

Article

Mild and Efficient Strontium Chloride Hexahydrate-Catalyzed Conversion of Ketones and Aldehydes into Corresponding *gem*-Dihydroperoxides by Aqueous H₂O₂

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Abstract: SrCl₂·6H₂O has been shown to act as an efficient catalyst for the conversion of aldehydes or ketones into the corresponding *gem*-dihydroperoxides (DHPs) by treatment with aqueous H₂O₂ (30%) in acetonitrile. The reactions proceed under mild and neutral conditions at room temperature to afford good to excellent yields of product.

Keywords: *gem*-dihydroperoxide; strontium chloride hexahydrate; ketone; aldehyde; hydrogen peroxide

1. Introduction

In recent years, much research has been directed towards *gem*-dihydroperoxides (DHPs) [1], due to their importance as useful intermediates in the synthesis of various peroxides, including tetraoxanes [2–9], and their analogues such as silatetroxanes [10], spirobisperoxyketals [11], and tetroxycycloalkanes [12], and epoxidation of α,β -unsaturated ketones [13]. These compounds have also recently been utilized as effective reagents in: (i) oxidation of various compounds [14] such as sulfides [15], (ii) enantioselective oxidation of 2-substituted 1,4-naphthoquinones [16], and (iii) as initiators in polymerization reactions [17,18]. It is also remarkable that *gem*-dihydroperoxides are relevant to peroxidic antimalarial drugs [2,19–23] possessing the *gem*-peroxy linkage as a salient structural feature [23,24–26] in common with many well-known antimalarial cyclic organic peroxides [1,2,27–35]. Most of the documented protocols for the synthesis of *gem*-dihydroperoxides in the

literature suffer from significant drawbacks such as the use of strong acidic media, concentrated H₂O₂ and low yields [1]. These methods mainly utilize a Brønsted or Lewis acid e.g., HCO₂H [12,20,36], NaHSO₄-SiO₂ [37], H₂SO₄ [38], F₃CCO₂H [39], H₂WO₄ [29,38], and BF₃·OEt₂ [30,39] to promote the conversion of ketones, ketals or enol ethers into the corresponding DHPs on treatment with aqueous H₂O₂. Other catalysts such as methyltrioxorhenium (prepared from Re₂O₇) [2], ceric ammonium nitrate (CAN) [32], and iodine [33] have also been reported to promote such transformations. However, these methods are not mild enough to offer general applicability and have limitations such as low yields, long reaction times, use of high concentration of H₂O₂ and incompatibility with sensitive functional groups. Recently, Dussault has reported a remarkably mild and highly efficient protocol for Re₂O₇-catalyzed conversion of ketones, aldehydes or acetals into 1,1-dihydroperoxides by H₂O₂ which represents a major improvement [34].

2. Results and Discussion

As part of our ongoing efforts to develop new methods for the synthesis of DHPs, we report here another new and highly efficient and inexpensive catalyst SrCl₂·6H₂O to promote the synthesis of *gem*-DHPs from ketones and aldehydes employing aqueous H₂O₂ (30%) at room temperature. To achieve suitable reaction conditions, *i.e.*, lower reaction times and higher yields, for the conversion of the ketones and aldehydes into their corresponding DHPs, various Lewis acid catalysts and solvents were investigated using 3-pentanone, cyclohexanone, acetophenone, and benzaldehyde as test compounds at room temperature (Table 1).

Table 1. Effects of catalyst and solvent in the synthesis of *gem*-DHPs.^a

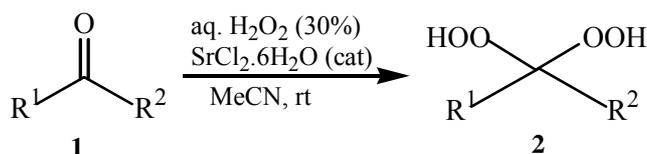
| Entry | Ketone 1/Aldehyde 3 | Catalyst | Solvent | Time (h) | Yield (%) ^b |
|-------|---------------------|--------------------------------------|---------------------------------|----------|------------------------|
| 1 | 3-pentanone | SrCl ₃ ·6H ₂ O | CH ₃ CN | 3 | 95 |
| 2 | 3-pentanone | SrCl ₃ ·6H ₂ O | CH ₂ Cl ₂ | 6 | 78 |
| 3 | 3-pentanone | SrCl ₃ ·6H ₂ O | Et ₂ O | 8 | 56 |
| 4 | 3-pentanone | SrCl ₃ ·6H ₂ O | AcOEt | 6 | 82 |
| 5 | 3-pentanone | SbCl ₃ | CH ₃ CN | 8 | 48 |
| 6 | 3-pentanone | CeO ₂ | CH ₃ CN | 10 | 45 |
| 7 | 3-pentanone | CrCl ₃ ·6H ₂ O | CH ₃ CN | 8 | 75 |
| 8 | 3-pentanone | KF-Al ₂ O ₃ | CH ₃ CN | 10 | Trace |
| 9 | Cyclohexanone | SrCl ₃ ·6H ₂ O | CH ₃ CN | 3 | 94 |
| 10 | Cyclohexanone | SbCl ₃ | CH ₃ CN | 7 | 55 |
| 11 | Cyclohexanone | CeO ₂ | CH ₃ CN | 8 | 50 |
| 12 | Cyclohexanone | CrCl ₃ ·6H ₂ O | CH ₃ CN | 6 | 70 |
| 13 | Cyclohexanone | KF-Al ₂ O ₃ | CH ₃ CN | 10 | Trace |
| 14 | Acetophenone | SrCl ₃ ·6H ₂ O | CH ₃ CN | 10 | 45 |
| 15 | Acetophenone | SbCl ₃ | CH ₃ CN | 12 | 23 |
| 16 | Acetophenone | CeO ₂ | CH ₃ CN | 12 | 15 |
| 17 | Acetophenone | CrCl ₃ ·6H ₂ O | CH ₃ CN | 10 | 28 |
| 18 | Acetophenone | KF-Al ₂ O ₃ | CH ₃ CN | 20 | 0 |
| 19 | Benzaldehyde | SrCl ₃ ·6H ₂ O | CH ₃ CN | 10 | 54 |
| 20 | Benzaldehyde | SbCl ₃ | CH ₃ CN | 15 | 32 |
| 21 | Benzaldehyde | CeO ₂ | CH ₃ CN | 15 | 15 |
| 22 | Benzaldehyde | CrCl ₃ ·6H ₂ O | CH ₃ CN | 12 | 22 |
| 23 | Benzaldehyde | KF-Al ₂ O ₃ | CH ₃ CN | 20 | 0 |

^a Conditions: Ketone and aldehyde (1 mmol), solvent (4 mL), catalyst (0.1 mmol), 30% aq. H₂O₂ (3 mL), reactions are carried out at rt. ^b Isolated yields.

As can be seen in Table 1, the reaction worked best in terms of yield and reaction time with aqueous H₂O₂ (30%) when SrCl₂·6H₂O (10 mol %) was used as a catalyst. The other catalysts such as SbCl₃, CeO₂ and CrCl₃·6H₂O gave moderate to low yields while KF-Al₂O₃ was found to be completely unsuitable for the synthesis of these DHPs. Effects of the solvents such as CH₂Cl₂, Et₂O, MeCN and AcOEt on the yields of the products were tested and the results are summarized in Table 1. Acetonitrile appeared as a much better solvent compared with other ones. This suggests that solvent polarity plays an important role in the synthesis of DHPs.

This success encouraged us to extend these reaction conditions to a variety of cyclic and acyclic aliphatic ketones **1a-g** using aqueous H₂O₂ (30%) in the presence of 10 mol% amount of SrCl₂·6H₂O as a chosen catalyst in acetonitrile at room temperature. The corresponding *gem*-dihydroperoxides **2a-g** were produced in high to excellent yields (90–98%) within 3–12 h (Table 2, Scheme 1). Similarly, aromatic ketones **1h-j** and aromatic aldehydes **1l-p** were converted to their corresponding *gem*-DHPs **2h-j** and **2l-p** in (45–68%) and (52–75%) yields respectively (Table 1). However, under the same reaction condition no conversion to *gem*-DHP was observed for benzophenone **1k** and it was recovered almost intact after 12 hours. This can possibly be accounted for by the strong resonance stabilization and steric effects exerted by two phenyl groups.

Scheme 1. Synthesis of *gem*-dihydroperoxides **2a-g**.



As previously reported by Rieche [40] and Žmitek *et al.* [41], we observed in the present protocol that simple, nonaromatic aldehydes such as octanal **3q** and dihydrocinnamaldehyde **3r**, which easily undergo hydration [42], reacted differently from the ketones and aromatic aldehydes. Under the same reaction conditions which converted ketones and aromatic aldehydes into their corresponding DHPs, both alkyl aldehydes—octanal **3q** and dihydrocinnamaldehyde **3r**—were not converted into their corresponding DHPs but instead into hydroxyl-hydroperoxides **4q** and **4r** in high yields (Table 1, Scheme 2), that is the addition of only one molecule of hydrogen peroxide to the carbonyl group has occurred. This implies that our protocol can furnish another hitherto unreported approach to 1,1-hydroxyhydroperoxides from aliphatic aldehydes.

Scheme 2. Synthesis of hydroxyl-hydroperoxides **4q** and **4r**.

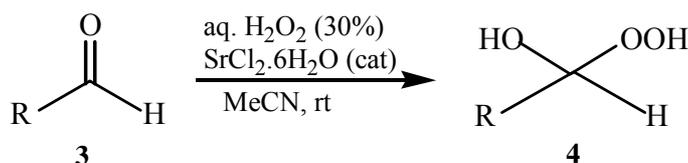


Table 2. Synthesis of *gem*-dihydroperoxides with SrCl₂·6H₂O (cat.)/30% aq. H₂O₂.^a

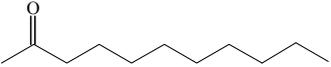
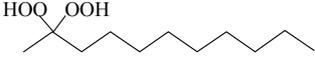
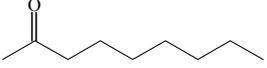
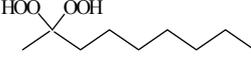
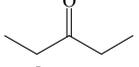
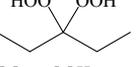
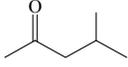
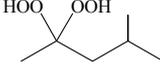
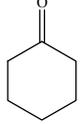
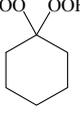
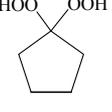
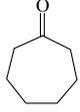
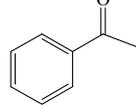
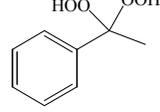
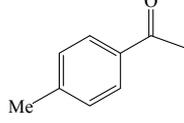
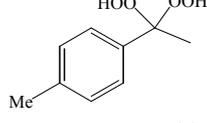
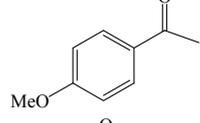
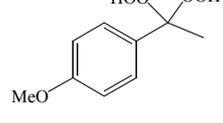
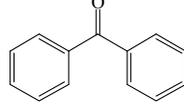
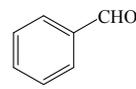
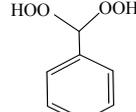
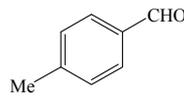
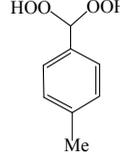
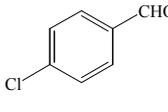
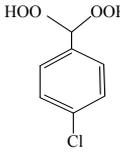
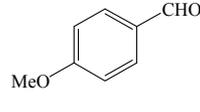
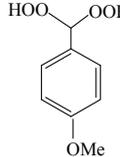
| Entry | Ketone 1/ Aldehyde 3 | Product 2 or 4 ^b | Time (h) | Yield (%) ^c |
|-------|---|---|----------|------------------------|
| a |  |  | 4 | 96 |
| b |  |  | 4 | 98 |
| c |  |  | 3 | 95 |
| d |  |  | 3 | 92 |
| e |  |  | 3 | 94 |
| f |  |  | 4 | 97 |
| g |  |  | 3 | 90 |
| h |  |  | 10 | 45 |
| i |  |  | 9 | 68 |
| j |  |  | 8 | 62 |
| k |  | — | 12 | — |
| l |  |  | 10 | 54 |
| m |  |  | 11 | 52 |
| n |  |  | 9 | 75 |
| o |  |  | 9 | 72 |

Table 2. Cont.

| | | | | |
|----------------------|--|--|----|----|
| P^d | | | 10 | 73 |
| q | | | 5 | 90 |
| r | | | 5 | 92 |

^a Conditions: Ketone and aldehyde (1 mmol), acetonitrile (4 mL), SrCl₂·6H₂O (0.1 mmol), 30% aq. H₂O₂ (3 mL), reactions are carried out at rt. ^b The structures of the products were established from their physical properties and spectral (¹H-, ¹³C-NMR and MS) analysis and compared with the literature. ^c Isolated Yield. ^d A new derivative.

3. Experimental

3.1. General

Chemicals were obtained from Merck. FT-IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ¹H- and ¹³C-NMR spectra were recorded on a 200 (50) MHz Varian or JEOL FX 90 MHz spectrometers in CDCl₃ and DMSO-d₆ solution, and are reported in δ units with TMS as internal standard. Melting points were determined in open capillary tubes in a Stuart SMP₃ apparatus and uncorrected.

3.2. General procedure for synthesis of gem-dihydroperoxides

Caution: Peroxidic compounds are potentially explosive and require precautions in handling (shields, fume hoods, absence of transition metal salts and heating).

A mixture of carbonyl substrates **1** or **3** (1 mmol), 30% aqueous H₂O₂ (3 mL) and SrCl₂·6H₂O (0.1 mmol) in MeCN (4 mL) was stirred at room temperature for 3-10 h (Table 1). After the completion of the reaction, the mixture was diluted with water (5 mL), extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate solution (3 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane-EtOAc) to afford pure gem-dihydroperoxides **2** or hydroxyl-hydroperoxides **4** (Table 1). The products were characterized on the basis of their physical properties and spectral (¹H-, ¹³C-NMR and MS) analyses and compared with literature data [32,33,37,40,41]. The spectral (¹H-, ¹³C-NMR and MS) data of some representative products are given below.

Undecane-2,2-dihydroperoxide (2a) [32]. ¹H-NMR (200 MHz, CDCl₃): δ 9.51 (br s, 2H), 1.76–1.60 (m, 2H), 1.38 (s, 3H), 1.32–1.19 (br s, 14H), 0.82 (t, *J* = 7 Hz, 3H); ¹³C-NMR (50 MHz, CDCl₃): 112.3, 33.4, 32.0, 29.4, 29.1, 28.4, 23.6, 22.5, 17.6, 13.8, 13.5; FABMS: *m/z* 243 [M+Na]⁺.

4-Methylpentane-2,2-dihydroperoxide (2d) [32]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.54 (br s, 2H), 1.80 (m, 1H), 1.62 (d, $J = 7$ Hz, 2H), 1.42 (s, 3H), 0.98 (d, $J = 7$ Hz, 6H); FABMS: m/z 173 $[\text{M}+\text{Na}]^+$.

Cyclohexane-1,1-dihydroperoxide (2e) [37]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.70 (br s, 2H), 1.93–1.70 (m, 4H), 1.67–1.39 (m, 6H); FABMS: m/z 171 $[\text{M}+\text{Na}]^+$.

Methy-phenyl-1,1-dihydroperoxide (2h) [33]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.16 (br s, 2H), 7.50–7.43 (m, 2H), 7.38–7.26 (m, 3H), 1.69 (s, 3H); FABMS: m/z 193 $[\text{M}+\text{Na}]^+$.

Phenylmethylene-1,1-dihydroperoxide (2l) [33]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.57 (br s, 2H), 7.42–7.28 (m, 5H), 6.24 (s, 1H); FABMS: m/z 179 $[\text{M}+\text{Na}]^+$.

(4-Methylphenyl)methylene-1,1-dihydroperoxide (2m) [41]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.71 (br s, 2H), 7.30 (d, $J = 8$ Hz, 2H), 7.15 (d, $J = 8$ Hz, 2H), 6.28 (s, 1H), 2.32 (s, 3H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 139.5, 129.4, 129.0, 126.7, 109.8, 21.1; FABMS: m/z 193 $[\text{M}+\text{Na}]^+$.

(4-Chlorophenyl)methylene-1,1-dihydroperoxide (2n) [32]. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.94 (br s, 2H), 7.85–7.34 (m, 4H), 6.26 (s, 1H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 139.6, 129.4, 129.0, 126.8, 10.02; FABMS: m/z 213 $[\text{M}+\text{Na}]^+$.

(4-Cyanophenyl)methylene-1,1-dihydroperoxide (2p). White solid; m.p. 107–110 °C; IR (KBr): 3,414, 2,916, 2,235, 1,611, 1,405, 1,333, 1,243, 1,199, 1,122, 1,083, 977, 824 cm^{-1} ; $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 10.08 (s, 2H), 8.04–7.78 (m, 4H), 7.24 (s, 1H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ 139.3, 129.4, 128.0, 126.1, 117.0, 112.1; FABMS: m/z 204 $[\text{M}+\text{Na}]^+$; Anal. Calcd for $\text{C}_8\text{H}_7\text{NO}_4$: C, 53.04; H, 3.86; N, 7.73. Found: C, 53.15; H, 3.98; N, 7.78.

Octane-1,1-hydroxyhydroperoxide (4q) [42]. Colorless oil; IR (KBr): 3,374, 3,028, 2,931, 2,863, 1,496, 1,454, 1,357, 1,242, 1,078, 1,030, 924, 748, 699 cm^{-1} ; $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 8.20 (br s, 1H), 7.00 (br s, 1H), 4.90 (t, $J = 7$ Hz, 1H), 2.10–0.70 (m, 15H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ 101.2, 32.6, 30.0, 28.5, 24.0, 20.1, 14.0; FABMS: m/z 185 $[\text{M}+\text{Na}]^+$.

3-Phenylpropane-1,1-hydroxyhydroperoxide (4r) [42]. Colorless oil; IR (KBr): 3384, 3062, 3027, 2902, 2861, 1496, 1457, 1376, 1242, 1079, 1031, 923, 747, 700 cm^{-1} ; $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 9.78 (br s, 1H), 8.65 (br s, 1H), 7.60–7.00 (m, 5H), 5.10 (t, $J = 7$ Hz, 1H), 2.60 (t, $J = 8$ Hz, 2H), 2.15–1.60 (m, 2H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ 141.5, 127.5, 125.0, 100.0, 32.2, 28.5; FABMS: m/z 191 $[\text{M}+\text{Na}]^+$.

4. Conclusions

In summary, a new efficient homogeneous catalyst $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ has been shown to promote the synthesis of *gem*-dihydroperoxides from aliphatic and aromatic ketones and aldehydes using aqueous H_2O_2 (30%) in acetonitrile at room temperature. The attractive features of this new approach are the readily available and non-expensive catalyst, high yields of the products, mild reaction conditions and the operational simplicity of the procedure.

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Sample Availability: Samples of the compounds are available from the authors.

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