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Full Papers

An Efficient Catalytic Method for the Beckmann Rearrangement of Ketoximes to Lactams by Cyanuric Chloride and Phosphazene Catalysts

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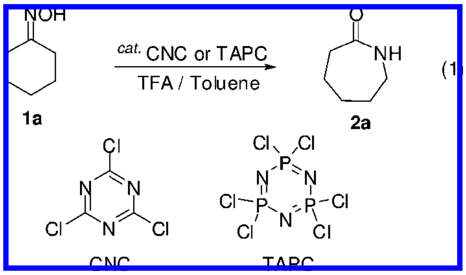
Abstract:

The Beckmann rearrangement of ketoximes to lactams was successfully achieved by a very small amount of cyanuric chloride and phosphazene by carrying out the reaction in a mixed solvent of trifluoroacetic acid and toluene under mild conditions. For instance, the Beckmann rearrangement of cyclohexanone oxime was completely performed under the influence of 0.5 mol % of cyanuric chloride (CNC) or phosphazene (1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride: TAPC) in a 3:2 mixed solvent of trifluoroacetic acid and toluene at 70 °C for 4 h to give ϵ-caprolactam, which is an important monomer of 6-Nylon, in almost quantitative yield. The same strategy could be applied to laurolactam synthesis from cyclododecanone oxime.

Introduction

The Beckmann rearrangement of cyclohexanone oxime (**1a**) with sulfuric acid to ϵ-caprolactam sulfate is a very important commercial process for producing the polymer material 6-nylon.[1] In 2005, about 4 million tons of ϵ-caprolactam sulfate was manufactured by this method. The drawback of this transformation is that the resulting lactam sulfate must be treated with a base such as ammonia to isolate ϵ-caprolactam (**2a**). As a result, a vast amount of undesired ammonium sulfate is simultaneously produced with lactam. In 2003, Sumitomo Chemical of Japan industrialized a sulfate-free process for **2a** which includes the conversion of cyclohexanone to **1a** upon treatment with H_2O_2 and NH_3 on TS-1 followed by the vapor-phase Beckmann rearrangement on high-silica zeolite catalyst.[2] On the other hand, Giacomelli et al. have recently reported that cyanuric chloride (CNC) induces stoichiometrically the Beckmann rearrangement of ketoximes to lactams.[3] Thereafter, Ishihara et al. have applied a catalytic reaction by using CNC with Lewis acid, $ZnCl_2$, and acetonitrile as a key solvent.[4] However, they reported that the yield of **2a** from **1a** was up to 30% even by the use of 10 mol % of CNC under refluxing acetonitrile. Quite recently, we have carried out the one-pot synthesis of lactam **2a** via oximation of cyclohexane using *tert*-butyl nitrite catalyzed by NHPI.[5,6] In addition, we showed that **1a** can be rearranged by the use of 10 mol % of CNC in 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) to **2a** (43%) and its condensate (**3a**) (22%) corresponding to 44% of **2a**.[6] Triphosphazene, like 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC), available from commercial sources, was found to promote efficiently the Beckmann rearrangement of ketoximes to lactams.[7] For example, the reaction of **1a** by TAPC (5 mol %) in HFP gave **2a** (40%) and its condensate (**3a**) (26%). However, one serious problem of our method is that HFP, which is much more expensive than acetonitrile, must be used as a solvent. Thus, a more efficient method that does not use expensive HFP is necessary to effect the Beckmann rearrangement of **1a** to **2a** in a large scale. In this contribution, we report a very efficient method for the Beckmann rearrangement of **1a** to **2a** by using CNC and TAPC as catalysts. A key of this method is the use of a mixed solvent of trifluoroacetic acid (TFA) and toluene (eq 1).



Results and Discussion

We previously reported that the rearrangement of **1a** by CNC and TAPC catalysts in HFP gives **2a** in satisfactory yields (Table 1, entries 1 and 2).[6,7] These results indicate that a fluorinated solvent such as HFP is suitable for the rearrangement

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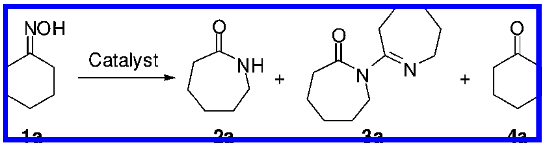
Table 1. **Beckmann rearrangement of cyclohexanone oxime to ϵ-caprolactam by CNC and TAPC catalyst under various conditions**[a]



entry	catalyst (mol %)	solvent (mL)	time (h)	conv (%)	yield (%)[b] 2a	3a	4a
1[c]	CNC (10)	HFP (2)	2	>99	43	22	trace
2[d]	TAPC (5)	HFP (2)	2	>99	40	26	trace
3	CNC (0.5)	TFA (2)	4	93	89	2	n.d.
4	–	TFA (2)	4	20	18	n.d.	trace
5	TAPC (0.5)	TFA (2)	4	86	84	1	trace
6	CNC (0.5)	TFA (1)	4	70	68	1	trace
7	CNC (0.5)	TFA (1.2)/toluene (0.8)	4	>99	99(95)	trace	trace
8[e]	CNC (0.5)	TFA (30)/toluene (20)	4	>99	93(89)	trace	trace
9	CNC (0.5)	TFA (1.0)/toluene (1.0)	4	81	80	trace	trace
10	CNC (0.5)	TFA (0.8)/toluene (1.2)	4	72	68	trace	trace
11	TAPC (0.5)	TFA (1.2)toluene (0.8)	4	60	59	trace	trace
12[f]	CNC (0.5)	TFA (1.2)/toluene (0.8)	4	37	30	trace	trace
13[g]	CNC (0.5)	TFA (1.2)/toluene (0.8)	1	98	96	trace	trace
14	CNC (0.25)	TFA (1.2)/toluene (0.8)	4	49	48	trace	trace
15[g]	CNC (0.25)	TFA (1.2)/toluene (0.8)	4	>99	97	1	trace

[a] Cyclohexanone oxime (**1a**) (2 mmol) was allowed to react in the presence of CNC or TAPC at 70 °C for 1–4 h. [b] Based on GC. Numbers in parenthesis show isolated yield. [c] Data from reference 6. [d] Data from reference 7. [e] **1a** (50 mmol) was used as substrate. [f] Reaction was performed at 50 °C. [g] Reaction was performed at 100 °C.

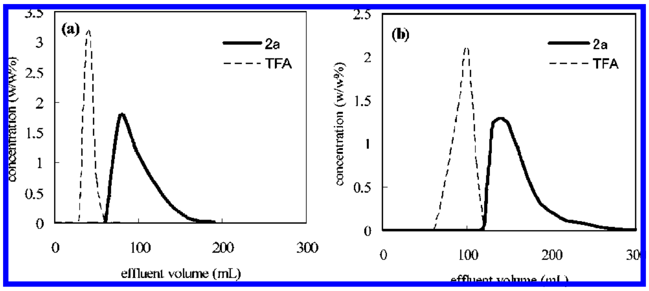


Figure 1. **Isolation of 2a from 2a-TFA salt by column chromatography on silica gel ((a) SiO_2 20 g, 2a-TFA 1.1 g, eluent: AcOEt:MeOH (10:1). (b) SiO_2 50 g, 2a-TFA salt 1.1 g, eluent: H_2O).**

of **1a** to **2a**. However, it is difficult to carry out the rearrangement in HFP in industrial scale, since the HFP is too expensive to use as a solvent in large-scale synthesis. Thus, we need to use other solvents which promote efficiently the rearrangement of **1a**. As a fluorous solvent such as HFP serves as a good solvent for this purpose, we tried the reaction of **1a** in several fluorinated solvents. Among the fluorinated solvents examined, we found that trifluoroacetic acid (TFA),[8] which is far cheaper than HFP, promotes the Beckmann rearrangement of **1a** to **2a** by CNC. The rearrangement of **1a** to **2a** in TFA by CNC under various conditions is summarized in Table 1.

Surprisingly, **2a** was obtained in high yield (89%) from **1a** even with the use of 0.5 mol % of CNC in TFA (entry 3). However, the reaction without CNC in TFA gave **2a** in low yield (18%) (entry 4). This indicates that the rearrangement is not induced by the use only of TFA as a solvent. In the reaction using TAPC catalyst in TFA, **1a** rearranged to **2a** in good yield (84%) (entry 5). From these results, TFA was found to be a good solvent to accelerate the rearrangement of **1a** to **2a** by CNC and TAPC. For the purpose of the reduction of TFA, when the amount of TFA was reduced to one-half, the yield of **2a** was found to decrease to 68%. Thus, the reaction was examined in a mixed solvent consisting of TFA and several other solvents. From the scrutiny of various mixed solvents, the reaction in a 3:2 mixture of TFA and toluene was found to progress the present rearrangement smoothly, giving **2a** in almost quantitative yield (entry 7). We performed the reaction on 50 mmol scale of **1a** and obtained **2a** in 89% isolated yield (entry 8). The most important feature of the reaction in a mixed solvent of TFA and toluene is that condensate **3a** which is formed in the reaction in HFP was negligibly small. Thus, several 3:2 mixed solvents consisting of TFA and one other solvent were examined, and the yield of **2a** was found to decrease in the following order: a 3:2 mixture of TFA and toluene (>99%), benzene (94%), MeCN (85%), acetone (82%), (n-Bu)$_2$O (66%), n-hexane (45%), AcOH (41%), and DMF (24%). However, when TAPC was employed as a catalyst, no positive effect by a mixed solvent was observed (entry 11). The reaction temperature considerably affected the rearrangement of **1a**. The reaction at 50 °C resulted in the decrease of the yield of **2a** (30%), whereas **2a** was obtained in high yield (96%) at 100 °C for 1 h (entries 12 and 13). When the amount of CNC was decreased from 0.5 mol % to 0.25 mol %, the yield of **2a** was considerably decreased, but the reaction temperature was raised to 100 °C to lead to **2a** in high yield (97%) and **3a** (1%) (entries 14 and 15).

Cyclododecanone oxime (**1b**) was also rearranged to laurolactam (**2b**), which is an important monomer of Nylon-12, in good yield in the presence of CNC (0.5 mol %) in a 3:2 mixture of TFA and toluene at 70 °C for 4 h (eq 2).

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(8) Price of TFA is approximately one-sixth that of HFP.

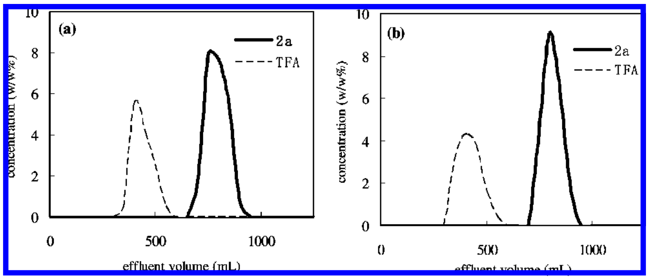


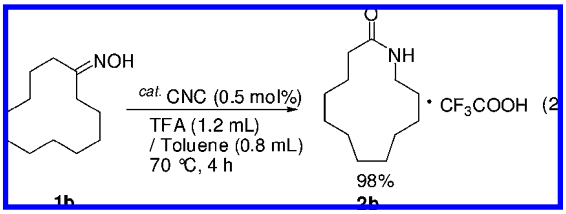
Figure 2. **Isolation of 2a from 2a-TFA salt by column chromatography on silica gel in preparative scale ((a) SiO_2 200 g, 2a-TFA 20 g, eluent: AcOEt:MeOH (10:1)/MeOH), effluent rate 10 mL/min). (b) Isolation of 2a by using recycled silica column under the conditions of Figure 2a.**

Table 2. **Isolation of 2a from 2a-TFA salt by using recycled silica column (SiO_2 20 g, 2a-TFA 1.1 g, eluent: AcOEt:MeOH (10:1))**

no. of uses	yield of **2a** (%)[a]	purity (%)[b]
1	94	>99
2	96	>99
3	96	>99
4	93	>99
5	92	>99

[a] Isolated yields. [b] Determined by GC and HPLC.

It is well-known that **2a** reacts with TFA to form a weak salt (**2a**-TFA) which behaves as an ionic liquid.[9] The **2a**-TFA salt was found to be easily separated into **2a** and TFA on silica gel, eluting with a mixed solvent or water. Figure 1 shows the result of the elution of the **2a**-TFA salt on silica gel with AcOEt:MeOH (10:1) (Figure 1a) or water (Figure 1b).

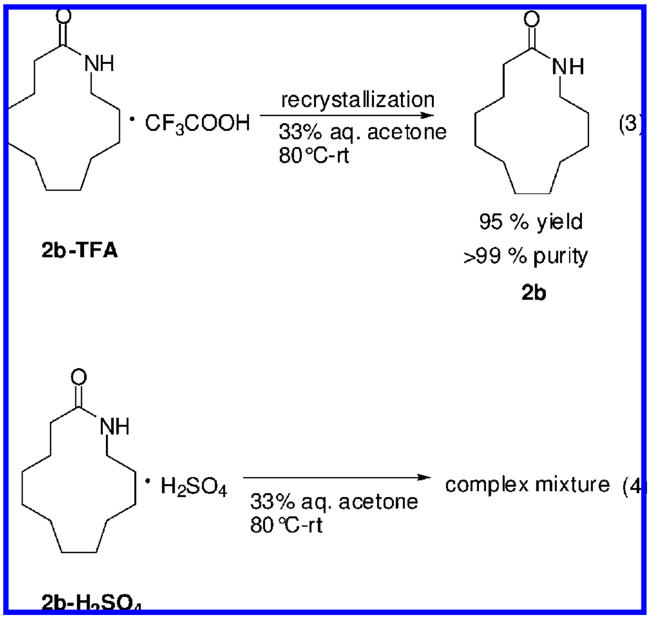


The first 50 mL of a mixed solvent of AcOEt and MeOH (10:1) contained only TFA, and then **2a** was eluted in a pure form in 94% yield (Figure 1a). It was found that water could be used as an eluent instead of the mixed solvent, although a slight excess of the eluent is needed to separate **2a** (Figure 1b). The silica gel column can be repeatedly used after separation of **2a**-TFA salt. After five uses, the result was almost the same as that using the fresh column (Table 2).

Thus, **2a** was obtained from the **2a**-TFA salt without treatment with a base.

In order to examine this method in preparative scale, we tried the isolation of **2a** from **2a**-TFA salt in 20-g scale (Figure 2a,b). To reduce the eluent volume, methanol was used as an eluent after elution of TFA with 300 mL of a 20:1 mixed solvent of ethyl acetate and methanol. As shown in Figure 2a, pure **2a** could be obtained by this method. After completion of the isolation of **2a**, we repeated the isolation of an additional 20 g of **2a-TFA** salt using the same column by this method. As shown in Figure 2b, **2a** was obtained in pure form, although the elution curve of TFA slightly broadened. Thus, the present method can be applicable to the large-scale synthesis and isolation of **2a**.

On the other hand, laurolactam **2b** was found to be easily isolated from **2b**-TFA. When the **2b**-TFA salt was dissolved in a 33% aqueous acetone at 80 °C, and the solution was allowed to stand at room temperature, laurolactam **2b** was gradually crystallized and isolated by filtration in 95% yield (>99% purity) (eq 3). However, laurolactam sulfate, prepared independently from **1b** and sulfuric acid, was dissolved in the aqueous acetone to result in a complex mixture without liberation of **2b**, owing to occurrence of the reaction of **2b** with the aqueous acetone (eq 4).



Conclusion

We reported the efficient method of Beckmann rearrangement of ketoximes to lactams. The reaction was achieved under the influence of CNC and TAPC catalyst by using a mixed solvent of trifluoroacetic acid and toluene.

Experimental Section

All starting materials were commercially available and used without any purification. Cyclododecanone oxime (**1b**) was prepared from cyclododecanone and hydroxylamine hydrochloride. GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^1H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra (EI, GC/MS) were measured with an Agilent 5973 Network Mass Selective Detector. HPLC was conducted using a Shimadzu Prominence with SPD-M20A diode array detector (column, ODS-H80). The yields of products were estimated from the peak areas based on the internal standard technique.

Compounds **2a** and **2b** are known compounds and have been reported previously.[7]

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Typical Procedure for the Reaction of 1a (Table 1, entry 7). A mixture of CNC (0.01 mmol, 1.8 mg) in TFA (1.2 mL) and toluene (0.8 mL) was placed in a 20 mL round-bottomed flask, and **1a** (2 mmol, 226 mg) was added to the flask. Then the mixture was stirred at 70 °C for 4 h. After removal of the solvent under reduced pressure, **2a** (214 mg) was isolated by column chromatography on silica gel (ethyl acetate:methanol = 20:1) in 95% yield.

Isolation of 2a from 2a-TFA Salt by Column Chromatography on Silica Gel (Figure 1 a). To a silica gel (20 g) column filled with eluents (AcOEt:MeOH = 10:1) was charged **2a**-TFA salt (1.10 g, 4.85 mmol). Concentration of **2a** and TFA of the effluent was monitored by GC and HPLC in every 10-mL effluent volume. The fraction containing **2a** was collected. After removal of the solvent under reduced pressure, **2a** (515 mg) was isolated as a white solid in 94% yield as a pure form (purity >99%).

Isolation of 2b from 2b-TFA Salt by Recrystallization from Aqueous Acetone (eq 3). **2b**-TFA (1.56 g, 5.0 mmol) was dissolved in 33% aqueous acetone (30 mL), and the mixture was heated to 80 °C. The resulting clear solution was allowed to stand at room temperature, and **2b** was gradually crystallized. The solid was collected by filtration and washed with H_2O (10 mL). After removal of the solvent under reduced pressure, **2b** (936 mg) was isolated as a white solid in 95% yield (>99% purity).

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