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Article

Mild and Efficient Strontium Chloride Hexahydrate-Catalyzed Conversion of Ketones and Aldehydes into Corresponding gem-Dihydroperoxides by Aqueous H$_2$O$_2$

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Abstract: SrCl$_2$·6H$_2$O 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 H$_2$O$_2$ (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], spirobisperoxycyclanals [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
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literature suffer from significant drawbacks such as the use of strong acidic media, concentrated H\textsubscript{2}O\textsubscript{2}
and low yields [1]. These methods mainly utilize a Brönsted or Lewis acid e.g., HCO\textsubscript{2}H [12,20,36],
NaHSO\textsubscript{4}-SiO\textsubscript{2} [37], H\textsubscript{2}SO\textsubscript{4} [38], F\textsubscript{3}CCO\textsubscript{2}H [39], H\textsubscript{2}WO\textsubscript{4} [29,38], and BF\textsubscript{3}·OEt\textsubscript{2} [30,39] to promote
the conversion of ketones, ketals or enol ethers into the corresponding DHPs on treatment with aqueous
H\textsubscript{2}O\textsubscript{2}. Other catalysts such as methyltrioxorhenium (prepared from Re\textsubscript{2}O\textsubscript{7}) [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 H\textsubscript{2}O\textsubscript{2} and incompatibility with sensitive functional
groups. Recently, Dussault has reported a remarkably mild and highly efficient protocol for Re\textsubscript{2}O\textsubscript{7}-
catalyzed conversion of ketones, aldehydes or acetals into 1,1-dihydroperoxides by H\textsubscript{2}O\textsubscript{2} 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 SrCl\textsubscript{2}·6H\textsubscript{2}O to promote the synthesis of
gem-DHPs from ketones and aldehydes employing aqueous H\textsubscript{2}O\textsubscript{2} (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\textsubscript{2}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 3        | 95              |
| 2     | 3-pentanone         | SrCl\textsubscript{2}·6H\textsubscript{2}O | CH\textsubscript{2}Cl\textsubscript{2} | 6        | 78              |
| 3     | 3-pentanone         | SrCl\textsubscript{2}·6H\textsubscript{2}O | Et\textsubscript{2}O | 8        | 56              |
| 4     | 3-pentanone         | SrCl\textsubscript{2}·6H\textsubscript{2}O | AcOEt | 6        | 82              |
| 5     | 3-pentanone         | SbCl\textsubscript{3} | CH\textsubscript{3}CN | 8        | 48              |
| 6     | 3-pentanone         | CeO\textsubscript{2} | CH\textsubscript{3}CN | 10       | 45              |
| 7     | 3-pentanone         | CrCl\textsubscript{3}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 8        | 75              |
| 8     | 3-pentanone         | KF-Al\textsubscript{2}O\textsubscript{3} | CH\textsubscript{3}CN | 10       | Trace           |
| 9     | Cyclohexanone       | SrCl\textsubscript{2}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 3        | 94              |
| 10    | Cyclohexanone       | SbCl\textsubscript{3} | CH\textsubscript{3}CN | 7        | 55              |
| 11    | Cyclohexanone       | CeO\textsubscript{2} | CH\textsubscript{3}CN | 8        | 50              |
| 12    | Cyclohexanone       | CrCl\textsubscript{3}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 6        | 70              |
| 13    | Cyclohexanone       | KF-Al\textsubscript{2}O\textsubscript{3} | CH\textsubscript{3}CN | 10       | Trace           |
| 14    | Acetophenone        | SrCl\textsubscript{2}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 10       | 45              |
| 15    | Acetophenone        | SbCl\textsubscript{3} | CH\textsubscript{3}CN | 12       | 23              |
| 16    | Acetophenone        | CeO\textsubscript{2} | CH\textsubscript{3}CN | 12       | 15              |
| 17    | Acetophenone        | CrCl\textsubscript{3}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 10       | 28              |
| 18    | Acetophenone        | KF-Al\textsubscript{2}O\textsubscript{3} | CH\textsubscript{3}CN | 20       | 0               |
| 19    | Benzaldehyde        | SrCl\textsubscript{2}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 10       | 54              |
| 20    | Benzaldehyde        | SbCl\textsubscript{3} | CH\textsubscript{3}CN | 15       | 32              |
| 21    | Benzaldehyde        | CeO\textsubscript{2} | CH\textsubscript{3}CN | 15       | 15              |
| 22    | Benzaldehyde        | CrCl\textsubscript{3}·6H\textsubscript{2}O | CH\textsubscript{3}CN | 12       | 22              |
| 23    | Benzaldehyde        | KF-Al\textsubscript{2}O\textsubscript{3} | CH\textsubscript{3}CN | 20       | 0               |

\(^{a}\) \textit{Conditions}: Ketone and aldehyde (1 mmol), solvent (4 mL), catalyst (0.1 mmol), 30\%aq. H\textsubscript{2}O\textsubscript{2} (3 mL),
reactions are carried out at rt. \(^{b}\) \textit{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 SrCl$_2$·6H$_2$O (cat.)/30% aq. H$_2$O$_2$ $^a$

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

3.1. General

Chemicals were obtained from Merck. FT-IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). \(^1\)H- and \(^13\)C-NMR spectra were recorded on a 200 (50) MHz Varian or JEOL FX 90 MHz spectrometers in CDCl\(_3\) and DMSO-d\(_6\) solution, and are reported in δ units with TMS as internal standard. Melting points were determined in open capillary tubes in a Stuart SMP\(_3\) 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 H\(_2\)O\(_2\) (3 mL) and SrCl\(_2\)·6H\(_2\)O (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 Na\(_2\)SO\(_4\) 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 (\(^1\)H-, \(^13\)C-NMR and MS) analyses and compared with literature data [32,33,37,40,41]. The spectral (\(^1\)H-, \(^13\)C-NMR and MS) data of some representative products are given below.

**Undecane-2,2-dihydroperoxide (2a) [32].** \(^1\)H-NMR (200 MHz, CDCl\(_3\)): 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); \(^13\)C-NMR (50 MHz, CDCl\(_3\)): 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]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 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 [M+Na]$^+$. 

Cyclohexane-1,1-dihydroperoxide (2e) [37]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 9.70 (br s, 2H), 1.93–1.70 (m, 4H), 1.67–1.39 (m, 6H); FABMS: $m/z$ 171 [M+Na]$^+$. 

Methy phenyl-1,1-dihydroperoxide (2h) [33]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 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 [M+Na]$^+$. 

Phenylmethylene-1,1-dihydroperoxide (2l) [33]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 9.57 (br s, 2H), 7.42–7.28 (m, 5H), 6.24 (s, 1H); FABMS: $m/z$ 179 [M+Na]$^+$. 

Methylphenylmethylene-1,1-dihydroperoxide (2m) [32]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 9.94 (br s, 2H), 7.85–7.34 (m, 4H), 6.26 (s, 1H); $^{13}$C-NMR (50 MHz, CDCl$_3$): 139.6, 129.4, 129.0, 126.8, 10.02; FABMS: $m/z$ 213 [M+Na]$^+$. 

(4-Chlorophenyl)methylene-1,1-dihydroperoxide (2n) [32]. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 9.94 (br s, 2H), 7.85–7.34 (m, 4H), 6.26 (s, 1H); $^{13}$C-NMR (50 MHz, CDCl$_3$): 139.6, 129.4, 129.0, 126.8, 10.02; FABMS: $m/z$ 213 [M+Na]$^+$. 

(4-Cyanophenyl)methylene-1,1-dihydroperoxide (2p). White solid; m.p. 107–110 ºC; 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$^{-1}$; $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 10.08 (s, 2H), 8.04–7.78 (m, 4H), 7.24 (s, 1H); $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 139.3, 129.4, 128.0, 126.1, 117.0, 112.1; FABMS: $m/z$ 204 [M+Na]$^+$. Anal. Calcd for C$_8$H$_7$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$^{-1}$; $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 8.20 (br s, 1H), 7.00 (br s, 1H), 4.90 (t, $J = 7$ Hz, 1H), 2.10–0.70 (m, 15H); $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 101.2, 32.6, 30.0, 28.5, 24.0, 20.1, 14.0; FABMS: $m/z$ 185 [M+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$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 141.5, 127.5, 125.0, 100.0, 32.2, 28.5; FABMS: $m/z$ 191 [M+Na]$^+$. 

4. Conclusions

In summary, a new efficient homogeneous catalyst SrCl$_2\cdot$6H$_2$O has been shown to promote the synthesis of $\text{gem}$-dihydroperoxides from aliphatic and aromatic ketones and aldehydes using aqueous H$_2$O$_2$ (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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