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Catalytic Oxidation of Alkylbenzenes with Molecular Oxygen under Normal Pressure and Temperature by *N*-Hydroxyphthalimide Combined with Co(OAc)$_2$

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A practical catalytic method to convert alkylbenzenes into the corresponding carboxylic acids under atmospheric dioxygen at ambient temperature using a combined catalytic system consisting of *N*-hydroxyphthalimide (NHPI) and Co(OAc)$_2$ was developed. For instance, the oxidation of toluene was completed by NHPI combined with Co(OAc)$_2$ under an oxygen atmosphere at room temperature to give benzoic acid in 81% yield. Under these conditions, *o*- and *p*-xylenes were selectively converted into the corresponding monocarboxylic acids without the formation of the dicarboxylic acids. ESR measurements showed that Co(II) species assists in the formation of phthalimide-*N*-oxyl (PINO), which is a key species in this oxidation, from NHPI.

Although there have been major advances in the oxidation of organic substrates using molecular oxygen, the development of effective and selective methods for the catalytic functionalization of saturated hydrocarbons still remains a major challenge in synthetic chemistry.[1] Effective large-scale processes for the transformation of alkanes with molecular oxygen have been limited because of the exceedingly low reactivity of alkanes. Typical examples of such processes are the autoxidation of cyclohexane and *p*-xylene. The reactions involve a free radical chain and hence are carried out under relatively harsh conditions, *i.e.*, higher oxygen pressure and more severe temperature (usually >150 °C).[2] As a consequence, the reactions are often difficult to control and exhibit poor product selectivity.

The selective catalytic oxidation of alkylbenzenes with molecular oxygen is a very important reaction for the production of bulk and fine chemicals such as benzoic acid and terephthalic acid.[2,3] Practically, the oxidation of toluene is carried out in the presence of a catalytic amount of cobalt(II) 2-ethylhexanoate under a pressure of 10 atm of air at 140−190 °C.[2e] If the direct aerobic oxidation of alkylbenzenes can be done under normal pressure and temperature, it will vastly contribute to industrial chemistry from technical, economical and environmental aspects since undesired reactions due to the higher pressure and temperature will be minimized. However, there is yet no way to carry out such oxidations under ambient conditions.

Although there are many reports on the catalytic oxidation of alkanes with dioxygen (1 atm), these reactions must be carried out in the presence of reducing reagent.[4−9] Recently, it is reported that metalloporphyrins are efficient catalysts for the autoxidation of organic substrates in the absence of any reducing reagents.[10−12] 3-Methylpentane was oxidized by dioxygen (1 atm) in the presence of 1/7500 equiv of the iron complex of halogenated porphyrin as a catalyst at 23 °C for 3 h, forming 3-hydroxy-3-methylpentane in 192% yield based on the catalyst.[12a]

[⊗] Abstract published in *Advance ACS Abstracts*, September 15, 1997.

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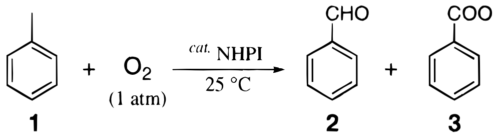
We have shown that the selective oxidation of alkanes[13] as well as alcohols and diols[14] with molecular oxygen was promoted by a new catalytic system, *N*-hydroxyphthalimide (NHPI) combined with Co(acac)$_n$ or Mn(acac)$_n$ (n = 2 or 3), which serves as the radical catalyst, at around 100 °C. Because of the important need to develop a new oxidation process for the production of bulk chemicals, we have focused on the NHPI-catalyzed aerobic oxidation of alkylbenzenes under ambient conditions. Thus, the oxidation of alkylbenzenes with dioxygen by the new catalytic system using NHPI combined with a transition metal was investigated.

Initially, the oxidation of toluene (**1**) was chosen as a model reaction and examined under several conditions (eq 1, Table 1).



(1)

Table 1. Aerobic Oxidation of Toluene (1) Catalyzed by NHPI at 25 °C under Various Conditions[a]

run	metal salts	solv	conv (%)	2	3
1	Co(OAc)$_2$	AcOH	84	2	81
2	Co(OAc)$_2$	CH$_3$CN	52	5	45
3	Co(acac)$_2$	AcOH	74	3	71
4	Co(acac)$_2$	CH$_3$CN	<1	nd[b]	nd
5	Co(acac)$_3$	AcOH		no reaction	

[a] Substrate **1** (3 mmol) was allowed to react in the presence of NHPI (0.3 mmol) and transition metal salts (0.015 mmol) under an oxygen atmosphere (1 atm) in solvent (5 mL) at 25 °C for 20 h. [b] None detected.

The oxidation of **1** in the presence of NHPI (10 mol %) and Co(OAc)$_2$ (0.5 mol %) in acetic acid under an oxygen atmosphere at ambient temperature (25 °C) for 20 h afforded benzaldehyde (**2**) and benzoic acid (**3**) in 2% and 81% yields, respectively (run 1). To our knowledge, this is the first example of the catalytic oxidation of toluene by dioxygen (1 atm) at room temperature. This finding is of great industrial importance, as it leads to development of a practical process which can operate the aerobic oxidation of toluene under ambient conditions (normal pressure and temperature). The oxidation of **1** in acetonitrile resulted in a lower yield (run 2). When Co(acac)$_2$ was used in place of Co(OAc)$_2$, **1** was oxidized to **3** in 71% yield (run 3). But this reaction did not proceed at all in acetonitrile (run 4). These results show that the NHPI-catalyzed aerobic oxidation of **1** is advantageously assisted by Co(OAc)$_2$ in acetic acid.

It is interesting to note that the oxidation of **1** did not entirely take place when Co(acac)$_3$ was employed instead of Co(acac)$_2$ (run 5).

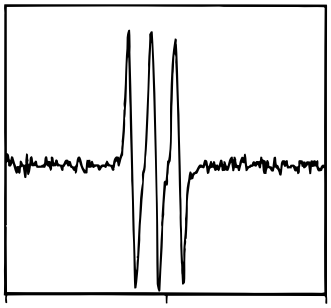


Figure 1. ESR spectrum of phthalimide-*N*-oxyl (PINO) obtained by exposing a mixture of 0.1 M NHPI, 5 × 10^{-3} M Co(OAc)$_2$, and 0.2 M toluene in MeCN under an oxygen atmosphere at 25 °C for 1 h.

In order to obtain further information on the role of the Co(II) species in the present oxidation, ESR measurements were carried out under similar conditions to those for the oxidation of **1**. In a preceding paper, we showed that the ESR signal attributed to the phthalimide-*N*-oxyl (PINO) radical is observed by exposing NHPI to dioxygen in benzonitrile at 80 °C for 45 min.[13b] Similarly, a acetonitrile solution of NHPI and toluene (**1**) was exposed to a dioxygen atmosphere at room temperature, but no ESR signal was observed over a 10 h period. However, when a very small amount of Co(OAc)$_2$ was added to this solution under ambient conditions, an ESR signal based on the PINO radical having hyperfine splitting (a_N = 0.423 mT) was observed at g = 2.0073 (Figure 1). No signal appeared when Co(acac)$_3$ was added in place of Co(OAc)$_2$ to the solution. These observations suggest that the complexation of Co(II) with dioxygen to generate a labile dioxygen complex such as superoxocobalt(III) or μ-peroxocobalt(III) complex is present during the oxidation step. Such cobalt−oxygen species are reported to be easily formed by the one-electron reduction of dioxygen using Co(II) (eqs 2 and 3).[15] Therefore, it is reasonable to assume that such cobalt species assist in the generation of the PINO radical from NHPI under ambient conditions.

$$\mathrm{LnCo^{II}} + \mathrm{O_2} \rightleftharpoons \underset{\text{superoxocobalt (III)}}{\mathrm{LnCo^{III}{-}O{-}O\bullet}} \quad (2)$$

$$\mathrm{LnCo^{III}{-}O{-}O\bullet} + \mathrm{LnCo^{II}} \rightleftharpoons \underset{\mu\text{-peroxocobalt (III)}}{\mathrm{LnCo^{III}{-}O{-}O{-}Co^{III}Ln}} \quad (3)$$

On the contrary, it seems reasonable that the oxidation of **1** by the combined system of NHPI and Co(acac)$_3$ did not take place, since a cobalt−oxygen complex cannot be generated from Co(acac)$_3$ and dioxygen under ambient conditions.[16] When the above reaction was carried out in the presence of a small amount of benzaldehyde, however, **1** was oxidized to **3** in 43% yield (48% conversion), because Co(III) species is reduced with benzaldehyde to Co(II) ion.[17]

A plausible reaction pathway for the aerobic oxidation of **1** by the combined use of NHPI and Co(OAc)$_2$ is illustrated as Scheme 1.

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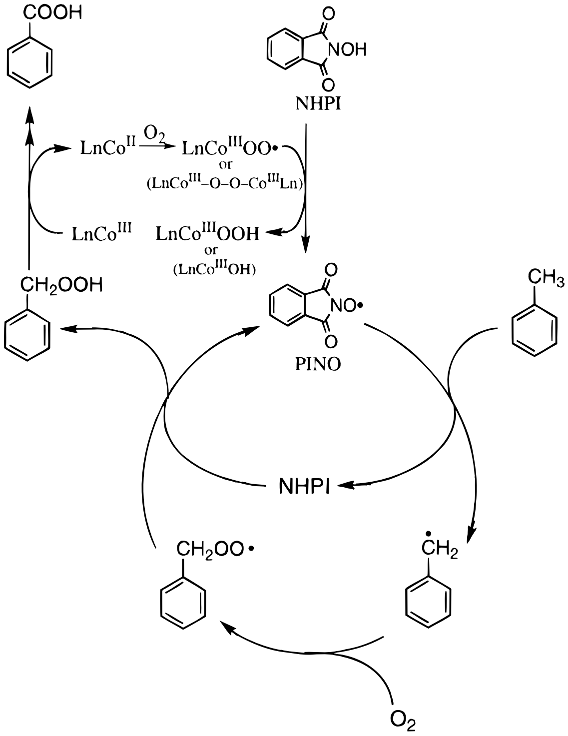
[16] In an earlier paper, we reported that toluene (**1**) can be oxidized by NHPI combined with Co(acac)$_3$ at 100 °C to give **3** in good yield. At higher temperature, Co(III) species is known to be gradually reduced by one-electron transfer from the aromatic ring of **1** to generate Co(II) species.[17] Therefore, a longer induction period was observed in the aerobic oxidation of alkylbenzenes by NHPI combined with Co(acac)$_3$ than with Co(acac)$_2$.[13b]

[17] Onopchenko, A.; Schultz, A. J. G. *J. Org. Chem.* **1973**, *38*, 3729, and references cited therein.

Scheme 1. A Plausible Reaction Path for the Aerobic Oxidation of Toluene (1) Catalyzed by NHPI Combined with Co(II)



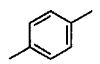
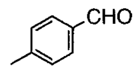
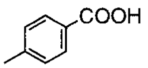
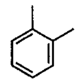
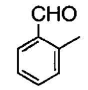
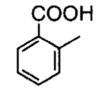
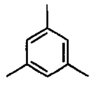
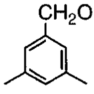
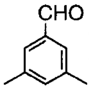
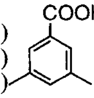
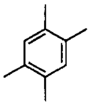
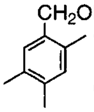
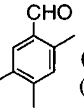
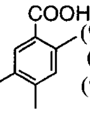
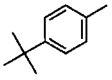
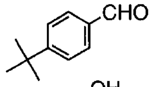
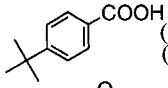
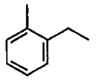
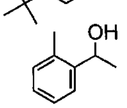
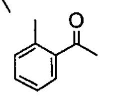
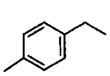
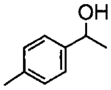
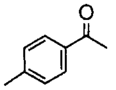
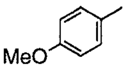
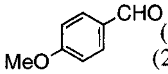
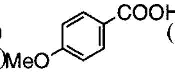
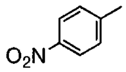
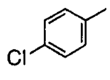
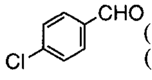
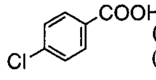
The generation of PINO by the reaction of the NHPI with the cobalt(III)–oxygen complex under ambient conditions would be the most important step in the present oxidation. The next step in the reaction involves the hydrogen abstraction from **1** by the PINO to form a benzyl radical which is readily trapped by dioxygen to provide the benzylperoxy radical followed by benzyl hydroperoxide and eventually the formation of **3**. The reaction of the benzylperoxy radical with Co(II) is known to lead to benzaldehyde as the primary product of **3**.[1a]

Table 2 shows the representive results for the aerobic oxidation of various alkyl benzenes catalyzed by NHPI and $Co(OAc)_2$ under ambient conditions (normal pressure and temperature). These observations suggest that the induction period markedly depended on the solvents and substrates used.

The time-dependence of **1** becoming **3**, catalyzed by NHPI combined with $Co(OAc)_2$, in acetonitrile was compared with that in acetic acid (Figure 2). A considerably longer induction period was observed during the oxidation of **1** in acetonitrile compared to that in acetic acid.

p-Xylene was selectively oxidized to *p*-toluic acid in good yields in both solvents. *o*-Xylene was converted into *o*-toluic acid with a satisfactory yield in acetic acid, but with a somewhat lower yield (63%) in acetonitrile. During these oxidations, dicarboxylic acids were not isolated at all. Although the oxidation of mesitylene was expected to take place more easily than that of toluene, the oxidation proceeded slowly to give 3,5-dimethylbenzoic acid (39%) and 3,5-dimethylbenzaldehyde (26%) as the main products.

Table 2. Aerobic Oxidation of Various Alkylbenzenes Catalyzed by NHPI Combined with $Co(OAc)_2$ in CH_3CN or AcOH at 25 °C[a]

run	substrate	conv. (%)	product (yield / %)					
1		94^b 95^c		(3) (2)				(83) (85)
2		70^b 93^c		(3) (2)				(63) (83)
3		73^b 73^c 81^{c,d}		(2) (2) (2)		(23) (26) (21)		(46) (39) (51)
4	 **4**	98 ^{b,e} 39 ^{c,e} 100^{c,f}	 **5**	(n.d.) (11) (n.d.)	 **6**	(5) (17) (n.d.)	 **7**	(93) (6) (93)
5		83^b 95^c		(4) (2)				(77) (91)
6		82^b 61^c		(21) (21)				(37) (25)
7		87^b 75^c		(12) (17)				(47) (31)
8		89^{b,g} 26^{c,g}		(9) (20)				(80) (0)
9		no reaction^b no reaction^c						
10		47^b 71^c		(7) (3)				(40) (67)

[a] Substrate (3 mmol) was allowed to react in the presence of NHPI (0.3 mmol) and $Co(OAc)_2$ (0.015 mmol) in solvent (5 mL) under an oxygen atmosphere (1 atm) at 25 °C for 20 h. [b] CH_3CN was used as solvent. [c] AcOH was used as solvent. [d] 30 h. [e] 3 h. [f] 12 h. [g] 6 h.

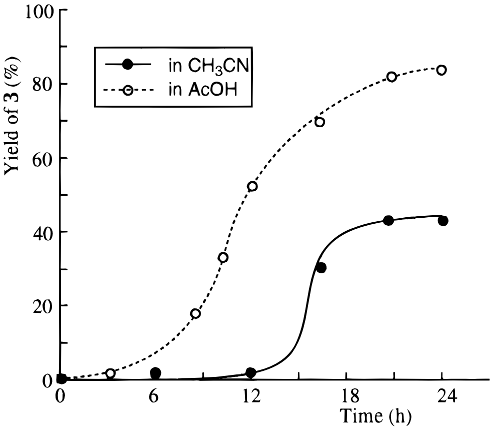


Figure 2. Time dependence curves for the formation of **3** by the aerobic oxidation of **1** catalyzed by NHPI combined with $Co(OAc)_2$ in CH_3CN or AcOH at 25 °C.

In the aerobic oxidation of **1** by the present NHPI–$Co(OAc)_2$ system, the reaction was faster in acetic acid than in acetonitrile, as shown in Table 1. In contrast, the oxidation of durene (**4**) in acetonitrile proceeded more rapidly than that in acetic acid and was completed within 3 h to form the corresponding monocarboxylic acid 2,4,5-trimethylbenzoic acid (**7**), in good yield along with a small amount of 2,4,5-trimethylbenzaldehyde (**6**) (run 4). It is interesting to compare the time-dependence for

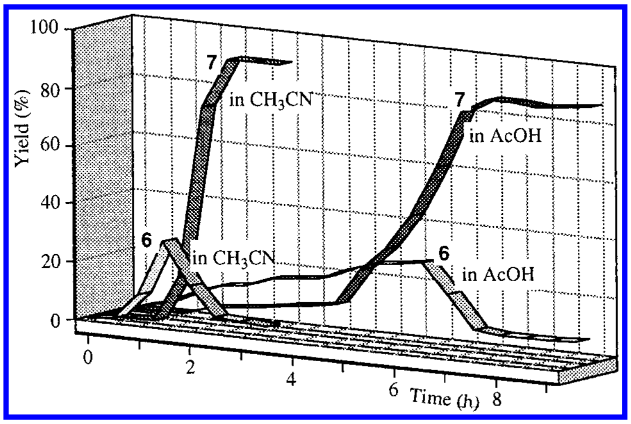


Figure 3. Time dependence curves for the aerobic oxidation of **4** catalyzed by NHPI combined with Co(OAc)$_2$ in CH$_3$CN or AcOH at 25 °C.

the oxidation of **4** in acetonitrile to that in acetic acid (Figure 3).

Figure 3 indicates that the oxidation product at the early stage of the reaction is the aldehyde **6** in both solvents. However, the conversion of **6** to acid **7** was very different between the two curves. The aldehyde **6** was more quickly converted into the acid **7** in acetonitrile than in acetic acid. Unfortunately, the question why **6** was much more slowly oxidized in acetic acid cannot explained at the present time.

p-*tert*-Butylbenzene was converted into *p*-*tert*-butylbenzoic acid in acetic acid in high yield. It is interesting that *o*-ethyltoluene, having different alkyl substituents on the benzene ring, underwent the reaction exclusively at the ethyl moiety to give 1-(2′-methylphenyl)ethanol and 2′-methylacetophenone in 21% and 37% yields, respectively. Similarly, *p*-ethyltoluene was converted into the corresponding alcohol and ketone in which the ethyl substituent was selectively oxidized.

To examine the electronic effect of the substituents on the aromatic ring, 4-methylanisole and *p*-nitrotoluene were allowed to react under the same conditions. 4-Methylanisole was smoothly oxidized in acetonitrile to give 4-methoxybenzoic acid in good yield (80%), but in acetic acid, the oxidation stopped at about 30% conversion. This is believed to be due to the formation of a phenol derivative which inhibits the radical reaction, based on the hydrolysis of anisole by acetic acid. *p*-Nitrotoluene was not oxidized under these conditions. However, *p*-chlorotoluene led to *p*-chlorobenzoic acid in 67% yield in acetic acid and 40% yield in acetonitrile.

In conclusion, a variety of alkylbenzenes can now be oxidized with molecular oxygen at normal pressure and temperature. The NHPI, a unique radical-producing catalyst from alkanes, vastly extends the scope of the oxidation of organic substrates with molecular oxygen beyond the conventional autoxidation. The present method is expected to provide a new methodology in the oxidation processes and promises to enhance commercial potentialities by the achievement of oxidation under ambient conditions.

Experimental Section

General Procedure. All starting materials and catalysts 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. ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, with tetramethylsilane as the internal standard. Infrared (IR) spectra were measured using NaCl or KBr plates. A GC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). GC−MS spectra were obtained at an ionization energy of 70 eV. ESR measurements were performed on a JEOL-FE-1X (X-band) with 100 kHz field modulation.

General Procedure for Oxidation of Alkylbenzene. An acetic acid or acetonitrile (5 mL) solution of substrate (3 mmol), NHPI (0.3 mmol, 10 mol%), and Co(OAc)$_2$ (0.015, 0.5 mol %) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 25 °C for 20 h. After removal of the solvent under reduced pressure, the products were purified by column chromatography on silica gel to give the corresponding oxygenated products. The products were identified through comparison of the isolated products with authentic samples.

ESR Measurement of Phthalimide-*N*-oxyl (PINO). An ESR spectrum of PINO was obtained under the following conditions: sweep width 327Å at 2.5 mT; modulation, 0.1 mT, and microwave power, 1 mW. Acetonitrile containing 10^{-1} M of NHPI and 5×10^{-1} M of Co(OAc)$_2$ was exposed under an O$_2$ atmosphere in the presence of toluene at 30 °C for 5 min, after the air in the ESR tube was replaced by O$_2$ gas using the freeze−pump−thaw method.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, IR, and MS spectra for compounds **5**, **6**, **7**, and 3,5-dimethylbenzaldyhyde (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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