Preparation of Hydroperoxides by *N*-Hydroxyphthalimide-Catalyzed Aerobic Oxidation of Alkylbenzenes and Hydroaromatic Compounds and Its Application

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Abstract: An efficient approach to phenols and aldehydes through the formation of hydroperoxides from alkylbenzenes was successfully achieved by aerobic oxidation using *N*-hydroxyphthalimide (NHPI) as a catalyst. The oxidation of various alkylbenzenes with dioxygen by NHPI followed by treatment with a Lewis acid or triphenylphosphine led to phenols or aldehydes, respectively, in good yields. For example, the aerobic oxidation of cumene in the presence of a catalytic amount of NHPI at 75 °C and subsequent treatment with H_2SO_4 gave phenol in 77% yield. 1,4-Dihydroxybenzene (61%) and 4-isopropylphenol (33%) were obtained from 1,4-diisopropylbenzene. On the other hand, dibenzyl ether was converted into phenol or benzaldehyde upon treatment of the resulting hydroperoxide with $InCl_3$ or PPh_3, respectively.

Keywords: homogeneous catalysis; oxidations, peroxides; radicals

Introduction

Hydroperoxides are used not only as oxidizing agents of olefins but also as important precursors for the synthesis of phenols. For instance, α-hydroperoxy-ethylbenzene obtained by aerobic oxidation of ethylbenzene is used as an active oxygen carrier in the epoxidation of propylene which is known as the Halcon process.[1] The cumene-phenol process (Hock process) based on the decomposition of cumene hydroperoxide with sulfuric acid to phenol and acetone is the current method for phenol synthesis used worldwide.[2]

Recently, we have shown that phthalimide *N*-oxyl (PINO), generated from *N*-hydroxyphthalimide (NHPI) and dioxygen assisted by a Co(II) species, smoothly abstracts a hydrogen atom from hydrocarbons to generate alkyl radicals which are readily trapped by O_2 to give oxygenated products such as alcohols, ketones and carboxylic acids through the redox decomposition of the resulting alkyl hydroperoxides by a Co ion.[3] It is well known that transition metal ions such as iron, copper and cobalt catalyze the redox decomposition of alkyl hydroperoxides.[4] In the conventional autoxidation of alkanes, the decomposition of alkyl hydroperoxides formed in the reaction course leads to alkylhydroperoxy and/or alkoxy radicals which promote the radical-chain process. Therefore, the alkyl hydroperoxides are usually difficult to obtain selectively in higher conversion under mild conditions by the conventional aerobic oxidation of hydrocarbons. Now we have found that alkyl hydroperoxides are easily prepared in high yields by aerobic oxidation of alkylbenzenes assisted by NHPI. In this paper, we wish to report on the preparation of alkyl hydroperoxides by the NHPI-catalyzed aerobic oxidation of alkylbenzenes and hydroaromatic compounds and their application to useful compounds like phenols (Scheme 1).
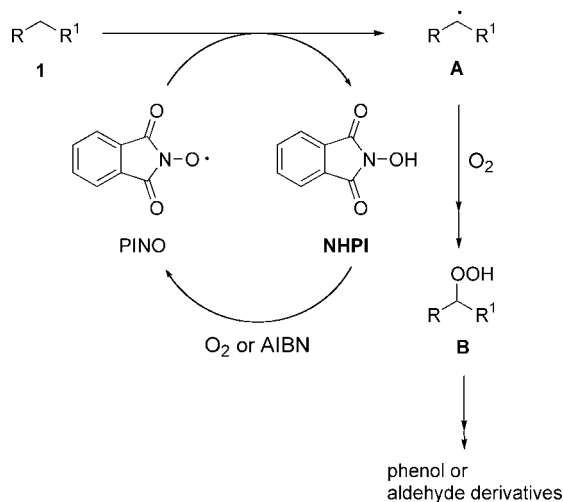
Scheme 1. Strategy for synthesis of phenol and aldehydes.

Results and Discussion

Initially, the aerobic oxidation of cumene (**1**) was examined under several reaction conditions (Table 1, Equation 1). The oxidation of **1** in the presence of NHPI (10 mol %) in CH_3CN under O_2 (1 atm) at 75 °C for 20 h followed by treatment with excess PPh_3 formed 2-phenyl-2-propanol (**2**) in 77% yield and triphenylphosphine oxide (77%) (Run 1). GC analysis of the same reaction mixture before the treatment with PPh_3 showed the formation of **2** (8%) at 90% conversion of **1** (Run 2). The resulting cumene hydroperoxide could not be detected by the GC measurements. From Runs 1 and 2, it was found that cumene hydroperoxide reacts easily with PPh_3 to yield **2** and triphenylphosphine oxide. When AIBN was added as an initiator, **2** was obtained in 75% yield at 76% conversion within 8 h (Run 3). The reaction by AIBN alone without NHPI under these conditions resulted in a significant decrease in the conversion of **1** (Run 4).
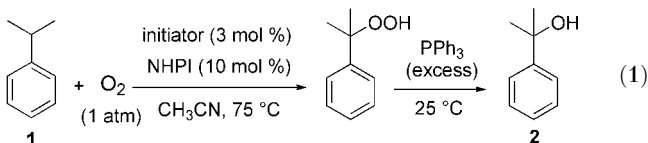

Table 1. Oxidation of **1** with O_2 by NHPI.[a]

Run	Initiator	Time (h)	Conversion (%)	Yield of **2** (%)
1	–	20	90	77
2[b]	–	20	90	8
3	AIBN	8	76	75
4[c]	AIBN	8	7	6

[a] Cumene (**1**) (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) and initiator (3 mol %) in CH_3CN (5 mL) at 75 °C, followed by treatment with excess of PPh_3.
[b] No treatment with PPh_3.
[c] Without NHPI.

Figure 1 shows time-dependence curves for the aerobic oxidation of **1** by the NHPI and the NHPI/AIBN systems. The oxidation of **1** by NHPI seems to proceed *via* two stages. It was found that the oxidation takes place very fast at the early stage of the reaction by both catalytic systems. This shows that the rapid radical chain transfer reaction can take place at the initial stage. The reaction at the later stage may be induced by radicals generated by decomposition of the resulting cumene hydroperoxide. The oxidation by the NHPI/AIBN system progressed faster than that by NHPI alone at the initial stage of the reaction, probably because the generation of PINO from NHPI was promoted by AIBN.

Table 2 shows the result for the conversion of cumene **1** to phenol **3** by the aerobic oxidation of **1** fol-
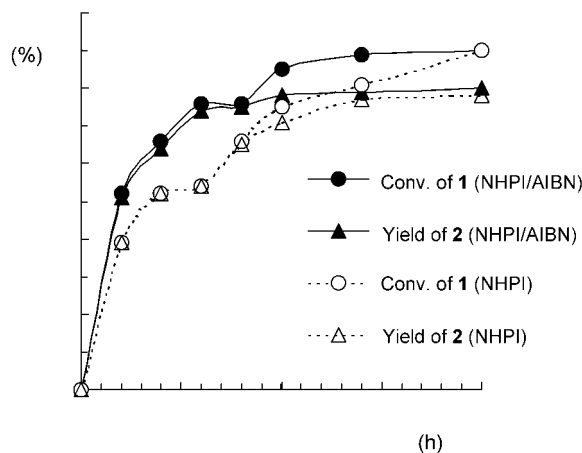

Figure 1. Time-dependence curves for the aerobic oxidation of **1** by NHPI (10 mol %) or NHPI (10 mol %)/AIBN (3 mol %) in CH_3CN under O_2 (1 atm) at 75 °C.

lowed by treatment with sulfuric acid or $InCl_3$ (Equation 2). The oxidation of **1** with O_2 (1 atm) in the presence of NHPI (10 mol %) in CH_3CN at 75 °C followed by treatment with 0.15 M H_2SO_4 solution in CH_3CN afforded **3** in 73% yield (Method A) (Run 1). Similarly, treatment of the reaction mixture with $InCl_3$ (10 mol %) in CH_3CN (1 mL) at 25 °C (Method B) gave **3** in almost the same yield (71%) as that with H_2SO_4 (Run 2). The reaction in acetic acid resulted in low conversion of **1**. This is believed to be due to the fact that a part of the cumene hydroperoxide formed is decomposed by acetic acid to give phenol **3** which serves as a radical inhibitor (Run 3).[5]
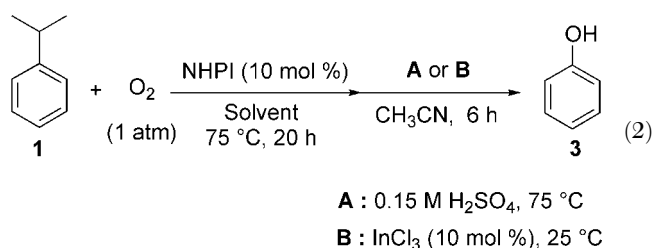

A : 0.15 M H_2SO_4, 75 °C

B : $InCl_3$ (10 mol %), 25 °C

Table 2. Oxidation of **1** with O_2 by NHPI followed by treatment with acids.[a]

Run	Solvent (mL)	Method[b]	Conversion (%)	Yield (%) of **3**
1	CH_3CN (5)	A	90	73
2	CH_3CN (5)	B	90	71
3	AcOH (5)	A	10	10
4[c,d]	CH_3CN (5)	A	78	68
5[c,e]	CH_3CN (3)	A	85	77

[a] **1** (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) in solvent at 75 °C for 20 h, followed by addition of various acids.
[b] A: 0.15 M H_2SO_4 in CH_3CN (2 mL), 75 °C, 4 h. B: $InCl_3$ (10 mol %) in CH_3CN (1 mL), 25 °C, 6 h.
[c] AIBN (3 mol %) was added.
[d] Aerobic oxidation step was carried out for 8 h.
[e] Aerobic oxidation step was carried out for 6 h.

The addition of a small amount of AIBN shortened the reaction time in the aerobic oxidation step and increased the selectivity of 3 (Run 4). In addition, when a smaller amount of CH₃CN was used, the yield of 3 was slightly improved (Run 5).

On the basis of these results, the oxidation of several alkylbenzenes with O_2 in the presence of a catalytic amount of NHPI and AIBN, followed by treatment with H_2SO_4 or $InCl_3$ was examined (Table 3).

Table 3. Oxidation of various substrates with O_2 by NHPI followed by treatment with acids.[a]

Run	Substrate	Conversion (%)	Method[b]	Product (Yield [%])
1	4	88	B	5 (47)
2	6	99	B	7 (16), 8 (56)
3	6	99	A	7 (17), 8 (36)
4	9	99	A	10 (33), 11 (61)
5	12	99	A	13 (63), 14 (1), 15 (11)
6	16	70	A	17 (28), 18 (3), 3 (30), 19 (11)
7[c]	20	–	A[d]	21 (50), 22 (30)

[a] Substrate (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) and AIBN (3 mol %) in CH₃CN (3 mL) at 75 °C for 20 h, followed the addition of various acids.
[b] See Table 2, footnote [b].
[c] The aerobic oxidation was carried out at 65 °C.
[d] Treatment with 0.15 M H_2SO_4 at 60 °C.

The oxidation of *p*-cymene (4) took place selectively at the isopropyl position to afford *p*-cresol 5 in 47% yield after treatment with $InCl_3$ (Run 1). Similarly, the oxidation of 1,3-diisopropylbenzene (6) followed by treatment with H_2SO_4 yielded resorcinol (8) (56%) and 3-isopropylphenol (7) (16%) (Run 2). By

treating with $InCl_3$, the yields of 8 and 7 were slightly decreased (Run 3). 1,4-Diisopropylbenzene (9) afforded 1,4-dihydroquinone (11) and 4-isopropylphenol (10) in 61% and 33% yields, respectively (Run 4). The oxidation of isochroman (12) led to 2-(2-hydroxyphenyl)ethyl formate (13) (63%) as a main product along with 1-hydroxyisochroman (14) and 1-isochromanone (15) (Run 5). These results suggest that the resulting alkyl hydroperoxide is decomposed by H_2SO_4 in the same fashion as 1. Dibenzyl ether (16) gave benzaldehyde (17) together with rearranged product 3 and benzyl alcohol (18) as well as benzyl formate (19) (Run 6). In addition, tetrahydrofuran (20) yielded butyrolactone (21) (50%) and hydrogen peroxide (22) (30%) as major products, although the reaction of 12 afforded the rearranged compound 13 as a main product (Run 7).

As mentioned above, since alkyl hydroperoxides readily react with PPh₃ to yield the corresponding alcohols, we next examined the preparation of aldehyde derivatives from alkyl hydroperoxides derived from ethers.

Table 4. Oxidation of various substrates with O_2 by NHPI followed by treatment with PPh₃.[a]

| Run	Substrate	Conversion (%)	Product (Yield [%])	
1	12	99	14 (62)	15 (13)
2	16	68	17 (92)	18 (23)
3	23	99	24 (29), 26 (34)	25 (14), 27 (1)

[a] Substrate (3 mmol) was allowed to react with O_2 (1 atm) in the presence of NHPI (10 mol %) and AIBN (3 mol %) in CH₃CN (3 mL) at 75 °C, followed by treatment with excess of PPh₃.

Table 4 summarizes the result for the oxidation of benzylic ethers followed by treatment with PPh₃. The reaction of 12 in the presence of NHPI (10 mol %) and AIBN (3 mol %) in CH₃CN (3 mL) at 75 °C for 8 h, followed by treatment with excess PPh₃ provided 14 in 62% yield and 15 in 13% yield (Run 1). The reaction of 16 gave selectively 17 as a main product (Run 2), in contrast to the treatment with acids where various products were formed (Table 3, Run 6). The oxidation of phthalane (23) afforded 1-hydroxyphthalane (24) (29%), phthalimide (25) (14%), phthalaldehyde (26) (34%) and a small amount of phthalic anhydride (27) (Run 3).

Mechanistically, the aerobic oxidation of ethers by the NHPI catalyst is rationally explained by Scheme 2. A hydroperoxide (**C**) formed by the oxidation of an

ether reacts with PPh₃ to lead to aldehyde and alcohol through the formation of a hemiacetal (**D**). On the other hand, the treatment of hydroperoxide **C** with acid gives rise to a formate and an aldehyde as products. It seems likely that the attack of a proton to the hydroperoxide **C** occurs *via* two different pathways to form two pairs of products, i.e., alcohol and formate from the path a, and aldehyde and H_2O_2 from path b. The rearrangement of the R^1 group of the **C** to the oxygen part followed by the attack of H_2O to a carbocation formed gave alcohol and formate (path a), while the addition of a proton to alcoholic oxygen and subsequent removal of alcohol from an intermediate **G** followed by addition of H_2O gave a α-hydroxyhydroperoxide (**I**) which eventually transformed to aldehyde and H_2O_2 (path b).
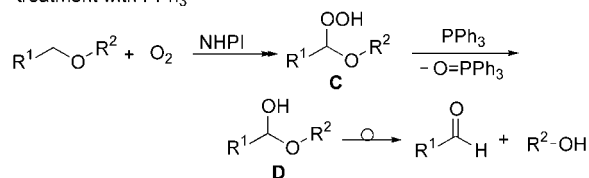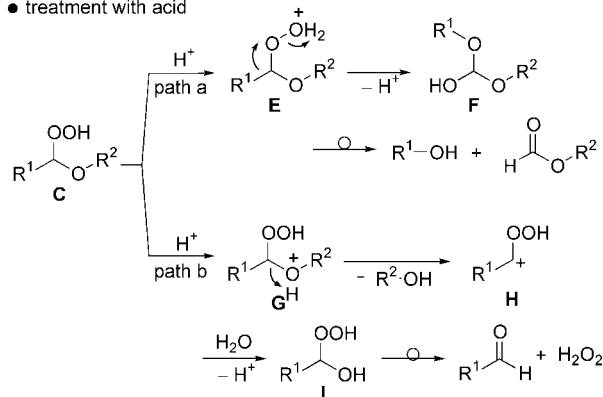
Scheme 2. A possible reaction path for aerobic oxidation of ethers catalyzed by NHPI followed by treatment with PPh₃ or acid.

In conclusion, we have achieved the selective production of alkyl hydroperoxides in high yields by aerobic oxidation of alkylbenzenes by NHPI under mild conditions, and demonstrate its potential application to organic synthesis.

Experimental Section

General Procedures

^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in CDCl₃ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plates or as KBr pressed disks. The GLC analysis was performed with a flame ionization detector using a

0.2 mm × 25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

General Procedure for the Oxidation of Various Substrates to the Phenol Derivatives

An acetonitrile (3 mL) solution of substrate (3 mmol), NHPI (10 mol %), and AIBN (3 mol %) was placed in a two-necked flask equipped with a balloon filled with O₂. **Caution:** *A balloon filled with oxygen can be hazardous, even with a small-scale reaction.* The mixture was stirred at 75 °C for 20 h. The reaction mixture was treated with various acidic solutions [0.15 M H_2SO_4 in CH₃CN (2 mL) or InCl₃ (10 mol %) in CH₃CN (1 mL)] at 75 °C or 25 °C for 6 h, respectively. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 3/2) to give the corresponding product. The products were characterized by ^{1}H and ^{13}C NMR, IR, and GC-MS, respectively.

Procedure for the Oxidation of Various Substrates to Aldehyde Derivatives

To the solution of substrate (3 mmol) in acetonitrile (3 mL) in a two-necked flask were added NHPI (10 mol %) and AIBN (3 mol %), and the flask was equipped with a balloon filled with O₂. **Caution:** *A balloon filled with oxygen can be hazardous, even with a small-scale reaction.* The solution was stirred at 75 °C for 20 h. The reaction mixture was treated with an excess amount of PPh₃. The work-up was performed by the same method as described above. All products except for **13**[6] and **24**[7] were commercially available, and were identified through comparison of the isolated product with an authentic sample.

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