

Production of Hydrogen Peroxide via Aerobic Oxidation of Alcohols Catalyzed by *N*-Hydroxyphthalimide

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Abstract:

An efficient method for production of hydrogen peroxide via aerobic oxidation of alcohols was achieved by the use of *N*-hydroxyphthalimide (NHPI) as a catalyst. For instance, the oxidation of benzhydrol in the presence of a catalytic amount of NHPI under dioxygen (1 atm) in ethyl acetate at 75 °C gave H₂O₂ in 51% yield along with benzophenone (72%). The production of H₂O₂ from various alcohols was also examined. The reaction proceeds through the formation of an α -hydroxy hydroperoxide as a transient intermediate derived from an alcohol and dioxygen by the action of NHPI.

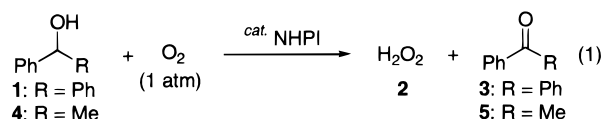
Introduction

Hydrogen peroxide (H₂O₂) is one of the most important and frequently used oxidants in the laboratory and in industry. Even many oxidants such as sodium perborate, percarbonate, potassium hydroperoxy sulfate, and organic peroxy acids are prepared from hydrogen peroxide.¹ In industrial chemistry, a large amount of H₂O₂ is used as an oxidant for bleaching of paper, textiles, and cellulose.² Recently, H₂O₂ has become more and more popular as an environmentally friendly reagent which leads to only water after the reaction.³

Current technology for the production of H₂O₂ is based on the autoxidation of anthrahydroquinones which is known as the AO process and is extensively employed.^{3b,4} The anthraquinones formed are reduced to the original hydroquinones with hydrogen. This process, therefore, leads to the net formation of H₂O₂ from gaseous hydrogen and oxygen. In addition to the AO process, the autoxidation of secondary alcohols is a powerful candidate for the production of H₂O₂ via formation of α -hydroxy hydroperoxides (**1**).^{3b,5} For instance, the autoxidation of 1-phenylethanol (Arco

process) produces H₂O₂ and acetophenone, although the oxidation must be carried out under relatively severe conditions (~160 °C, 10~20 atm of air or O₂).^{5a} After the isolation of H₂O₂, the resulting mixture involving acetophenone is subjected to the hydrogenation to form the original 1-phenylethanol.^{5a}

In previous papers, we reported that *N*-hydroxyphthalimide (NHPI) which serves as a radical catalyst promotes aerobic oxidations of various hydrocarbons in the presence or absence of a transition metal under mild conditions.⁶ The NHPI-catalyzed aerobic oxidation of alkanes proceeds via a radical process involving the hydrogen abstraction from alkanes by phthalimide *N*-oxyl (PINO) generated in situ from NHPI and O₂, producing hydroperoxides which eventually are converted into oxygen-containing products such as alcohols and ketones as well as carboxylic acids. Recently, we have found that α -hydroxy hydroperoxides **1** formed in situ from alcohols and O₂ by the action of NHPI can be applied as oxidants to the selective oxidation of sulfides to sulfoxides⁷ and alkenes to epoxides.⁸ In continuation of our study on the NHPI-catalyzed autoxidation of alcohols, we wish to report here a novel approach for the production of H₂O₂ by the aerobic oxidation of benzhydrol or 1-phenylethanol under mild conditions (eq 1).



Results and Discussion

At the beginning, benzhydrol (**1**) was chosen as a model alcohol and allowed to react under various conditions (Table 1). When **1** was reacted under dioxygen (1 atm) in the presence of a catalytic amount of NHPI (10 mol %) in AcOEt at 75 °C for 12 h, H₂O₂ (**2**) was obtained in 51% yield at 72% conversion of **1** along with benzophenone (**3**) (72%) (run 1). This indicates that ~70% of **1** was oxidized to **3** to liberate H₂O₂.⁹ The formation of H₂O₂ by the present method

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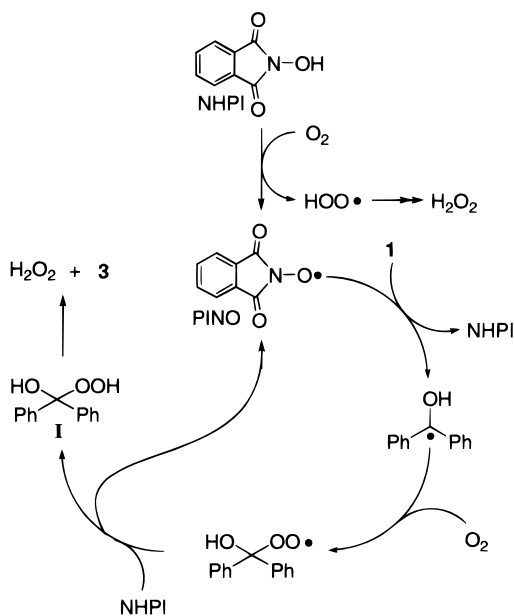
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Table 1. Production of H₂O₂ (**2**) via oxidation of benzhydrol (**1**) in AcOEt under various conditions^a

run	[alcohol] ^b (M)	NHPI (mol %)	time (h)	conv. (%)	yield %	
					2 ^c	3
1	1	10	12	72	51 (70)	72
2	2	10	12	76	48 (64)	73
3	2	5	12	61	37 (62)	60
4 ^d	2	10	12	71	60 (85)	70
5 ^e	1	10	8	94	21 (22)	92
6 ^{e,f}	1	10	12	61	33 (55)	60

^a **1** (5 mmol) was allowed to react with molecular oxygen in the presence of NHPI in AcOEt at 75 °C. ^b Concentration of **1** (mol/L). ^c Selectivity based on **1** reacted is in parentheses. ^d 40 mmol of **1** was used. ^e Co(OAc)₂ (0.02 mol %) was added. ^f Reaction was conducted at 50 °C.

Scheme 1



is illustrated by Scheme 1. The reaction using 5 mol % of NHPI under these conditions gave H₂O₂ in slightly lower yield (37%) (run 3). To evaluate whether the present method can be used as a practical method, it was important to carry out the reaction in large-scale. Thus, 40 mmol of **1** (7.36 g) was allowed to react under these reaction conditions, and it was found that H₂O₂ was obtained in good selectivity (85%) and conversion (71%) (run 4). It is interesting to note that the large-scale reaction gave better results than that on small-scale.

In a previous paper, we reported that the aerobic oxidation of various alcohols was markedly enhanced in the presence of a small amount of a Co species such as Co(OAc)₂.¹⁰ Thus, the effect of the Co ion on the formation of H₂O₂ from **1** was investigated (runs 5 and 6). Despite the higher conversion of alcohol **1** into ketone **3**, H₂O₂ was formed in low yield. This shows that the formed H₂O₂ is readily decom-

Table 2. Production of H₂O₂ (**2**) via oxidation of **1** to **3** in various solvents^a

run	solvent	time (h)	conv. (%)	yield (%)	
				2 ^b	3
1	AcOEt	12	72	51 (70)	72
2	AcOBu ⁿ	12	71	44 (62)	71
3	CH ₃ CN	18	48	42 (87)	48
4	CH ₃ CN	24	77	55 (72)	76
5	PhCN	18	70	42 (60)	70
6 ^c	PhCN	18	79	43 (54)	78
7 ^{c,d}	PhCN	18	55	38 (69)	54
8 ^e	PhCN	3	58	34 (60)	58
9 ^e	PhCN	10	82	34 (41)	82
10	PhCl	12	21	14 (60)	21
11	PhCF ₃	12	15	<9	15

^a **1** (5 mmol) was allowed to react with molecular oxygen in the presence of NHPI (10 mol %) in solvent (5 mL) at 75 °C. ^b Selectivity based on **1** reacted is in parentheses. ^c PhCN (2.5 mL) was used. ^d Reaction was carried out at 60 °C. ^e Reaction was carried out at 85 °C.

posed through the redox pathway by the cobalt ion. It is well-known that transition metal ions such as iron and cobalt prompt the redox decomposition of H₂O₂ and hydroperoxides.¹¹ When the reaction temperature was lowered from 75 to 50 °C, the decomposition of H₂O₂ was suppressed to some extent (run 6). The effect of other metal ions such as Cu(OAc)₂ and VO(acac)₂ on the formation of H₂O₂ was also examined, but satisfactory results were not obtained by the addition of these metals.

The choice of solvent is important not only to carry out efficiently the reaction but also to extract the resulting H₂O₂ from the solvents. The aerobic oxidation of **1** was run in several solvents (Table 2). The reaction in AcOBuⁿ having higher lipophilicity than AcOEt tends to decrease the selectivity to H₂O₂ (run 2). The oxidation of **1** in CH₃CN led to H₂O₂ in the highest selectivity (87%) at 48% conversion, although longer reaction time was needed (runs 3 and 4). For the production of aqueous H₂O₂, however, CH₃CN may be undesirable, since it is miscible with water.¹² Thus, the oxidation of **1** in PhCN which is immiscible with water was carried out. However, the reaction in PhCN gave H₂O₂ in lower selectivity (60%) than that in CH₃CN (run 5). The selectivity of H₂O₂ was somewhat improved at 60 °C (69%) (run 7). The same oxidation at 85 °C for 3 h resulted in H₂O₂ (60%) in 58% conversion (60%) (run 8). The aerobic oxidation of **1** in chlorobenzene or trifluoromethylbenzene proceeded slowly to give **2** in poor yields (runs 10 and 11).

To extend the present method, various alcohols were allowed to react under the same reaction conditions (Table 3). From the aerobic oxidation of aromatic alcohols such as 1-phenylethanol (**4**) and benzoin, H₂O₂ was obtained in high

(9) A part of NHPI was found to be converted into phthalimide during the reaction. After the evaporation of AcOEt, NHPI and phthalimide were isolated by filtration and then washed with cold ether. Treatment of the recovered phthalimide with hydroxylamine gave the NHPI in almost quantitative yield.

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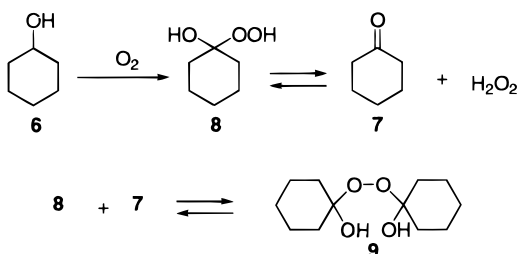
(12) The in situ generation of H₂O₂ seems to be a great advantage in the chemical industry, because the storage and transportation of explosive hydrogen peroxide can be omitted. For storage and transportation of H₂O₂: Goor, G.; Kunkel, W. In *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Elvers, B., Hawkins, S., Ravenscroft, M., Schulz, G., Eds.; VCH: Weinheim, 1989; Vol. A 13, pp 461–463.

Table 3. Production of H₂O₂ (2) via Oxidation of Various Alcohols to Ketones by NHPI–O₂ system^a

run	alcohol	conv. (%)	yield (%) ^b	
			H ₂ O ₂	ketone
1	benzhydrol (1)	72	51 (70)	72
2 ^c	1-phenylethanol (4)	49	40 (81)	48
3	benzoin	54	40 (74)	49
4 ^d	cyclohexanol (6)	20	14 (70)	19
5 ^{d,e}	6	58	12 (21)	38
6 ^d	2-propanol		<5	

^a Alcohol (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) in AcOEt (5 mL) at 75 °C for 12 h. ^b Selectivity based on alcohol reacted is in parentheses. ^c 18 h. ^d 20 h. ^e CH₃CN was used as solvent.

Scheme 2



selectivities at moderate conversions (runs 2 and 3).¹³ The production of H₂O₂ from 1-phenylethanol **4** seems to be a very attractive route, since a large quantity of the **4** is formed as a coproduct along with propylene oxide during the epoxidation of propylene with α -hydroperoxy ethylbenzene by the Halcon process.¹⁴

The selectivity of the oxidation of cyclohexanol (**6**) in AcOEt was considerably different from that in CH₃CN. In AcOEt, H₂O₂ was formed in higher selectivity (70%). However, in CH₃CN the selectivity to H₂O₂ became very low (21%). This is believed to be due to the fact that the resulting H₂O₂ reacted with cyclohexanone (**7**) leading to peroxide (**9**) through α -hydroxy hydroperoxide as shown in Scheme 2 (runs 4 and 5).¹⁵ ¹H NMR measurement of the reaction mixture obtained from the aerobic oxidation of alcohol **4** under the influence of NHPI in CD₃CN indicated a broad peak attributed to the proton of H₂O₂ at around δ 8.3 and several peaks assigned to **4** and acetophenone (**5**), but no peaks assigned to the α -hydroxy hydroperoxides were observed. In the aerobic oxidation of **6**, however, ¹H NMR of the reactant showed many peaks in the range δ 8.4–9.8 which are assigned to hydroperoxides and peroxides derived from **7** and H₂O₂.

(13) The Arco process is operated at 140 °C under 21 kg/cm² of air leading to 30% conversion of **4**. On the other hand, the present oxidation of **1** or **4** proceeds smoothly even under 1 atm of O₂ or air at moderate temperature (70–80 °C) to give H₂O₂ (71% conversion and 85% selectivity) comparable to those obtained by the Arco process. Thus, from the safety point of view, this oxidation method has great advantages in the chemical industry.

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Although we also examined the oxidation of 2-propanol under these conditions, low yield of H₂O₂ was obtained (run 6). We believe that the oxidation of secondary alcohols by the present catalytic system is difficult to occur. From the practical and synthetic points of view, 2-propanol is not suited for the production of pure hydrogen peroxide, because of the complication of isolation of H₂O₂ from a mixture of acetone/2-propanol/water/ H₂O₂.

On the basis of these results, benzhydrol **1** and 1-phenylethanol **4** were found to be good alcohols for the production of H₂O₂ by the present method.

To carry out the present reaction in industrial scale, the employment of air instead of molecular oxygen as the oxidant is important for economical and safety reasons. With this in mind, the production of H₂O₂ by the NHPI-catalyzed oxidation of benzhydrol **1** and 1-phenylethanol **4** using air was evaluated (Table 4).

Even under 1 atm of air, the reaction proceeded smoothly to give H₂O₂ in 36% yield (63% selectivity) (run 1). When the same oxidation was conducted under 5 and 10 atm of air, the yield of H₂O₂ was improved to 50 and 57%, respectively (runs 2 and 4). The oxidation at 65 °C under these conditions produced H₂O₂ in 35% yield (84% selectivity) (run 5). Even when the amount of NHPI was halved (5 mol %), **1** afforded H₂O₂ in 41% yield (run 6). However, the oxidation at higher temperature (85 °C) resulted in H₂O₂ in lower selectivity (run 7).

Similarly, the aerobic oxidation of 1-phenylethanol **4** was examined (runs 8–10). In all cases, H₂O₂ was obtained in satisfactory yields along with acetophenone **5**, although the oxidation took place more slowly than that of **1**.

In conclusion, we have developed an alternative efficient route for the production of H₂O₂ via the aerobic oxidation of alcohols assisted by the NHPI catalyst. H₂O₂ could be prepared by the aerobic oxidation of benzhydrol catalyzed by NHPI. The resulting H₂O₂ can be easily separated from the reaction mixture by extraction with water. Further investigations to extend the present system to the oxidation of various substrates with the in situ generated H₂O₂ are in progress.

Experimental Section

¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively, using CDCl₃ with tetramethylsilane as the internal standard. Flash chromatography was performed with use of silica gel (MERCK, Silica gel 60, 70–230 mesh). Gas chromatography was carried out on Shimadzu GC-17A with a flame ionization detector using a 0.22 mm × 25 m capillary column (SGE BP-10).

All starting materials, solvents and catalysts were purchased from commercial sources and used without further treatment. The yield of oxidation products except for H₂O₂ was estimated from the peak areas based on the internal standard technique.

General Procedure for the Oxidation of **1 and Isolation of Hydrogen Peroxide.** An ethyl acetate (5 mL) solution of **1** (920 mg, 5 mmol), NHPI (82 mg, 0.5 mmol) was placed in a two-necked flask equipped with a balloon filled with O₂. The mixture was stirred at 75 °C for 12 h. After the reaction, water (5 mL) and toluene (10 mL) were added to

Table 4. Production of H₂O₂ (2) via aerobic oxidation of 1 or 4 to 3 or 5 in AcOEt under air pressure^a

run	alcohol	air (atm)	[alcohol] ^b (M)	NHPI (mol %)	temp. (°C)	time (h)	conv. (%)	yield (%)		select. (%)	
								2	3	2	3
1	1	1	1	10	75	12	57	36	48	63	84
2	1	5	1	10	75	12	66	50	66	76	99
3	1	10	1	10	75	8	63	51	63	81	99
4	1	10	1	10	75	12	75	57	75	76	99
5	1	5	1	10	65	12	42	35	42	84	99
6 ^c	1	5	2	5	75	12	50	41	50	82	99
7 ^c	1	5	2	5	85	8	45	33	45	73	99
8 ^c	4	5	2	10	75	24	42	35	42 ^d	83	99 ^d
9 ^c	4	10	2	10	75	24	51	40	50 ^d	78	98 ^d
10	4	5	1	10	75	24	40	35	40 ^d	86	99 ^d

^a **1** (5 mmol) was allowed to react in the presence of NHPI under pressure of air in AcOEt (5 mL). ^b Concentration of alcohol employed. ^c Alcohol (10 mmol) was used. ^d Acetophenone **5**.

the reactant, and then the aqueous phase was separated. The quantity of hydrogen peroxide in the aqueous solution was determined by iodometry.¹⁶ The slight amount of AcOEt was found to be involved in aqueous H₂O₂ by GC analysis. The organic layer was dried over MgSO₄ and analyzed by GLC with an internal standard. The products were separated from the solvent under reduced pressure and purified by column chromatography on silica gel (*n*-hexane/AcOEt = 5/1) to give the corresponding ketones. Ketones were identified through the comparison of their ¹H and ¹³C NMR with those of authentic samples.

Oxidation of 1 on a Large Scale. An ethyl acetate (20 mL) solution of **1** (7.36 g, 40 mmol), NHPI (0.652 g, 4 mmol) was placed in a two-necked flask (100 mL) equipped with a balloon filled with O₂. The mixture was stirred at 75 °C for 12 h. The workup was performed using the same method as previously described.

General Procedure for Oxidation of 1 under Air Pressure. To a solution of **1** (1.84 g, 10 mmol) in AcOEt (5

mL) placed in a 50 mL stainless steel autoclave was added NHPI (82 mg, 0.5 mmol). The autoclave was pressured with 5 or 10 atm of air, with stirring, at 75 °C. After 12 h, the autoclave was cooled in an ice bath, and then the residual air was ventilated. The workup was performed using the same method as previously described.

¹H NMR Measurement in the Oxidation of 4. A CD₃CN (2 mL) solution of **4** (244 mg, 2 mmol), NHPI (32 mg, 0.2 mmol) was placed in a two-necked flask equipped with a balloon filled with O₂. The mixture was stirred at 75 °C for 24 h. After the reaction, the mixture was subjected to the ¹H NMR measurement.

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