Cesium nitrate: As an efficient catalyst for synthesis of gem-dihydroperoxides from aldehydes and ketones using aqueous 30% H₂O₂

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Cesium nitrate: As an efficient catalyst for synthesis of gem-dihydroperoxides from aldehydes and ketones using aqueous 30% H$_2$O$_2$

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**Abstract:** Gem-dihydroperoxides (DHPs), as key intermediates of aldehydes and ketones, are important precursors in synthesis of anti-malaria drugs and have been used as a solid and powerful oxidant in many oxidation organic reactions. For the importance of gem-DHPs, in this work, cesium nitrate has been used as an efficient and commercially available solid catalyst for catalysis peroxidation of aldehydes and ketones to corresponding gem-DHPs by 30% aqueous hydrogen peroxide at room temperature. The reactions carry on with short time and the products were obtained in excellent yields and high purity. In all reaction, no by-product was observed. This methodology is new, easy, effective, and usable.

**Subjects:** Clinical Chemistry; Drug Design & Development; Organic Chemistry

**Keywords:** gem-dihydroperoxide; aldehyde; ketones; cesium nitrate; hydrogen peroxide

1. **Introduction**

Gem-dihydroperoxides (DHPs) which have been known as nearly steady derivatives of ketones and aldehydes have been considered because of their roles in the synthesis of peroxide anti-malarial drugs (Iskra, Bonnet-Delpon, & Bégué, 2003; Tang, Dong, & Vennerstrom, 2004; Žmitek, Zupan, & Iskra, 2007). Additionally, these compounds are key intermediates in the synthesis of some peroxides such as tetraoxanes (Amewu et al., 2006; Franco et al., 2012; Terent’ev et al., 2004), silateraoxans (Terent’ev, Platonov, Tursina, Chernyshev, & Nikishin, 2008), spirobisperoxyketals (Ghorai, Dussault, & Hu, 2008; Hang, Li, & Wu, 2007), bisperoxyketals (Hamada et al., 2002), and 1,2,4,5-tetraoxacycloalkanes (Kim et al., 2001; Masuyama, Wu, Nojima, Kim, & Wataya, 2005). Also, gem-DHPs have been employed as the initiators for radical polymerization reactions (Hansma & Schroeder, 1978) and as the precursors for synthesis of dicarboxylic acid esters (Terent’ev, Platonov, & Kutkin, 2006). As well as, this category of peroxide have been utilized as the powerful solid oxidant for...
several oxidation reactions including epoxidation of \( \alpha,\beta \)-unsaturated ketones (Azarifar & Khosravi, 2010a; Jakka, Liu, & Zhao, 2007), enantioselective oxidation of 2-substituted 1,4-naphtoquinones (Bunge, Hamann, McCalmon, & Liebscher, 2009), oxidation of sulfides (Azarifar & Khosravi, 2010b; Jon Paul Selvam et al., 2008), and in some other oxidative organic reactions (Adam, 2000; Ando, 1992; Khosravi, Mobinikhaledi, Kazemi, Azarifar, & Rahmani, 2014). Generally, for synthesis of gem-DHPs, three conventional methods including (i) ozonolysis of ketone enol ethers or \( \alpha \)-olefines in the presence of aqueous \( \text{H}_2\text{O}_2 \) (Ito, Tokuyasu, Masuyama, Nojima, & McCullough, 2003; Kim et al., 2001; (Kim et al., 1999), (ii) reaction of ketals with \( \text{H}_2\text{O}_2 \) in the presence of tungstic acid (Jefford, Li, Jaber, Jaber, & Boukouvalas, 1990), or BF\(_3\).Et\(_2\)O (Terent’ev, Kutkin, Troizky, Ogibin, & Nikishin, 2005), and (iii) peroxidation of ketones using an acidic solvent have been reported (Ledaal & Solbjör, 1967). However, unfortunately, these methods suffer from certain drawbacks such as needing of concentrated \( \text{H}_2\text{O}_2 \) and extra acid, generation of mixes of peroxide products, low yield, and limited substrate range (Kharasch & Sosnovsky, 1958). Furthermore, one of the limitations in ozonolysis reaction is the presence of ozone-sensitive groups in the substrates and poor selectivity. Therefore, to modify these defects, reactions of ketones and aldehydes with \( \text{H}_2\text{O}_2 \) in the presence of I\(_2\), (Zmitek, Zupan, Stavber, & Iskra, 2006; Zmitek, Zupan, Stavber, & Iskra, 2007) in acetonitrile as the solvent have been reported. Several Lewis or Bronsted acids including Ceric ammonium nitrate (CAN) (Das, Krishnaiyah, Veeranjaneyulu, & Ravikan, 2007), CSA (Bunge, Hamann, & Liebscher, 2009), \( \text{NaHSO}_4 \).SiO\(_4\) (Das, Veeranjaneyulu, Krishnaiah, & Balasubramanyam, 2008), ReO\(_3\) (Ghori & Dussault, 2008), and PMA (Li, Hao, Zhang, & Wu, 2009) have been employed as the catalyst in the synthesis of gem-DHPs by aqueous \( \text{H}_2\text{O}_2 \). As the importance of gem-DHPs and in continuation of our attempts to analyze new catalysts for synthesis of these compounds (Azarifar, Khoresponse, & Soleimanei, 2009; Azarifar, Najminejad, & Khosravi, 2013), herein, we like to present the cesium nitrate as a nearly cheap and efficient solid catalyst in the synthesis of gem-DHPs from aldehydes and ketones with 30% aqueous \( \text{H}_2\text{O}_2 \) at room temperature (Scheme 1).

Cesium nitrate is commercially available solid that is nearly soluble in water and has been used widely as an effective catalyst in different reactions (Ovsienko, 2012; Jacobsen, 2000).

2. Experimental

2.1. Caution
Although we did not encounter any problem with gem-DHPs, peroxides are potentially explosive and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood, and transition metal salts or heating should be avoided.

Nuclear magnetic resonance spectra were recorded on a JEOL FX 90Q spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Perkin Elmer GX FT IR spectrometer (KBr pellets).

2.2. General procedure for synthesis of gem-dihydroperoxides
To a mixture of carbonyl compound (1 mmol) and cesium nitrate (0.1 mmol, 0.0194 g) in MeCN (4 ml), 30% aqueous \( \text{H}_2\text{O}_2 \) (1 ml) was added, and the mixture was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction as monitored by thin-layer chromatography (TLC), the mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 × 5 ml). Organic layer that contains products was separated, dried over Mg\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was purified by silica-packed column chromatography (hexane-EtOAc) to afford pure gem-DHPs if it was needed (Table 2). The
products were characterized on the basis of their melting points, elemental analysis and IR, \(^1\)H NMR, and \(^{13}\)C NMR spectral analysis. Also the amount of peroxide in products has been determined by iodometry or manganometry titration.

2.3. Spectroscopic data of unknown products are given below

4-(dihydroperoxymethyl)-N,N-dimethylaniline (Table 2, entry x):
Sticky brown oil. IR (Nujol mull): 3400, 3092, 1592, 1425, 1363, 1221, 1111, 979 cm\(^{-1}\); \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 3.00 (s, 6H), 6.28 (s, 1H), 7.32–7.42 (m, 2H), 7.97–8.17 (m, 2H), 9.37 (br, s, 2H); \(^{13}\)C NMR (22.5 MHz, DMSO-d\(_6\)) \(\delta\): 38.50, 101.00, 127.75, 130.56, 138.06, 143.42; Anal. Calcd for C\(_9\)H\(_{13}\)NO\(_4\): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.44; H, 6.83; N, 7.30.

2-(dihydroperoxymethyl)thiophene (Table 2, entry y):
White solid, m.p: 200–202 \(^\circ\)C. IR (KBr pellet): 3420, 2922, 2829, 1635, 1558, 1458, 1363, 1271, 987, 721, 599, 435, 353 cm\(^{-1}\); \(^1\)H NMR (90 MHz, CDCl\(_3\)) \(\delta\): 6.49 (s, 1H), 6.60 (s, 1H), 7.06 (s, 1H), 7.28 (s, 1H), 9.17 (br, s, 2H). \(^{13}\)C NMR (22.5 MHz, DMSO-d\(_6\)): \(\delta\)C: 100.42, 126.75, 138.01, 139.00, 146.15; Anal. Calcd for C\(_6\)H\(_8\)O\(_4\)S: C, 37.03; H, 3.73; S, 19.77. Found: C, 37.15; H, 3.80, S, 20.02.

3. Results and discussion

In an attempt to arrange the reaction conditions, all reaction parameters for synthesis of 1,1-dihydroperoxycyclohexane as the model reaction were studied and the results are summarized in Table 1. As we have seen, the best result in terms of yield and reaction time was provided using MeCN as solvent at room temperature with 10 mol% of catalyst loading (entry 6, Table 1).

In optimized conditions (aq 30% H\(_2\)O\(_2\) (2 ml), 0.1 mmol of catalyst, MeCN (4 ml), r.t), we started to analyze the potential of the reaction using a different aliphatic and aromatic aldehydes and ketones (Table 2). According to the obtained results summarized in Table 2, generally, aliphatic ketones g-l react faster than aromatic ketones a-e to generate the corresponding gem-DHPs in higher yields. Surprisingly, the aromatic aldehydes and ketones substituted by power electron-withdrawing substituent were not reacting at all or reacted in a very long time with nearly low yields. Also, it was interesting that in cases of aliphatic aldehydes such as z and z' entries (Table 2), addition of only one molecule of hydrogen peroxide to carbonyl group occurs and generates 1,1-hydroxyhydroperoxide derivatives instead of their expected DHPs (Scheme 2).

| Entrya | Solvent | Cesium nitrate (mmol) | Time (min) | Yield (%)b |
|--------|---------|-----------------------|------------|------------|
| 1      | n-hex   | 0.1                   | 120        | 5          |
| 2      | EtOAc   | 0.1                   | 30         | 82         |
| 3      | CH\(_2\)\(_2\)Cl | 0.1       | 100        | 50         |
| 4      | CHCl\(_3\) | 0.1                   | 120        | 45         |
| 5      | CCl\(_4\) | 0.1                   | 120        | 40         |
| 6      | CH\(_2\)CN | 0.1                   | 20         | 97         |
| 7      | CH\(_2\)CN | 0.05                  | 35         | 91         |
| 8      | CH\(_2\)CN | 0.15                  | 15         | 91         |
| 9      | CH\(_2\)CN | 0.2                   | 15         | 75         |

\(^a\)mmol cyclohexanone, amount of H\(_2\)O\(_2\) in all entries is 1 ml.
\(^b\)Isolated yields.
### Table 2. Synthesis of gem-DHPs catalyzed by cesium nitrate

| Entry | Ketone or aldehyde | Producta | Time (min) | Yield (%)c | Mp (°C) | Ref |
|-------|--------------------|----------|------------|------------|---------|-----|
| a     | ![Ketone or aldehyde](image1) | ![Product](image2) | 200 | 67 | 75–77 | 36 |
| b     | ![Ketone or aldehyde](image1) | ![Product](image2) | 200 | 72 | Oil | 36 |
| c     | ![Ketone or aldehyde](image1) | ![Product](image2) | 205 | 75 | Oil | 36 |
| d     | ![Ketone or aldehyde](image1) | ![Product](image2) | 190 | 74 | Oil | 36 |
| e     | ![Ketone or aldehyde](image1) | ![Product](image2) | 90 | 85 | Oil | 36 |
| f     | ![Ketone or aldehyde](image1) | ![Product](image2) | 300 | - | - | - |
| g     | ![Ketone or aldehyde](image1) | ![Product](image2) | 20 | 97 | Oil | 36 |
| h     | ![Ketone or aldehyde](image1) | ![Product](image2) | 25 | 92 | Oil | 30 |
| i     | ![Ketone or aldehyde](image1) | ![Product](image2) | 30 | 93 | Oil | 30 |
| j     | ![Ketone or aldehyde](image1) | ![Product](image2) | 28 | 96 | Oil | 33 |
| k     | ![Ketone or aldehyde](image1) | ![Product](image2) | 29 | 93 | 64–66 | 36 |
| l     | ![Ketone or aldehyde](image1) | ![Product](image2) | 18 | 95 | Oil | 36 |
| m     | ![Ketone or aldehyde](image1) | ![Product](image2) | 20 | 93 | Oil | 36 |

(Continued)
Furthermore, we have successfully converted 2-thiophenecarbaldehyde as a heterocyclic aldehyde to corresponding gem-dihydroperoxide without any by-product (Table 2, entry y) for the first time. Again, similar to other reports, benzophenone was recovered intact after 200 min (Table 2, entry f).

It seems that cesium cation as an efficient Lewis acid activates carbonyl group to electrophilic attack by hydrogen peroxide.
Moreover, this method for peroxidation of cyclohexanone as a model method (entry a, Table 2) is compared with other reported methodologies in Table 3. From the given results, it is shown that this methodology evidently improved time reaction, yields, and reaction conditions.

### Table 3. Comparing reported results for peroxidation of cyclohexanone

| Entry | Catalyst | Condition | Concentration of H₂O₂ (%) | Time (min) | Yield (%) | Ref |
|-------|----------|-----------|---------------------------|------------|-----------|-----|
| 1     | This method (cesium nitrate) | r. t | 30 | 20 | 97 | – |
| 2     | Silica sulfuric acid | r. t | 30 | 20 | 98 | 36 |
| 3     | Bi(OTf)₃ | r. t | 18 | 150 | 95 | 34 |
| 4     | phosphomolybdic acid | r. t | 50 | 30 | 79 | 33 |
| 5     | CAN reagent | r. t | 50 | 120 | 87 | 30 |
| 6     | NaHSO₄·SiO₂ | r. t | 50 | 20 | 98 | 32 |

Moreover, this method for peroxidation of cyclohexanone as a model method (entry a, Table 2) is compared with other reported methodologies in Table 3. From the given results, it is shown that this methodology evidently improved time reaction, yields, and reaction conditions.

### 4. Conclusion

In conclusion, cesium nitrate has been utilized as a highly efficient, commercially available and nontoxic catalyst for conversion of ketones and aldehydes to corresponding gem-DHPs. These reactions go on smoothly with short reaction times at room temperature to produce products from high to excellent yields. Cesium nitrate as a nearly cheap and nontoxic catalyst makes the process less contaminant, cost-effective, and environmentally friendly.

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### Cover image

Conversion of ketones and aldehydes to corresponding gem-dihydroperoxides.

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