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Beckmann Rearrangement of Ketoximes to Lactams by Triphosphazene Catalyst[†]

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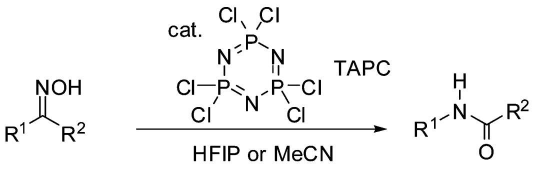
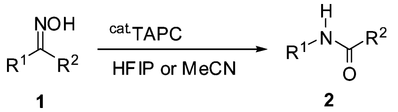


Triphosphazene, 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC), was found to be an efficient catalyst for the Beckmann rearrangement of cyclohexanone oxime and cyclododecanone oxime to ε-caprolactam and laurolactam, which are raw materials of nylon-6 and nylon-12, respectively.

The Beckmann rearrangement of oximes to lactams is a very important commercial process for the production of raw materials of polyamides such as nylon-6 and nylon-12.[1,2] Currently, the Beckmann rearrangement is carried out using oleum as a catalyst, which results in undesired sulfates as byproducts.[3] It is generally said that at least 1.7 tons of sulfates are formed to obtain a ton of the ε-caprolactam. In the year 2005, ca. 4 million tons of ε-caprolactam was manufactured in the world. As a result, vast amounts of sulfates are co-produced with the lactam. Therefore, much effort has been devoted so far to the development of the sulfate-free synthetic method of lactams, in particular, in industrial chemistry. In recent years, Sumitomo Chemical of Japan has developed a new process for sulfate-free lactam synthesis, involving the oximation of cyclohexanone with NH_3 and H_2O_2 on TS-1 and then the vapor-phase Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam using a high-silica zeolite catalyst,[4] and has operated since 2003. On the other hand, Ishihara and co-workers reported the first successful Beckmann rearrangement of ketoximes to lactams by an organocatalyst, cyanuric chloride (CNC), without formation of any sulfate.[5] This method provides a convenient route to lactams from oximes, but the rearrangement of cyclohexanone oxime to ε-caprolactam, which is the most important Beckmann rearrangement in industrial chemistry, was difficult to carry out in satisfactory yield by CNC catalyst: even by the use of 10 mol % of CNC, the yield of ε-caprolactam was only 30% under refluxing acetonitrile.

Recently, we have developed the one-pot synthesis of lactams from cycloalkanes such as cyclohexane and cyclododecane,[6] which consists of the nitrosation of cycloalkanes with *tert*-butyl nitrite using *N*-hydroxyphthalimide (NHPI) catalyst followed by the isomerization to oximes and then the Beckmann rearrangement by CNC.[7] Furthermore, we disclosed that the Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam by CNC catalyst can be improved by carrying out the reaction in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent. During the course of this study, our attention is focused on the development of a new catalyst other than the Ishihara catalyst, CNC, for the Beckmann rearrangement of oximes to lactams under mild conditions. Fortunately, we have now found that triphosphazene, 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC), is an efficient catalyst for the Beckmann rearrangement of various ketoximes to lactams (eq 1). Interestingly, TAPC promotes efficiently the Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam, which is difficult to achieve satisfactorily by CNC.



(1)

The Beckmann rearrangement of cyclododecanone oxime (**1a**) to laurolactam (**2a**) which is an important raw material of nylon-12 was chosen as a model reaction and was examined using several candidate catalysts which seem to promote the Beckmann rearrangement of oximes (Table 1).

The activity of various catalysts for the rearrangement of **1a** to **2a** was compared with that of cyanuric chloride (CNC) reported by Ishihara et al.[5] The reaction of **1a** by CNC (1 mol %) in MeCN (2 mL) at 70 °C for 2 h afforded **2a** in 22% yield (entry 1), while the same reaction by TAPC (1 mol %) gave **2a** in 64% (entry 2). In order to improve the catalytic efficiency of the reaction, we examined the effect of various solvents in this transformation. From reactions in various solvents, the rearrangement was found to proceed smoothly by allowing the reaction in fluorinated solvents. For instance, the reaction in

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[†] This paper is dedicated to the memory of the late Professor Yoshihiko Ito.

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(2) For recent examples of transition-metal-catalyzed Beckmann rearrangement of oximes, see: (a) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599. (b) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 73. (c) Park, S.; Choi, Y.; Han, H.; Yang, S. H.; Chang, S. *Chem. Commun.* **2003**, 1936.

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(4) (a) Takahashi, T.; Kai, T.; Nakao, E. *Appl. Catal. A* **2004**, *262*, 137. (b) Forni, L.; Fornasari, G.; Giordano, G.; Lucarelli, C.; Katovic, A.; Trifirò, F.; Perri, C.; Nagy, J. B. *Phys. Chem. Chem. Phys.* **2004**, *6*, 1842 and references cited therein.

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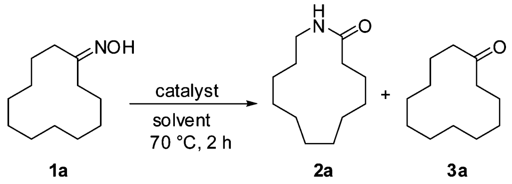
10.1021/jo702277g CCC: $40.75

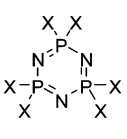
TABLE 1. The Beckmann Rearrangement of 1a to 2a by Various Catalysts[a]



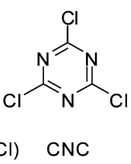
entry	catalyst (mol %)	solvent	conv/%[b]	yield/%[b]	
				2a	3a
1	CNC (1)	MeCN	22	22	trace
2	TAPC (1)	MeCN	68	64	trace
3	CNC (1)	HFIP	>99	>99	trace
4	TAPC (1)	HFIP	>99	>99	0
5[c]	CNC (0.1)	HFIP	20	19	trace
6[c,d]	CNC (0.1)	HFIP	47	47	trace
7[d,e]	TAPC (0.1)	HFIP	86	86	trace
8[d]	TAPC (0.3)	HFIP	>99	99(96)	trace
9	CNC (1)	$CF_3CF_2CH_2OH$	20	11	4
10	TAPC (1)	$CF_3CF_2CH_2OH$	74	71	1
11	CNC (1)	AcOH	4	1	1
12	TAPC(1)	AcOH	8	4	2
13	CNC(1)	^{t}BuOH	19	10	5
14	TAPC(1)	^{t}BuOH	13	6	4
15	TAPF (2)	HFIP	5	3	0
16	TICNA (1)	HFIP	96	94	2
17	TICNA (1)	MeCN	8	6	1
18	CNA (5)	HFIP	no reaction		
19	NBS[f] (1)	HFIP	25	22	trace
20	NCS[g] (1)	HFIP	26	25	trace

[a] **1a** (1.0 mmol) was allowed to react in the presence of catalyst in solvent (2 mL) at 70 °C (bath temperature) for 2 h. [b] By GLC. The number in the parentheses shows isolated yield. [c] **1a** (10 mmol) and HFIP (10 mL) were used. [d] Reaction time was 6 h. [e] **1a** (5 mmol) and HFIP (5 mL) were used. [f] *N*-Bromosuccinimide. [g] *N*-Chlorosuccinimide.

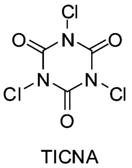
HFIP instead of MeCN gave **2a** in quantitative yields by both CNC and TAPC catalysts (entries 3 and 4). However, when the amount of CNC or TAPC was reduced to 0.1 mol % with respect to **1a**, the yield of **2a** was 47% by CNC and 86% by TAPC (entries 6 and 7). By the use of 0.3 mol % of TAPC, **1a** was completely rearranged to **2a** in 6 h (entry 8). The reaction of **1a** by CNC (1 mol %) in 2,2,3,3,3-pentafluoro-1-propanol resulted in **2a** (11%) and cyclododecanone (**3a**) (4%), while by TAPC, **2a** was obtained in 71% yield and **3a** was less than 1% (entries 9 and 10). The reaction in common solvents such as acetic acid and *tert*-butyl alcohol led to **2a** in poor yields (entries 11−14). The catalytic performance of several catalysts for the rearrangement of **1a** to **2a** was examined in HFIP and MeCN (entries 15−20). 1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-fluoride (TAPF), which is an analogue of TAPC, was found to be inactive, and the starting TAPF was recovered unchanged after the reaction (entry 15). Trichloroisocyanuric acid (TICNA) indicated relatively high catalytic activity in HFIP but low in MeCN (entries 16 and 17). Cyanuric acid (CNA) was inactive, but NBS and NCS indicated low catalytic activities (entries 18 and 20).



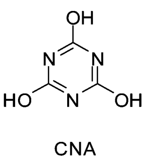
TAPC (X = Cl)
TAPF (X = F)



CNC



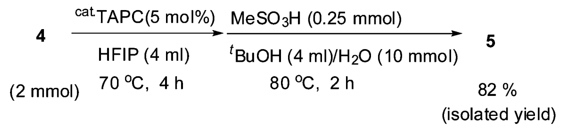
TICNA



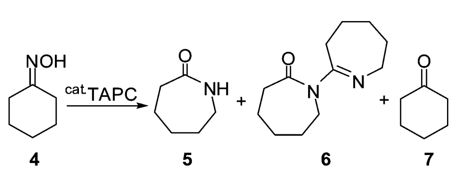
CNA

On the basis of these results, we next examined the Beckmann rearrangement of various ketoximes to lactams using TAPC catalyst (Table 2). 1-Phenylethanone oxime (**1b**) was reacted under several conditions (entries 1−4). It was found that **1b** was perfectly rearranged to *N*-phenylacetamide (**2b**) by TAPC (1 mol %) in HFIP at 70 °C, while the same reaction in MeCN gave **2b** in moderate yield (44%) (entries 1 and 2). However, the reaction by the use of 2 mol % of TAPC under refluxing temperature (ca. 80 °C) of MeCN led to **2b** in quantitative yield (entry 4). 1-(4-Methylphenyl)ethanone oxime (**1c**) and 1-(2-naphthalenyl)ethanone oxime (**1d**) were smoothly rearranged by TAPC even in MeCN to *N*-(4-methylphenyl)acetamide (**2c**) at 70 °C and *N*-(2-naphthyl)acetamide (**2d**) at refluxing temperature, respectively (entries 5−8). 2,4-Dimethyl-3-pentanone oxime (**1e**) was also rearranged to 2-methyl-*N*-(1-methylethyl)-propanamide (**2e**) in quantitative yield (entries 9 and 10). These results indicate that TAPC possesses high catalytic activity for the Beckmann rearrangement of ketoximes to lactams. The most attractive application of TAPC to the Beckmann rearrangement is the reaction of cyclohexanone oxime (**4**) to ϵ-caprolactam (**5**) (Scheme 1, eq 2). Thus, **4** was allowed to react in the presence of TAPC under several reaction conditions (Table 3).

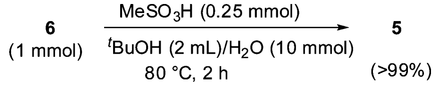
SCHEME 1. One-Pot Synthesis of 5 from 4



Treatment of **4** with 1−2 mol % of TAPC in HFIP led to only small amounts of **5** (7−13%) and its condensate (**6**) (3−7%) as well as cyclohexanone (**7**) (1%) (entries 1 and 2). When the amount of TAPC was increased to 5 mol %, **4** was rearranged to **5** (40%) and **6** (26%) in 4 h (entry 4). The condensate product **6** was found to be easily hydrolyzed to 2 equiv of **5** in quantitative yield (98% isolated yield) (Scheme 1, eq 3). This means that **4** can be rearranged to **5** in an overall yield of 92% by TAPC. In order to compare the catalytic activity of TAPC with that of CNC,[5] the reaction using CNC under the same conditions was used, but the reaction gave only **5** (16%), **6** (7%), and **7** (1%) (entry 5). These results indicate that TAPC is more active than CNC for the Beckmann rearrangement of **4** to **5** under these conditions. In addition, one-pot synthesis of **5** from **4** was performed under the same conditions as those described in Table 3, entry 4, followed by the hydrolysis according to the method as shown in eq 3. As a result, **5** was obtained in 82% isolated yield.



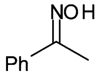
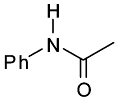
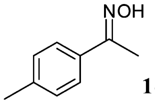
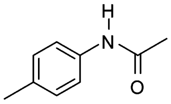
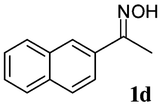
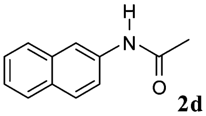
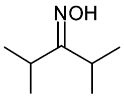
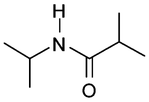
(2)



(3)

Scheme 2 shows a plausible reaction path for the Beckmann rearrangement of **4** by TAPC. It was found that no product was formed by the reaction of TAPC with HFIP at 70 °C for 2 h. Rosini et al. reported that a stoichiometric reaction of oxime **4** with TAPC affords *O*-(pentachlorocyclotriphosphazatriene)-

TABLE 2. The Beckmann Rearrangement of Various Ketoximes by TAPC[a]

entry	oxime (**1**)	solvent	temp./ °C	conv. / %[b]	product	yield/ %[b]
1	 **1b**	HFIP	70	>99	 **2b**	99
2	**1b**	MeCN	70	44	**2b**	44
3	**1b**	MeCN	reflux	87	**2b**	87
4[c]	**1b**	MeCN	reflux	>99	**2b**	>99 (93)
5	 **1c**	HFIP	70	>99	 **2c**	99
6	**1c**	MeCN	70	>99	**2c**	99 (97)
7	 **1d**	HFIP	70	>99	 **2d**	>99
8	**1d**	MeCN	reflux	>99	**2d**	>99 (90)
9	 **1e**	HFIP	70	>99	 **2e**	>99
10	**1e**	MeCN	reflux	>99	**2e**	>99 (96)

[a] Oxime (**1**) (1 mmol) was allowed to react with TAPC (1 mol %) in solvent (2 mL) at 70 °C (bath temperature) or refluxing temp (ca. 80 °C) for 2 h. [b] By GLC. The numbers in the parentheses show isolated yields. [c] TAPC (2 mol %) was used.

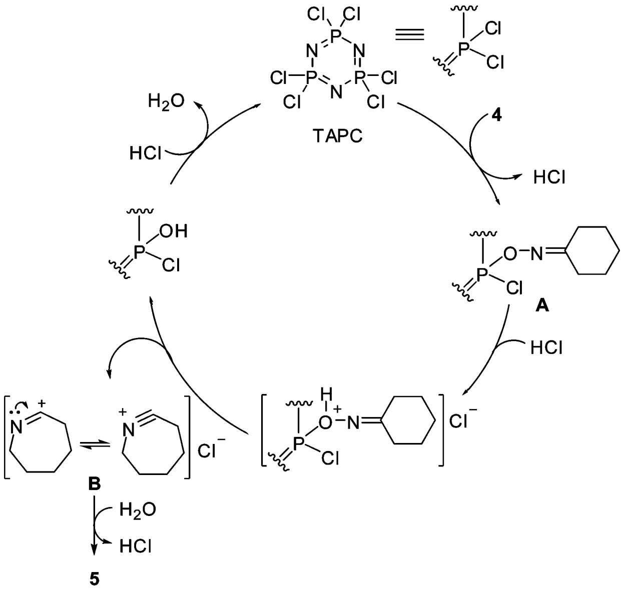
TABLE 3. The Beckmann Rearrangement of Cyclohexanone Oxime (4) by TAPC or CNC under Various Conditions[a]

entry	catalyst (mol %)	solvent	conv/%[b]	yield/%[b] 5	6	7
1	TAPC (1)	HFIP	22	7	3	1
2	TAPC (2)	HFIP	33	13	7	1
3	TAPC (5)	HFIP	88	34	18	2
4[c]	TAPC (5)	HFIP	>99	40	26	trace
5[c]	CNC (5)	HFIP	49	16	7	1
6	TAPC (5)	MeCN	39	11	3	5
7[d]	TAPC (5)	MeCN	67	20	1	13
8[e]	TAPC (5)	HFIP	56	25	4	8

[a] **4** (1.0 mmol) was allowed to react in the presence of catalyst in solvent (2 mL) at 70 °C (bath temperature) for 2 h. [b] By GLC. [c] Reaction time was 4 h. [d] Refluxing temp (ca. 80 °C). [e] H_2O (0.2 mL) was added.

cyclohexanone (**A**) in 63% yield.[8] Therefore, we thought that the compound **A** is a key intermediate to lactam **5**. Thus, **4** was reacted in the presence of a catalytic amount (0.1 equiv) of **A** prepared independently by modified Rosini's procedure under several conditions. It is interesting to note that the reaction of **4** (1 mmol) in the presence of **A** (0.1 equiv) in HFIP (2 mL) at 70 °C for 2 h afforded **5** (47%) and **6** (15%), while the same reaction in MeCN gave very low yield of **5** (5%).

SCHEME 2. A Plausible Reaction Path for the Beckmann Rearrangement by TAPC



The rearrangement from **A** to lactam **5** is considered to proceed through the formation of nitrilium ion **B** followed by nucleophilic attack of H_2O to produce **5**. The dimeric condensate **6** seems to be formed through the reaction of the resulting **5**

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(8) (a) Rosini, G.; Baccolini, G.; Cacchi, S. *J. Org. Chem.* **1973**, *38*, 1060. (b) Trunbull, J. H. *Chem. Ind.* **1956**, 350.

with **B**. In fact, the addition of water in HFIP resulted in a considerable decrease of the condensate **6** (Table 3, entry 8). We confirmed that **6** is not produced by the reaction of oxime **4** with lactam **5** even in the presence of HFIP (eq 4).

$$\mathbf{4} + \mathbf{5} \xrightarrow[\text{HFIP, reflux, 2 h}]{} \underset{\text{not detected}}{\mathbf{6}} \qquad (4)$$

In conclusion, we have found that TAPC, easily available from commercial source, serves as an efficient catalyst for the Beckmann rearrangement of ketoximes to lactams. The rearrangement of cyclohexanone oxime (**4**) to ϵ-caprolactam (**5**) which was not fully succeeded by CNC was achieved by TAPC. The present method provides an environmentally friendly route to nylon-6 without formation of any salt.

Experimental Section

All starting materials were commercially available and used without any purification. GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5 or BP-25). ^{1}H NMR and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (Me_4Si) in $CDCl_3$.

Typical Procedure for the Reaction of 1a (Table 1, entry 8): A mixture of TAPC (0.01 mmol, 3.5 mg) and HFIP (2 mL) was placed in a 20 mL round-bottomed flask, and **1a** (1 mmol, 197 mg) was added to the flask. Then the mixture was stirred at 70 °C for 2 h. After removal of the solvent under reduced pressure, **2a** (190 mg) was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate = 1/1) in 96% yield.

Synthesis of 5 from 6 (eq 3): A mixture of **6** (1 mmol, 208 mg), methanesulfonic acid (0.25 mmol, 24 mg), H_2O (10 mmol, 180 mg), and ^{t}BuOH (2 mL) was placed in a 20 mL round-bottomed flask. Then the mixture was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure, extracted with diethyl ether, and the compound **5** (221 mg, 98%) was obtained by evaporation of ether.

One-Pot Synthesis of 5 from 4 (Scheme 1): A mixture of TAPC (0.1 mmol, 35 mg) and HFIP (4 mL) was placed in a 30 mL round-bottomed flask, and **4** (2 mmol, 226 mg) was added to the flask. Then the mixture was stirred at 70 °C for 4 h. After the solvent was removed under vacuum, methanesulfonic acid (0.25 mmol, 24 mg), H_2O (10 mmol, 180 mg), and ^{t}BuOH (4 mL) were added to this concentrate, then the reaction mixture was stirred at 80 °C for 2 h. Removal of the solvent under reduced pressure and purification by column chromatography on silica gel (ethyl acetate/MeOH = 10/1) gave a fraction of **5** containing HFIP. H_2O (ca. 2 mL) was added to this and evaporated the solvent, giving **5** in 82% yield (186 mg).

The products **2a**,[5] **2b**,[5] **2c**,[9] **2d**,[5] **2e**,[5] **5**,[10] and **6**[10] are known compounds and have been reported previously.

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Supporting Information Available: Copies of ^{1}H and ^{13}C spectra for **2a**−**e**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Mazurkiewicz, R. *Acta Chim. Hung.* **1990**, *127*, 439; *Chem. Abstr.* **1991**, *114*, 206 693.