvalas, J. *Heterocycles*, **1989**, *28*, 673. (g) Fujisaka, T.; Miura, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. I.* **1989**, 1031.
4. (a) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *Heteroatom Chemistry* **1995**, *6*, 105. (b) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459. (c) Oh, H.; Kang, J. H.; Posner, G. H. *Bull. Kor. Chem. Soc.* **1996**, *17*, 581-582. (d) Oh, H.; Posner, G. H. *Bull. Kor. Chem. Soc.* **1997**, *18*, 644-648.
5. (a) Adam, W.; Rios, A. *J. Chem. Soc., Chem. Commun.* **1971**, 822. (b) Subramanyam, V.; Brizuela, C. L.; Soloway, A. H. *J. Chem. Soc., Chem. Commun.* **1976**, 508-509. (c) Singh, C. *Tetrahedron Lett.* **1990**, *31*, 6901-6902.
6. Bloodworth, A. J.; Shah, A. *J. Chem. Soc., Chem. Commun.* **1991**, 947-948.
7. Miura, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Chem. Commun.* **1981**, 581-582
8. Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459.
9. (a) Jefford, C. W.; Velarde, J.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *30*, 4485. (c) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D.; Milhous, W. K. *J. Med. Chem.* **1990**, *33*, 1516.
10. Bunnelle, W. H.; Isbell, T. A.; Barnes, C. L.; Qualls, S. *J. Am. Chem. Soc.* **1991**, *113*, 8168-8169.
11. (a) Adam, W.; Duran, N. J. Chem. Soc., Chem. Commun. 1972, 798. (b) Dussault, P. H.; Davies, D. R. Tetrahedron Lett. 1996, 37, 463. (c) Ushigoe, Y.; Torao, Y.; Masuyama, A.; Nojima, M. J. Org. Chem. 1997, 62, 4949. (d) Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron Lett.* **1997**, *38*, 8753-8756.
12. Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071-1074.
13. Spectral data of the product **3e** are as follow: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.13 (dd, J=11.7, 3.6 Hz, 1H), 4.11 (ddd, J=12.6, 12.0, 1.2 Hz, 1H), 3.82 (td, J=3.5, 12.6 Hz, 1H), 2.28 (m, 1H), 2.01 (bd, J=14.4 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.25, 128.54, 128.49, 127.24, 106.58, 86.06, 60.64, 38.72, 24.83, 22.04; IR ($CHCl_3$, cm^{-1}) 2955, 1485, 1445, 1360, 1205; EIMS (rel. intensity) 208 (M^+, 71), 176 (25), 151 (100); EIHRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1099. All the other new compounds have been fully characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and HRMS.