

A simple and efficient approach for highly selective preparation of nitrocyclohexane from cyclohexane with tert-butyl nitrite catalyzed by *N*-hydroxyphthalimide

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Abstract A simple and effective approach for highly selective preparation of nitrocyclohexane from cyclohexane using tert-butyl nitrite as a nitrating agent under atmospheric pressure has been successfully developed in this work. The results indicate that the *N*-hydroxyphthalimide catalyst gave the best results with 27.3 % of cyclohexane conversion and 88.0 % of selectivity to nitrocyclohexane under optimal reaction conditions. The present reaction provides a novel strategy for the synthesis of nitroalkanes from the nitration of low-carbon alkanes because of the mild reaction condition, simple experimental procedure and high selectivity towards the desired product. This method may be very significant to establish such a synthesis method for aliphatic nitro-compounds from the low-carbon alkanes in organic fields.

Keywords Cyclohexane · Nitrocyclohexane · Tert-butyl nitrite · NHPI · Nitration

Introduction

The nitration of alkanes to nitroalkanes is an important process since nitroalkanes are not only chemical commodities but also very important intermediates for synthesis of a variety of chemicals such as pharmaceuticals and agrochemicals [1].

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The nitro group on alkanes can be easily replaced selectively with maintenance of other functional groups and reduced to afford various nitrogen-containing compounds [2]. For instance, nitrocyclohexane can be partly hydrogenated into cyclohexanone oxime, a raw material of ε -caprolactam, which in turn leads to nylon-6 [3]. Also, it can be completely hydrogenated into cyclohexylamine that is mainly used for fuel, pigments and pharmaceuticals or is further oxidized into cyclohexanone oxime.

Compared with nitration of aromatic hydrocarbons, the selective nitration of aliphatic hydrocarbons and cycloalkanes are very difficult because of their exceedingly low reactivity [4]. Traditionally, there are the following two synthetic routes for nitrocyclohexane. Firstly, the nitration of benzene by nitric acid can be used for production of nitrobenzene [5, 6], which is hydrogenated to nitrocyclohexane. Secondly, benzene can be completely hydrogenated to cyclohexane, which can be converted into nitrocyclohexane by nitric acid or nitrogen dioxide [7, 8] (as shown in Scheme 1). However, these methods suffer a series of disadvantages, such as generation of large numbers of waste acids, low selectivity towards the desired product and consumption of a large quantity of Lewis acid as activators [9]. Meanwhile, those acids are environmentally unfriendly and costly to treat. Therefore, the development of highly selective preparation of nitrocyclohexane from cyclohexane has been desired for a long time in the chemical industry.

Currently, the nitrations of cyclohexane to nitrocyclohexane by nitrogen dioxide or nitric acid as a nitrating reagent are performed at fairly high temperatures (250–400 °C), and they proceed by free radical chain reactions involving C–H bond homolysis or cleavage of the C–C skeleton [10, 11]. Therefore, it is very difficult to obtain high selectivity of nitrocyclohexane. Ishii et al. [12, 13] developed a novel catalytic method for the nitration of aliphatic hydrocarbons and low-carbon cycloalkanes with nitric acid or nitrogen dioxide using *N*-hydroxyphthalimide (NHPI) as a key catalyst under mild conditions. Yamaguchi et al. [14] also reported a catalytic method for the nitration of various alkanes with nitric acid using $[VO(H_2O)_5]H[PMo_{12}O_{40}]$ as a key catalyst in acetic acid. However, the control of selectivity to nitroalkanes is still difficult issues. Ishii et al. also put forward synthesis of nitrosocycloalkanes or cycloalkanone oximes from cyclohexanes and tert-butyl nitrite (TBN) by using NHPI as key catalyst in the presence of acetic acid under argon [15–17].



Scheme 1 The routes for the manufacture of nitrocyclohexane

NHPI is a cheap, nontoxic catalyst easily prepared by the reaction of phthalic anhydride and hydroxylamine [18]. The use of NHPI in free radical reactions is suitable not only for classical oxidations but also for some important synthetic transformations such as carbon–carbon and carbon–nitrogen bond formation reactions [19]. Phthalimido-*N*-oxyl radical (PINO, derived from NHPI) serves as a carbon-radical-producing catalyst and can abstract hydrogen atoms from the C–H bonds in saturated hydrocarbons, forming the corresponding alkyl radicals under relatively mild conditions [20].

Herein, we report a simple and effective approach for highly selective preparation of nitrocyclohexane from cyclohexane by using commercially available TBN as a safe and effective nitrating agent with the help of NHPI in this work, as is shown in Scheme 2. Compared with the existing nitration methods, the most promising feature of the approach are more environmentally friendly because of TBN instead of nitric acid or nitrogen dioxide as a nitrating agent. Generally, several alkyl nitrites are industrially produced from the corresponding alcohols and gaseous NO under O_2 atmosphere [21, 22]. The TBN was found to be converted into tert-butyl alcohol and gaseous NO. And it could be prepared in good to excellent yield by treating tert-butyl alcohol with nitrous acid or other nitrosating agents. This method may be very significant to establish such a synthesis method for aliphatic nitro-compounds from the low-carbon alkanes in organic fields.

Experimental

Reagents and instrument

Cyclohexane (AR) was purchased from Shanghai Chemical Co., Ltd., China. Tertbutyl nitrite (AR) (TBN) was purchased from Shanghai Adamas Reagent Co., China. The other reagents were purchased from Aladdin Industrial Corporation. Except where specified, all chemicals were of analytical grade and used as received. Gas chromatography (GC) was performed on a Shimadzu GC-2010 plus equipped with a DB-5 (30 m × 0.25 mm × 0.25 µm) column for quantitative analysis by using chlorobenzene as internal standard. Gas chromatography–mass spectrometry (GC–MS) was run on a Shimadzu GCMS-QP2010 PLUS for qualitative analysis of products.

Typical experimental procedure

The nitration reaction of cyclohexane with TBN was carried out in liquid-phase at a certain set temperature in a 100 ml round-bottomed flask reactor equipped with a



Scheme 2 The novel preparation route of nitrocyclohexane from the nitration of cyclohexane with TBN

reflux condenser and a magnetic stirrer. The reactor was immersed in an oil bath. A typical reaction procedure was as follows: 0.2 g catalyst and 20 mmol TBN were added in a certain amount of cyclohexane. The obtained mixture was heated to the reaction temperature and stirred for 24 h. After cooling to room temperature, the catalyst was separated by filtration and the resulting mixture was analyzed by using an Agilent 7890 gas chromatography with hydrogen flame ion detector (FID). The quantitative analysis of products was calculated by internal standard methods. The conversion of cyclohexane and selectivity of products were calculated using the following formulas [Eqs. (1) and (2)]. All raw material and products were established mass balances (including carbon mass balance and nitrogen mass balance).

Conversion of cyclohexane (%) =
$$\frac{\text{the amount (mol) of cyclohexane converted}}{\text{the amount (mol) of TBN}} \times 100\%$$
 (1)

Selectivity of product (%) =
$$\frac{\text{the amount (mol) of product}}{\text{the amount (mol) of cyclohexane converted}} \times 100\%$$
(2)

Results and discussion

Effects of various catalysts on nitration reaction of cyclohexane with TBN

Effects of various catalysts on the conversion of cyclohexane and selectivity of products in the nitration reaction of cyclohexane were examined, and the results were summarized in Table 1. In this catalytic system, the catalytic performances of the present catalysts were different.

Catalyst	Conversion (%)	Selectivity	Selectivity (%)				
		CH-ol	CH-one	CH-ONO ₂	CH-NO ₂		
None	3.2	38.5	_	_	61.5		
NiV ₂ O ₆	3.4	24.3	-	8.3	67.3		
VPO	4.6	21.2	-	20.0	58.8		
SBA-15	3.8	52.4	_	_	47.6		
HPW	4.4	82.0	_	_	18.0		
NHPI	27.3	0.9	5.1	6.0	88.0		

Table 1 Effects of various catalysts on nitration reaction of cyclohexane with TBN

Reaction conditions: the molar ratio of cyclohexane to TBN is 4:1, the mass of cyclohexane is 6.72 g, reaction time is 24 h, reaction temperature is 80 °C and the mass of catalyst is 0.2 g. CH–ol, CH–one, CH–ONO₂ and CH–NO₂ stands for cyclohexanol, cyclohexanone, cyclohexyl nitrate and nitrocyclohexane, respectively

Nitrocyclohexane could be formed from cyclohexane with TBN in the absence of any catalysts and the conversion of cyclohexane was only 3.2 %. When the oxidation catalyst NiV₂O₆ and VPO were used, the conversion of cyclohexane and selectivity to nitrocyclohexane is not significantly improved. When the solid acid catalyst (phosphotungstic acid, HPW) is introduced to nitration reaction, the selectivity to oxygenated product cyclohexanol was increased obviously, while the selectivity to nitrocyclohexane was only 18.0 %. Among these catalysts, the NHPI catalyst gave the best results. Under our conditions, 27.3 % of conversion with 88.0 % of the selectivity to nitrocyclohexane was obtained. This result showed that free radical catalyst was very suitable for the nitration reaction.

Effects of reaction temperature on nitration reaction of cyclohexane with TBN

Table 2 shows the effects of reaction temperature on the nitration reaction of cyclohexane with TBN. It is clearly found that there is significant influence of reaction temperature on the conversion and selectivity. The conversion of cyclohexane increased rapidly from 9.6 to 27.8 % and the selectivity to nitrocyclohexane decreased gradually from 93.5 to 83.7 % when the reaction temperature was elevated from 50 to 90 °C. Obviously, the selectivity of oxygenated product cyclohexanol and cyclohexanone were found to increase with elevated temperatures, while the selectivity of nitrocyclohexane showed the decline trend. This may be due to the following reason. The nitration and oxidation reaction of cyclohexane with TBN catalyzed by NHPI happened simultaneously and were competitive reaction in this process. Maybe the reaction rate of oxidation reaction to form cyclohexanol and cyclohexanone became faster when reaction temperature was raised from 70 °C. While the reaction rate of the nitration reaction to form nitrocyclohexane remains substantially unchanged. Thus, the selectivity of nitrocyclohexane was declined. Therefore, elevating temperature was not beneficial to the selectivity of nitrocyclohexane. And a range of favorable reaction temperature were about 70-80 °C from the points of the conversion of cyclohexane and selectivity of nitrocyclohexane.

Table 2 Effects of reactiontemperature on nitration reaction	Reaction temperature (°C)	Conversion	Select	ctivity (%)		
of cyclohexane		(%)	CH– ol	CH- one	CH– ONO ₂	CH– NO ₂
	50	9.6	0.5	1.4	4.7	93.5
Reaction conditions: the molar	60	16.8	0.7	1.6	6.5	91.2
4:1. the mass of cyclohexane is	70	27.2	0.8	2.7	8.4	88.1
6.72 g, reaction time is 24 h,	80	27.3	0.9	5.1	6.0	88.0
and the amount of NHPI catalyst is 0.2 g	90	27.8	1.9	6.6	7.8	83.7

Effects of molar ratio of cyclohexane to TBN on nitration reaction

Table 3 summarized the representative results of different molar ratio of cyclohexane to TBN on nitration reaction. It can be seen that the conversion of cyclohexane increases with raising the molar ratio. The selectivity of nitrocyclohexane increases gradually from 81.3 to 88.0 % with the molar ratio from 0.5 to 4. The selectivity to nitrocyclohexane shows the decline trend when the molar ratio of cyclohexane to TBN is elevated to 8. These results show that the molar ratio is also an important factor to affect the conversion and selectivity in the nitration reaction. From the points of the conversion of cyclohexane and selectivity of nitrocyclohexane, it is clearly found that the favorable molar ratio of cyclohexane to TBN is 4:1 under the reaction time of 24 h and the reaction temperature of 70 °C.

Effects of reaction time on nitration reaction of cyclohexane with TBN

Figure 1 shows the effects of different reaction time on nitration reaction of cyclohexane with TBN at 70 °C. It can be seen that conversion of cyclohexane gradually increases with prolonged reaction time, while the selectivity to nitrocyclohexane is not changed obviously. These results show that the reaction time mainly affects on the conversion of cyclohexane and the selectivity to nitrocyclohexane almost remains unchanged. From the points of the conversion and the selectivity, a suitable reaction time should not be beyond 24 h at 70 °C from Fig. 1.

Effects of the amount of catalyst on nitration reaction of cyclohexane with TBN

Table 4 shows the effects of the amount of catalyst on nitration reaction under the reaction temperature of 70 °C and the reaction time of 24 h. It can be seen that the conversion of cyclohexane seems to increase slowly with the elevated amount of catalyst. The conversion of cyclohexane reached 27.3 % with 88.0 % of selectivity

Molar ratio	Conversion (%)	Selectivity (%)				
		CH-ol	CH-one	CH-ONO ₂	CH–NO ₂	
0.5:1	9.4	5.9	1.2	11.6	81.3	
1:1	12.7	3.6	0.9	11.7	83.8	
2:1	17.5	3.4	1.4	11.0	84.2	
4:1	27.3	0.9	5.1	6.0	88.0	
8:1	27.7	2.4	9.3	10.1	78.3	

Table 3 Effects of molar ratio of cyclohexane to TBN on nitration reaction

Reaction conditions: the mass of TBN is 2.06 g, reaction temperature is 70 $^{\circ}$ C, reaction time is 24 h, and the mass of NHPI catalyst is 0.2 g

Molar ratio stands for the molar ratio of cyclohexane to TBN



Fig. 1 Effects of reaction time on nitration reaction. Reaction conditions: molar ratio of cyclohexane to *TBN* is 4:1, the mass of cyclohexane is 6.72 g, reaction temperature is 70 $^{\circ}$ C, and the mass of NHPI catalyst is 0.2 g

to nitrocyclohexane when reaction was added 0.2 g of NHPI. However, the selectivity to nitrocyclohexane decreased obviously when the amount of catalyst exceeded 0.4 g. This reason might be that the reaction rate of oxidation reaction to form cyclohexanol and cyclohexanone became faster when the amount of catalyst was relatively high under these reaction conditions. Therefore, the suitable amount of catalyst adequately and efficiently catalyzed the nitration of cyclohexane with TBN to nitrocyclohexane. From the points of the conversion and the selectivity, a suitable amount of catalyst should be 0.2 g.

In summary, from the single factor experiment results, the optimal reaction conditions were obtained that the reaction time was 24 h, reaction temperature was 70 °C, the amount of NHPI catalyst was 0.2 g, and the molar ratio of cyclohexane to TBN was 4:1 in the nitration reaction.

Amount of catalyst (g)	Conversion (%)	Selectivity (%)			
		CH-ol	CH-one	CH-ONO ₂	CH-NO ₂
0.1	24.1	2.7	_	9.8	87.8
0.2	27.3	0.9	5.1	6.0	88.0
0.4	27.7	2.7	12.8	10.4	74.2

Table 4 Effects of the amount of catalyst on nitration reaction of cyclohexane

Reaction conditions: molar ratio of cyclohexane to TBN is 4:1, the mass of cyclohexane is 6.72 g, reaction temperature is 70 °C, reaction time is 24 h, and catalyst is NHPI

Effects of different environment on nitration reaction of cyclohexane with TBN

Table 5 shows the effects of different environment on nitration reaction under the reaction temperature of 70 °C and the reaction time of 24 h. It is clearly found that there is significant influence of reaction environment on the conversion and selectivity. The conversion of cyclohexane reached 27.3 % with 88.1 % of selectivity to nitrocyclohexane when reaction was under air. Obviously, the conversion of cyclohexane could be increased under oxygen atmosphere, however, the selectivity to nitrocyclohexane was not ideal. This might be due to the following reason. The formed NO in the reaction was very easily converted into NO₂ under oxygen atmosphere. Owing to the higher concentration of NO₂ than under air, cyclohexane could react selectively with NO₂ to give oxygenated products in preference to nitrocyclohexane. Meanwhile, the formed cyclohexanol could react with HNO₃ to form cyclohexyl nitrate.

The nitration of linear alkane (*n*-hexane) and alkylbenzene (toluene) with TBN

The results of the nitration of *n*-hexane and toluene with TBN by the present method are shown in Table 6. Owing to the oxidizing ability of TBN, the nitration of toluene with TBN led to oxygenated products benzaldehyde (58 %) and benzoic acid (42 %). While *n*-hexane afforded a 11:51:38 regio-isomeric mixture of nitrohexane, 2-nitrohexane, and 3-nitrohexane in 20.66 % conversion. These results demonstrate the nitration of linear alkane and alkylbenzene with TBN are different in nitration process.

Recyclability of the NHPI catalyst and purification of the target product

Stability and recyclability of catalyst is a key issue in catalysis reaction. After the reaction, the NHPI could be easily separated from the reaction mixture by filtration. The results indicated the recovered NHPI could be reused directly and the results obtained in the optimal reaction conditions indicated that the selectivity to nitrocyclohexane remained substantially unchanged and the conversion of cyclohexane decreased slightly.

Since TBN generated only volatile residual products, such as tert butyl alcohol and gaseous NO, almost pure nitrating product was easily obtained by simple

Environment	Conversion (%)	Selectivity (%)				
		CH-ol	CH-one	CH-ONO ₂	CH-NO ₂	
Air	27.3	0.9	5.1	6.0	88.0	
Oxygen	47.21	2.3	16.7	44.95	36.05	

Table 5 Effects of different environment on nitration reaction of cyclohexane

Reaction conditions: molar ratio of cyclohexane to TBN is 4:1, the mass of cyclohexane is 6.72 g, reaction temperature is 70 $^{\circ}$ C, reaction time is 24 h, and the mass of NHPI catalyst is 0.2 g

Substrate	Conversion (%)	Selectivity of product (%)				
n-Hexane	20.66	Nitrohexane	2-Nitrohexane	3-Nitrohexane		
		11.0	51.0	38.0		
Toluene	19.0		Benzaldehyde	Benzoic acid		
			58.0	42.0		

Table 6 NHPI-catalyzed nitration of different substrate with TBN under selected conditions

Reaction conditions: the molar ratio of substrate to TBN is 4:1, the mass of TBN is 2.06 g, reaction temperature is 70 $^\circ$ C, reaction time is 24 h, and the mass of NHPI catalyst is 0.2 g

distillation of the reaction mixtures. The reaction product was distilled by using a rotary evaporator under the condition that vacuum degree was 0.09 Mpa and bath temperature was raised from 40 to 80 °C. The mass fraction of nitrocyclohexane could reach 95 % in the obtained sample by using a gas chromatography. This was a meaningful superiority especially in the case of large scale reactions.

The possible reaction path of cyclohexane with TBN catalyzed by NHPI

On the basis of these results in this work, the possible formation pathway of products in the catalytic nitration reaction of cyclohexane with TBN was proposed in Scheme 3. Firstly, the nitration might be initiated by hydrogen-atom abstraction from the hydroxyimide group of NHPI by TBN to generate a PINO radical. The PINO radical readily abstracted a hydrogen atom from cyclohexane to form a cyclohexyl radical, which undergoed nitration with NO₂ to give a nitrocyclohexane. TBN was decomposed to produce NO and tert-butyl alcohol via the O–N bond cleavage under the action of NHPI. The formed NO was very easily converted into NO₂ under air. And cyclohexane also could react with NO₂ to form a cyclohexyl free radical and HNO₂. The formed HNO₂ could be converted into HNO₃, H₂O and NO [23]. And the formed cyclohexyl free radical reacted with O₂ to form



Scheme 3 Possible reaction path of cyclohexane with TBN catalyzed by NHPI

cyclohexanol, which was further oxidized to cyclohexanone. Meanwhile, the formed cyclohexanol also reacted with HNO₃ to form cyclohexyl nitrate.

Conclusions

In conclusion, a novel approach for highly selective preparation of nitrocyclohexane from the nitration reaction of cyclohexane with TBN had been developed successfully under atmospheric pressure in this work. The results indicated that high selectivity (over 88 %) for nitrocyclohexane with 27.3 % of cyclohexane conversion was obtained. And the possible reaction path had been proposed and further studies for the optimization of the reaction conditions are now in progress. Assuming that better catalysts can be developed, this method may be very significant to establish such a synthesis method for aliphatic nitro-compounds from the low-carbon alkanes in organic fields.

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