Catalysis Communications 11 (2010) 758–762

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Metal and solvent-free oxidation of α-isophorone to ketoisophorone by molecular oxygen

Congmin Wang, Guoliang Wang, Jianyong Mao, Zhen Yao, Haoran Li *

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

ARTICLE INFO

Article history:
Received 24 November 2009
Received in revised form 4 February 2010
Accepted 9 February 2010
Available online 12 February 2010

ABSTRACT

The metal and solvent-free oxidation of α-isophorone to ketoisophorone (KIP) using *N*-hydroxy phthalimide (NHPI) as the catalyst under atmospheric oxygen was studied, eliminating the isomerization process of α-isophorone to β-isophorone. The effect of co-catalyst, temperature, time, amount of NHPI, and recycling on the oxidation was investigated. The oxidation of α-isophorone proceed well without any co-catalyst under 60 °C for 10 h, which was different with the traditional oxidation of α-isophorone at high temperature. Furthermore, NHPI can be easily separated and reused with a slight loss on its activity. This aerobic oxidation process by NHPI provides a good alternative way for the industrial synthesis of KIP.

1. Introduction

Selective allylic oxidation of cyclic olefins is a fundamental and important functional transformation in synthetic chemistry [1]. As a typical allylic oxidation, the oxidation of 3,5,5-trimethyl-2-cyclohexen-1-one (α-isophorone, α-IP, 1) to 3,5,5-trimethyl-2-cyclohexen-1,4-dione (ketoisophorone, KIP, 3) has received considerable attention (Scheme 1), because KIP is a key intermediate for the synthesis of various carotenoids and flavoring fine chemicals [2]. The conventional method for the production of KIP (3) in industry is the homogeneous liquid oxidation of 3,5,5-trimethyl-3-cyclohexen-1-one (β-isophorone, β-IP, 2), which is prepared by the isomerization process of α-IP (1) [3–9]. However, the isomerization temperature is very high, and the conversion of α-IP (1) to β-IP (2) is no more than 2% [10]. The selective oxidation of α-IP is an interesting route to prepare KIP, eliminating the isomerization step of α-IP (1) to β-IP (2).

Accordingly, a variety of catalytic systems including phosphomolybdic acid [11,12], Pd(OAc)$_2$ [13], molybdovanadophosphate [14,15], and metal supported MgAl hydrotalcite [16,17] have been extensively investigated for the oxidation of α-IP (1) to KIP (3). For the selective oxidation of α-IP (1) to KIP (3), molecular oxygen as an oxidant is more convenient for both economical and environmental benefits. Murphy and Baiker [11] described an efficient and selective aerobic oxidation of α-IP (1) to KIP (3) catalyzed by homogeneous phosphomolybdic acid system. However, these oxidation processes were mainly catalyzed by metallic compounds contained molybdenum, vanadium, chromium, copper, etc., which suffered the drawbacks such as relatively harsh conditions, metallic toxicity, and high expense. Therefore, selective metal-free oxidation of α-IP (1) to KIP (3) with molecular oxygen under relatively mild condition becomes particularly desirable.

Recently, aerobic oxidation catalyzed by metal-free catalyst such as *N*-hydroxyphthalimide (NHPI) was attractive because of its high efficiency and relatively mild reaction condition [18–22]. It was found that NHPI combined with metal or organic co-catalyst to be a remarkable catalytic system, which exhibited high activity in the oxidation of hydrocarbons [22,23], and some olefins such as cyclohexene and styrene [24–27]. However, to the best of our knowledge, the metal and solvent-free aerobic oxidation of the olefins such as α-IP (1) and 2-cyclohexen-1-one, which is conjugated with the carbonyl group, has not been reported.

Herein, we report a metal and solvent-free aerobic oxidation of α-IP (1) to KIP (3) with molecular oxygen in the presence of NHPI. The effect of co-catalyst, temperature, time, amount of NHPI, and recycling on the conversion and selectivity was investigated. The possible oxidation pathways of α-IP (1) catalyzed by NHPI were estimated. This metal and solvent-free aerobic oxidation process provides a good alternative way for the industrial synthesis of KIP (3).

2. Experimental section

2.1. Materials

The commercial-grade α-IP (1), β-IP (2), and KIP (3) were supplied by Zhejiang NHU Co., Ltd. NHPI, benzoyl peroxide (BPO), tetrabutylammonium bromide (TBAB), anthraquinone (AQ), Ethyl benzoate, and dichloromethane were analytical reagents

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* Corresponding author. Fax: +86 571 8795 1695.
E-mail address: lihr@zju.edu.cn (H. Li).

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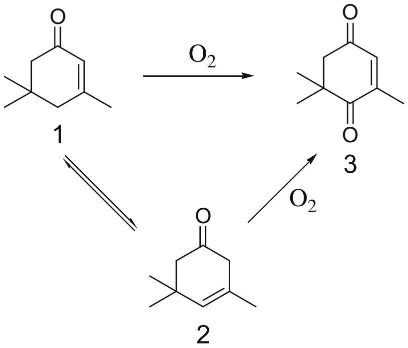
doi:10.1016/j.catcom.2010.02.010



Scheme 1. Catalytic oxidation of isophorone to ketoisophorone with dioxygen.

purchased from commercial sources, and were all used as received unless otherwise stated.

2.2. Experimental methods

In a typical oxidation procedure, a batch reactor, which composed of a four-neck flask connected with a reflux condenser, gas bubbler, mechanical stirrer, and a water bath equipped with a thermostat, was used for catalytic reactions. A mixture of NHPI (0.8 g, 5 mmol) and α-IP (13.6 g, 100 mmol) was placed in the flask and heated at 60 °C under vigorous stirring, then a stream of dioxygen was conducted into the reaction solution for 10 h. After the reaction finished, the reaction mixture cooled down to about 0 °C. The resulting finely crystalline precipitate was removed by centrifuging to produce the recycled NHPI (0.68 g). The filtrate was evaporated, treated, and analyzed regularly to monitor the oxidation reaction by gas chromatography. The oxidation products and intermediates were identified by HP5973 GC–MS with DP17 column (30 m × 0.25 mm × 0.25 μm) by comparing retention times and fragmentation patterns with authentic samples. The conversion and selectivity were determined using GC equipped with column ATSE-54 (50 m × 0.53 mm × 1 μm). Ethyl benzoate (99.9%) was applied as internal standard for quantitative analysis.

3. Results and discussion

The co-catalysts are generally indispensable in the aerobic oxidation of hydrocarbons catalyzed by NHPI as a function of initiator [25,28–30]. Therefore, the aerobic oxidation of α-IP (1) catalyzed by NHPI with different co-catalysts at 80 °C for 10 h was investigated at first. It was seen in Table 1 that the selectivity and conversion did not increase remarkably when different co-catalysts were used. For example, the KIP (3) selectivity of 47.5%, 42.9%, and conversion of 41.0%, 39.6%, were obtained when benzoyl peroxide (BPO) and anthraquinone (AQ) were used as the co-catalysts, while the KIP (3) selectivity of 48.3% and conversion of 39.0% were obtained in the absence of co-catalyst. Hence, the results showed that the co-catalyst was not necessary in the aerobic oxidation of α-IP (1) catalyzed by NHPI. This feature may be related to the structure of KIP (3), which is similar to that of quinone [31]. The study on the reason why the oxidation did not need co-catalyst is in progress.

Different with the traditional oxidation of α-IP (1) catalyzed by metallic catalyst, which carried out at high temperature (>100 °C) because of the thermodynamic stability of α-IP (1) [12], the oxida-

Table 1
The effect of different catalyst on the oxidation of α-isophorone.

Entry	Catalyst	Conversion (%)	Selectivity (%)	
			KIP	HIP
1	NHPI/BPO	41.0	47.5	4.8
2	NHPI/TBAB	20.0	46.2	4.0
3	NHPI/AQ	39.6	42.9	4.5
4	NHPI	39.0	48.3	5.5
5	–	Trace	–	–

Reaction conditions: 100 mmol α-IP, 5 mmol NHPI, 0.3 mmol co-catalyst, 80 °C, 10 h.
BPO: benzoyl peroxide.
TBAB: tetrabutylammonium bromide.
AQ: anthraquinone.

Table 2
The effect of temperature on the oxidation of α-isophorone catalyzed by NHPI.

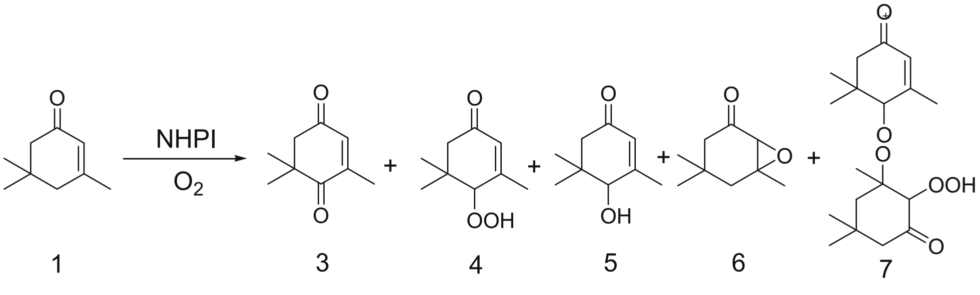
Entry	Temperature (°C)	Conversion (%)	Selectivity (%)	
			KIP	HIP
1	80	39.0	48.3	5.5
2	70	26.1	56.0	5.4
3	60	15.4	77.2	4.5
4	50	10.4	53.2	4.2
5	40	4.1	45.5	3.7

Reaction conditions: 100 mmol α-IP, 5 mmol NHPI, 10 h.

Table 3
The effect of time and the amount of NHPI on the oxidation of α-isophorone.

Entry	Time (h)	NHPI (mol%)	Conversion (%)	Selectivity (%)	
				KIP	HIP
1	5	5	10.9	81.7	4.9
2	10	5	15.4	77.2	4.5
2	15	5	17.3	68.0	4.0
3	20	5	24.8	57.7	3.4
4	25	5	29.2	51.8	3.0
5	10	3	10.1	70.0	4.2
6	10	4	11.9	75.7	4.2
7	10	6	15.8	67.4	4.4
8	10	7	16.1	65.8	4.6

Reaction conditions: 100 mmol α-IP, 60 °C.



Scheme 2. The oxidation of α-isophorone catalyzed by NHPI with dioxygen.

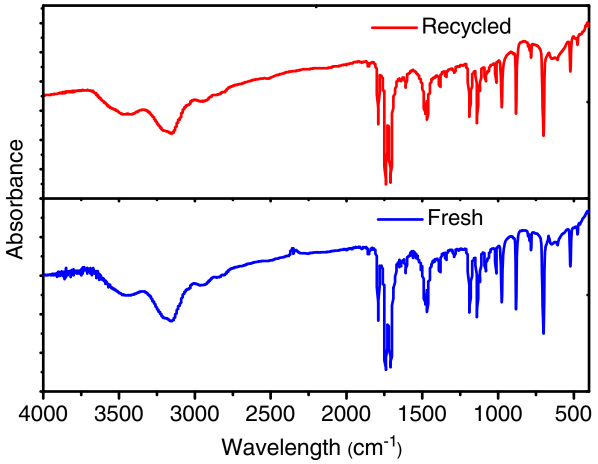


Fig. 1. The comparison of IR spectrum between the fresh NHPI and recycled NHPI. ▬, fresh NHPI; ▬, recycled NHPI.

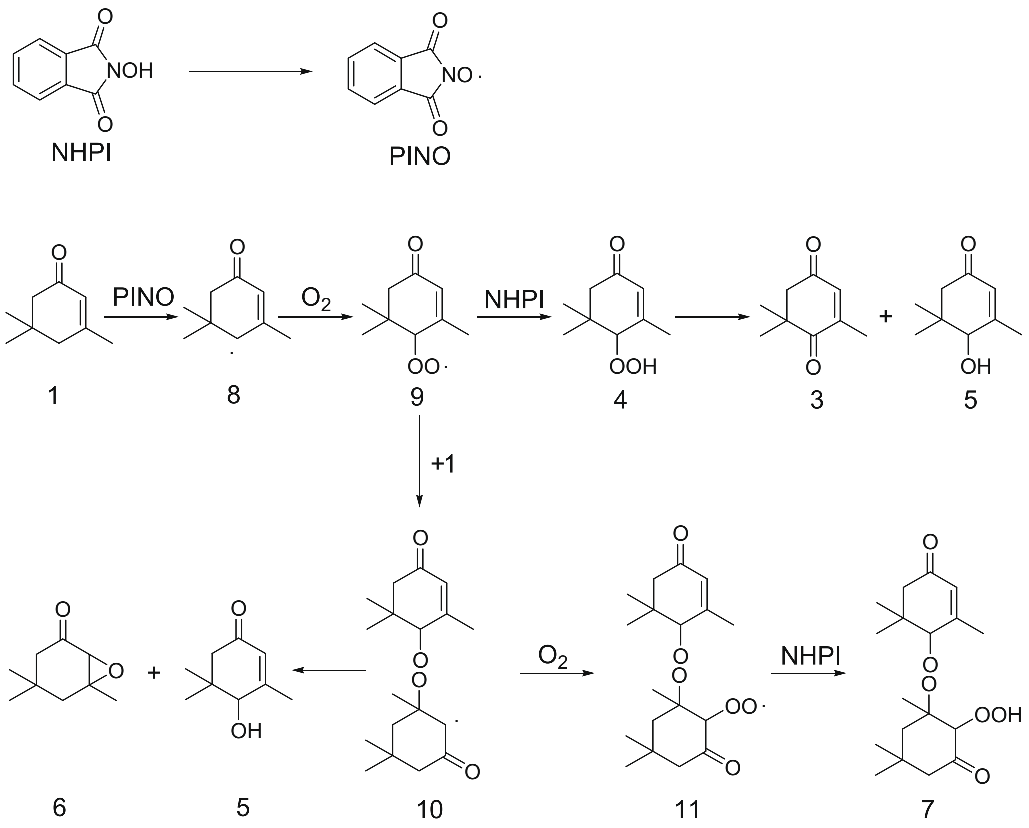
Table 4
The effect of reused NHPI on the oxidation of α-isophorone.

Entry	Recycling	Conversion (%)	Selectivity (%)	
			KIP	HIP
1[a]	0	15.4	77.2	4.5
2	1	14.2	69.0	4.2
3	2	14.7	67.0	4.4
4	3	14.5	70.0	4.3
5	4	14.1	69.6	4.0

Reaction conditions: 100 mmol α-IP, 60 °C, 10 h.
[a] NHPI (5 mmol).

tion catalyzed by NHPI proceed well under relatively mild temperature (Scheme 2). It was clear in Table 2 that the effect of temperature on the oxidation of α-IP (1) was significant. When the temperature of the oxidation was higher than 60 °C, the selectivity would decrease remarkably because of the formation of the undesired byproducts such as dimer and polymers, which were detected by ESI-MS. On the other hand, the KIP (3) selectivity would reduce from 77.2% to 45.5% when the temperature of the oxidation decreased from 60 °C to 40 °C because the active intermediate PINO was not easy to produce at low temperature [32]. In contrast, the desired KIP (3) was obtained with high selectivity of 77.2% at 60 °C. An important feature of the oxidation is that there is no evidence for the formation of over-oxidation products such as formyisophorone, which may be related to the low temperature [14]. During the oxidation, besides the main product KIP (3), 4-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (HIP) (5) of about 4% and 4,4,6-trimethyl-7-oxobicyclo [4.1.0]-heptan-2-one (OIP) (6) of about 2% were also produced, which were identified by GC–MS.

It should be noted that the time had strong effect on the oxidation, which was shown in Table 3. The conversion of α-IP (1) increased from 10.9% to 24.8%, and selectivity of KIP (3) decreased continuously from 81.7% to 57.7% with the increasing of the time from 4 h to 20 h. Selectivity of KIP (3) decreased remarkably when the time of the oxidation was longer than 15 h because of the formation of the byproducts. Considering the separation of α-IP (1) and KIP (3) is easy, 10 h might be the best for the oxidation catalyzed by NHPI at 60 °C. In addition, we also studied the influence of amount of NHPI on the oxidation. It can be seen in Table 3 that the conversion and selectivity increased when amount of NHPI enhanced from 3 mol% to 5 mol%. On the other hand, the conversion changed very little, but the selectivity decreased remarkably as the



Scheme 3. Proposed reaction pathways for α-isophorone oxidation with dioxygen in the presence of NHPI.

Table 5
The comparison of different allylic oxidation in the presence of NHPI.

Entry	Substance	Time (h)	Conversion (%)	Selectivity (%)			
				Ketone	Alcohol	Epoxy	Other
1	α-IP	10	15.4	77.2	4.5	2.6	15.7
2[a]	β-IP	10	45.6	91.1	1.4	Trace	1.0
3	Cyclohexene	5	64.8	55.4	9.7	3.6	31.3
4[b]	Cyclohexenone	10	4.4	46.4	6.8	5.4	41.4

Reaction conditions: 100 mmol substrate, NHPI 5.0 mmol, 60 °C.

[a] Pyridine (40 ml) was used as solvent.

[b] BPO (0.3 mmol) was added as co-catalyst.

amount of NHPI increases up to 7 mol%. Therefore, 5 mol% is considered as a preferable amount of NHPI.

The separation of NHPI and KIP (3) is very easy because NHPI is immiscible with α-IP (1) and KIP (3) at low temperature. When the oxidation finished, after cooling down the reaction mixture to 0 °C, NHPI was separated from the organic phase by centrifuging, which could be used in the subsequent reaction. The structure of recycled NHPI was confirmed using IR spectra, 1H NMR, and ESI-MS, which was shown in Fig. 1. It was clear that there was not obvious difference between the recycled NHPI and the fresh NHPI. In order to access the influence of the recycled NHPI on the oxidation, five recycling runs were carried out under the same condition. It was seen in Table 4 that the NHPI could be recycled with a slight loss of its activity. It seemed that the NHPI could have the potential to be used more than five times.

Based on previous reports and the observed reaction products, the possible oxidation pathways of α-IP catalyzed by NHPI could be postulated, which was shown in Scheme 3. Firstly, NHPI can be converted to phthalimide N-oxylradical (PINO). The hydrogen atom of α-IP (1) was abstracted by PINO to produce α-IP radical (8), which further led to the formation of α-IP peroxy radical (9) and the corresponding α-IP hydroperoxide (4). Then α-IP hydroperoxide (4) was directly decomposed to KIP (3) and HIP (5). It is well known that alkyl hydroperoxide (4) is the initial intermediate in the oxidation of hydrocarbon [33–35]. In the oxidation of α-IP to KIP catalyzed by NHPI, it was confirmed by the addition of triphenyl phosphate (TPP) because α-IP hydroperoxide (4) could be quantitatively reduced to the HIP (5) by TPP at room temperature [34,35]. On the other hand, α-IP peroxy radical (9) can add to the double bond in α-IP to produce the more stable β-peroxy radical (10) [36]. The β-peroxy radical (10) reacted with O_2 to give the new peroxy radical (11) and further converted to the dimer hydroperoxide (7) and polymer, which was detected by ESI-MS. It is reported that the greater the stability of β-peroxy alkyl radical, the more likely it is to react with oxygen rather than to undergo unimolecular decomposition to produce OIP (6) [37]. Thus the dimer hydroperoxide (7) and polymer are main products, and OIP (6) is trace in the oxidation of α-IP (1).

For further verifying of the mechanism of catalytic oxidation, the oxidation of β-IP (2), cyclohexene, and cyclohexenone catalyzed by NHPI was also carried out, which was given in Table 5. It was clear that the selectivity of KIP (3) was more than 90%, and the other byproducts such as polymer were only about 1% when β-IP (2) was oxidized in the same condition, while the selectivity of KIP (3) was only 77.2%, and the other byproducts such as polymer were more than 15% for α-IP (1). The difference between α-IP (1) and β-IP (2) is the position of carbon–carbon double bond. The former is conjugated with carbonyl group, but the latter is not. Similarly, the higher selectivity of ketone and the lower other byproducts were obtained for cyclohexene, compared with that of cyclohexenone. Therefore, the results showed that the addition which resulted in the dimer and polymer is favored over the abstraction of an allylic hydrogen when the double bond is conjugated with carbonyl group, which is the reason why the selectivity of KIP (3) in the oxidation of α-IP (1) decreased with the increasing of the time [37].

4. Conclusion

In summary, α-IP (1) can be directly oxidized to KIP (3) with atmospheric oxygen by NHPI. The effect of co-catalyst on the oxidation was investigated and the results showed that the co-catalyst was not necessary in the aerobic oxidation of α-IP (1) catalyzed by NHPI. Especially, the oxidation of α-IP (1) catalyzed by NHPI was carried out well under 60 °C for 10 h, while the traditional oxidation of α-IP (1) was usually at high temperature. Furthermore, the separation and recycling of NHPI were easy with a slight loss on its activity. Possible reaction pathways for the oxidation of α-IP (1) were presented, which indicated that the byproducts such as dimer and polymers produced easily when the double bond is conjugated with carbonyl group. Considering the advantage such as aerobic oxidation, metal and solvent-free process, this oxidation catalyzed by NHPI provided a potentially new way for the synthesis of KIP (3) in industry.

Acknowledgement

This work was supported by National Natural Science Foundation of China (Nos. 20990221, 20704035).

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