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A simple and efficient synthesis of *gem*-dihydroperoxides from ketones using aqueous hydrogen peroxide and catalytic ceric ammonium nitrate☆

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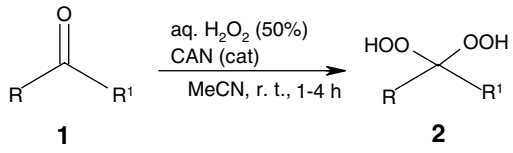
Abstract—Ketones were efficiently converted into the corresponding *gem*-dihydroperoxides in high yields within a short period of time on treatment with aqueous H_2O_2 (50%) in the presence of a catalytic amount of CAN in acetonitrile at room temperature.

gem-Dihydroperoxides have gained much importance in recent years due to their relevance to peroxidic antimalarial drugs.[1] They are useful intermediates in the synthesis of various peroxides such as tetraoxanes[1a,2] and endoperoxides.[3] They have also recently been utilized as oxidants.[4] *gem*-Dihydroperoxides can be prepared by ozonolysis of ketone enol ethers or α-olefins in the presence of H_2O_2[5] or by hydroperoxide rearrangement of bicyclic alcohols.[6] However, these methods suffer from disadvantages such as the requirement of suitable starting materials, use of concentrated H_2O_2 and excess acid and unsatisfactory yields. Recently, a method for the conversion of ketones into *gem*-dihydroperoxides using aqueous H_2O_2 in the presence of iodine was reported.[7] The time required for this conversion was typically 24 h.

In continuation of our work[8] on the development of useful synthetic methodologies we have observed that *gem*-dihydroperoxides can be prepared from ketones on treatment with aqueous H_2O_2 (50%) using a catalytic amount of CAN (Scheme 1).

Various ketones were successfully converted into the corresponding *gem*-dihydroperoxides at room temperature



1 2

Scheme 1.

(Table 1). The conversions were complete within 1–4 h. CAN, being a Lewis acid, activates the carbonyl group and increases the electrophilic character of the carbonyl C-atom. It also enhances the nucleophilic character of H_2O_2. Both acylic and cyclic aliphatic ketones afforded the desired products in excellent yields. Cyclododecanone was converted into the corresponding *gem*-dihydroperoxide in 1 h in 92% yield (Table 1, entry l). Previously, the same conversion using H_2O_2/I_2 required[7] 24 h to form the same product in only 60% yield (Scheme 2).

The present method was also applied for the hydroperoxidation of aromatic ketones. Thus acetophenone afforded the corresponding *gem*-dihydroperoxide within 2 h in a yield of 48% (entry o). Previously, hydroperoxidation of acetophenone using aqueous H_2O_2/I_2 required 24 h and the yield was only 16%.[7] Different acetophenone derivatives containing both electron-donating (e.g., OMe and Cl, entries p and q) and electron-withdrawing groups (e.g., NO_2, entry r) afforded the corresponding dihydroperoxides in appreciable quantities. However, purification of the product derived from acetophenone with an electron-withdrawing group

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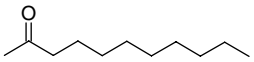
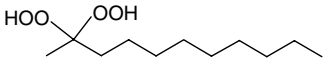
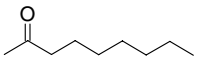
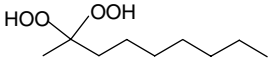
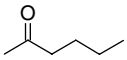
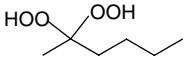
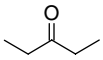
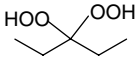
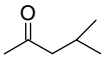
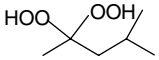
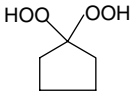
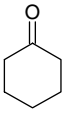
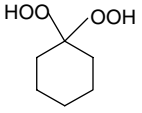
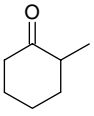
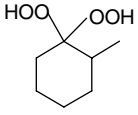
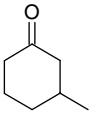
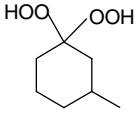
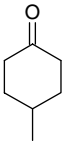
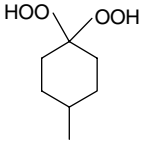
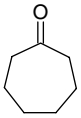
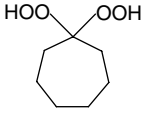
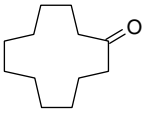
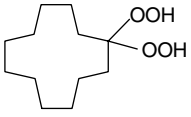
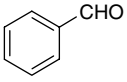
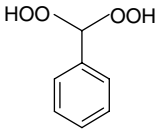
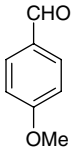
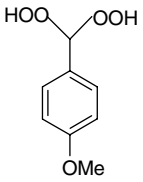
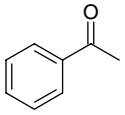
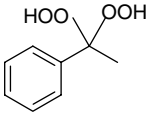
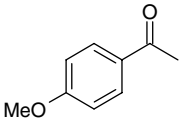
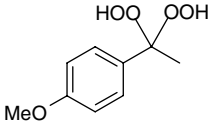
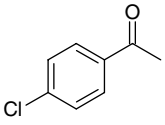
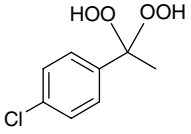
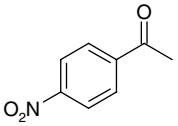
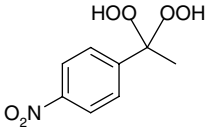
Table 1. Synthesis of dihydroperoxides with CAN/50% aq H_2O_2[a]

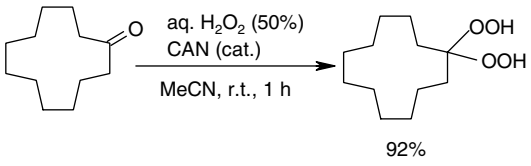
Entry	Ketone/aldehyde **1**	Product **2**	Time (h)	Yield[b] (%)
a			1	96
b			1	95
c			2	96
d			3	89
e			2	90
f			3	85
g			2	87
h			2.5	82
i			2	85
j			2	90
k			2	86
l			1	92
m			4	51

(*continued on next page*)

Table 1 (*continued*)

Entry	Ketone/aldehyde **1**	Product **2**	Time (h)	Yield[b] (%)
n			4	74
o			2	48
p			2	60
q			2	62
r			4	25[c]

[a] The structures of the products were established from their spectral (^{1}H, ^{13}C NMR and MS) data.
[b] Isolated yield.
[c] The crude ^{1}H NMR spectrum of the reaction mixture showed formation of the product in a yield of 55%, however, it decomposed during isolation.



Scheme 2.

by column chromatography using silica gel resulted in decomposition.

Hydroperoxidation of aldehydes is quite difficult. Benzaldehyde was earlier converted using aqueous H_2O_2/I_2 into the corresponding *gem*-dihydroperoxide in 24 h in a yield of 55%.[7] In the present method the same conversion was carried out in 4 h to furnish the *gem*-dihydroperoxide in 51% yield (entry m). The presence of an electron-donating group (e.g., OMe) on benzaldehyde afforded the product in higher yield (entry n) while the presence of an electron-withdrawing group (e.g., NO_2) resulted in no product.

In conclusion, we have developed a simple and highly efficient method for the synthesis of *gem*-dihydroperoxides from the corresponding ketones on treatment with aqueous H_2O_2 and a catalytic amount of CAN. The high yields of products, mild reaction conditions, short conversion times and the use of less costly reagents are notable advantages of the present method.

General procedure: A mixture of ketone (1 mmol), 50% aqueous H_2O_2 (1 mL) and CAN (0.1 mmol) in MeCN (4 mL) was stirred at room temperature for 1–4 h. The reaction was quenched with water (5 mL) and the mixture was extracted with EtOAc (3×5 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue, on purification by column chromatography (silica gel, hexane–EtOAc), afforded pure *gem*-dihydroperoxide.

The spectral (^{1}H, ^{13}C NMR and MS) data of some representative products are given below.

Compound **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.52 (2H, br s), 1.78–1.62 (2H, m), 1.39 (3H, s), 1.34–1.20 (14H, br s), 0.83 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 112.5, 33.5, 32.0, 29.5, 29.0, 28.5, 23.8, 22.6, 17.8, 13.9; LC–MS: m/z 243 $[M+Na]^+$.

Compound **2d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.35 (2H, br s), 1.62 (4H, q, $J = 7.0$ Hz), 0.85 (6H, t, $J = 7.0$ Hz); LC–MS: m/z 159 $[M+Na]^+$.

Compound **2e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.56 (2H, br s), 1.82 (1H, m), 1.63 (2H, d, $J = 7.0$ Hz), 1.44 (3H, s), 0.98 (6H, d, $J = 7.0$ Hz); LC–MS: m/z 173 $[M+Na]^+$.

Compound **2i**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.22 (2H, br s), 2.20 (2H, br d, $J = 13.0$ Hz), 1.80–1.22 (5H, m), 1.12–0.81 (2H, m) 0.98 (3H, d, $J = 7.0$ Hz); LC–MS: m/z 185 $[M+Na]^+$.

Compound **2l**: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 10.39 (2H, br s), 1.62–1.24 (m, 22H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 112.4, 25.9, 25.8, 25.5, 24.2, 23.8, 21.7, 21.5, 21.4, 21.3, 19.2, 18.5; LC–MS: m/z 255 $[M+Na]^+$.

Compound **2m**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.59 (2H, br s), 7.44–7.30 (5H, m), 6.26 (1H, s); LC–MS: m/z 179 $[M+Na]^+$.

Compound **2o**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.18 (2H, br s), 7.52–7.44 (2H, m), 7.40–7.28 (3H, m), 1.71 (3H, s); LC–MS: m/z 193 $[M+Na]^+$.

Acknowledgement

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