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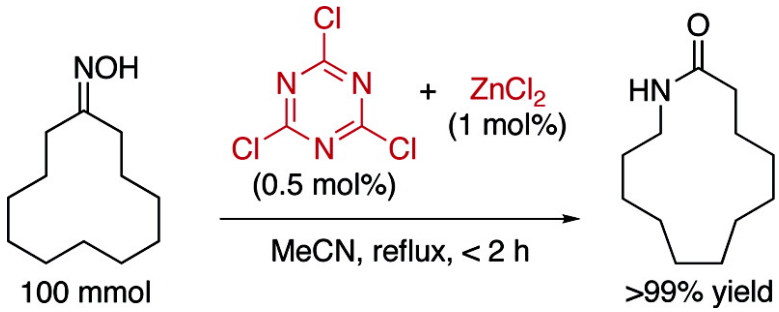
*J. Am. Chem. Soc.*, **2005**, 127 (32), 11240-11241• DOI: 10.1021/ja053441x • Publication Date (Web): 23 July 2005



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# Cyanuric Chloride as a Mild and Active Beckmann Rearrangement Catalyst

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The Beckmann rearrangement is commonly used in organic chemistry to transform ketoximes into amides.[1,2] The reaction generally requires high reaction temperatures and strongly acidic and dehydrating media.[1,2] Thus, this reaction leads to large amounts of byproducts and cannot be used with sensitive substrates. We report here that 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, **9a**)[3,4] is a highly effective catalyst for the Beckmann rearrangement under reflux in acetonitrile or nitromethane. To the best our knowledge, this is the first example of an organocatalytic Beckmann rearrangement.

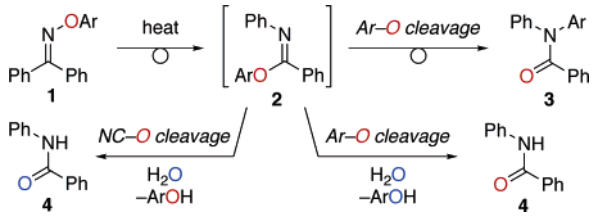
The Beckmann rearrangement of *O*-picrylbenzophenone oxime (**1**) is known to give *N*-picrylbenzanilide (**3**) and benzanilide (**4**) via a common intermediate, picryl *N*-phenylbenzimidate (**2**), under heating conditions in anhydrous and aqueous solvents, respectively (Scheme 1).[5] Product **3** is formed through a 1,3-shift of the picryl cation of **2** (Ar−O cleavage), while **4** is formed through hydrolysis of **2** (Ar−O or NC−O cleavage).

If the above Beckmann rearrangement is performed in the presence of excess benzophenone oxime in place of water in an anhydrous solvent, **1** may be reproduced with **4** through the nucleophilic attack of benzophenone oxime to **2** (Ar−O cleavage). On the basis of this assumption, a new strategy for organocatalyzed Beckmann rearrangement was proposed, as shown in Scheme 2. We expected that chloroarenes bearing several strong electron-withdrawing groups, such as picryl chloride (**8a**), might catalytically promote Beckmann rearrangement via the corresponding *O*-aryl ketoxime **5**, *O*-aryl imidate intermediate **6**, and Meisenheimer complex **7**.[6]

First, several chloroarenes (5 mol %) were examined as catalysts for the Beckmann rearrangement of acetophenone oxime in acetonitrile under reflux conditions for 2 h (Table 1). As expected, the use of **8a** gave acetanilide in 45% yield. **8a** was the most active catalyst among chlorobenzenes bearing electron-withdrawing groups (e.g., entries 2 and 3). By further screening of chloroarenes, we found that cyanuric chloride **9a** was much more effective than **8a** (entry 4). In contrast, 4,6-dimethoxy-2-chloro-1,3,5-triazine (**9b**) was inert (entry 5). This result can be easily understood by the electron-donating effect of the two methoxy groups. Although 4,6-dichloro-5-nitropyrimidine (**10**) and 2-chloro-3,5-dinitropyridine (**11**) were also as effective as **8a** (entries 7 and 8), **9a** exhibited outstanding catalytic activity. The solvent effect was also investigated (entries 8−11). Polar and nucleophilic solvents, such as acetonitrile and nitromethane, were suitable for this catalysis.

Next, several Lewis acids and Brønsted acids were examined as cocatalysts for **9a** to further increase the catalytic activity of **9a**. Representative results are shown in Table 2. The Beckmann rearrangement of acetophenone oxime proceeded quantitatively in the presence of **9a** (2 mol %) and mild Lewis acids (2 mol %), such as $ZnCl_2$, $FeCl_3$, $CoCl_2$, and $BiCl_3$, within 2 h (entries 2−5). However, this rearrangement was quite slow in the presence of 2 mol % of **9a** without any cocatalysts (entry 1). Furthermore, these weak Lewis acids and Brønsted acids were inert or less active for this rearrangement in the absence of **9a** (entries 2−5 and 11). Brønsted acids, such as TsOH and HCl, were also effective, but less effective than the above Lewis acids (entries 10 and 11). Therefore, less-expensive $ZnCl_2$ was the best choice as a cocatalyst for **9a**. The addition of more than 2 equiv of $ZnCl_2$ per **9a** further activated the rearrangement (entries 12−14). Thus, the rearrange-

***Scheme 1.*** Beckmann Rearrangement of **1** (Ar = 2,4,6-$(NO_2)_3C_6H_2$)




***Scheme 2.*** A New Strategy for Organocatalyzed Beckmann Rearrangement

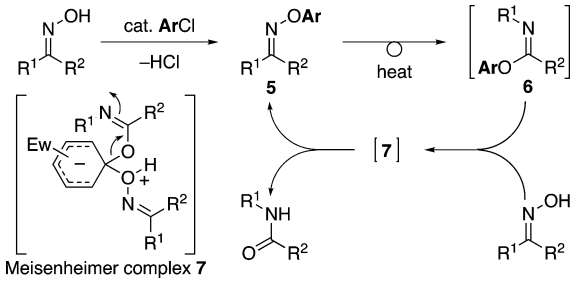
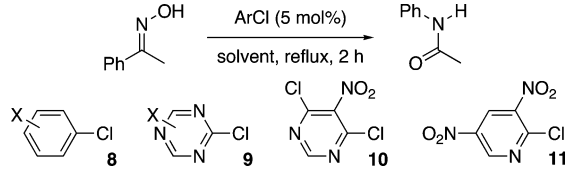



***Table 1.*** ArCl-Catalyzed Beckmann Rearrangement of Acetophenone Oxime[a]




| entry | ArCl | solvent (bp) | yield (%) |
|---|---|---|---|
| 1 | **8a** [X = 2,4,6-$(NO_2)_3$] | MeCN (82 °C) | 43 |
| 2 | **8b** [X = 2,6-$(NO_2)_2$-4-CN] | MeCN (82 °C) | 15 |
| 3 | **8c** [X = 2,6-$(NO_2)_2$-4-$CF_3$] | MeCN (82 °C) | 0 |
| 4 | **9a** [X = 4,6-$Cl_2$] | MeCN (82 °C) | 100 |
| 5 | **9b** [X = 4,6-$(OMe)_2$]] | MeCN (82 °C) | 0 |
| 6 | **10** | MeCN (82 °C) | 58 |
| 7 | **11** | MeCN (82 °C) | 44 |
| 8 | **9a** | $MeNO_2$ (101 °C) | 100 |
| 9 | **9a** | 1,4-dioxane (101 °C) | 5 |
| 10 | **9a** | acetone (56 °C) | 16 |
| 11 | **9a** | toluene (110 °C) | 8 |

[a] The rearrangement of acetophenone oxime (2 mmol) was carried out in a solvent (4 mL) in the presence of 5 mol % of ArCl.

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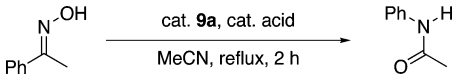
10.1021/ja053441x CCC: $30.25 

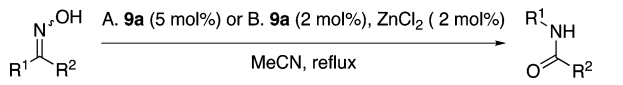
***Table 2.*** Effect of Acids as Cocatalysts on the **9a**-Catalyzed Beckmann Rearrangement of Acetophenone Oxime[a]




| entry | 9a (mol %) | acid (mol %) | yield (%) | entry | 9a (mol %) | acid (mol %) | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 2 | | 31 | 9 | 2 | $CuCl_2$ (2) | 10 |
| 2 | 2 | $ZnCl_2$ (2) | 100 [0][b] | 10 | 2 | TsOH (2) | 69 |
| 3 | 2 | $FeCl_3$ (2) | 100 [0][b] | 11 | 2 | HCl (2)[c] | 50 [3][b] |
| 4 | 2 | $CoCl_2$ (2) | 100 [0][b] | 12 | 1 | $ZnCl_2$ (1) | 67 |
| 5 | 2 | $BiCl_3$ (2) | 100 [13][b] | 13 | 1 | $ZnCl_2$ (2) | 97 |
| 6 | 2 | $GeCl_4$ (2) | 83 | 14 | 1 | $ZnCl_2$ (3) | 98 |
| 7 | 2 | $FeCl_2$ (2) | 49 | 15 | 1 | $FeCl_3$ (1) | 59 |
| 8 | 2 | $MgCl_2$ (2) | 32 | 16 | 1 | $CoCl_2$ (1) | 70 |

[a] The rearrangement of acetophenone oxime (5 mmol) was carried out in MeCN (10 mL). [b] The results in the absence of **9a** are indicated in brackets. [c] 4 M HCl solution in 1,4-dioxane was used.

***Table 3.*** Generality and Scope of the Beckmann Rearrangement Catalyzed by **9a** or **9a**−$ZnCl_2$[a]




| entry | $R^1$ | $R^2$ | time (h), yield (%)[b] condition A | condition B |
|---|---|---|---|---|
| 1 | Ph | Me | 2, 97 | 2, 99 |
| 2 | *o*-(MeO)$C_6H_4$ | Me | 1, 98 | 1, 99 |
| 3 | *m*-(MeO)$C_6H_4$ | Me | 6, 93 | 2, 96 |
| 4 | *p*-(MeO)$C_6H_4$ | Me | 2, 94 | 1, 99 |
| 5 | *p*-$FC_6H_4$ | Me | 4, 92 | 2, 97 |
| 6 | 3,4-($CH_2O_2$)$C_6H_3$[c] | Me | | 2, 98 |
| 7 | 2-naphthyl | Me | 4, 96 | 2, 98 |
| 8 | Ph | *i*-Pr | | 1, 97[d] |
| 9 | Ph | $(CH_2)_2CO_2Me$ | | 2, 95 |
| 10 | $C_8H_{17}$ | Me | 4, 94 | 2, 96 |
| 11 | *i*-Pr | *i*-Pr | | 1, 97 |
| 12 | $(CH_2)_{11}$ | | 1, 98 | 1, 97 **[2, >99]**[e] |
| 13 | $(CH_2)_{10}$ | | | 1, 95 |
| 14 | $(CH_2)_9$ | | | 1, 96 |
| 15 | $(CH_2)_7$ | | | 6, 27 |
| 16 | $(CH_2)_5$ | | 2, 30[f] | |

[a] The rearrangement of ketoxime (2 mmol) was carried out in MeCN (4 mL). [b] Isolated yield. [c] 3,4-Methylenedioxyphenyl. [d] *N*-Phenylisobutyramide and *N*-isopropylbenzamide were obtained in 49 and 48%, respectively. [e] The rearrangement of ketoxime (100 mmol) in MeCN (50 mL) was carried out using **9a** (0.5 mol %) and $ZnCl_2$ (1 mol %). [f] 10 mol % of **9a** was used.

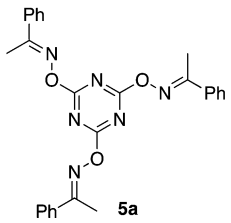
ment gave acetanilide in 97% yield within 2 h in the presence of **9a** (1 mol %) and $ZnCl_2$ (2 mol %) (entry 13).

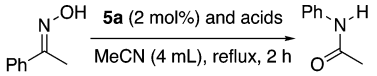
To explore the generality and scope of the Beckmann rearrangement catalyzed by **9a** or **9a**−$ZnCl_2$, representative ketoximes as substrates were examined under reflux conditions in acetonitrile (Table 3). Not only aromatic but also aliphatic ketoximes were smoothly rearranged under both conditions A and B. In particular, the rearrangement of most substrates was complete within 2 h under condition B. Acetal and ester groups in ketoximes were tolerable under these conditions (entries 6 and 9). Large cycloalkanone oximes were also very reactive and were transformed to the corresponding lactams, which were useful as starting materials for nylons.[7] Unfortunately, the reaction of six- to eight-membered cycloalkanone oximes gave the desired lactams in poor yield (entries 15 and 16).[8]

The applicability of the present protocol to a large-scale process was examined. The Beckmann rearrangement of cyclododecanone oxime (100 mmol) was complete within 2 h in the presence of **9a** (0.5 mol %) and $ZnCl_2$ (1 mol %) (entry 12, Table 3).

To ascertain that the present organocatalytic Beckmann rearrangement occurred via *O*-aryl ketoxime **5**, the rearrangement of acetophenone oxime was attempted in the presence of 2 mol % of **5a** in place of **9a** (Table 4). **5a** was almost inert in the absence of

***Table 4.*** Beckmann Rearrangement of Acetophenone Oxime Catalyzed by **5a** and Acids




| acids (mol%) | yield (%) of acetanilide |
|---|---|
| – | 2 |
| HCl (6) | 68 |
| $ZnCl_2$ (2) | 12 |
| HCl (6) + $ZnCl_2$ (2) | 96 |

acids. On the other hand, **5a** acted as an organocatalyst in the presence of HCl (6 mol %) or $ZnCl_2$ (2 mol %). Finally, this rearrangement was extremely accelerated by the combined use of **5a** (2 mol %), HCl (6 mol %), and $ZnCl_2$ (2 mol %), as well as the use of **9a** (2 mol %) and $ZnCl_2$ (2 mol %) (see entry 2, Table 2). These experimental results suggested that HCl, which is generated in situ from ketoximes and **9a**,[9] plays a very important role in this organocatalysis of **9a**: HCl and $ZnCl_2$ probably promote the rearrangement of **5a** by their chelation with nitrogen atoms of **5a**.[4b,10]

In summary, we have realized the first general organocatalytic Beckmann rearrangement of ketoximes into amides. Commercially available **9a** was the most effective organocatalyst, and acids such as HCl and $ZnCl_2$ were effective as cocatalysts for **9a**. Further studies are in progress to achieve the Beckmann rearrangement of six- to eight-membered cycloalkanone oximes.

**Acknowledgment.** Financial support for this project was provided by SORST, JST, the 21st Century COE Program of MEXT, and the Iwatani Naoji Foundation. We thank Mr. Toshikatsu Maki† for helpful experiments.

**Supporting Information Available:** Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The catalyses in entries 12 and 13 were inhibited by side-reaction of **6a** with nucleophilic small-ring lactams to give *N*-aryllactams instead of **5a**.

(9) The generation of **5a**·$(HCl)_3$ salt from ketoximes and **9a** proceeded very rapidly even at room temperature.

(10) Cyanuric fluoride was a much less effective catalyst than **9a** because the acidity ($pK_a = 3.2$) of HF was weaker than that ($pK_a = -7.0$) of HCl.

JA053441X