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One-Pot Synthesis of Lactams from Cycloalkanes and *tert*-Butyl Nitrite by Using *N*-Hydroxyphthalimide as Key Catalyst

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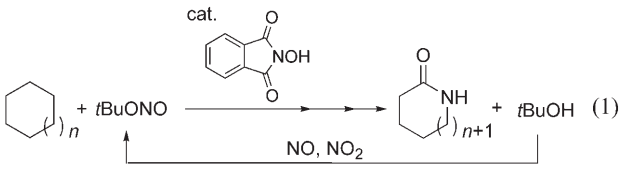
Abstract: Lactams were successfully synthesized in the one-pot reaction of cycloalkanes and *t*BuONO in the presence of *N*-hydroxyphthalimide as a key catalyst. Cyclododecane and cyclohexane were treated with *t*BuONO followed by triethylamine and then cyanuric chloride in a one-pot manner to give laurolactam and ε-caprolactam, respectively, in good yields. The Beckmann rearrangement of oximes by cyanuric chloride was found to be accelerated by the use of 1,1,1,3,3,3-hexafluoro-2-propanol as solvent. The method provides the first successful environmentally benign direct synthetic route to lactams from cycloalkanes without the formation of any salt.

Keywords: Beckmann rearrangement · homogeneous catalysis · lactams · oximes · triazines

Introduction

Lactams are very important raw materials for the synthesis of polyamides such as nylon-6 and nylon-12. In 2000, worldwide production of polyamides amounted to 3.31×10^6 tons.[1] Over the last several decades, considerable effort has been devoted to develop a sulfate-free lactam synthesis, but it still remains an important subject. Although there have been several methods to obtain lactams, the most popular route involves the following sequential reactions: 1) aerobic oxidation of cycloalkanes to give a mixture of cyclic alcohols and ketones, 2) dehydrogenation of alcohols to ketones, 3) oxime formation from cycloalkanones with hydroxylamine, and 4) Beckmann rearrangement of oximes in the presence of oleum to give lactams. Another possibility is oxime formation by the photochemically initiated reaction of cycloalkanes with NOCl followed by treatment of the resulting oximes with oleum. However, these methods produce vast amounts of ammonium sulfate as by-product. It is generally said that 1.6–2.2 tons of ammonium sulfate are produced to obtain 1 ton of ε-caprolactam.[2] Although the resulting ammonium sulfate is used as a fertilizer and gypsum material, the development of a method that avoids the formation of ammonium sulfate is a goal in lactam synthesis, particularly in industrial chemistry. In fact, Sumitomo Chemical Co. have industrialized a salt-free lactam synthesis involving the vapor-phase Beckmann rearrangement of cyclohexanone oxime derived from cyclohexanone, H_2O_2, and NH_3 on TS-1 catalyst.[1,3]

In a previous paper, we described the *N*-hydroxyphthalimide (NHPI)-catalyzed nitrosation of cycloalkanes with *tert*-butyl nitrite (*t*BuONO) to give nitrosocycloalkanes.[4] We have now succeeded in the synthesis of lactams from cycloalkanes in a one-pot reaction without any salt formation, which has been a long-term goal in industrial chemistry, by using NHPI as a key catalyst [Eq. (1)]. As *t*BuONO can be regenerated by treatment of the resulting *t*BuOH with NO and NO_2,[5] the present method can be regarded as an atom-economical lactam synthesis from cycloalkanes.



(1)

Results and Discussion

We first tried to improve the nitrosation of cycloalkanes with *t*BuONO in the presence of NHPI under various reaction conditions (Table 1). Cyclododecane (**1a**) (5 mmol), *t*BuONO (1 mmol), and NHPI (0.1 mmol) in benzene

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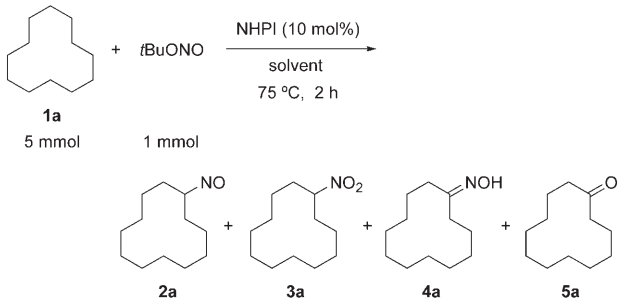
Table 1. Nitrosation of **1a** with *t*BuONO in the presence of NHPI under various conditions.[a]



Entry	Solvent ([mL])	Yield [%]			
		2a	**3a**	**4a**	**5a**
1	benzene/AcOH (2/0.5)	75	1	<1	1
2[b]	benzene/AcOH (2/0.5)	37	13	<1	2
3	benzene (2)	16	1	<1	1
4	AcOH (0.5)	50	13	<1	2
5	PhF/AcOH (2/0.5)	83	1	<1	1
6	PhCl/AcOH (2/0.5)	48	11	<1	2
7[c]	PhF/AcOH (2/0.5)	<1	<1	<1	<1
8[d]	PhF/AcOH (2/0.5)	60	10	<1	1

[a] See text. [b] Ar pressure: 760 Torr. [c] AIBN (0.5 mmol) instead of NHPI was used. [d] NO (≈0.2 mmol) was added.

(2 mL) containing a small amount of acetic acid (0.5 mL) were added to a 20-mL Schlenk tube under Ar. After frozen-evacuation below 1 Torr at liquid-nitrogen temperatures, the reaction mixture was allowed to warm to room temperature and stirred at 75 °C for 2 h to produce nitrosocyclododecane (**2a**) in 75% yield based on consumed *t*BuONO (Table 1, entry 1). The reaction under normal pressure (760 Torr) of Ar resulted in a considerable decrease in **2a** (37%) along with nitrocyclododecane (**3a**) in 13% yield (Table 1, entry 2). As the pressure of the reaction system was found to be an important factor to obtain **2a** selectively, all reactions except that in Table 1, entry 2 were carried out after frozen evacuation below 1 Torr. The reaction in benzene without acetic acid afforded **2a** in low yield (16%; Table 1, entry 3), whereas nitrosation in acetic acid without benzene gave **2a** in relatively good yield (50%) as well as **3a** (13%) (Table 1, entry 4). The best yield (83%) of **2a** was obtained when fluorobenzene containing a small amount of acetic acid was employed (Table 1, entry 5). However, the use of chlorobenzene instead of fluorobenzene resulted in a considerable decrease in **2a** (from 80 to 48%), whereas the yield of **3a** increased from 1 to 11% (Table 1, entry 6). Only trace amounts of **3a** were formed when using 2,2′-azobisisobutyronitrile (AIBN) instead of NHPI as a radical initiator (Table 1, entry 7).

It is important to recover the NHPI, which is used in 10 mol%, from the reaction solution after nitrosation. In a previous paper, we showed that 80% of NHPI can be recovered from the reaction solution after the nitrosation of cyclohexane.[4] Efforts are ongoing to decrease the amount of the catalyst used and to develop more-efficient catalyst systems.

To investigate the effect of NO gas, the reaction was examined by the addition of NO (≈0.2 mmol) after frozen evacuation—the yield of **2a** decreased to 60%, and the formation of **3a** increased to 10% yield. This shows that the concomitant generation of NO and phthalimide *N*-oxyl radical (PINO) from *t*BuONO and NHPI is important to obtain **2a**.[4]

As the nitrosation of **1a** with *t*BuONO in the presence of NHPI was considerably affected by the initial pressure, the nitrosation of **1a** and cyclohexane (**1b**) was examined under varying Ar pressures (Figure 1a and b). The yields of nitrocycloalkanes **3a**,**b** were affected considerably by the initial Ar pressure, but the effects of the pressure on the nitrosation of **1a** and **1b** were almost the same. The yields of **2a**,**b** decreased gradually with increasing Ar pressure, in contrast to the increased yields of **3a**,**b**. Nitrosation at pressures below 1 Torr led to **2a**,**b** in yields of 83 and 88%, respectively, based on *t*BuONO consumed.

We previously showed sequential reaction pathways for the nitrosation of **1b** with *t*BuONO in the presence of NHPI,[4] and the most important step is the concomitant generation of NO and PINO, as the resulting PINO abstracts the hydrogen atom from **1b** to give a cyclohexyl radical, which readily reacts with NO to produce **2b**. Therefore, the concentration of NO in the reaction solution seems to be a very important factor governing the formation of **2b**.

It is difficult to account clearly for the pressure effect in the nitrosation of cycloalkanes. It seems reasonable to assume that the solubility of NO, evolved from *t*BuONO by the action of NHPI, in the reaction solution is influenced by the pressure of the reaction system. In the present system in which a strong interaction between the solvent molecules (acetic acid) and radical molecules such as NO is predicted, the solubility of NO in the reaction solution probably increases with pressure. As a result, the concentration of NO in the solution under higher Ar pressure may become higher than that under lower pressure. It was reported that **2b** reacts with NO to give **3b** and a complex mixture of by-products.[6] Therefore, if the concentration of NO in the reaction solution is high, the amount of nitrocycloalkanes **3a** and **3b** may increase in the present reaction.[7] The results

Abstract in Japanese:

N-ヒドロキシフタルイミドを鍵触媒としたシクロアルカンと*t*-BuONOの反応によるラクタムのワンポット合成に成功した。シクロドデカンおよびシクロヘキサンを*t*BuONOと反応させた後、トリエチルアミン、続いて塩化シアヌールで処理すると、それぞれラウロラクタムおよびε-カプロラクタムを良好な収率で与えた。塩化シアヌールによるオキシムのベックマン転位反応は、1,1,1,3,3,3-ヘキサフルオロ-2-プロパノールを溶媒に用いることによって促進されることを見出した。本法は、塩の副生を伴わない環境にやさしいシクロアルカンからラクタムの新規な合成ルートを提供するものである。

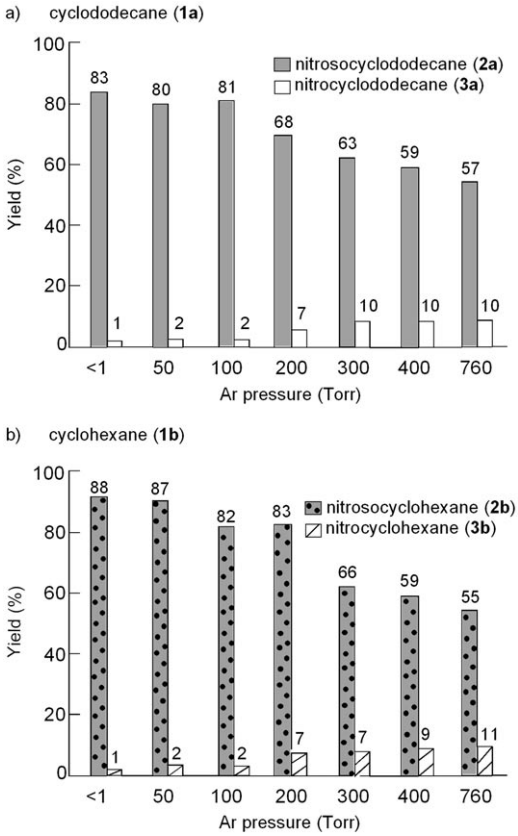
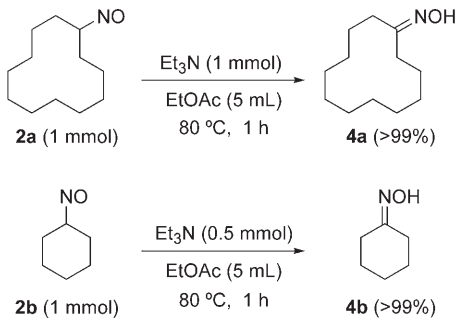


Figure 1. Effect of Ar pressure on the NHPI-catalyzed nitrosation of **1a**,**b** with *t*BuONO. Reaction conditions: **1a** (10 mmol) or **1b** (4 mL) were treated with *t*BuONO (1 mmol) and NHPI (0.1 mmol) in fluorobenzene (2 mL) and AcOH (0.1 mL or 0.5 mL, respectively) at 75 °C for 2 h under varying pressures of Ar.

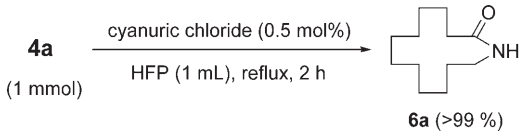
shown in Figure 1 a, b reflect the influence of the concentration of NO on the nitrosation of cycloalkanes under varying Ar pressures.

As nitrosocycloalkanes are converted into oximes in the reaction with amines,[8] treatment of **2a** or **2b** with Et_3N in EtOAc forms cyclododecanone oxime (**4a**) or cyclohexanone oxime (**4b**) in quantitative yields [Eq. (2)].



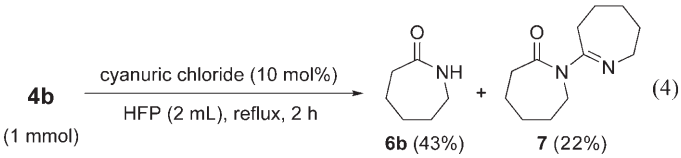
(2)

Recently, Yamamoto and Ishihara[9] reported an efficient method for the Beckmann rearrangement of oximes by using 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) as a key catalyst. We found that the Beckmann rearrangement of oxime **4a** by cyanuric chloride is considerably facilitated by carrying out the reaction in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP). Treatment of **4a** (1 mmol) in the presence of even a very small amount of cyanuric chloride (0.5 mol %) in HFP (1 mL) at reflux for 2 h afforded laurolactam (**6a**) in quantitative yield (>99 %) without any by-products [Eq. (3)].



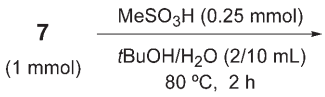
(3)

On the other hand, it was reported that the Beckmann rearrangement of **4b** is more difficult than that of **4a**,[9] and that the reaction of **4b** (2 mmol) with cyanuric chloride (10 mol %) in MeCN (4 mL) at reflux for 2 h affords **5a** in only 30 % yield. However, the same treatment of **4b** with cyanuric chloride in HFP instead of MeCN produced **6b** (43 %) and its condensate **7** (22 %) [Eq. (4)].



(4)

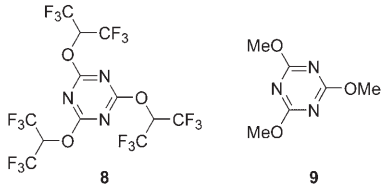
The condensate **7** was found to be easily hydrolyzed to give **6b** in almost quantitative yield [Eq. (5)], which corresponds to an overall yield of 87 % from **4b**.



(5)

To clarify the role of HFP in the Beckmann rearrangement of oximes, 2,4,6-tris[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]-1,3,5-triazine (**8**) and 2,4,6-trimethoxy-1,3,5-triazine (**9**) were prepared by the reaction of cyanuric chloride with HFP. The Beckmann rearrangement of **4a** in the presence of **8** under several conditions is summarized in Table 2. The reaction of **4a** in the presence of **8** (1 mol %) in HFP at reflux for 2 h afforded **6a** in 17 % yield (Table 2, entry 1). When **8** (5 mol %) was used, the yield of **6a** improved to 80 % (Table 2, entry 2). By adding *p*-TsOH to this system, **6a** was obtained in 94 % yield, even in the presence of only 1 mol % of **8** (Table 2, entry 3). To avoid the use of expensive HFP as a solvent, the reaction was carried out in toluene instead of in HFP in the presence or absence of *p*-TsOH to give **6a** in 1 % and 63 % yields, respectively, and small amounts of cyclododecanone (Table 2, entries 4 and 5). Interestingly, the rearrangement of **4a** in the presence of cyanuric chloride in CH_3CN was found to be inhibited by

Table 2. Beckmann rearrangement of **4a** in the presence of triazine **8** (or **9**) to give **6a**.[a]



8

9

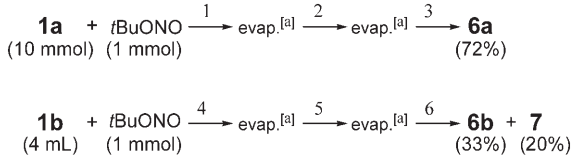
Run	Solvent	Additive	Conv. [%]	Yield [%][b]	
1	HFP	none	25	17	(<1)
2[c]	HFP	none	99	80	(<1)
3	HFP	*p*-TsOH	96	94	(1)
4[c]	toluene	none	19	1	(2)
5[c]	toluene	*p*-TsOH	87	63	(5)
6[d]	HFP	none	>99	>99	(<1)
7[d]	CH_3CN	Et_3N	3	1	(<1)
8[d]	HFP	Et_3N	96	92	(1)
9[e]	HFP	*p*-TsOH	no reaction		

[a] Reaction of **4a** (1 mmol) in the presence of **8** (1 mol%) and *p*-TsOH (15 mol%) or Et_3N (3 mol%) in solvent (1 mL) at 70°C (bath temp.) for 2 h. [b] Value in parentheses indicates the yield of cyclododecanone. [c] **8**: 5 mol%. [d] Cyanuric chloride (1 mol%) was used instead of **8**. [e] **9** was used instead of **8**.

adding triethylamine to the catalytic system, but the same reaction in HFP proceeded smoothly, even in the presence of triethylamine (Table 2, entries 7 and 8). This shows that the HCl may be formed by the reaction of **4a** with cyanuric chloride, and that the resulting HCl serves as an important promoter for the rearrangement of **4a** to give **6a**. In the former case, however, the HCl was trapped by triethylamine as triethylamine hydrochloride and the subsequent reaction of cyanurate with **4a** may be inhibited. In contrast, in the reaction in HFP, a transient active cyanuric intermediate such as **8** may be derived from cyanuric compounds and HFP during the course of the reaction, and the reaction of the active cyanuric species with **4a** was assisted by HFP which probably serves as a weak acid to give **6a**. On the other hand, the use of **9** instead of **8** did not lead to the rearrangement of **4a**, even in the presence of *p*-TsOH in HFP (Table 2, entry 9). This indicates that the reaction between **9** and HFP as well as oxime **4a** is difficult because of the poor reactivity of **9**. In fact, catalyst **9** was recovered unchanged after this reaction, whereas it was difficult to recover catalyst **8**.

On the basis of these results, it is probable that the hexafluoroisopropoxy group in **8** undergoes rapid exchange by the hydroxy group in **4a** to form a transient intermediate, which is converted entirely into **6a**, whereas the methoxy group in **9** is stable and difficult to react with **4a** or HFP.

A salt-free one-pot synthesis of lactams **6a**,**b** from cycloalkanes **1a**,**b**, respectively, would be very attractive. The reaction of **1a** with *t*BuONO under the same conditions as those described in Figure 1a and the isomerization of the resulting **2a** with triethylamine followed by the Beckmann rearrangement in the presence of cyanuric chloride in HFP led to laurolactam **6a** in 72% yield based on consumed *t*BuONO. Similarly, **1b** and *t*BuONO gave lactam **6b** (33%) and its condensate **7** (20%) corresponding to 40% of **6b** (Scheme 1).



Scheme 1. Reaction conditions: 1) NHPI (0.1 mmol), fluorobenzene/AcOH (2/0.1 mL), 75°C, Ar (<1 Torr), 2 h; 2) Et_3N (1 mmol), EtOAc (5 mL), 80°C, 1 h; 3) cyanuric chloride (0.05 mmol), HFP (1 mL), 70°C, 2 h; 4) NHPI (0.1 mmol), AcOH (0.5 mL), 75°C, Ar (<1 Torr), 2 h; 5) Et_3N (0.5 mmol), EtOAc (5 mL), 80 °C, 1 h; 6) cyanuric chloride (0.15 mmol), HFP (2 mL), 70°C, 2 h. [a] evap = evaporation.

This is the first successful one-pot synthesis of lactams **6a**,**b** from **1a**,**b**, respectively, without the formation of any undesired salts.

Conclusions

An efficient synthetic route to the oxime and/or lactam derivatives from cyclododecane **1a** and cyclohexane **1b** was established by the use of the NHPI/*t*BuONO system. In particular, the rearrangement of oximes into lactams in the presence of cyanuric chloride was markedly facilitated by the use of HFP as a solvent. This could provide a novel salt-free lactam synthesis from the corresponding cycloalkanes, which has been long-term goal in organic and industrial chemistry.

Experimental Section

All starting materials were commercially available and were used without purification. GLC analysis was performed with a flame ionization detector and a 0.2 mm × 25 m capillary column (OV-1). ^1H and ^{13}C NMR spectra were measured at 270 or 400 MHz and 67.5 or 100 MHz, respectively, in $CDCl_3$, with Me_4Si as the internal standard.

Nitrosation of **1a** with *t*BuONO catalyzed by NHPI: NHPI (0.1 mmol) was added to a solution of **1a** (5 mmol) and *t*BuONO (1 mmol) in benzene (2 mL) and AcOH (0.5 mL) in a 20-mL Schlenk tube. The tube was cooled to liquid-nitrogen temperatures to freeze the solvent and degassed in vacuo. The reaction mixture was allowed to stand at room temperature and then heated at 75°C for 2 h. After the reaction, NMR spectroscopic analysis was performed. The yield of **2a** was estimated from the peak areas based on the internal standard technique by NMR spectroscopy.

Transformation of **2a** into **4a**: Et_3N (1 mmol) was added to a solution of **2a** (1 mmol) in EtOAc (5 mL) in a 30-mL round-bottomed flask. The reaction mixture was heated at 80°C for 1 h. The yield of **4a** was estimated from the peak areas based on the internal standard technique by GC.

Transformation of **4a** into **6a**: Compound **4a** (1 mmol) was added to a solution of cyanuric chloride (0.005 mmol) in HFP (1 mL) in a 30-mL round-bottomed flask. The reaction mixture was heated at reflux for 2 h. The yield of **6a** was estimated from the peak areas based on the internal standard technique by GC.

One-pot synthesis of **6a** from **1a:** NHPI (0.1 mmol) was added to a solution of **1a** (10 mmol) and *t*BuONO (1 mmol) in fluorobenzene (2 mL) and AcOH (0.1 mL) in a 20-mL Schlenk tube. The tube was cooled to liquid-nitrogen temperatures to freeze the solvent and degassed in vacuo. The reaction mixture was allowed to stand at room temperature and then

heated at 75 °C for 2 h. After the evaporation, a solution of Et_3N (1 mmol) in EtOAc (5 mL) was added to the crude mixture, then the mixture was heated at 80 °C for 1 h. After evaporation, a solution of cyanuric chloride (0.05 mmol) in HFP (1 mL) was added to the crude mixture, and the mixture was then heated at 70 °C for 2 h.

The products, **2a**,[4] **2b**,[4,10] **4a**,[11] and **7**,[12] were reported previously.

Preparation of 2,4,6-tris[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]-1,3,5-triazine (**8**) and 2,4,6-trimethoxy-1,3,5-triazine (**9**): Cyanuric chloride (3 mmol), K_2CO_3 (10 mmol), and 3-Å molecular sieves (200 mg) were added to a solution of HFIP (10 mL). The mixture was stirred at room temperature for 15 h. Removal of solids by filtration and evaporation under reduced pressure gave crude **8** in almost quantitative yield as a white solid. Similarly, the reaction of cyanuric chloride in methanol under the same conditions as above afforded **9** in almost quantitative yield. Compounds **8** and **9** are known compounds, and **9** is available from Aldrich.

Acknowledgements

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