Synthesis Techniques

A New Route to Lactam Precursors from Cycloalkanes: Direct Production of Nitrosocycloalkanes or Cycloalkanone Oximes by Using *tert*-Butyl Nitrite and *N*-Hydroxyphthalimide**

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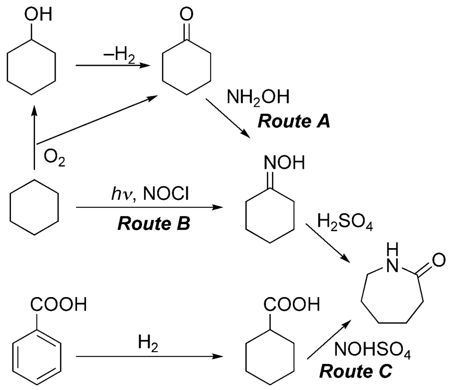
The development of an innovative methodology for the production of bulk and commodity chemicals, in particular one that takes account of effects on the environment, becomes more and more important in industrial chemistry worldwide.[1,2] ε-Caprolactam is one of the monomers most widely used for the production of nylon 6; the world production capacity of ε-caprolactam in 1998 was about 4.2 million tons.[3] Currently, ε-caprolactam is produced by the following methods (Scheme 1): 1) Beckmann rearrangement of cyclohexanone oxime derived from cyclohexanone and hydroxylamine (Route A) or from cyclohexane and NOCl by the photonitrosation of cyclohexane (PNC) process (Route B), or 2) nitrosation of cyclohexane carboxylic acid with $NOHSO_4$ (Route C). Of these approaches, Route A is most often employed and accounts for about 70 % of the total production of ε-caprolactam worldwide. However, this method has several drawbacks. Cyclohexanone is supplied by the aerobic oxidation of cyclohexane, which leads to a mixture of cyclohexanone and cyclohexanol (K/A oil), but the conversion of cyclohexane must be kept at only 3–6 % to avoid the formation of further oxidation products such as adipic acid and glutaric acid.[4] Another serious drawback of this method is the coproduction of a large amount of ammonium sulfate waste in both the hydroxylamine production and the Beckmann rearrangement processes.[3]



Scheme 1. The routes currently used for the manufacture of ε-caprolactam.

Several new approaches to the synthesis of ε-caprolactam and its precursors have recently been developed. Researchers at EniChem Co. have synthesized the oxime by ammoximation of cyclohexanone with hydrogen peroxide and ammonia catalyzed by titanium silicate-1 (TS-1), followed by Beckmann rearrangement in the presence of a high-content silicate catalyst developed by Sumitomo Chemical Co.[3,5] Thomas and co-workers have reported that a bifunctional transition-metal-ion-substituted aluminophosphate molecular sieve promotes the reaction of cyclohexanone with ammonia and hydrogen peroxide or molecular oxygen to give cyclohexanone oxime along with a small amount of ε-caprolactam.[6] These methods, however, require cyclohexanone as the starting material. If direct conversion of cyclohexane into ε-caprolactam precursor could be achieved, the reaction would represent an innovative method. Although the PNC process fits this purpose, very corrosive NOCl must be used as a key compound together with HCl.[1] In addition, cyclohexanone oxime is obtained as its hydrochloric acid salt and the formation of NOCl is very troublesome. Therefore, the development of a new system for the nitrosation or oximation of cyclohexane that overcomes these disadvantages is desirable.

We have shown previously that the phthalimide *N*-oxyl radical (PINO; generated in situ by reaction of *N*-hydroxyphthalimide (NHPI) with dioxygen in the presence or absence of a transition-metal salt or nitrogen dioxide) serves as a carbon-radical-producing catalyst (CRPC) and abstracts hydrogen atoms from C–H bonds in hydrocarbons under relatively mild conditions.[7] For example, cyclohexane was oxidized in the presence of a catalytic amount of NHPI combined with $[Mn(acac)_2]$ (acac = acetylacetonate) under dioxygen to give a cyclohexyl radical, which was eventually converted into adipic acid in high yield.[8] Cyclohexane was also efficiently nitrated by treatment with nitrogen dioxide and NHPI to form nitrocyclohexane.[9] In the course of our studies on the NHPI-catalyzed functionalization of cyclohexane, we have now found that the nitrosation of cyclohexane

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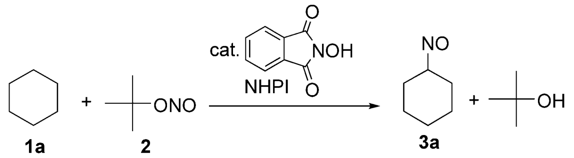
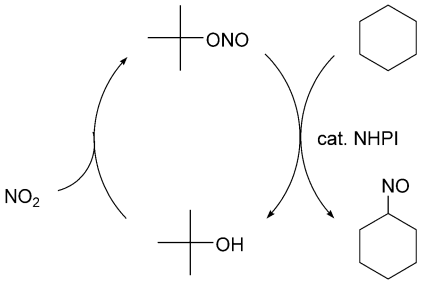
by *tert*-butyl nitrite can be successfully achieved without photoirradiation and under halogen-free conditions by using NHPI as a catalyst (Scheme 2).



Scheme 2. Nitrosation of cyclohexane under halogen-free conditions, catalyzed by NHPI in AcOH at 80 °C under argon.

Cyclohexane (**1a**; 8 mmol, 1 mL) was allowed to react with *tert*-butyl nitrite (**2**; 1 mmol) in the presence of NHPI (0.1 mmol) in AcOH (1 mL) at 80 °C for 2 h under argon (standard conditions). Evaporation of the solvent and remaining starting materials followed by short column chromatography on acidic alumina (hexane/ethyl acetate, 5:1) gave nitrosocyclohexane (**3a**; 0.51 mmol) as a dimer. The yield of isolated **3a** was 51 % based on the amount of **2** used. This process is the first catalytic transformation of **1a** into **3a** under relatively mild conditions (at 80 °C for 2 h). The majority of **2** was found to be converted into *tert*-butyl alcohol (see below). Since *tert*-butyl alcohol is known to react with NO_2 or sodium nitrite to produce **2**,[10] reagent **2** may be regenerated from the *tert*-butyl alcohol formed. This fact suggests that this nitrosation of **1a** with **2** provides a "green" route to **3a** (Scheme 3). LC-MS analysis of the reactant showed that most of the NHPI catalyst remains in the reaction mixture after the reaction and is not decomposed. In fact, 80 % of the NHPI catalyst used could be recovered from the reaction mixture.



Scheme 3. A new route to ε-caprolactam precursors.

Figure 1 shows the ^1H and ^{13}C NMR spectra of the reactant after reaction in CD_3COOD under standard conditions. Signals at $\delta = 5.06$ ppm and $\delta = 66.0$ ppm in the ^1H and ^{13}C NMR spectrum, respectively, were assigned to protons and carbon atoms in **3a**. The signals at $\delta = 7.79$–7.67 ppm in the ^1H spectrum and $\delta = 163.9$, 133.6, 129.1, and 122.7 ppm in the ^{13}C spectrum were attributed to NHPI and small amounts of phthalimide and phthalic anhydride, which were detected by LC-MS analysis. The ^{13}C signal at $\delta = 69.5$ ppm corresponds to the tertiary carbon atom of the *tert*-butyl alcohol derived from **2**. The signals around $\delta = 4.40$ ppm in the ^1H spectrum were ascribed to a trace amount of nitrocyclohexane (**4a**), which was confirmed by GC-MS analysis. Compound **2** was not detected at all after the reaction. Part of **2** seems to cleave to form NO_2, which was observed as a brown gas during the reaction. HNO_2 and HNO_3 generated from NO_2 made the reaction solution very acidic.

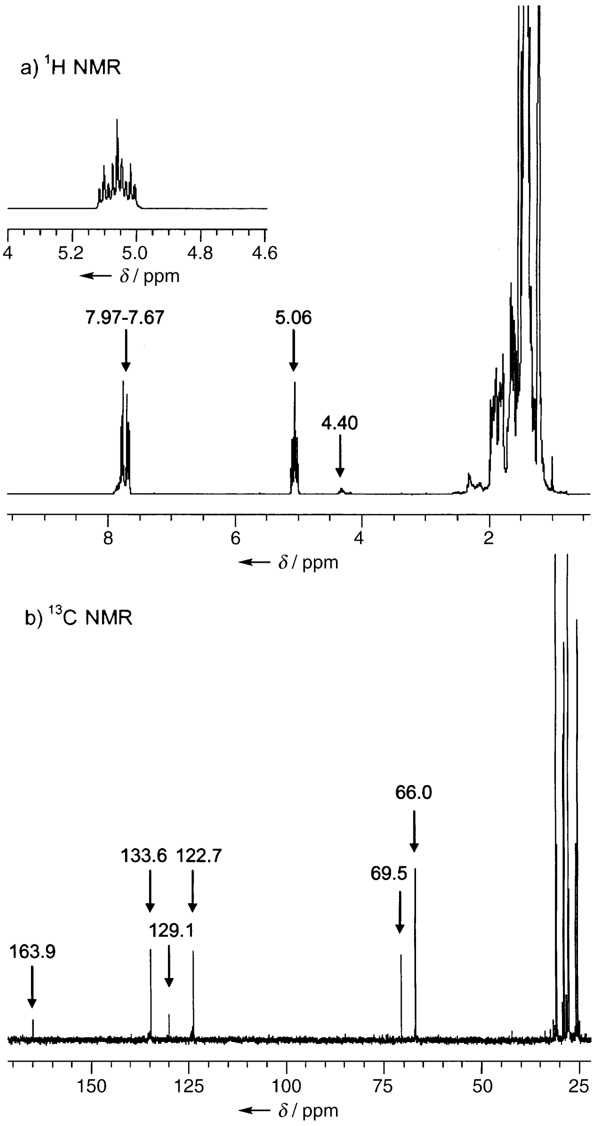


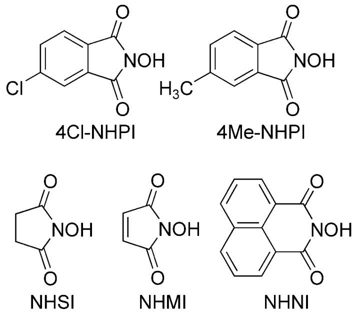
Figure 1. The NMR spectra of the reaction mixture after reaction of cyclohexane (**1a**) with *tert*-butyl nitrite (**2**) catalyzed by NHPI in CD_3COOD under standard conditions.

Table 1 summarizes representative results for the nitrosation of **1a** by treatment with **2** to form **3a** under various reaction conditions. The yield of **3a** was determined by ^1H NMR spectroscopy by using a known amount of nitromethane as an internal standard. Among the *N*-hydroxyimide analogues shown in Scheme 4, NHPI and *N*-hydroxy-4-chlorophthalimide (4Cl-NHPI) were found to be effective catalysts (entries 1–6). Compound **3a** was obtained in 51 % yield within only 1 h when 4Cl-NHPI was used as a catalyst (entry 3). The reaction proceeded even at 70 °C (entry 7). Recovered NHPI was also efficient when reused for a further

Table 1: Nitrosation of cyclohexane (**1a**) by treatment with *tert*-butyl nitrite (**2**), catalyzed by NHPI.[a]

Entry	Catalyst[b]	*t* [h]	Yield of **3a** [%]
1	NHPI	2	58
2	NHPI	1	33
3	4Cl-NHPI	1	51
4	4Me-NHPI	2	19
5	NHSI	2	32
6	NHNI	2	20
7[c]	NHPI	2	63
8[d]	NHPI	2	56
9[e]	NHPI	2	40
10[f]	NHPI	2	52
11[g]	NHPI	2	0
12[h]	NHPI	2	< 1
13[i]	NHPI	2	28
14[j]	NHPI	2	64
15[k]	NHPI	2	1
16[l]	NHPI	6	18

[a] **1a** (4 mmol, 0.5 mL) was allowed to react with *tert*-butyl nitrite (**2**; 0.5 mmol) in the presence of NHPI (0.05 mmol) in CD_3COOD (0.5 mL) at 80 °C under argon for 2 h. The yield of **3a** based on the amount of **2** was determined by ^1H NMR spectroscopy with a known amount of nitromethane as an internal standard and is given as the average of two runs. [b] The abbreviations refer to the structures in Scheme 4. [c] The reaction was carried out at 70 °C. [d] The catalyst recovered from the reaction described in entry 1 was used. [e] 2 mmol (0.25 mL) of **1** was used. [f] 0.25 mL of CD_3COOD was used. [g] In the absence of CD_3COOD. [h] CD_3CN (0.5 mL) was used instead of CD_3COOD. [i] The reaction was carried out in an O_2 atmosphere. [j] The reaction was carried out in the dark. [k] *n*-Butyl nitrite (**5**, 0.5 mmol) was used instead of **2**. [l] See the text for details.

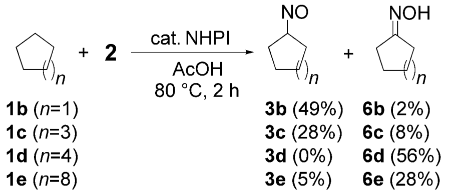


Scheme 4. The catalysts involved in the reactions listed in Table 1. 4Cl-NHPI = *N*-hydroxy-4-chlorophthalimide, 4Me-NHPI = *N*-hydroxy-4-methylphthalimide, NHSI = *N*-hydroxysuccinimide, NHMI = *N*-hydroxymaleimide, NHNI = *N*-hydroxynaphthalimide.

nitrosation (entry 8). When the amount of **1a** or CD_3COOD was halved, **3a** was formed in slightly lower yield (entries 9 and 10). The reaction did not take place at all in the absence of CD_3COOD (entry 11). Almost no reaction occurred when CD_3CN was employed in place of acetic acid (entry 12). No reaction was observed in other solvents such as PhCl, AcOEt, and α,α′,α″-trifluorotoluene.

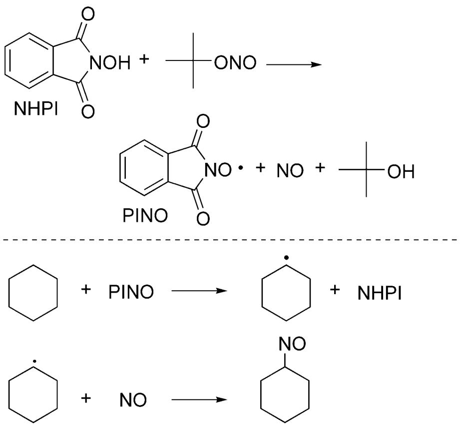
The reaction carried out in an O_2 atmosphere was accompanied by the formation of **3a** (28 %) and considerable amounts of **4a** (19 %), as well as oxygenated products (< 5 %) such as cyclohexanol and cyclohexanone (entry 13). This result may be caused by trapping of the generated cyclohexyl radical by NO_2 derived from NO and O_2, or by O_2 itself to form **4a** and the oxygenated products, respectively. The reaction carried out in the dark gave the same results as that in the light, which indicates that the nitrosation is not initiated by photoirradiation (entry 14). When **1a** was allowed to react with *n*-butyl nitrite (**5**) instead of **2**, only a trace amount of **3a** was produced because of the formation of *n*-butyl acetate by the ready reaction of **5** with acetic acid (entry 15). A prolonged reaction time (6 h) led to a complex mixture of products other than **3a** (18 %) and cyclohexanone oxime **6a** (8 %; entry 16).

On the basis of these results, the reactions of several cycloalkanes with **2** catalyzed by NHPI under standard conditions were examined (Scheme 5). Cyclopentane (**1b**) was nitrosated in a similar manner to **1a** to afford nitrosocyclopentane (**3b**) in 49 % yield. A small amount (2 %) of cyclopentanone oxime (**6b**) was also obtained. Interestingly, the reaction of cyclooctane (**1d**) produced cyclooctanone oxime (**6d**) as a major product (56 %). A longer reaction time (4 h) led to **6d** in 65 % yield. Direct transformation of cycloalkanes to cycloalkanone oximes, which has so far been very difficult to carry out by conventional methods, was thus achieved. It seems likely that the nitrosocyclooctane (**3d**) formed is rapidly isomerized into **6d** under these reaction conditions, probably as a result of the lower stability of nitroso dimer **3d** compared to **6d**.



Scheme 5. The reactions of cycloalkanes with **2**, catalyzed by NHPI under standard conditions.

ESR measurements were made to obtain information on the reaction pathway. After reaction of **2** with NHPI for 15 minutes under standard conditions, ESR measurement of the reaction mixture showed a triple signal at $g = 2.0073$ with $A_N = 4.23$ G, which we attributed to the phthalimide *N*-oxyl radical. The nitrosation process is complex and the reaction pathway is difficult to explain clearly at this stage, but a plausible reaction pathway is outlined in Scheme 6. In this suggested pathway, the reaction is initiated by the formation of PINO and NO through the reaction of NHPI with **2**. Since NHPI is easily oxidized by a weak oxidizing agent, *tert*-butyl nitrite (**2**) may serve as an oxidizing agent for NHPI and allow the formation of PINO and NO. A brown gas (nitrogen dioxide) was observed upon heating **2** with NHPI in acetic acid in the presence or absence of **1a**, which suggests that **2** decomposed to form NO and reaction with a small amount of the dissolved dioxygen gave NO_2. The PINO thus generated abstracts a hydrogen atom from **1a** to form a cyclohexyl radical and NHPI. Subsequently, the cyclohexyl radical is trapped by NO to produce nitrosocyclohexane (**3a**).



Scheme 6. A plausible reaction pathway for the reaction of **1a** with **2**, catalyzed by NHPI.

According to this reaction pathway, nitrosation of **1a** under an NO atmosphere instead of under Ar should improve the yield of **3a**. However, it was found to be difficult to obtain **3a** selectively by NHPI-catalyzed reaction of **1a** with **2** under NO. When **1a** was allowed to react with **2** in the presence of NHPI at 80 °C for 2 h under an NO atmosphere, the reaction resulted in a complex mixture of several products. We have previously shown that the reaction of an alkane in the presence of the catalyst NHPI under an NO atmosphere proceeds by the formation of an alkyl cation intermediate that is produced when the alkyl radical generated from the alkane is oxidized by excess amounts of NO.[11] We therefore suggest that transformation of the cyclohexyl radical into the cyclohexyl cation may occur as a side reaction in the nitrosation of **1a** with **2** in the presence of excess amounts of NO. The cyclohexyl cation generated could be converted into cyclohexyl acetate by trapping with AcOH, into cyclohexene by β-proton elimination, and into several reaction products of the resulting cyclohexene. As a consequence, the reaction of **1a** with **2** in an NO atmosphere would lead to a complex mixture of products. We think that NO may be generated slowly from **2** during nitrosation of **1a** by treatment with **2** under an Ar atmosphere and that this explains why **3a** was obtained in only moderate yield. Further investigations aiming to optimize the reaction conditions are now in progress.

In conclusion, we have developed a novel, clean procedure for the nitrosation of **1a** by treatment with **2** in the presence of NHPI as a catalyst. This method has some advantages over conventional methods, such as the halogen-free, relatively mild reaction conditions, good product selectivity (almost no organic byproducts), and high recovery of the catalyst.

Experimental Section

Representative procedure: NHPI (0.1 mmol) was added to a solution of **1a** (1 mL, 8 mmol) and **2** (1 mmol) in AcOH (1 mL) in a Schlenk tube. The tube was cooled to −78 °C to freeze the solvent, degassed in vacuo, then filled with Ar gas. The frozen solvent was melted at room temperature and refrozen to repeat the evacuation/Ar purge procedure. The series of operations was repeated three times. The reaction mixture was allowed to react under an atmospheric pressure of argon at 80 °C for 2 h. After the reaction, GC and GC-MS analyses were performed. The yields of products were estimated from the areas under the peaks in the spectra by incorporating an internal standard.

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