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A mild and efficient catalyst for the Beckmann rearrangement, BOP-Cl

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Abstract—BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) was found to be very active as the first organophosphorus catalyst (1–5 mol % loading) for the Beckmann rearrangement of various ketoximes to the corresponding amides in anhydrous acetonitrile at refluxing temperature.

The Beckmann rearrangement (BKR) is an important reaction for transformation of ketoxime into amide, which has been successfully utilized to produce ω-caprolactam and laurolactam in industry.[1–3] However, it often suffers from the co-production of large amount of undesired ammonium sulfate and suffers from serious corrosion problems in conventional liquid-phase industrial process. To solve the problems, catalytic version of the Beckmann rearrangement have been mainly focused on vapor-phase processes[3g–m] by developing solid catalyst such as metal oxides, clays, and zeolites, which often suffer from high reaction temperature and decay of activity of catalyst. In liquid-phase, Deng's group[4] have developed a series of catalysts such as PCl_5, chlorosulfonic acid, and ionic supported sulfonyl chloride. Other catalysts such as sulfamic acid,[5] lanthanide triflate,[6] and $RuCl_3$[7] have also been reported. However, few reports focus on small organomolecule[8] catalyzed BKR. Recently, Yamamoto and Ishihara's group[9] reported that cyanuric chloride is a mild and active catalyst for the BKR. Herein, we would like to report our preliminary results on the first highly effective organophospho BOP-Cl (**6**) catalyzed Beckmann rearrangement of ketoxime to amide.

Although PCl_5[4a] and P_2O_5[10] have been reported to be good catalysts (normally 10–20 mol % loading is required) for the Beckmann rearrangement of cyclohexanone oxime in ionic liquid or DMF, further studies on new catalyst still need to be done since they are all corrosive and not easy to handle. Furthermore the mechanism of these two catalysts in the BKR is still not clear, although PCl_5 and P_2O_5 may act as dehydration reagents according to the classical BKR mechanism. BOP-Cl (**6**)[11] is a well known excellent dehydration reagent in peptide synthesis, which is more stable, less corrosive and easy to handle. Initially we would like to know if BOP-Cl could also act as an effective dehydration reagent in the Beckmann rearrangement. To our delight, it did catalyze the BKR of acetophone oxime to *N*-acetyl aniline very well (10 mol % of **6**, 99% yield). Interestingly, according to the classical BKR mechanism and dehydration pathway of BOP-Cl, a maximum 10% of conversion should be obtained by using 10 mol % of BOP-Cl. The mechanism therefore needed to be addressed.

Recently, Yamamoto and Ishihara proposed a novel BKR mechanism for the cyanuric chloride catalyzed BKR.[9] On the basis of this mechanism, we propose here a similar mechanism (Scheme 1) for BOP-Cl catalytic Beckmann rearrangement, which accounts for the excellent catalytic behavior of BOP-Cl. If this is true, decrease of the BOP-Cl loading to 5 mol % would also catalyze this rearrangement efficiently. As expected, *N*-acetyl aniline was obtained in 94% of yield within 1 h. Then a series of phosphinic chloride catalysts were tested, however only moderate catalytic activity was found. These were probably less active than BOP-Cl due to an undetermined electronic effect on the phosphorous center caused by different substituents on

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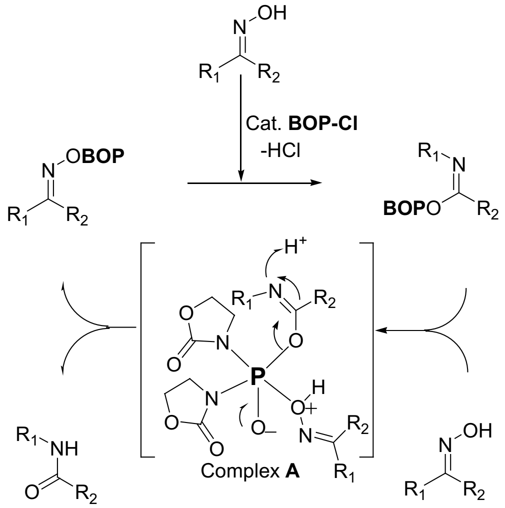
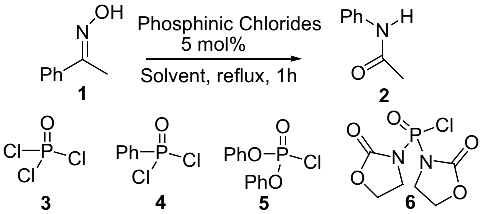


Scheme 1. Proposed mechanism for BOP-Cl catalyzed BKR.

the phosphorous atom. Solvent effects were also investigated and the results summarized in Table 1. Polar solvent acetonitrile gave the best result (Table 1, entries 4 and 5).

It has been reported that Lewis acids such as $ZnCl_2$ are good co-catalysts for cyanuric chloride catalyzed BKR, which is not active in the absence of cyanuric chloride.[9] In order to understand whether this Lewis acid effect works similarly in our BOP-Cl system, a series of Lewis acids were investigated. A similar Lewis acid effect was found. From Table 2, it is clear that $ZnCl_2$ showed the best co-catalytic effect, and BOP-Cl could be further decreased to 2 mol % by using 2 mol % of $ZnCl_2$ as co-catalyst to maintain the catalytic activity. In the course of our study, we also noticed that using anhydrous solvent is the key to achieving high catalytic activity. When 0.33 equiv of water and 1 equiv of water (based on oxime) were added to reaction system respectively in the presence of 5 mol % of BOP-Cl, *N*-acetyl aniline was obtained in 55% and 5% of yield, respectively (entries 8 and 9).

Table 1. Phosphinic chlorides (5 mol %) catalyzed Beckmann rearrangement of acetophenone oxime[a]



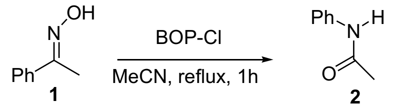
Entry	Catalyst	Solvent	Yield[c] (%)
1	**3**	MeCN	55
2	**4**	MeCN	50
3	**5**	MeCN	48
4	**6**	MeCN	94
5[b]	**6**	MeCN	99
6	**6**	THF	50
7	**6**	Toluene	5
8	**6**	Dioxane	5

[a] 2 mmol of acetophenone oxime was used for the BKR in anhydrous solvent (4 mL) and in the presence of 5 mol % of catalysts at refluxing temperature.

[b] 10 mol % of catalyst BOP-Cl was used.

[c] Isolated yield.

Table 2. Influences of Lewis acids and water on the BOP-Cl catalyzed Beckmann rearrangement of acetophenone[a]



Entry	BOP-Cl (mol %)	Additive[b] (%) (mol %)	Yield[c] (%)
1	5	No	94
2	5	$ZnCl_2$ (2)	99
3	2	$ZnCl_2$ (2)	92
4	2	No	40
5	2	$InCl_3$ (2)	56
6	2	$In(OTf)_3$ (2)	85
7	2	$Sc(OTf)_3$ (2)	73
8	5	H_2O (33)	55
9	5	H_2O (100)	5

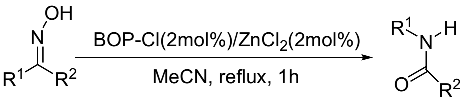
[a] 2 mmol of acetophenone oxime was used for BKR in anhydrous MeCN (4 mL).

[b] Lewis acids were dissolved in anhydrous MeCN to make 1 M solution, which were then added into reaction mixture via syringe.

[c] Isolated yield.

Next we examined the generality of the BOP-Cl (2 mol %) catalyzed BKR with $ZnCl_2$ (2 mol %) as co-catalyst in anhydrous acetonitrile (Table 3). The Beckmann rearrangement of various ketoximes proceeded smoothly with complete reaction within 1 h to give the corresponding amides in good to excellent yield in most cases. Interestingly, 1 mol % BOP-Cl in the absence of $ZnCl_2$ was extremely active in the rearrangement of benzophenone to the corresponding amide (entry 1). Cyclododecanone oxime was also very reactive and converted to the corresponding laurolactam in 99% of yield (entry 9), which is a very useful monomer material

Table 3. Scope of BOP-Cl/$ZnCl_2$ catalyzed Beckmann rearrangement[a]



Entry	R^1	R^2	Yield[c] (%)
1[b]	Ph	Ph	99
2	Ph	Me	92
3	*p*-(Me)C_6H_4	Me	97
4	*o*-(MeO)C_6H_4	Me	96
5	*m*-(MeO)C_6H_4	Me	95
6	*p*-(MeO)C_6H_4	Me	99
7	Ph	Et	97
8	$CH_3(CH_2)_7$	Me	95
9	$(CH_2)_{11}$		99
10	$(CH_2)_5$		<5

[a] 2 mmol of ketoximes were used for the Beckmann rearrangement in anhydrous MeCN (4 mL) in the presence of BOP-Cl (2 mol %) and $ZnCl_2$ (2 mol %).

[b] Only 1 mol % of BOP-Cl was used in the absence of $ZnCl_2$.

[c] Isolated yield.

for nylons.[12] However, cyclohexanone oxime was extremely unreactive to BOP-Cl (entry 10), which behaved similarly to cyanuric chloride.[9]

In summary, we have developed the first generation of organophosphinic chloride, commercially available BOP-Cl (5 mol %) or BOP-Cl (2 mol %)/$ZnCl_2$ (2 mol %) system,[13] as highly effective catalyst for the Beckmann rearrangement of ketoximes to corresponding amides. This finding will broaden the scope of catalytic Beckmann rearrangement. Further modifications of substituents on the phosphorous center will be pursued in an effort to increase catalyst performance. Further studies are in progress in our laboratories to clarify the catalytic mechanism and to explore more versatile catalysts for the Beckmann rearrangement of various ketoximes to corresponding amides.

Acknowledgements

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13. *General procedure for the BOP-Cl catalyzed Beckmann rearrangement reaction*: A solution of ketoxime (2 mmol), 1–5 mol % of BOP-Cl **6** and/or 2 mol % Lewis acid in 4 mL of dry MeCN was refluxed under a nitrogen atmosphere. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated aqueous sodium hydrogen carbonate. The organic layer was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel to give the corresponding amide in high yield. Typical example: Acetanilide (Table 1, entry 1) **2**.[10] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.17 (s, 3H), 7.10 (t, $J = 7.4$ Hz, 1H), 7.30–7.35 (m, 3H), 7.50 (d, $J = 8.0$ Hz, 2H).