

Aerobic oxidation of alcohols using a novel combination of *N*-hydroxyphthalimide (NHPI) and CuBr

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Abstract A new catalytic system for oxidation of alcohols with oxygen by *N*-hydroxyphthalimide (NHPI) combined with CuBr has been developed. The reaction results showed that this catalytic system can effectively catalyze the oxidation of alcohols to the corresponding carboxylic acids or ketones. We obtained 100% selectivity for acetophenone at 94.2% conversion of phenylethanol at 75 °C for 20 h. A mechanism of oxidation of alcohols catalyzed by NHPI/CuBr was proposed.

Keywords Oxidation · Alcohol · NHPI · Copper · Oxygen

Introduction

The selective oxidation of alcohols into their corresponding carbonyl compounds is an important functional group transformation in organic synthesis [1–3]. The resulting carbonyl compounds are of paramount importance as synthetic intermediates for fine chemicals and pharmaceuticals. Traditionally, permanganate, manganese (IV) oxide, chromium (VI) oxide, dichromate, and ruthenium (VIII) oxide are used as the stoichiometric oxidants [4–10]. However, they are all hazardous oxidizing agents. From both an economic and environmental point of

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view [11, 12], the catalytic oxidation process represents a promising improvement in this protocol. The use of molecular oxygen as the oxidant is particularly attractive.

Recently, *N*-hydroxyphthalimide (NHPI) has emerged as a powerful and popular catalyst for the efficient aerobic oxidation of various organic compounds under mild conditions using some metallic compounds as co-catalysts. Among a number of transition metals, complexes of Co and V have shown the positive effect on the catalytic activity for the aerobic alcohol oxidation. Ishii and coworkers [13, 14] reported that NHPI/Co (II or III) catalytic system showed good catalytic activity for the primary and secondary alcohol oxidation with O₂ as oxidant using acetonitrile or ethyl acetate as the solvent. In this catalytic system, the oxidation of 2-octanol in ethyl acetate at 70 °C in the presence of NHPI (10 mol%) and Co(OAc)₂ (0.5 mol%) under dioxygen (1 atm) gave rise to 2-octanone in quantitative yield. Benzoic acids such as *m*-chlorobenzoic acid (MCBA) enhance the oxidation of alcohols to carbonyl compounds. 2-Octanol can be converted into 2-octanone with O₂ even at room temperature by adding a catalytic amount of MCBA to the NHPI/Co(OAc)₂ system. Minisci and coworkers [15] found that the aerobic oxidation of primary benzylic alcohol catalyzed by NHPI and Co salts under mild conditions in acetonitrile solution leads to aromatic aldehydes with high selectivities, without appreciable formation of carboxylic acids. Sobczak and coworkers [16–18] reported two catalytic systems based on NHPI/VO(acac)₂ with LiCl or NHPI/[Bu₄N]VO₃ for the alcohol oxidation in acetonitrile at 75 °C and 1 atm of O₂. The results indicated that two catalytic systems are effective in oxidation of primary and secondary alcohols.

According to the literature, the effect of metal ions on the hydroperoxide decomposition is different in the cumene oxidation in the presence of NHPI [19]. Hydroperoxide also is the intermediate in the alcohol oxidation catalyzed by NHPI. Copper salts combined with NHPI showed good activity for the oxidation of benzylic compounds [19–21], but no example of this system used for aerobic oxidation of alcohols was reported. In this paper, the alcohol oxidation catalyzed by NHPI and CuBr using O₂ as oxidant was investigated. Primary and secondary alcohols can be oxidized to the corresponding carboxylic acids and ketones by this catalytic system, respectively.

Results and discussion

For the initial experiments, phenylethanol was chosen as a model substrate and allowed it to react with catalytic amount of copper salts and NHPI in the presence of oxygen at 75 °C for 20 h. The reaction conversions and selectivities were determined by GC analysis using an internal standard. As shown in Table 1, NHPI and Cu salts are essential for the oxidation, without them there is very little reaction taking place (Table 1, entries 1–3). The solvent has an important effect on the reaction. Ethyl acetate as a solvent could obtain good catalytic activity compared to other solvents such as DMF, acetonitrile, dichloroethane, and trifluorotoluene (Table 1, entries 4–8). A variety of copper salts were evaluated with ethyl acetate as a solvent. CuBr and CuBr₂ as catalysts can obtain high conversions and selectivities

Table 1 Oxidation of phenylethanol catalyzed by NHPI/Cu

| Entry | Solvent | NHPI | Cu salt | Conversion (%) ^a | Selectivity (%) ^a |
|-------|------------------|------|--|-----------------------------|------------------------------|
| 1 | Ethyl acetate | – | – | Trace | Trace |
| 2 | Ethyl acetate | – | CuBr | Trace | Trace |
| 3 | Ethyl acetate | + | – | Trace | Trace |
| 4 | Ethyl acetate | + | CuBr | 94.2 | 100 |
| 5 | Acetonitrile | + | CuBr | 100 | 61.1 |
| 6 | DMF | + | CuBr | 70.0 | 87.3 |
| 7 | Dichloroethane | + | CuBr | 70.5 | 32.4 |
| 8 | Trifluorotoluene | + | CuBr | 47.8 | 94.7 |
| 9 | Ethyl acetate | + | CuBr ₂ | 94.6 | 99.0 |
| 10 | Ethyl acetate | + | CuCl | 69.2 | 99.4 |
| 11 | Ethyl acetate | + | CuCl ₂ ·2H ₂ O | 62.0 | 79.3 |
| 12 | Ethyl acetate | + | Cu(OAc) ₂ ·H ₂ O | 17.6 | 12.6 |
| 13 | Ethyl acetate | + | CuSO ₄ ·5H ₂ O | 17.8 | 53.9 |

Reaction conditions: phenylethanol (1 mmol), NHPI (10 mol%), Cu salts (5 mol%), solvent (3 mL), 0.15 MPa O₂, 75 °C, 20 h

^a Conversion and selectivity were based on GC analysis using biphenyl as an internal standard

(Table 1, entries 4, 9). CuCl and CuCl₂·2H₂O give the moderate conversions and selectivities (Table 1, entries 10, 11). Cu(OAc)₂·H₂O, CuSO₄·5H₂O were the least active catalysts only yielding 17.6 and 17.8% conversions, respectively (Table 1, entries 12, 13). The results suggested that the copper counterion had a great effect on the oxidation of phenylethanol.

The NHPI/CuBr catalytic system exhibits good catalytic activity for primary and secondary benzylic alcohols. As shown in Table 2, primary benzylic alcohol was easily oxidized into the corresponding carboxylic acid with high conversion and yield (Table 2, entry 1). It is clear that non-substituted and substituted secondary benzylic alcohols were efficiently oxidized to their corresponding ketones with excellent conversions and yields (>90%) (Table 2, entries 2–5). Compared to benzylic alcohols, aliphatic alcohols were less reactive. Under the same reaction conditions, secondary aliphatic alcohol only gave modest yields (48–80%) (Table 2, entries 6–8).

It was reported that the phthalimide *N*-oxyl (PINO) radical generated in situ from the reaction of O₂ and NHPI in the presence of metal co-catalyst [14] is able to abstract a hydrogen atom from the alcohol in the NHPI catalyzed alcohol oxidation. The newly formed carbon radical then rapidly reacts with O₂ to give ultimately oxygenated products. Based on the above-mentioned description, a plausible mechanism of the alcohol oxidation with O₂ catalyzed by NHPI/CuBr was proposed (Scheme 1). We suppose that in the alcohol oxidation catalyzed by NHPI and CuBr as a co-catalyst, PINO radical will be generated in oxidation of the NHPI by O₂ and CuBr. The PINO radical can in turn abstract the hydrogen atom from the phenylethanol to produce the α -hydroxy carbon radical (A) and regenerate the NHPI. The resulting carbon-centered radical (A) reacts with O₂ to form a peroxy radical (B), which is further converted to acetophenone.

Table 2 Alcohol oxidation catalyzed by NHPI/CuBr

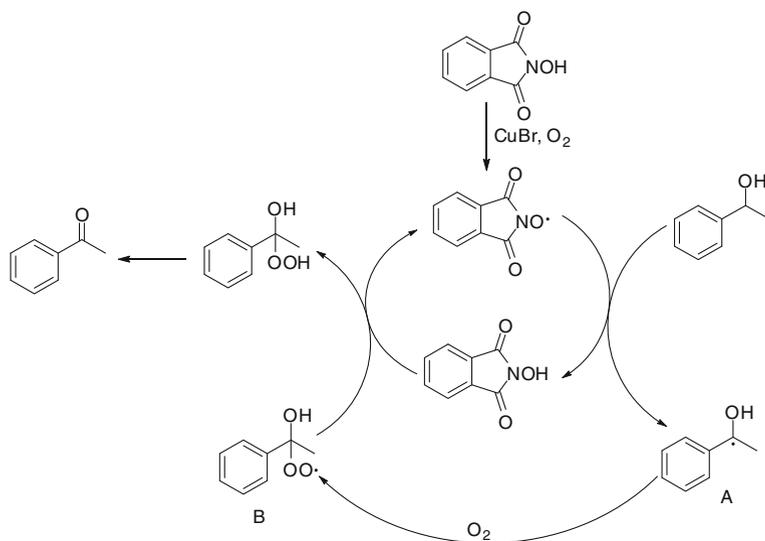
| Entry | Substrate | Product | Conversion (%) ^a | Yield (%) ^a |
|-------|-----------|---------|-----------------------------|------------------------|
| 1 | | | 99.0 | 99.0 |
| 2 | | | 94.2 | 94.2 (87.7) |
| 3 | | | 93.6 | 90.7 (84.6) |
| 4 | | | 99.0 | 99.0 (91.7) |
| 5 | | | 98.9 | 98.9 (93.1) |
| 6 | | | 75.3 | 48.0 |
| 7 | | | 80.8 | 67.6 |
| 8 | | | 97.2 | 80.1 |

Reaction conditions: substrate (1 mmol), NHPI (10 mol%), CuBr (5 mol%), ethyl acetate (3 mL), 0.15 MPa O₂, 75 °C, 20 h

^a Conversion and yield were based on GC analysis using biphenyl as an internal standard. The values in parentheses are the yields of the isolated products

It was reported that the UV-Vis spectrum of the PINO radical generated in situ from the reaction of NHPI and $[n\text{-Bu}_4\text{N}]\text{VO}_3$ in acetonitrile has two absorptions at 321 and 386 nm [18]. In our case, as shown in Fig. 1, the UV/Vis spectrum of CuBr, NHPI and O₂ in ethyl acetate has two absorptions at 306 and 358 nm, which confirmed the formation of PINO radical. A small difference value was probably due to solvent polarity [22].

The CuBr/NHPI system and Co(OAc)₂/NHPI system were compared using the aerobic oxidation of phenylethanol at the same reaction conditions (Table 3). The selectivity for acetophenone was 100% in acetonitrile and 72.8% in ethyl acetate



Scheme 1 Proposed mechanism of alcohol oxidation catalyzed by NHPI/CuBr with O₂

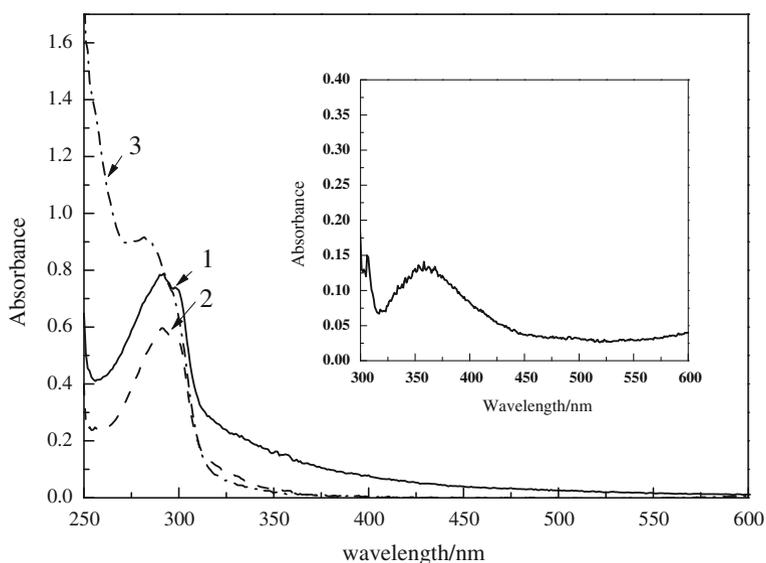


Fig. 1 UV-Vis spectra of ethyl acetate solutions: (1) NHPI; (2) NHPI, and CuBr; (3) Reaction mixture of NHPI and CuBr with 1 atm O₂ at 75 °C for 1 h. The inset shows a difference spectrum obtained by subtraction of the spectra of 2 from that of 3; it represents the spectrum of PINO radical

using Co(OAc)₂ as a co-catalyst; while CuBr as a co-catalyst the selectivity for acetophenone was 71.3% in acetonitrile and 100% in ethyl acetate, respectively. The major byproduct was benzoic acid due to the cleavage of the C–C bond. These

Table 3 Oxidation of phenylethanol catalyzed by NHPI/Cu and NHPI/Co

| Metal salt | Solvent | Conversion ^a | Selectivity ^a |
|-----------------------------------|---------------|-------------------------|--------------------------|
| CuBr | Acetonitrile | 95.3 | 71.3 |
| Co(OAc) ₂ | Acetonitrile | 95.6 | 100 |
| CuBr ^b | Ethyl acetate | 94.2 | 100 |
| Co(OAc) ₂ ^b | Ethyl acetate | 100 | 72.8 |

Reaction conditions: phenylethanol (1 mmol), NHPI (10 mol%), metal salt (2 mol%), solvent (3 mL), 0.1 MPa O₂, 75 °C, 20 h

^a Conversion and selectivity were based on GC analysis using biphenyl as an internal standard

^b Metal salt (5 mol%), solvent (3 mL), 0.15 MPa O₂, 75 °C, 20 h

studies indicated that the type of metal salt and the solvent used can influence the composition of the resulting products. Figures 2 and 3 are the influence of CuBr and Co(OAc)₂ on the aerobic oxidation reaction of phenylethanol in acetonitrile and ethyl acetate, respectively. The results indicated that acetonitrile Co(OAc)₂ used as a co-catalyst in the oxidation of phenylethanol catalyzed by NHPI showed better activity than the reaction using CuBr as a co-catalyst (Fig. 2). However, in ethyl acetate both showed similar activity (Fig. 3).

In conclusion, a new catalytic system based on NHPI and CuBr for aerobic alcohol oxidation was developed. This catalytic system is useful for the oxidation of secondary alcohol, especially for the oxidation of secondary benzylic alcohols to ketones with excellent conversions and selectivities.

Experimental

General methods

All experiments were carried out in Teflon-lined 316L stainless-steel autoclave equipped with a magnetic stirring. The initial air in the autoclave was exchanged three times with oxygen. ¹H NMR and ¹³C NMR spectrum were recorded on a 400-MHz NMR spectrometer using CDCl₃ as the solvent with tetramethylsilane as an internal reference. ¹H and ¹³C positive chemical shifts (δ) in ppm are downfield from tetramethylsilane (CDCl₃: δ_C = 77.0 ppm; residual CHCl₃ in CDCl₃: δ_H = 7.26 ppm). GC analysis of determination of conversions and yields was performed on an Agilent 7890A with a flame ionization detector. All products were confirmed by GC-MS with Agilent 6890N GC/5973 MS detector and the comparison of their GC retention time with those of authentic samples. UV-Vis spectra were recorded from 240 to 900 nm on UV-2550 spectrophotometer. SE-54 capillary column, 30 m × 250 μm × 1 μm; FID detector, 300 °C; injection: 250 °C; carrier gas: nitrogen; carrier gas rate: 2.8 mL/min. All substrates and their corresponding products were detected under a condition as: column temperature: 100 °C for 7 min, rising to 250 °C in a rate of 15 °C/min.

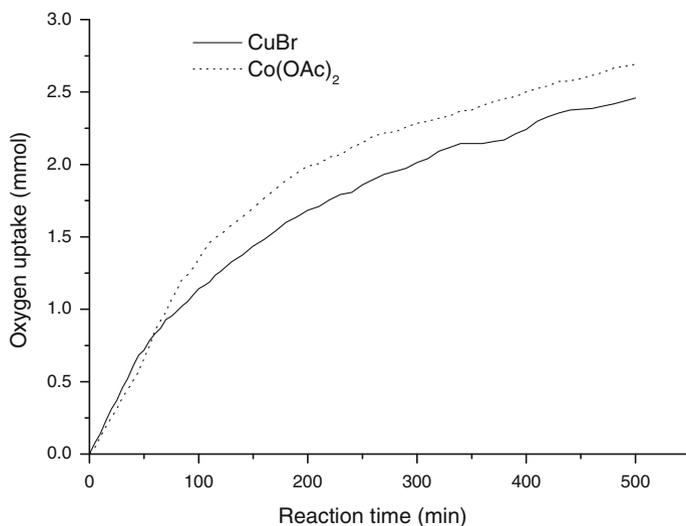


Fig. 2 Aerobic oxidation of phenylethanol in acetonitrile. Reaction conditions: phenylethanol (5 mmol), NHPI (10 mol%), metal salt (2 mol%), acetonitrile (15 mL), 0.15 MPa O₂, 75 °C

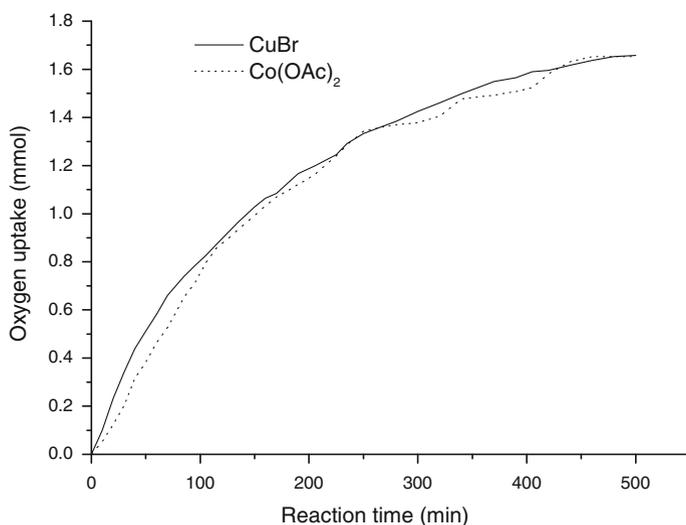


Fig. 3 Aerobic oxidation of phenylethanol in ethyl acetate. Reaction conditions: phenylethanol (5 mmol), NHPI (10 mol%), metal salt (5 mol%), ethyl acetate (15 mL), 0.15 MPa O₂, 75 °C

A typical example for alcohol oxidation

Typically, phenylethanol (1 mmol), NHPI (0.1 mmol) and CuBr (0.05 mmol) were added into the autoclave followed by 3 mL of ethyl acetate. After the autoclave was closed, oxygen was charged to 0.15 MPa. The autoclave was put into a water bath

that was preheated to 75 °C. The reaction mixture was monitored by GC. When the reaction was finished, the autoclave was cooled to room temperature and carefully depressurized. The solvent was concentrated in vacuo and the product was further purified by column chromatography over silica gel (*n*-hexane: ethyl acetate, 10:1) to afford acetophenone (106.1 mg, yield, 87.7%) as a light yellow liquid. Purity was confirmed by GC and ¹H NMR, ¹³C NMR. ¹H NMR (400 MHz, CDCl₃): δ 2.55 (s, 3H), 7.42 (t, ³J_{H, H} = 7.6 Hz, 2H), 7.52 (t, ³J_{H, H} = 7.2 Hz, 1H), 7.93 (d, ³J_{H, H} = 8.0 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 198.3, 137.4, 133.4, 128.9, 128.6, 26.9.

Spectral data of the isolated products

4'-Methoxyacetophenone: white crystal, ¹H NMR (400 MHz, CDCl₃): δ 2.54 (s, 3H), 3.86 (s, 3H), 6.92 (d, ³J_{H, H} = 8.4 Hz, 2H), 7.93 (d, ³J_{H, H} = 8.4 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.4, 164.1, 131.2, 131.0, 114.3, 56.1, 27.0.

4'-Chloroacetophenone: white liquid, ¹H NMR (400 MHz, CDCl₃): δ 2.54 (s, 3H), 7.38 (d, ³J_{H, H} = 8.4 Hz, 2H), 7.84 (d, ³J_{H, H} = 8.0 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.4, 140.1, 136.1, 130.4, 129.5, 27.2.

2'-Chloroacetophenone: colorless liquid, ¹H NMR (400 MHz, CDCl₃): δ 2.59 (s, 3H), 7.40 (t, ³J_{H, H} = 8.0 Hz, 1H), 7.52 (d, ³J_{H, H} = 7.6 Hz, 1H), 7.82 (d, ³J_{H, H} = 8.0 Hz, 1H), 7.91 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.3, 139.2, 135.5, 133.7, 130.6, 129.0, 127.1, 27.3.

Sample preparation of UV-Vis investigation of PINO radical formation

Preparation of NHPI solution (1)

A total of 16.3 mg NHPI was added into a 10-mL A-grade volumetric flask, followed by 5 mL of ethyl acetate. The mixture was swirled vigorously for approximately 3–5 min and then diluted to volume. Then, 0.1 mL of this solution was transferred to a fresh 10-mL A-grade volumetric flask and diluted to volume. This final solution was then immediately analyzed.

Preparation of NHPI and CuBr solution at 25 °C (2)

A total of 16.3 mg NHPI and 7.2 mg CuBr were added into a 10-mL A-grade volumetric flask, followed by 5 mL of ethyl acetate. The mixture was swirled vigorously for approximately 1 h at 25 °C and diluted to volume. Then, 0.1 mL of this solution was transferred to a fresh 10-mL A-grade volumetric flask and diluted to volume. This final solution was then immediately analyzed.

Preparation of NHPI and CuBr solution at 75 °C (3)

A total of 16.3 mg NHPI and 7.2 mg CuBr were added into a 10-mL A-grade volumetric flask, followed by 5 mL of ethyl acetate. The mixture was swirled vigorously for approximately 3–5 min, and diluted to volume. Then, 5 mL of this

solution was transferred to a 25-mL Teflon-lined 316L stainless-steel autoclave equipped with a magnetic stirring. After the autoclave was closed, oxygen was charged to 0.15 MPa. The autoclave was put into an oil bath that was preheated to 75 °C for 1 h. The autoclave was cooled to room temperature and carefully depressurized. Then, 0.1 mL of the reaction mixture was transferred to a fresh 10-mL A-grade volumetric flask and diluted to volume. This final solution was then immediately analyzed.

O₂-uptake kinetics for the CuBr/NHPI system

A typical reaction was conducted as follows. Phenylethanol (5 mmol), CuBr (0.25 mmol), and 10 mL of ethyl acetate were added to the 150-mL Teflon-lined 316L stainless-steel autoclave. The autoclave was attached to an apparatus with a pressure transducer designed to measure the O₂ pressure. The air in the autoclave was exchanged ten times with O₂, and then filled with O₂ to 0.15 MPa. The autoclave was put into a water bath that was preheated to 75 °C. When the pressure stabilized in the apparatus, 0.5 mmol of NHPI in 5 mL of ethyl acetate was added via a syringe through a septum. The mmol of oxygen that reacted was calculated using volume, actual temperature, and pressure from the ideal gas equation.

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