

An Efficient and Mild Oxidation of α -Isophorone to Ketoisophorone Catalyzed by *N*-Hydroxyphthalimide and Copper Chloride

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N-hydroxyphthalimide (NHPI) and copper chloride (CuCl_2) were first utilized for aerobic oxidation of α -isophorone (α -IP) to ketoisophorone (KIP) and the effects of co-catalysts, temperature, reaction time, solvent, amount of CuCl_2 and pressure of oxygen were investigated extensively. NHPI/ CuCl_2 turned out to be highly efficient to this oxidation with up to 91.3% conversion and 81.0% selectivity under mild conditions. And various hydrocarbons including benzylic compounds, cycloalkene and its derivatives were also oxidized smoothly under optimized conditions. Moreover, the possible reaction mechanism was proposed and verified by FT-IR spectra.

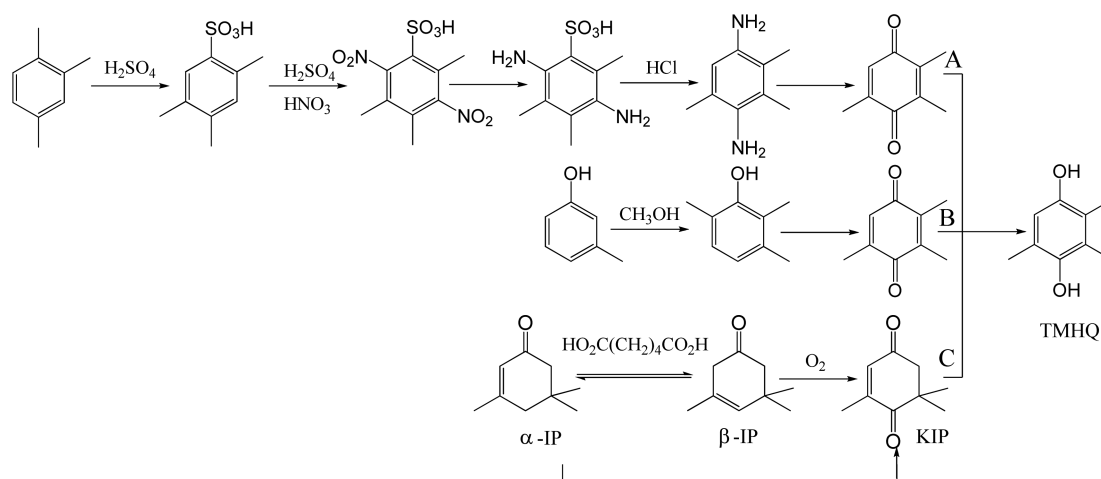
Key Words : α -Isophorone, *N*-Hydroxyphthalimide, Copper chloride, Aerobic oxidation

Introduction

Selective allylic oxidation of alkenes is considered as a fundamental and critical reaction for its extensive applications in synthetic chemistry.¹ As a typical allylic oxidation, the transformation of α -isophorone (3,5,5-trimethylcyclohex-2-enone, α -IP) to ketoisophorone (3,5,5-trimethylcyclohex-2-ene-1,4-dione, KIP) has attracted enormous attention in recent years since KIP is not only an important flavoring, but also a vital intermediate for synthesis of pharmaceuticals.² For example, Vitamin E, one of the most important antioxidants, is synthesized from the reaction of isophytol and trimethylhydroquinol (TMHQ). TMHQ was mainly prepared from 1,2,4-trimethylbenzene (Scheme 1-A) or 3-methylphenol (Scheme 1-B). Both of these two routes were not practical in view of either environmental or economic consideration. As for Route A, its synthetic route was tediously long and the employment of highly corrosive substances such as H_2SO_4 and HNO_3 caused the environmental pollution; regarding to Route B, the relatively ex-

pensive raw material (3-methylphenol) had to be used. An alternative strategy using α -isophorone to synthesize TMHQ has also been developed (Scheme 1-C),³ in which the transformation of α -IP to KIP is the crucial step and the following rearrangement of KIP to THMQ is relatively mature process.⁴ However, high temperature is required in the isomerization of α -IP to β -IP, in which the conversion is low due to the thermodynamic stability of α -IP with the conjugated system of double bond and carbonyl group. Therefore, the direct oxidation of α -IP to KIP without the isomerization step has become intrinsically attractive.⁵

Various catalytic systems for the oxidation of α -IP to KIP have been developed. Unfortunately, long reaction time (around 5d) and high temperature ($> 100\text{ }^\circ\text{C}$) were necessary for this autooxidation. Liquid phase oxidations of α -IP employing simple salts of first row transition metals as catalysts typically gave KIP in poor yield (ca. 21%).^{6,7} Molecular oxygen has been considered as an ideal oxidant for both economical and environmental benefits. But it is less reactive toward the strong C-H bond. Murphy and



Scheme 1. Different routes for the synthesis of TMHQ.

coworkers⁸ reported the aerobic oxidation of α -IP to KIP catalyzed by the homogeneous phosphomolybdic acid system (PMA/DMSO/ KO_tBu) with 99.1% conversion and 77.1% selectivity. However, it was very difficult to purify the desired product due to the presence of the high boiling point solvent DMSO and the severe dimerization catalyzed by the acid PMA under reduced pressure distillation.

N-Hydroxyphthalimide (NHPI) is a powerful and efficient catalyst towards aerobic oxidation under mild conditions via the generation of the phthalimide-*N*-oxyl (PINO) radical. Wang *et al.*⁹ utilized NHPI alone to catalyze the aerobic oxidation of α -IP to KIP in solvent-free system with only 15.4% conversion. To the best of our knowledge, NHPI combined with metal or organic co-catalyst is a remarkable catalysis system, which exhibits high activity in the oxidation of hydrocarbons.¹⁰ Orlinska¹¹ applied NHPI in combination with copper (II), cobalt (II) and manganese (II) acetylacetonate, acetate or chloride to the aerobic oxidation of cumene. The use of NHPI in combination with copper salts at 90 °C resulted in the formation of ketone in high selectivity. Herein, we employed NHPI/ CuCl_2 as the catalytic system for the aerobic oxidation of α -IP to KIP. The effects of co-catalyst, temperature, reaction time, solvent, amount of CuCl_2 and pressure of oxygen were investigated. Moreover, oxidations of benzylic compounds, cyclohexene and its derivatives to the corresponding oxy-compounds were also studied.

Experimental

All the chemicals were analytical grade except for the industrial-grade α -isophorone and they were all used without further treatment. Gas Chromatograph-Mass Spectra (GC-MS) were obtained on AGILENT QP2010 with an ionization energy of 70 eV. Gas Chromatograph (GC) were performed with a flame ionization detector using OV-1701 column (50 m \times 0.25 mm \times 0.25 μm) and ethyl benzoate (99.9%) was applied as internal standard for quantitative analysis. Infrared spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrophotometer using KBr discs in the 400–4000 cm^{-1} region. ¹H-NMR spectra was measured with a Bruker-400MHz nuclear magnetic resonance spectrometer with CDCl_3 as solvent and TMS as internal reference.

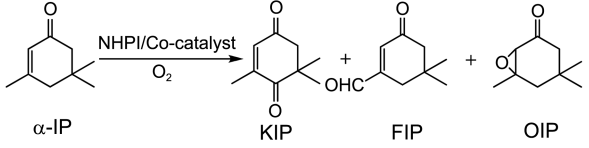
A typical reaction was performed in a 100 mL auto-clave with a magnetic stirrer. A mixture of α -isophorone (10 mmol), NHPI (10 mol %) and CuCl_2 (2.5 mol %) in acetonitrile (10 mL) was placed into the auto-clave and heated to 75 °C under stirring. Oxygen was introduced to replace the atmospheric air in the reactor for three times and the pressure was maintained at 1.2 MPa by feeding O_2 . After completion of the reaction, the reactor was cooled to the ambient temperature. The mixture was then diluted with 10 mL of ethyl acetate and washed with distilled water (3 \times 10 mL). And the combined organic phase was dried over anhydrous Na_2SO_4 , and concentrated to provide an oily residue, which was analyzed by GC-MS. The desired product ketoisophorone was obtained under reduced pressure

distillation. bp 97–98 °C (10 mm Hg); MS: m/z = 152 (M^+), 137, 109, 96, 68, 40; IR (cm^{-1}): 2969, 2932, 2873, 1681, 1623, 1279, 1187; ¹H-NMR (CDCl_3 , ppm): δ 1.25 (s, 6H), δ 2.01 (s, 3H), δ 2.73 (s, 2H), δ 6.57 (s, 1H).

Results and Discussions

NHPI has been considered to be effective in activating C-H bond of hydrocarbons since it can generate PINO radical with the assistance of co-catalysts such as aldehyde,¹² quinone,¹³ α,α' -azobisisobutyronitrile (AIBN),¹⁴ transition metal salts¹⁵ *etc.* Therefore, the oxidation of α -IP catalyzed by NHPI with different co-catalysts was investigated (Table 1). KIP was obtained as the major product with a small amount of 3-formyl-5,5-dimethyl-2-cyclohexen-1-one (FIP) and 4,4,6-trimethyl-7-oxobicyclo [4.1.0]-heptan-2-one (OIP). When using formaldehyde or AIBN as organic co-catalysts, both the conversion and KIP selectivity decreased (entries 1, 2). The use of tetrachlorobenzoquinone (TCBQ) raised the conversion slightly but the selectivity dropped to 48.6% (entry 3), compared with NHPI as the sole catalyst under the same condition (35.1% conversion, 59.5% selectivity, entry 4). Presumably, the organic co-catalysts could not enhance the catalytic ability of NHPI in α -IP oxidation. Similar results were also observed by Wang *et al.*⁹ Satisfyingly, NHPI combined with CuCl_2 was found to catalyze the aerobic oxidation of α -IP to KIP with 91.3% conversion and 81.0% selectivity (entry 5). In contrast, only trace amount of α -IP was converted to KIP with CuCl_2 as the sole catalyst (entry 10), which indicated that the catalytic ability depended on the interaction of NHPI and CuCl_2 . When the anion Cl^- was replaced by AcO^- or SO_4^{2-} , the conversion slightly dropped to 80.4% and 84.1%, respectively (entries 6, 7); while the

Table 1. The aerobic oxidation of α -IP catalyzed by NHPI combined with co-catalyst



Entry	Catalyst	Conversion (%) ^a	Selectivity (%) ^a		
			KIP	FIP	OIP
1	NHPI/ CH_2O	21.3	58.2	5.2	1.0
2	NHPI/AIBN	32.8	55.5	3.4	4.6
3	NHPI/TCBQ	43.2	48.6	11.3	2.5
4	NHPI	35.1	59.5	5.0	8.1
5	NHPI/ CuCl_2	91.3	81.0	5.6	1.8
6	NHPI/ $\text{Cu}(\text{OAc})_2$	80.4	81.1	8.6	1.9
7	NHPI/ CuSO_4	84.1	80.4	9.0	6.5
8	NHPI/ ZnCl_2	26.8	81.1	4.6	2.3
9	NHPI/ CaCl_2	56.3	77.7	2.5	15.4
10	CuCl_2	Trace	-	-	-

Reaction conditions: 10 mmol α -IP, 10 mol % NHPI and 2.5 mol % Co-catalyst, 10 mL CH_3CN , 1.2 MPa O_2 , 75 °C, 5 h. ^aAnalyzed by GC-MS or GC.

Table 2. The effects of reaction time and temperature on α -IP oxidation catalyzed by NHPI/CuCl₂

Entry	t (h)	T (°C)	Conversion (%) ^a	Selectivity (%) ^a		
				KIP	FIP	OIP
1	0.5	75	65.7	87.2	3.5	0.6
2	1.5	75	79.7	86.9	5.0	0.6
3	3	75	88.5	81.7	5.1	0.9
4	5	75	91.3	81.0	5.6	1.8
5	10	75	91.9	75.7	8.1	2.3
6	5	40	61.6	90.3	3.9	-
7	5	60	80.9	82.1	4.5	1.6
8	5	75	91.3	81.0	5.6	1.8
9	5	85	91.6	66.5	7.1	2.7
10	3	100	92.1	65.8	8.3	2.6

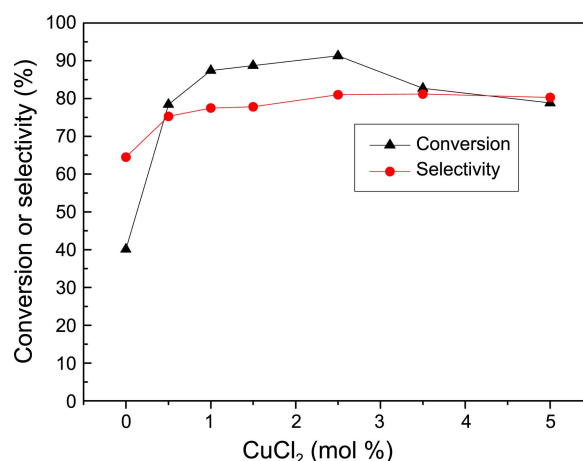
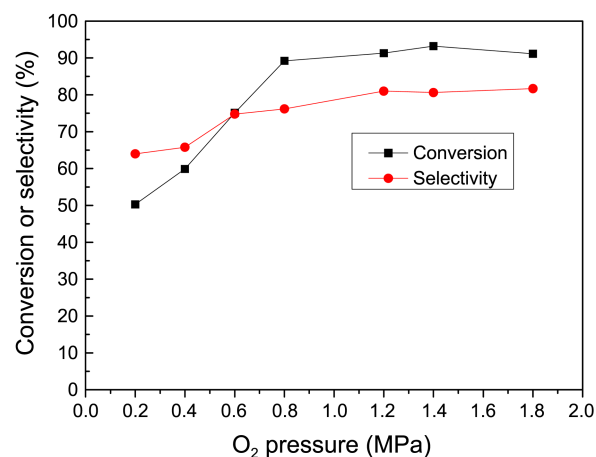
Reaction conditions: 10 mmol α -IP, 10 mol % NHPI and 2.5 mol % CuCl₂, 10 mL CH₃CN, 1.2 MPa O₂. ^aAnalyzed by GC.

cation Cu²⁺ was replaced by Zn²⁺ or Ca²⁺, the conversion sharply declined to 26.8% and 56.3% (entries 8, 9). These results indicated that the anions of metal salts had no obvious effect on the catalytic ability of NHPI while the cation Cu²⁺ is the key for α -IP oxidation catalyzed by NHPI.

The effects of reaction time and temperature on the oxidation were examined using 10 mol % NHPI and 2.5 mol % CuCl₂, and the results were summarized in Table 2. The reaction proceeded just within 0.5 h at 75 °C with 65.7% conversion and 87.2% selectivity (entry 1), which was significant improvement compared to the traditional catalytic system.^{6,7} The conversion went up while the selectivity went down slightly with the lapse of time and 5 h was suitable for this oxidation. In addition, it was found that the reaction didn't occur at room temperature, which indicated that the active intermediate PINO could not be generated at low temperature.¹⁶ However, when the temperature was increased to 40 °C, 61.6% conversion and 90.3% selectivity were obtained (entry 5). With the temperature increasing, the conversion increased but the KIP selectivity decreased since more of the over-oxidation products such as formylisophorone (FIP) was formed at higher temperature (entries 6-10). Taking both conversion and selectivity into consideration, 75 °C might be the suitable reaction temperature.

The oxidation results using 10 mol % NHPI and different amount of CuCl₂ at 75 °C under 1.2 MPa O₂ for 5 h were displayed in Figure 1. When using 0.5 mol % CuCl₂ as co-catalyst, both of the conversion and selectivity increased remarkably in comparison with NHPI as the sole catalyst. Obviously, CuCl₂ promoted this oxidation. The catalytic efficiency was achieved to the maximum with 2.5 mol % of CuCl₂. The conversion decreased and the selectivity remained unchanged even though more of CuCl₂ was added.

It was noted that O₂ pressure had significant effect on the oxidation of α -IP (Figure 2). Only 42.1% conversion and 61.6% selectivity were observed under atmospheric pressure for the reason that the concentration of dioxygen in the solvent was low and only a small amount of dioxygen participated in the reaction. It is generally believed that concen-

**Figure 1.** The effect of amount of CuCl₂ on α -IP oxidation. Reaction conditions: 10 mmol α -IP, 10 mol % NHPI, Co-catalyst: CuCl₂, and 10 mL CH₃CN, 1.2 MPa O₂, 75 °C, 5 h.**Figure 2.** The effect of O₂ pressure on α -IP oxidation. Reaction conditions: 10 mmol α -IP, 10 mol % NHPI and 2.5 mol % CuCl₂, 10 mL CH₃CN, 75 °C, 5 h.

tration of dioxygen increases with the increase of O₂ pressure. Both the conversion and selectivity kept increasing until the O₂ pressure reached 1.2 MPa. So 1.2 MPa O₂ pressure was preferable for this oxidation.

Then, the α -IP oxidation was carried out in different solvents and the results were illustrated in Figure 3. The reaction proceeded well in acetonitrile (91.3% conversion, 81.0% selectivity) and moderately in acetone (77.6% conversion, 74.8% selectivity) and ethylacetate (59.3% conversion, 73.5% selectivity). 37.2% of α -IP was converted with 75.5% selectivity in the absence of solvent. Only 15.2% conversion was given in the presence of hexane. Low conversion was obtained in acetic acid while no reaction was observed in ethanol. In conclusion, the studies on various solvents showed that aprotic solvents favored this oxidation. Constantini¹⁷ also reported the similar results that only aprotic solvents are suitable for the oxidation, while protic solvents lead to the formation of by-products through undesired reactions, thereby decreasing the KIP selectivity. The reason may be that the solvent participates in reaction

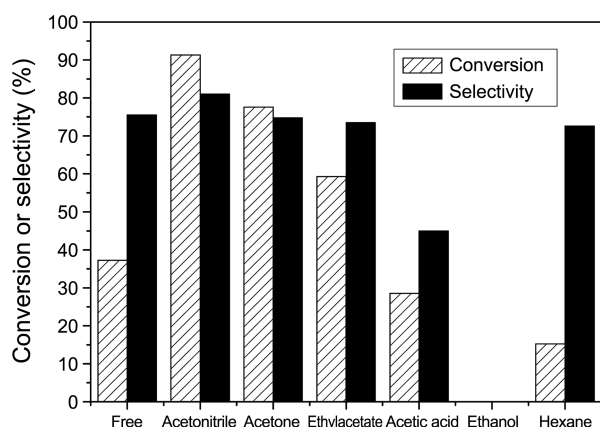


Figure 3. The effect of solvents on α -IP oxidation. Reaction conditions: 10 mmol α -IP, 10 mol % NHPI and 2.5 mol % CuCl_2 , 10 mL solvent, 1.2 MPa O_2 , 75 °C, 5 h.

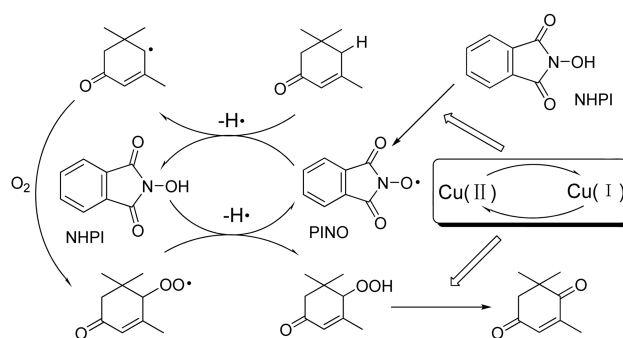
Table 3. The aerobic oxidation of various hydrocarbons catalyzed by NHPI/ CuCl_2

Entry	Substrate	Conversion (%) ^a	Main products	selectivity (%) ^a
1		100		81.8
2		87.4		82.3
3		17.5		66.3
4		100		93.9
5		100		46.3

Reaction conditions: 10 mmol substrates, 10 mol % NHPI and 2.5 mol % CuCl_2 , 10 mL CH_3CN , 1.2 MPa O_2 , 75 °C, 5 h. ^aDetermined by GC-MS.

by creating a medium that facilitates electron transfer among the reaction species involved¹⁸ to enhance the oxidation activity.

Furthermore, a series of allylic aerobic oxidation of hydrocarbons were studied under the optimized conditions (Table 3). Surprisingly, terpinolene was oxidized to 2-(4-methylphenyl)-propan-2-ol rather than 3-terpinolone in 81.8% conversion, which might be attributed to the rearrangement-aromatization (entry 1). This method was feasible for the oxidation of cyclohexene to 2-cyclohexen-1-one with 87.4% conversion and 82.3% selectivity (entry 2). However, due to the steric and electrophilic effects of the acetyl group, only 17.5% of 1-acetylcyclohexene was converted (entry 3). This



Scheme 2. The possible reaction mechanism.

method was also effective for the oxidation of aromatic substrates. Toluene was converted to benzoic acid with 100% conversion and 93.9% selectivity (entry 4) and 100% of tetralin was converted to tetralone with 46.3% selectivity and other undetermined products (entry 5).

It is generally accepted that NHPI catalyzes oxidation reaction through initial generation of the PINO radical by abstraction of the O-H hydrogen in NHPI.¹⁹ Therefore, as shown in Scheme 2, a plausible reaction mechanism was proposed for the allylic oxidation of α -IP catalyzed by NHPI/ CuCl_2 . The key step is the *in situ* generation of PINO from NHPI through the redox reaction of copper salts.²⁰ The next step involves the hydrogen atom abstraction from α -IP by PINO to form α -IP radicals and synchronously, PINO becomes NHPI again during this step. Trapping the resulting α -IP radical by dioxygen provides peroxy radical, which is eventually converted into oxygenated products through α -IP hydroperoxide. Meanwhile, Cu (I) comes back to Cu (II).

For further verifying the mechanism of catalytic oxidation, FT-IR spectroscopy was performed and the spectra are shown in Figure 4. The intense broad peak at 3443 cm^{-1} was assigned to the stretching vibration of -OH of non-hydrogen bonding association. While the peak at 3134 cm^{-1} was observed in spectra of NHPI/ CuCl_2 in acetonitrile in the presence of O_2 , but it was not present in the spectrum of

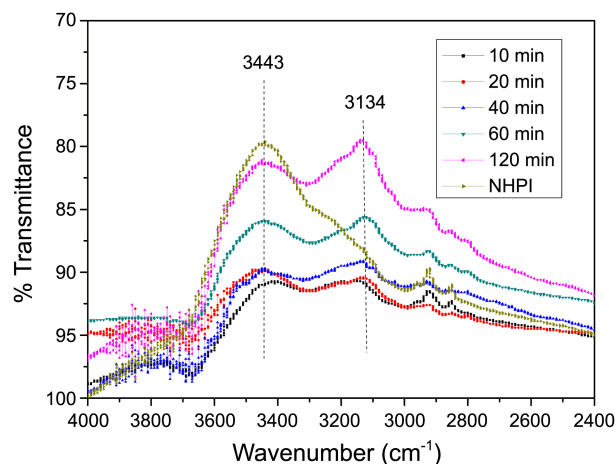


Figure 4. FT-IR spectra of NHPI in CH_3CN , and the mixture of NHPI/ CuCl_2 in CH_3CN in the presence of O_2 collected at different times.

NHPI alone in acetonitrile. It could be assigned to the ν (OH) in $>O-H \cdots O-N<$ because the nitroxyl function of PINO had high dipole moment (6.7 D) and could easily form intermolecular or intramolecular hydrogen bonds with proton donors.²¹ Thus, it could be concluded PINO radicals were generated through the interaction of NHPI with $CuCl_2$. Moreover, the peak intensity increased with the lapse of time from 10 min to 120 min, which meant that more PINO radicals were generated and therefore more hydrogen bonds were formed with NHPI.

Conclusions

In conclusion, NHPI/ $CuCl_2$ is a highly efficient catalytic system to the aerobic oxidation of α -IP to KIP. 91.3% conversion and 81.0% selectivity were obtained under the optimized conditions (10 mmol α -IP, 10 mol % NHPI, 2.5 mol % $CuCl_2$, 75 °C, 1.2 MPa O_2 pressure, 5 h). This method significantly improved the reaction condition of α -IP oxidation compared with the traditional pathways. Furthermore, it is also applicable to oxidation of other hydrocarbons such as benzylic compounds, cycloalkene and its derivatives.

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