JOC*Note*

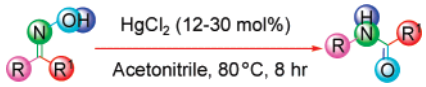
Mercury-Catalyzed Rearrangement of Ketoximes into Amides and Lactams in Acetonitrile

Chennan Ramalingan and Yong-Tae Park*

Department of Chemistry, Kyungpook National University, Taegu 702-701, Korea

ytpark@knu.ac.kr

Received February 13, 2007

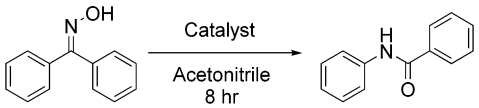


An acetonitrile solution of mercury(II) chloride has been found to catalyze efficiently the conversion of a diverse range of ketoximes into their corresponding amides/lactams.

The Beckmann rearrangement for the transformation of ketoximes into amides/lactams constitutes a fundamental tool in organic synthesis.[1] This rearrangement, however, traditionally requires harsh conditions such as a large amount of a strong acid and high reaction temperature. The transformation of sensitive oximes into amides/lactams is usually impeded in the above condition, and the formation of a large amount of the byproduct ammonium sulfate is a serious drawback in the rearrangement. Hence, extensive efforts have been devoted to circumvent the harsh conditions; various procedures in liquid phase,[2] in vapor phase,[3] in supercritical water,[4] and in ionic liquids[5] have been developed. In the liquid phase,[6,7] ferric chloride impregnated silicagel, known as silferc catalyst, and ferric chloride impregnated montmorillonite K10 were used as catalysts for the Beckmann rearrangement. Application of the former method to most of the acetophenone oximes gave their corresponding amides as isomeric mixtures. For the latter method, limited numbers of diarylketoximes were investigated. Recently, an efficient catalytic method using in situ generation of a transition metal complex (rhodium complex) as catalyst has been reported.[8] Although this elegant method efficiently catalyzes acyclic ketoximes into their corresponding amides, this method failed to give lactams from cyclic ketoximes. Hence, more efficient and milder catalytic methods for the transformation of ketoximes into amides/lactams as well as diversification of the rearrangement are highly desirable. We recently reported the Beckmann rearrangement of a diverse range of ketoximes into their corresponding amides/lactams by mesitylenesulfonyl chloride in one pot.[9] In continuation of the research directed toward an efficient and mild methodology for the Beckmann rearrangement, we described herein a mercury-catalyzed Beckmann rearrangement of ketoximes into amides/lactams in neutral condition.

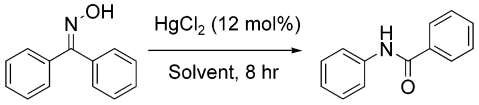
We initially hypothesized that some of electrophilic transition metal halides might efficiently catalyze the transformation of ketoximes into amides/lactams by forming a better leaving group as a metallic complex with the hydroxyl group of the oxime. This method also would alleviate the harsh conditions of the

TABLE 1. Effect of Temperature and Catalyst on the Rearrangement of Benzophenone Oxime



entry	catalyst (mol %)	reaction temp (°C)	yield (%)
1	$HgCl_2$ (12)	80	96
2	$HgCl_2$ (12)	50	74
3	$HgCl_2$ (10)	80	81
4	$ZnCl_2$ (12)	80	0
5	$CdCl_2$ (12)	80	15
6	$CoCl_2.6H_2O$ (12)	80	10
7	$NiCl_2.6H_2O$ (12)	80	13
8	$FeCl_3$	80	38
9	$MnCl_2.4H_2O$ (12)	80	35

TABLE 2. Effect of Solvents on the Rearrangement of Benzophenone Oxime



entry	solvent	reaction temp (°C)	yield (%)
1	acetonitrile	80	96
2	THF	reflux	0
3	DMF	80	0
4	acetone	reflux	5
5	DMA	80	0
6	1,4-dioxane	80	8
7	DMSO	80	6
8	*n*-hexane	reflux	0
9	DCE	80	5
10	toluene	80	0

(1) (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; pp 1415 and references therein. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1−424 and references therein.

(2) (a) Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 11240−11241. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272−6274. (c) Kusama, H.; Yamashita, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 373−377. (d) Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. *Tetrahedron Lett.* **2004**, *45*, 3369−3372. (e) Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* **2005**, *46*, 671−674. (f) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2002**, *43*, 2455−2457. (g) Dongare, M. K.; Bhagwat, V. V.; Ramana, C. V.; Gurjar, M. K. *Tetrahedron Lett.* **2004**, *45*, 4759−4762.

(3) (a) Ghiaci, M.; Abbaspur, A.; Kalbasi, R. *Appl. Catal. A* **2005**, *287* (1), 83−88. (b) Forni, L.; Fornasari, G.; Giordano, G.; Lucarelli, C.; Katovic, A.; Trifiro, F.; Perri, C.; Nagy, J. B. *Phy. Chem. Chem. Phy.* **2004**, *6* (8), 1842−1847.

(4) (a) Boero, M.; Ikeshoji, T.; Liew, C. C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* **2004**, *126* (20), 6280−6286. (b) Ikushima, Y.; Hatakeda, K.; Sato, M.; Sato, O.; Arai, M. *Chem. Commun.* **2002**, *19*, 2208−2209. (c) Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *Angew. Chem., Int. Ed.* **1999**, *38* (19), 2910−2914.

(5) (a) Guo, S.; Du, Z.; Zhang, S.; Li, D.; Li, Z.; Deng, Y. *Green Chem.* **2006**, *8* (3), 296−300. (b) Guo, S.; Deng, Y. *Catal. Commun.* **2005**, *6* (3), 225−228.

(6) Khadilkar, B. M.; Upadhyaya, D. J. *Synth. Commun.* **2002**, *32* (12), 1867−1873.

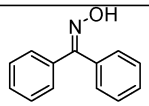
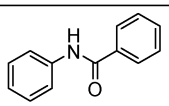
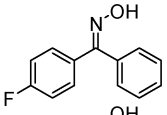
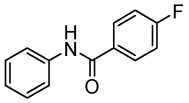
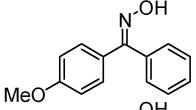
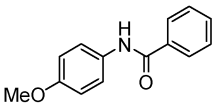
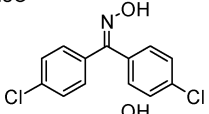
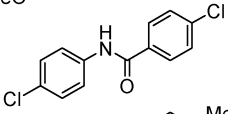
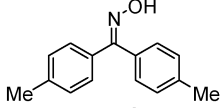
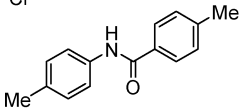
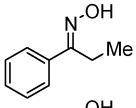
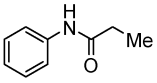
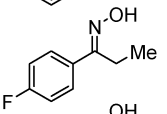
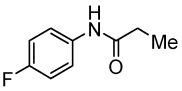
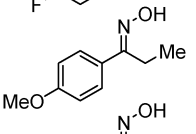
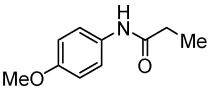
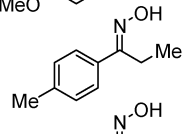
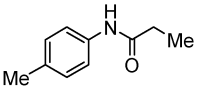
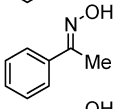
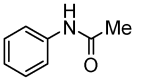
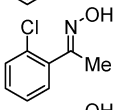
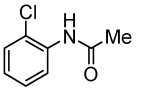
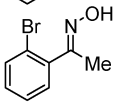
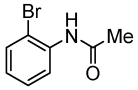
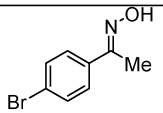
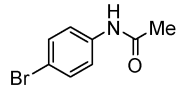
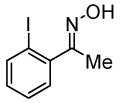
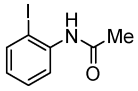
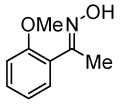
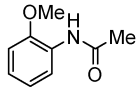
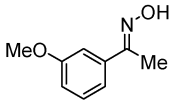
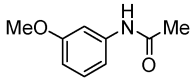
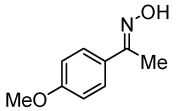
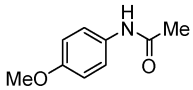
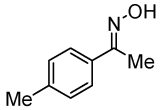
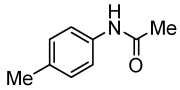
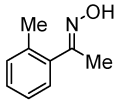
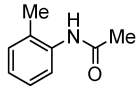
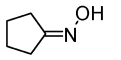
(7) Pai, S. G.; Bajpai, A. R.; Deshpande, A. B.; Samant, S. D. *Synth. Commun.* **1997**, *27* (3), 379−384.

(8) Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311−312.

(9) Ramalingan, C.; Park, Y.-T. Unpublished results.

10.1021/jo070297k CCC: $37.00
Published on Web 05/05/2007

TABLE 3. Mercury-Catalyzed Beckmann Rearrangement of Acyclic and Cyclic Ketoximes

entry	substrate	$HgCl_2$ (mol%)	product	yield (%)
1		12		96
2		12		82[a]
3		12		85[b]
4		12		89
5		12		97
6		12		98
7		12		85
8		12		89
9		12		94
10		12		98
11		12		83
12		12		79
13		12		84
14		12		74
15		12		71
16		12		82
17		12		90
18		12		93
19		12		77
20		30		84
21		30		92
22		30		89
23		30		48

[a] Overall yield of isomeric mixtures (0.8 : 1.0)

[b] Overall yield of isomeric mixtures (1.0 : 0.7)

Beckmann rearrangement and reduce the byproduct yield. A preliminary examination showed that acetonitrile solution of $HgCl_2$ among several transition metal halides effectively catalyzed the Beckmann rearrangement of benzophenone oxime as a model.

When an acetonitrile solution of benzophenone oxime and $HgCl_2$ (12 mol %) was stirred at 80 °C for 8 h under nitrogen atmosphere, the rearrangement product, *N*-phenylbenzamide was produced in high yield (96%, entry 1 in Table 1). The above reaction condition was appropriate for the transformation because lowering the reaction temperature from 80 to 50 °C and decreasing the amount of catalyst from 12 to 10 mol % lowered the amide yield (entries 2 and 3).

The catalytic activities of diverse transition metal halides on the transformation of benzophenone oxime in acetonitrile were examined (entries 4−9). No conversion was observed when $ZnCl_2$ (12 mol %) was used as a catalyst (entry 4). Although some of the other transition metal halides exhibited measurable activities for the transformation of benzophenone oxime, their yields were not appreciable compared to that of $HgCl_2$ (12 mol %). For example, the use of $CdCl_2$ (12 mol %) afforded *N*-phenylbenzamide in low yield (15%, entry 5). The other transition metal halides such as $CoCl_2 \cdot 6H_2O$ and $NiCl_2 \cdot 6H_2O$ (12 mol %) produced *N*-phenylbenzamide in 10−13% yield (entries 6 and 7). However, $FeCl_3$ and $MnCl_2 \cdot 4H_2O$ (12 mol %) afforded *N*-phenylbenzamide in better yield (entries 8 and

9) albeit lower than that of $HgCl_2$. Thus, the procedure using $HgCl_2$ (12 mol %) as a catalyst in acetonitrile at 80 °C proved to be optimal for the rearrangement.

Solvent effects on the transformation were studied (Table 2). In place of acetonitrile, other solvents such as aprotic polar solvents and nonpolar solvents did not accomplish the rearrangement effectively (less than 10% yield, Table 2). Probably acetontrile helps the reaction by forming an acetonitrile complex with mercury ion since this complexation is known.[10,11]

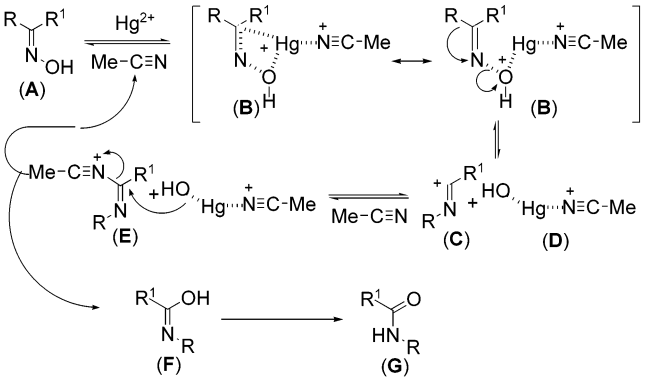
To illustrate the general applicability of Beckmann rearrangement catalyzed by an acetonitrile solution of $HgCl_2$, a diverse range of ketoximes[12] were examined; the results are shown in Table 3. A striking feature is that regardless of the electronic properties of the substituents, all of the oximes, benzophenone oximes (entries 1−5), propiophenone oximes (entries 6−9), and acetophenone oximes (entries 10−19) were efficiently transformed into their corresponding N-substituted amides in neutral condition. The oximes with *ortho* substituents afforded their corresponding amides with yields comparatively lower (entries 11, 12, 14, 15, and 19) than those of the oximes with *para* substituents or without substituents. Probably, the substituent group at the *ortho* position partially hinders complexation between the mercuric ion and the oxime moiety and/or impedes a migration of the aryl group due to steric effect.

The unsymmetrical benzophenone oxime (4-fluorophenyl)-phenylmethanone oxime gave a mixture of isomeric amides *N*-(4-fluorophenyl)benzamide and 4-fluoro-*N*-phenylbenzamide in the ratio of 0.8/1.0 (entry 2). Similarly, (4-methoxyphenyl)-phenylmethanone oxime produced *N*-(4-methoxyphenyl)benzamide and 4-methoxy-*N*-phenylbenzamide as an isomeric mixture in the ratio of 1.0/0.7 (entry 3). In the reactions of the unsymmetric propiophenone oximes and acetophenone oximes, aryl groups migrated exclusively in preference to the alkyl group. These results imply that electron-rich aryl groups have better migrating aptitude than the alkyl group toward the oximino nitrogen terminus and, thus, cationic species of the oximino nitrogen terminus is involved (vide infra).

An investigation with cyclic ketoximes possessing several ring size such as five-, six-, and seven-membered rings showed that higher loading of the catalyst was required to transform the cyclic ketoximes into their corresponding lactams with good to better yield. The higher loading (30 mol %) of $HgCl_2$ on the reaction effected the conversion of cyclopentanone oxime, cyclohexanone oxime, and 2-*tert*-butylcyclohexanone oxime into piperidin-2-one, azepan-2-one, and 7-*tert*-butylazepan-2-one, respectively, with excellent yields (84−92%), whereas its application to the transformation of cycloheptanone oxime produced azocan-2-one in relatively lower yield (48%). In the case of unsymmetrical α-substituted cyclohexanone oxime, exclusive migration of an electron-rich α-carbon carrying an alkyl substituent toward the imino nitrogen of the oxime occurred (entry 22).

The following mercury-catalyzed rearrangement mechanism for the transformation of the oxime into amide is proposed on the basis of the above preparative reactions and solvent and catalyst effects (Scheme 1). Electrophilic mercury ion is stabilized by forming a mercury complex with acetonitrile.[10,11] The mercury

SCHEME 1. Mechanism for the Mercury-Catalyzed Rearrangement of Ketoximes



ion is coordinated to the oximino moiety of the oxime (**A**) and to the lone pair electrons of acetonitrile to give complex **B** in the presence of acetonitrile, which is in resonance with the oxo mercury complex. The hydroxide group of complex **B**, which has a strong leaving propensity, moves to the mercury ion to give oxo mercury complex **D**. Concomitantly the *anti* periplanar alkyl or aryl group, *trans* to the oxime oxygen, migrates to the cationic species of the oximino nitrogen terminus to give the carbocation of imine **C**. The carbocation **C** is solvated with acetonitrile to give intermediate **E** or reacts with a hydroxide ion from oxo mercury complex **D** to directly give imidol **F**. The acetonitrile group of the intermediate **E** is substituted with the hydroxyl ligand of mercury complex **D** to provide imidol form of amide **F**. Amide **G** is produced from imidol form **F** by tautomerization.

In the presence of small amount of methanol in acetonitrile the rearranged product was not obtained. A plausible reason is that methanol inhibits the formation of the complex **B** by coordination with the mercury ion, thus suppressing further reaction.

In summary, an acetonitrilomercury(II) complex efficiently catalyzes the rearrangement of a variety of acyclic and cyclic ketoximes with good to excellent yields under essentially neutral condition.

Experimental Section

The procedure for the catalytic conversion of benzophenone oxime into *N*-phenylbenzamide using mercury(II) chloride is representative. To a solution of benzophenone oxime (197 mg, 1 mmol in 5 mL of acetonitrile) in a two-necked flask equipped with a reflux condenser under a nitrogen atmosphere was added mercury(II) chloride (33 mg, 0.12 mmol). After being stirred at 80 °C for 8 h, the reaction mixture was allowed to cool, and then acetonitrile (5 mL) was added to dissolve the solid formed. The solvent was stripped off, and the organic material was dissolved in dichloromethane (4 × 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated under reduced pressure, and the residue obtained was purified by flash column chromatography over silica gel (230−400 mesh) with a dichloromethane−methanol (100:4) eluent system to afford *N*-phenylbenzamide as a colorless solid (189 mg, 96%), mp 162−163 °C.

Acknowledgment. Financial support from Korea Research Foundation (KRF-2006-005-J02401) is gratefully acknowledged.

Supporting Information Available: Experimental details and characterization data for all lactams and amides. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070297K

(10) Danil de Namor, A. F.; Chahine, S.; Kowalska, D.; Castellano, E. E.; Piro, O. E. *J. Am. Chem. Soc.* **2002**, *124*, 12824−12836.

(11) Sze, Y. K.; Irish, D. E. *Can. J. Chem.* **1975**, *53* (3), 427−436.

(12) All of the oxime substrates used in this investigation (entries 1−23 in Table 3) were quantitatively synthesized by refluxing a mixture of 1 equiv of the corresponding ketones, 2.3 equiv of hydroxylamine hydrochloride, and 2.5 equiv of sodium acetate trihydrate in aqueous methanol.