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Boric Acid: As a Green Catalyst for the Conversion of Aldehydes and Ketones to *Gem*-Dihydroperoxides Using Aqueous 30% H₂O₂

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Gem-dihydroperoxides as nearly stable peroxidic derivatives of aldehydes and ketones are known important intermediates in synthesis of anti-malaria drugs. Also, because containing high concentration of peroxidic oxygen, recently, some of these compounds have been used as solid, efficient and powerful oxidants in many oxidation organic reactions. Generally, these compounds are synthesized *via* peroxidation of aldehydes and ketones. So, regarding the importance of *gem*-dihydroperoxides, in this work, boric acid has been explored as an effective, inexpensive, commercially available, green and homogenous solid catalyst for catalyze peroxidation of aldehydes and ketones to corresponding *gem*-dihydroperoxides by 30% aqueous hydrogen peroxide at room temperature in acetonitrile as the solvent. Both aromatic and aliphatic aldehydes and ketones were studied in this work. The reactions were carried on in short times. The products were obtained in high yields and good purity. In all reaction, no any by-product was observed. This methodology is easy, mild, nearly green, efficient and available.

Keywords: *Gem*-dihydroperoxide, Aldehyde, Ketones, Boric acid, Hydrogen peroxide

INTRODUCTION

Gem-dihydroperoxides (DHPs) have been studied as nearly steady derivatives of ketones and aldehydes [1] that have been considered because of their participation in peroxide anti-malarial drugs [2,3]. In addition, these compounds are significant key intermediates in the synthesis of some peroxides such as tetraoxanes [4-6], silatetraoxanes [7], spirobisperoxyketals [8,9], bisperoxyketals [10] and 1,2,4,5-tetraoxacycloalkanes [11,12]. *Gem*-dihydroperoxides have been also used as the initiators for radical polymerization reactions [13], as the forerunners for synthesis of dicarboxylic acid esters [14] and as the oxidant for oxidation reactions such as epoxidation of α,β -unsaturated ketones [15,16], enantioselective oxidation of 2-substituted 1,4-naphthoquinones [17], oxidation of sulfides [18-19] and as the desirable oxidative reagents in some other oxidative organic reactions [20-22]. There are three major reported methods for synthesis of *gem*-dihydro-

peroxides including: (i) ozonolysis of ketone enol ethers or α -olefines in the presence of aqueous H₂O₂ [11,23,24], (ii) reaction of ketals with H₂O₂ in the presence of tungstic acid [25], or BF₃.Et₂O [26], and (iv) peroxidation of ketones using an acidic solvent [27]. All the same, unfortunately, these methods have sure disadvantages including use of concentrated H₂O₂ and excess acid, formation of mixtures of peroxide products, poor yield and limited substrate range [28]. In addition, presence of ozone sensitive groups in the substrates and low selectivity is further limitations in ozonolysis reaction. So, to avoid these disadvantages, recently, reactions of ketones and aldehydes with H₂O₂ in the presence of Lewis acids in acetonitrile as the solvent have been reported. So, I₂ [29,30], Ceric ammonium nitrate (CAN) [31], CSA [32], NaHSO₄.SiO₂ [33], Re₂O₇ [34] and PMA [35] have been employed as the catalyst in the synthesis of *gem*-dihydroperoxides by aqueous H₂O₂. In continuation of our attempts to find new catalysts for synthesis of *gem*-dihydroperoxides [35,36], herein, we like to introduce the boric acid as a low-cost, green and effective solid catalyst in synthesis of *gem*-dihydroperoxides from

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ketones and aldehydes with 30% aqueous H₂O₂ at room temperature (Scheme 1).

Boric acid is commercially available that is solvable in water and has been used widely as an effective catalyst in organic synthesis [38].

EXPERIMENTAL

Caution

Although we did not encounter any problem with *gem*-dihydroperoxides, 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).

General Procedure for Synthesis of Gem-Dihydroperoxides

To a mixture of aldehyde or ketones (1 mmol) and boric acid (0.1 mmol, 0.0062 g) in MeCN (4 ml), 30% aqueous H₂O₂ (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 was separated and dried by anhydrous Mg₂SO₄ and evaporated under reduced pressure to obtain pure *gem*-dihydroperoxides (Table 2). The products were characterized on the basis of their melting points, elemental analysis and IR, ¹H NMR and ¹³C NMR spectral analyses and the amount of peroxide in products was determined by iodometry or manganometry titration.

Spectral Data of Unknown Products are Given Below

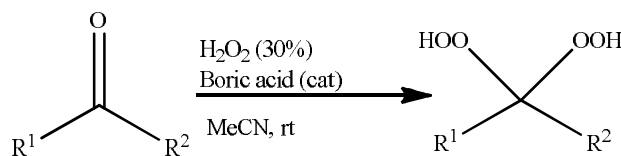
4-(Dihydroperoxymethyl)-*N,N*-dimethylaniline (Table 2, Entry s): Sticky brown oil. IR (nujol mull): 3400, 3092, 1592, 1425, 1363, 1221, 1111, 979 cm⁻¹. ¹H NMR (90 MHz, CDCl₃) δ: 3.00 (s, 6H), 6.28 (s, 1H), 7.32-7.42 (m, 2H), 7.97-8.17 (m, 2H), 9.37 (br, s, 2H). ¹³C NMR (22.5 MHz, DMSO-*d*₆) δ: 38.50, 101.00, 127.75, 130.56, 138.06, 143.42. Anal. Calcd. for C₉H₁₃NO₄: 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 t): White solid, m.p.: 98-101 °C. IR (KBr pellet): 3420, 2922, 2829, 1635, 1558, 1458, 1363, 1271, 987, 721, 599, 435, 353 cm⁻¹. ¹H NMR (90 MHz, CDCl₃) δ: 6.49 (s, 1H), 6.60 (s, 1H), 7.06 (s, 1H), 7.28 (s, 1H), 9.17 (br, s, 2H). ¹³C NMR (22.5 MHz, DMSO-*d*₆): δC: 100.42, 126.75, 138.01, 139.00, 146.15. Anal. Calcd. for C₆H₈O₄S: C, 37.03; H, 3.73; S, 19.77. Found: C, 37.15; H, 3.80, S, 20.02.

RESULTS AND DISCUSSION

In an effort to set up the reaction conditions, all reaction parameters for the synthesis of 1,1-dihydroperoxy-cyclohexane as the model reaction were studied and the results are summarized in Table 1. As noted, the best result in terms of yield and reaction time was provided using MeCN as a solvent at room temperature with 10 mol% of catalyst loading (Entry 6, Table 1).

In optimized conditions (aq. 30% H₂O₂ (1 ml), 0.1 mmol of boric acid, MeCN (4 ml), r.t) we began to study the potential of the reaction using a variety of aliphatic and aromatic aldehydes and ketones (Table 2). According to the summarized results in Table 2, generally, aliphatic ketones g-l react faster than aromatic ketones v-z” to produce the corresponding *gem*-dihydroperoxides in higher yields. In



Scheme 1. Conversion of ketones and aldehydes to the corresponding *gem*-dihydroperoxides

Table 1. Screening of the Reaction Parameters for the Formation of 1,1-Dihydroperoxycyclohexane

Entry ^a	Solvent	Boric acid (mmol)	Time (min)	Yield (%) ^b
1	Et ₂ O	0.10	60	78
2	EtOAc	0.10	40	80
3	CH ₂ Cl ₂	0.10	120	40
4	CHCl ₃	0.10	110	47
5	CCl ₄	0.10	140	45
6	CH ₃ CN	0.10	30	96
7	CH ₃ CN	0.05	45	90
8	CH ₃ CN	0.15	25	92
9	CH ₃ CN	0.20	25	73

^a1 mmol cyclohexanone, amount of H₂O₂ in all entries is 1 ml. ^bIsolated yields.

Table 2. Synthesis of *Gem*-dihydroperoxides Catalyzed by Boric Acid

Entry	Ketone or aldehyde	Product ^b	Time (min)	Yield (%) ^c	M.P. (°C)	Ref.
a			30	96	Oil	[37]
b			40	90	Oil	[31]
c			35	92	Oil	[31]
d			33	95	Oil	[34]
e			35	91	64-66	[37]
f			31	95	Oil	37

Table 2. Continued

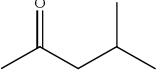
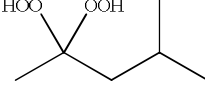
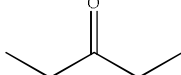
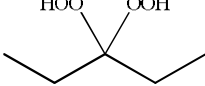
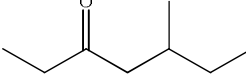
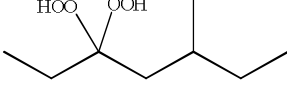
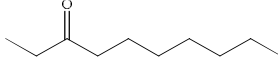
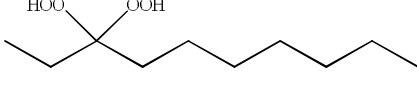
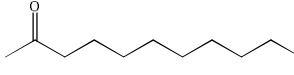
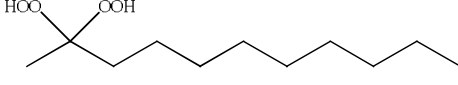
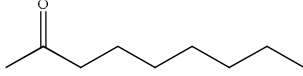
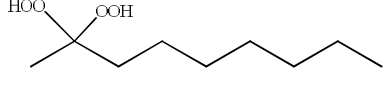
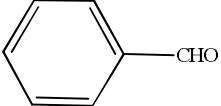
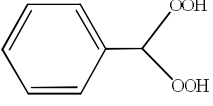
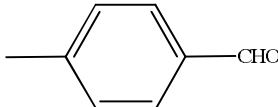
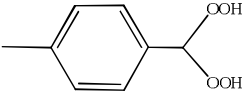
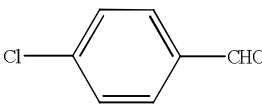
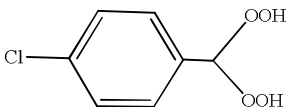
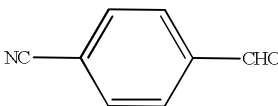
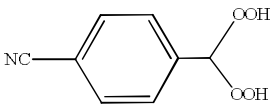
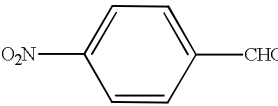
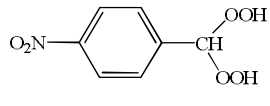
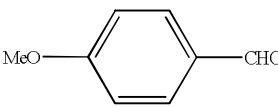
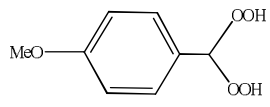
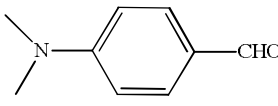
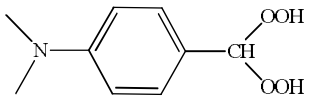
g			25	92	Oil	[37]
h			25	92	Oil	[37]
i			26	93	Oil	[29]
j			32	90	31-33	[29]
k			31	94	Oil	[37]
l			30	92	Oil	[31]
m			90	80	Oil	[37]
n			90	82	54-56	[37]
o			100	83	72-74	[37]
p			240	15	105-107	[37]
q			250	-	-	-
r			75	89	Oil	[37]
s			150	72	Sticky brown oil	New

Table 2. Continued

t			140	84	98-101	New
u			120	90	Oil	[37]
v			100	91	Oil	[37]
w			220	70	75-77	[37]
x			210	72	Oil	[37]
y			220	74	Oil	[37]
z			200	67	Oil	[37]
z'			100	90	Oil	[36]
z''		-	300	-	-	-

^aConditions: ketone and aldehyde (1 mmol), CH₃CN (4 ml), Boric acid (0.1 mmol, 0.0062 g), 30% aq. H₂O₂ (1 ml), reactions are carried out at rt. ^bThe structures of the products were established from their physical properties and spectral (¹H NMR, ¹³C NMR and IR) analysis and compared with the data reported in the literature and the amount of peroxide is determined by iodometry or manganometry titration. ^cIsolated Yield.

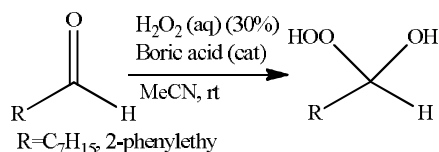
aromatic substrates, conjugation of carbonyl group to phenyl ring reduces its activity towards nucleophile's attack compared to that in aliphatic carbonyls, therefore benzophenone (Table 2, Entry z'') was recovered intact after 300 min. Interestingly, the aromatic aldehydes and ketones substituted by electron-withdrawing groups were not reacting at all or reacted in a very long time with nearly low yields (Table 2, Entries p and q). Zmitek and CO-workers suggested that transition state in peroxidation of aldehydes and ketones has positive charge [28], therefore, powerful electron-withdrawing groups destabilizes the transition state. In Addition, it was interesting that addition of only one molecule of hydrogen peroxide to the carbonyl group occurs in reactions of aliphatic aldehydes such as u and v entries (Table 2) to result in formation of 1,1-hydroxyhydroperoxide derivatives instead of their expected DHPs (Scheme 2). This observation has been reported before in all corresponding published documents.

As shown in suggested mechanism, Scheme 3, boric

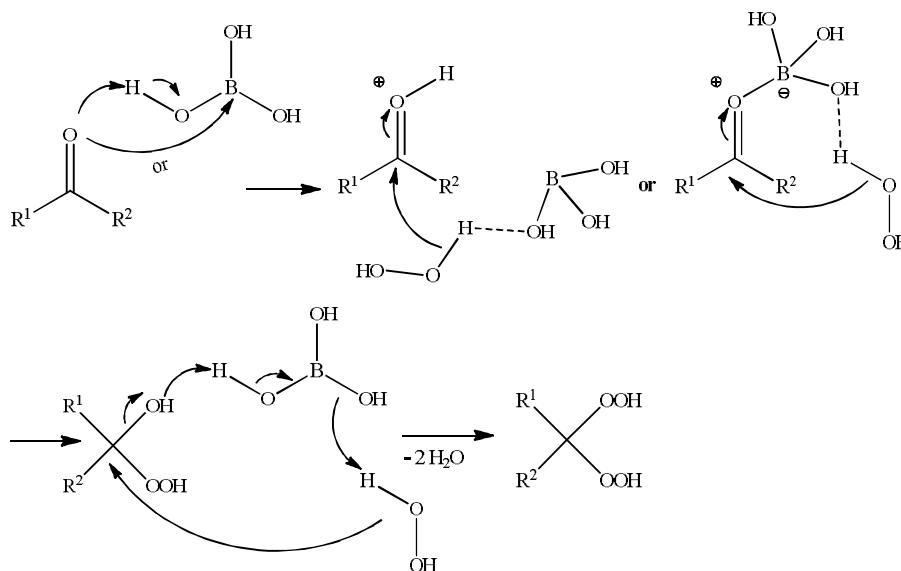
acid activates carbonyl group, through protonation of this group, for nucleophilic attack by hydrogen peroxide. On the other hand, the boron atom as a Lewis acid also can do this carbonyl's activation. Also, this procedure helps the hydroxyl group to live and displacement by hydrogen peroxide. Finally, it is possible that, thorough hydrogen bonding, boric acid activate hydrogen peroxide as a nucleophile.

Equally important, we have successfully converted 2-thiophenecarbaldehyde as a heterocyclic aldehyde to the corresponding *gem*-dihydroperoxide without any by-product for the first time (Table 2, Entry t). Also, like our other reports, benzophenone was recovered intact after 300 min (Table 2, Entry z'')

Finally, this method for peroxidation of cyclohexanone (Entry a, Table 2) was compared with other reported methodologies in the Table 3. As shown by the results, this methodology obviously improves the reaction time, yields and reaction conditions.



Scheme 2. Aliphatic aldehydes have been converted to 1,1- hydroxyhydroperoxide



Scheme 3. Suggested mechanism for catalytic effect of boric acid in peroxidation of ketones and aldehydes

Table 3. Comparing Reported Results for Peroxidation of Cyclohexanone

Entry	Catalyst	Condition	Concentration of H ₂ O ₂ (%)	Time (min)	Yield (%)	Ref.
1	This method (boric acid)	r. t	30	30	96	-
2	Silica sulphuric acid	r. t	30	20	98	[36]
3	Bi(OTf) ₃	r. t	30	18	78	[39]
4	phosphomolybdic acid	r. t	50	150	95	[34]
5	Re ₂ O ₇	r. t	50	30	79	[33]
6	CAN reagent	r. t	50	120	87	[30]
7	NaHSO ₄ ·SiO ₂	r. t	50	20	98	[32]

CONCLUSIONS

In conclusion, boric acid has been used as a high activity, commercially available and non-toxic catalyst for conversion of ketones and aldehydes to the corresponding *gem*-dihydroperoxides. These reactions go on smoothly with short reaction times at room temperature to produce products in high to excellent yields. Boric acid as an inexpensive and non-toxic catalyst makes the process less contaminant, cost-effective and environmentally friendly.

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