Tin(IV) Chloride Promoted Reaction of Oxiranes with Hydrogen Peroxide

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Received: 11.12.2012; Accepted after revision: 22.01.2013

Abstract: A group of substituted oxiranes were readily transformed to the corresponding β-hydroxyhydroperoxides (HHP) in good yields in ethereal $SnCl_4$–H_2O_2 system in which $SnCl_4$ acts as catalyst. Alternatively, treating oxiranes with $SnCl_4$ first, followed by addition of ethereal H_2O_2 solution achieved primary *gem*-dihydroperoxides (DHP) in moderate yields. In the case of preparing DHP, $SnCl_4$ first promoted the rearrangement of oxiranes to aldehydes, followed by condensation with hydrogen peroxide to provide DHP as final products.

Key words: $SnCl_4$, oxirane, β-hydroxyhydroperoxide, *gem*-dihydroperoxide

Synthetic endoperoxides, 1,2,4-trioxanes and 1,2,4,5-tetraoxanes, have been discovered as novel antimalarial drug candidates.[1] Some of these endoperoxides, for example **1**[2] and **2**[3] (Figure 1), display activity against *Plasmodium falciparum* malaria comparable to that of the first-line antimalarial drug artemisinin (**3**). Besides antimalarial activity, recent studies also emphasized their other important biological activities, including antitumor,[4] antituberculosis,[4c,5] and fasciocidal.[6]

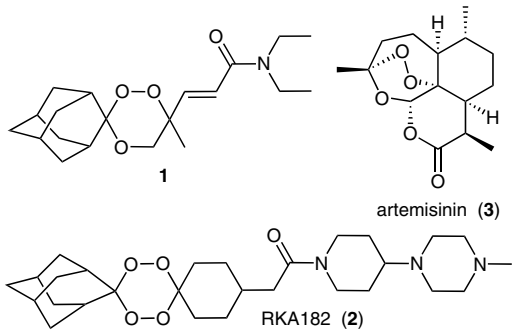


Figure 1 Endoperoxides with potent antimalarial activity

β-Hydroxyhydroperoxides (HHP) and *gem*-dihydroperoxides (DHP) are important reaction intermediates for preparing 1,2,4-trioxanes and 1,2,4,5-tetraoxanes. These hydroperoxides were conveniently converted into the corresponding 1,2,4-trioxanes and 1,2,4,5-tetraoxanes through a condensation reaction with carbonyl compounds (or ketals) under acidic conditions.[7]

To prepare HHP, two general approaches were reported. One is the addition of singlet oxygen to allylic alcohols,[8] which was restricted to an allylic specific alcohol skeleton. Alternatively, the ring-opening reaction of oxiranes by H_2O_2 can afford a variety of substitued HHP.[7b,9] This approach can also avoid the use of the oxygen gas tank. However, a high concentration of H_2O_2 (>50%) as reactant is dangerous,[7b,9d,e] and the lack of efficient catalysts limited further application of this method. A few reported catalysts include $MoO_2(acac)_2$,[7b] $SbCl_3/SiO_2$,[9b] and phosphomolybdic acid (PMA).[9a] $MoO_2(acac)_2$ was applied to very few substrates. $SbCl_3/SiO_2$ was mainly used for the ring opening of substituted styrene oxides. PMA was widely applicable, but the low reaction yield and prolonged reaction time can not satisfy the general demand. Therefore, more efficient methods for preparing HHP are required.

Ketone-derived DHP (secondary DHP) were readily formed in high yield by the reaction of ketones or ketals with H_2O_2 using an acidic catalyst, such as PMA,[10] Re_2O_7,[11] ceric ammonium nitrate,[12] I_2,[13] $SrCl_2{\cdot}6H_2O$,[14] and $SnCl_2{\cdot}2H_2O$,[15] or sometimes even without catalyst.[16] Some secondary DHP could also be obtained in low to moderate yield by the reaction of ketones with molecular oxygen and anthracene under light irradiation.[17]

Acid-catalyzed reactions of aromatic aldehydes with H_2O_2 could provide aromatic primary DHP. However, under the same conditions, aliphatic aldehydes would give α-hydroxyhydroperoxides other than the corresponding primary DHP.[13b,14–17] Recently, a general method for preparing aliphatic primary DHP was reported by reactions of aliphatic aldehydes and hydrogen peroxide employing camphorsulfonic acid (CSA) as catalyst.[18] Some drawbacks of this method include the use of highly concentrated H_2O_2 (70%), a long reaction time (16–40 h), and undesirable yield (28–77%). Alternatively, ozonolysis of enol ethers in ethereal H_2O_2 solution could prepare some type of aliphatic primary DHP,[19] but the use of ozone is troublesome and the yield is not good (33–43%) either. Considering aliphatic primary DHP were the key intermediates for the preparation of some biologically important 1,2,4,5-tetraoxanes,[18,19] efficient synthetic methods for this kind of DHP are valuable.

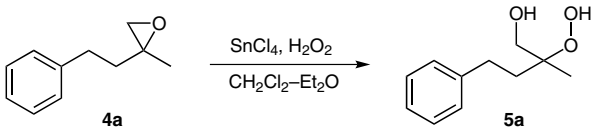
$SnCl_4$ is a strong Lewis acid and highly soluble in organic solvents. It interacts preferentially with hard base like oxygen. It has been reported that $SnCl_4$ was involved in many important organic reactions by activating the C–O bond through coordinating with oxygen atom.[20] Although

SYNLETT 2013, 24, 0502–0506
Advanced online publication: 06.02.2013
DOI: 10.1055/s-0032-1318213; Art ID: ST-2012-W1040-L

previous research found that $SnCl_4$ could not catalyze the formation of HHP at ambient temperature through the ring-opening reaction of oxiranes in ethereal H_2O_2 solution,[9a] our present work show that HHP could be efficiently achieved under optimized conditions. Interestingly, we demonstrated that the same reaction system could also afford the aliphatic primary DHP by changing reaction conditions. Herein, we report our results about preparing HHP by direct ring opening of oxiranes and the preparation of primary DHP by a tandem rearrangement–condensation reaction.

To prepare the HHP, our initial investigation started from the reaction shown in Table 1 (entry 1). HHP **5a** was readily formed by adding a dichloromethane solution of **4a** to a mixture of $SnCl_4$–CH_2Cl_2 and H_2O_2–Et_2O solution, which was prepared according to a literature procedure[21] (method A). Next, we optimized the $SnCl_4$ and H_2O_2 ratio, reaction temperature, and time. We discovered that at room to ice-bath temperature, a catalytic amount (0.1 equiv) of $SnCl_4$ could efficiently promote the conversion of oxirane into HHP by using 5.0 equivalents of H_2O_2 in an ethereal solution (Table 1, entries 6 and 7).

Table 1 Yield of HHP **5a** under Different Conditions (Method A)

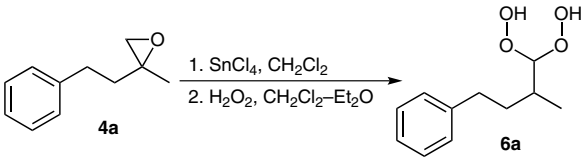


Entry	$SnCl_4$ (equiv)[a]	H_2O_2 (equiv)[b]	Temp (°C)	Time (h)	Yield (%)[c]
1	1.1	3.0	0	0.5	66
2	1.1	3.0	–30	0.5	64
3	1.0	3.0	0	0.5	74
4	1.0	5.0	0	0.5	79
5	2.0	5.0	0	0.5	74
6	0.1	5.0	0	2.5	80
7	0.1	5.0	r.t.	1.0	79

[a] Conditions: 1.0 mol L^{-1} in CH_2Cl_2.
[b] Conditions: 1.4 mol L^{-1} in Et_2O.
[c] Isolated yield.

Interestingly, when **4a** and a stoichiometric amount of $SnCl_4$ (1.0 equiv) were mixed first, followed by addition of an ethereal H_2O_2 solution (method B), DHP **6a** was obtained as product rather than the expected HHP **5a** (Table 2). Subsequent optimization of the reaction conditions disclosed that the order of addition of the reaction components, as well as the amount of $SnCl_4$, was crucial to the reaction outcome. While 1.0 equivalent or more than 1.0 equivalent of $SnCl_4$ afforded **6a** as the sole product, using a substoichiometric amount of $SnCl_4$ (0.9 equiv) resulted in a mixture of **5a** and **6a**, and a catalytic amount (0.1 equiv) of $SnCl_4$ could not afford **6a** at all (Table 2, entry 3). Besides, addition of $SnCl_4$ and H_2O_2 at low temperature (lower than –30 °C) favored the formation of **6a**.

Table 2 Yield of DHP under Various Conditions (Method B)



Entry	$SnCl_4$ (equiv)[a]	H_2O_2 (equiv)[b]	Temp (°C)	Yield (%)[c]
1	2.0	3.0	0	31
2	1.0	3.0	0	38
3	0.1	3.0	0	0
4	1.0	5.0	0	21
5	1.0	5.0	–30 to r.t.	71
6	1.0	5.0	–70 to r.t.	70

[a] Conditions: 1.0 mol L^{-1} in CH_2Cl_2.
[b] Conditions: 1.4 mol L^{-1} in Et_2O.
[c] Isolated yield.

We then tested the substrate compatibility under these two reaction conditions. As shown in Table 3, using method A, all selected oxiranes **4b–l** with different functional groups could afford the corresponding HHP **5b–l** in moderate to good yields. Compared to reactions catalyzed by PMA,[9a] the $SnCl_4$-catalyzed reaction time was substantially shortened (0.2–2 h vs. 2–12 h) without yield compromise. Moreover, the $SnCl_4$–H_2O_2 system is broadly applicable and can tolerate some commonly used protecting groups (Bn, TBS) and functional group (COOEt).

In terms of reaction regioselectivity of method A, the 2,2-disubstituted oxiranes **4b–h** (Table 3, entries 1–7, method A) underwent perhydrolysis exclusively at the quarternary carbon, which is in agreement with the PMA-catalyzed reaction.[9a] But 2-monosubstituted oxiranes **4i** and **4j** gave HHP with different regioselectivity (Table 3, entries 8 and 9, method A). The electron-donating butyl group at the 2-position of **4j** may function to stabilize the intermediate carbocation, giving the main products **5j–1** with the hydrogen peroxide group being added at the 2-position as the major product (**5j-1**/**5j-2** = 10:1 by ^1H NMR analysis). This result is different from that reported by another group for the longer alkyl chain oxirane.[9b] This may be due to the different reaction catalyst employed in the two systems. Accordingly, the electron-withdrawing oxygen atom at the β-position in oxirane **4i** would lose this stabilizing effect, providing **5i** as the main product with the hydrogen peroxide group being added at the less hindered terminal carbon, which was consistent with published report.[9a] To verify the regiochemistry, **5i** was further transformed to 1,2,4-trioxane **7** (Scheme 1) after reaction with 2,2-dimethoxypropane, the ^1H NMR and ^{13}C NMR spectra of the product were consistent with the data reported in

the literature.[9a] Finally, symmetric 2,3-disubstituted oxirane **4k** (Table 3, entry 10, method A) gave the *trans*-isomer **5k** in good yield,[20] the asymmetric **4l** afforded the HHP **5l** with the hydrogen peroxide group being added to the benzyl position in moderate yield.

Table 3 Products and Yield in Two Methods[21]

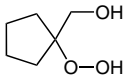
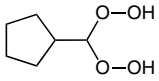
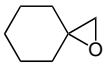
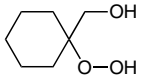
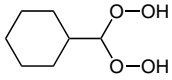
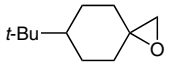
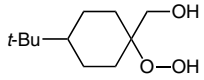
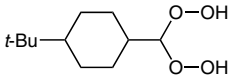
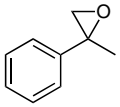
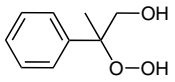
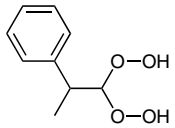
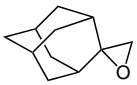
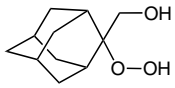
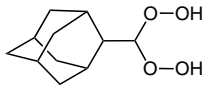
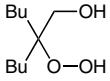
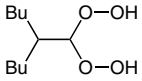
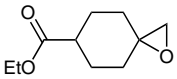
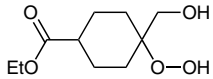
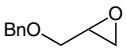
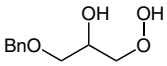
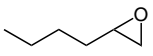
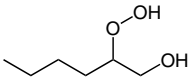
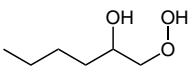
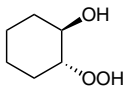
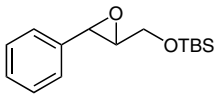
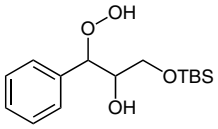
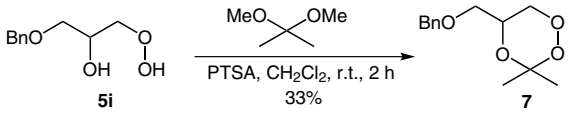
Entry	Oxiranes	Products of method A, yield[a]	Products of method B, yield[b]
1	 **4b**	 **5b** 75%	 **6b** 47%
2	 **4c**	 **5c** 81%	 **6c** 54%
3	 **4d**	 **5d** 61%	 **6d** 53%
4	 **4e**	 **5e** 74%	 **6e** 33%
5	 **4f**	 **5f** 37%	 **6f** 74%
6	 **4g**	 **5g** 49%	 **6g** 80%
7	 **4h**	 **5h** 66%	**5h** 55%[c]
8	 **4i**	 **5i** 60%	**5i** 61%
9	 **4j**	 **5j-1** major  **5j-2** minor 54% total	**5j-1** and **5j-2** 20% total
10	 **4k**	 **5k** 67%	**5k** 30%

Table 3 Products and Yield in Two Methods[21] (continued)

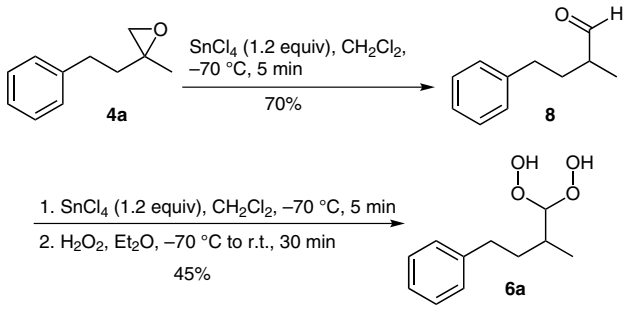
Entry	Oxiranes	Products of method A, yield[a]	Products of method B, yield[b]
11	 **4l**	 **5l** 55%	**5l** 17%

[a] Reaction conditions: 0.2–2 h, 0 °C to r.t., $SnCl_4$ (0.1 equiv), H_2O_2 (5.0 equiv).
[b] Reaction conditions: 30 min, –70 °C to r.t., $SnCl_4$ (1.2 equiv), H_2O_2 (5.0 equiv).
[c] 2.0 and 3.0 equiv of $SnCl_4$ gave similar results.



Scheme 1 Preparation of 1,2,4-trioxane **7** from **5i**

Using method B, 2,2-disubstituted oxiranes **4a**–**g** were transformed to the corresponding DHPs **6a**–**g** in good yields. This reaction outcome could be explained by a one-pot tandem rearrangement–condensation reaction: the oxiranes that were primarily catalyzed by $SnCl_4$ underwent a Meinwald-type rearrangement to form the aldehyde **8**,[22] followed by condensation with two molecules of hydrogen peroxide. Using **4a** as substrate, the above proposed two-step reaction process was confirmed. We first isolated the corresponding first-step reaction product, aldehyde **8**, which was further converted into DHP by treatment with hydrogen peroxide in the presence of $SnCl_4$ (Scheme 2). Obviously, the overall yield (32%) of two separated steps was much lower than that from a tandem reaction (71%), demonstrated the advantage of the one-pot reaction.



Scheme 2 Formation of DHP **6a** from oxirane **4a** in method B via an intermediate aldehyde **8**

2,2-Disubstituted oxirane **4h** with an ester group at the 4-position of the cyclohexyl ring gave HHP **5h** rather than the expected DHP, indicating the ester carbonyl may disturb the coordination of $SnCl_4$ with the oxirane oxygen atom, then prevent the oxirane to rearrange giving aldehyde. In addition, oxiranes **4i**–**l** would not afford the corresponding DHP products, suggesting this rearrangement reaction could not smoothly proceed for certain substrates using method B. Consequently, the $SnCl_4$-promoted hydroperoxidation of oxiranes would provide the same reaction product as method A.

In brief, we have disclosed an oxirane–$SnCl_4$–H_2O_2 system which could convert oxiranes into either HHP or primary DHP in moderate to good yields by adjusting the order of addition, reaction temperature, and the amount of $SnCl_4$. $SnCl_4$ acted as an efficient catalyst in the preparation of HHP. In the case of preparing primary DHP, $SnCl_4$ first promoted the rearrangement of oxirane to aldehyde, then catalyzed the condensation reaction of aldehyde with hydrogen peroxide. This is the first report that primary DHP could be efficiently prepared from the corresponding oxirane via a two-step, one-pot tandem reaction, even though the substrate scope is currently limited.

Acknowledgment

This work was supported by the Chinese National Science Foundation (81072514) to Professor Chunhua Qiao at Soochow University. Foundation from the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions and funding No. CXZZ12_0851 are also acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **Representative Procedure for Preparing β-Hydroxyhydroperoxides (Method A, Conversion of 4a into 5a)**
To the ethereal H_2O_2 solution (1.4 mol·L^{-1}, 2.2 mL, 3.08 mmol, 5.0 equiv) was added $SnCl_4$–CH_2Cl_2 solution (1.0 mol·L^{-1}, 0.062 mL, 62 μmol, 0.1 equiv) in an ice-bath. The mixture was stirred for 5 min. A solution of **4a** (0.1 g, 0.62 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added slowly at this temperature. Then the mixture was warmed up to r.t. and stirred for about 1 h till the reaction was complete (TLC). The reaction mixture was diluted with Et_2O (20 mL) and washed with H_2O (5 mL). The organic phase was separated, the aqueous solution was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (PE–EtOAc = 5:1) to afford **5a** as a white solid (95 mg, 79% yield). R_f = 0.2 (PE–EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (br s, 1 H), 7.31–7.09 (m, 5 H), 3.70 (d, J = 11.9 Hz, 1 H), 3.59 (d, J = 12.0 Hz, 1 H), 3.48 (br s, 1 H), 2.78–2.54 (m, 2 H), 2.00–1.84 (m, 1 H), 1.79–1.63 (m, 1 H), 1.21 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 128.5 (2 C), 128.4 (2 C), 125.9, 84.67, 65.7, 35.6, 29.6, 18.3. ESI-HRMS: *m/z* calcd for $C_{11}H_{16}O_3Na$ [M + Na]$^+$: 219.0992; found: 219.0994.
Representative Procedure for Preparing Primary *gem*-Dihydroperoxides (Method B, Conversion of 4a into 6a)
The solution of **4a** (0.1 g, 0.62 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was cooled to –70 °C. $SnCl_4$–CH_2Cl_2 solution (1.0 mol·L^{-1}, 0.62 mL, 0.62 mmol, 1.0 equiv) was added, and the mixture was stirred for 5 min. Then ethereal H_2O_2 solution (1.4 mol·L^{-1}, 2.2 mL, 3.08 mmol, 5.0 equiv) was added quickly. The mixture was stirred for 5 min at –70 °C. The reaction vessel was warmed to r.t., and the reaction mixture was stirred for 30 min and diluted with Et_2O (30 mL), washed with H_2O (5 mL), sat. $NaHCO_3$ solution (5 mL), and brine (5 mL), dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (PE–EtOAc = 10:1) to afford **6a** as a colorless liquid (92 mg, 70% yield). R_f = 0.4 (PE–EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 2 H), 7.33–7.12 (m, 5 H), 5.08 (d, J = 7.2 Hz, 1 H), 2.76–2.66 (m, 1 H), 2.63–2.52 (m, 1 H), 2.05–1.86 (m, 2 H), 1.60–1.48 (m, 1 H), 1.06 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 128.4 (4 C), 125.9, 114.5, 33.9, 33.2, 32.8, 14.9. ESI-HRMS: *m/z* calcd for $C_{11}H_{16}O_4Na$ [M + Na]$^+$: 235.0941; found: 235.0943.
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