Cyanuric Chloride/ Manganese Chloride Tetrahydrate Catalyzed Beckmann Rearrangement of Ketoximes

ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

In order to find an efficient catalytic system for Beckmann rearrangement of ketoximes, cyanuric chloride and Lewis acids were screened, and the cyanuric chloride /manganese chloride tetrahydrate system with good catalytic effect has been discovered. Using 2 mol% cyanuric chloride and 2 mol% $MnCl_2 \cdot 4H_2O$ as catalyst, the yield of Beckmann rearrangement of benzophenone oxime was 96% after refluxing for 2 h in acetonitrile. A variety of ketoximes underwent the Beckmann rearrangement to afford the corresponding amides in moderate to high yields.

Keywords: Beckmann rearrangement; ketoximes; cyanuric chloride; manganese chloride tetrahydrate; amides

1. INTRODUCTION

Beckmann rearrangement of ketoximes, which includes an intramolecular rearrangement in the presence of catalyst, is an important method for the synthesis of amides in organic chemistry. [1-3] This rearrangement traditionally needs high temperature, a large number of strong acids and dehydrating agents, which leads to many by-products and acidic wastewater, and is not suitable for unstable ketoximes. Therefore, enormous efforts have been devoted to find more mild and effective versions in this field.

Cyanuric chloride is an efficient catalyst for Beckmann rearrangement reaction. Cyanuric chloride in DMF, acetonitrile and ionic liquids have showed high to excellent catalytic effects in this reaction. [4-7] Cyanuric chloride accompanying with trifluoroacetic acid in toluene can efficiently catalyze cyclohexanone oxime to caprolactam,[8] which has poor yield in cyanuric chloride/acetonitrile system. Lewis acids represented by $ZnCl_2$ as cocatalyst can increase the calalytic activity of Cyanuric chloride.[5] In this paper, we reported a very efficient method for Beckmann rearrangement reaction by using $MnCl_2 \cdot 4H_2O$ and cyanuric chloride as catalysts. In addition, the applicability of the catalytic system in different solvents and to different ketoxime substrates was also studied.

2. MATERIAL AND METHODS

2.1 Reagents and instruments

NMR spectra were recorded at Advance III HD 500 MHz or 400 MHz NMR Spectrometer (Bruker, Switzerland) in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard, and chemical shift values (δ) were given in ppm. Flash chromatograph was performed with silica gel (200-300 mesh). The melting points were determined on a WRR Melting Point Instrument (Shanghai Precision Scientific Instruments Co., Ltd.) and were uncorrected. Reagents were all analytically pure and purchased from SAN Chemical Technology (Shanghai) Co., Ltd. and Shanghai Aladdin Biochemical Technology Co., Ltd. All solvents and liquid reagent were dried by standard methods in advance and distilled before use.

2.2 Synthesis

Benzophenone oxime was synthesized according to the literature.[9] Benzophenone (50.00 g, 0.275 mol) and hydroxylamine hydrochloride (30.00 g, 0.43 mol) were dissolved in a mixture of 100 mL 95% ethanol and 20 mL water. Sodium hydroxide (55.00 g, 1.375 mol) was added in portions under stirring. After all the sodium hydroxide has been added, the flask is connected to a reflux condenser, heated to boiling, and refluxed for five minutes. After cooling to room temperature, the obtained white turbid liquid was poured into a mixture of 150 mL concentrated hydrochloric acid and 1 L water to precipitate white solid. The precipitate is filtered and washed with water. The crude product was recrystallized with methanol and white crystals were obtained. The melting point was 142.8-143.8 ℃, and the yield was 90%. ^{1}H NMR (500 MHz，DMSO-d_6) δ: 11.36 (br s, 1H, OH), 7.48-7.35 (m, 8H, Ar-H), 7.29-7.27 (m, 2H, Ar-H). ^{13}C NMR (125 MHz，DMSO-d_6) δ: 155.2, 136.8, 133.6, 128.9, 128.8, 128.4, 128.3, 128.2, 127.0.

The mixture of ketoxime (4 mmol), $MnCl_2{\cdot}4H_2O$ (2 mol%) and cyanuric chloride (2 mol%) was added into 8 mL acetonitrile and refluxed. The reaction was monitored by TLC, then saturated sodium bicarbonate solution (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (20 mL*3). Anhydrous sodium sulfate was added to the combining organic phase. After removal of organic solvents by rotary evaporator, the crude products were obtained, then flash chromatography was used for further purification to afford the target amides.

N-phenylbenzamide, white solid, yield 96%，m. p. 162.5-163.6℃, ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.27 (s, 1H, NH), 7.98-7.96 (m, 2H, Ar-H), 7.81 (d, 2H, *J*=8.0 Hz, Ar-H), 7.61-7.58 (m, 1H, Ar-H), 7.55-7.52 (m, 2H, Ar-H), 7.36 (t, 2H, *J*=8.0 Hz, Ar-H), 7.11 (t, 1H, *J*=7.5 Hz, Ar-H)。^{13}C NMR(125MHz，DMSO-d_6) δ: 165.6, 139.2, 135.0, 131.5, 128.6, 128.4, 127.7, 123.7, 120.4。

N-phenylacetamide, white solid, yield 85%，m. p. 113.9-115.1℃, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (s, 1H, NH), 7.55-7.53 (m, 2H, Ar-H), 7.30-7.27 (m, 2H, Ar-H), 7.10 (t, 1H, *J*=7.5 Hz, Ar-H), 2.14 (s, 3H, CH_3)。^{13}C NMR(125MHz，$CDCl_3$) δ : 169.3, 138.1, 128.8, 124.2, 120.2, 24.2。

N-(p-tolyl)acetamide, white solid, yield 85%, m. p. 149.0-151.0℃，^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (s, 1H, NH), 7.37 (d, 2H, *J*=8.4 Hz, Ar-H), 7.10 (s, 2H, *J*=8.2 Hz, Ar-H), 2.30 (s, 3H, CH_3-Ar), 2.13 (s, 3H, CH_3CO)。

N-(4-methoxyphenyl)acetamide, white solid, yield 80%，m. p. 113.9-115.1℃，^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (s, 1H, NH), 7.39 (d, 2H, *J*=8.8 Hz, Ar-H), 6.84 (d, 2H, *J*=8.8 Hz, Ar-H), 3.78 (s, 3H, CH_3O), 2.13 (s, 1H, CH_3CO)。

N-(4-hydroxyphenyl)acetamide, white solid, yield 86%，m. p. 169.0-170.0℃，^{1}H NMR (400 MHz，DMSO-d_6) δ: 8.99 (s, 1H, OH), 8.20 (s, 1H, NH), 7.45 (d, 2H, *J*=8.0 Hz, Ar-H), 6.77 (s, 2H, *J*=8.0 Hz, Ar-H), 2.07 (s, 3H, CH_3)。

N-(4-chlorophenyl)acetamide, white solid, yield 70%，m. p. 177.2-178.5℃，^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, 2H, *J*=8.0 Hz, Ar-H), 7.39 (s, 1H, NH), 7.27 (d, 2H, *J*=8.0 Hz, Ar-H), 2.17 (s, 3H, CH_3)。

N-(4-fluorophenyl)acetamide, white solid, yield 75%，m. p. 153.5-155.0℃，^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 1H, NH), 7.47-7.43 (m, 2H, Ar-H), 7.01-6.97 (m, 2H, Ar-H), 2.15 (s, 3H, CH_3)。

N-(o-tolyl)acetamide, white solid, yield 70%，m. p. 111.0-112.5℃，^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H, NH), 7.43 (d, 1H, *J*=6.9 Hz, Ar-H), 7.29-7.14 (m, 2H, Ar-H), 7.09 (t, 1H, *J*=6.9 Hz, Ar-H), 2.23 (s, 3H, Ar-CH_3), 2.09 (s, 3H, CH_3)。

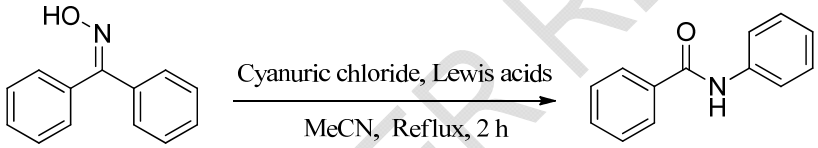
4-Methyl-N-(p-tolyl)benzamide, white solid, yield 85% , m. p. 231.0-233.0℃ , ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H, NH), 7.88 (d, 2H, *J*=8.2 Hz, Ar-H), 7.67 (d, 2H, *J*=8.4 Hz, Ar-H), 7.33 (d, 2H, *J*=8.0 Hz, Ar-H), 7.15 (d, 2H, *J*=8.2 Hz, Ar-H), 2.39 (s, 3H, CH_3), 2,28 (s, 3H, CH_3)。

Aepan-2-one, white solid, yield 50% , m. p. 69.0-71.2℃ , ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.47 (s, 1H, NH), 3.23-3.19 (m, 2H, CH_2), 2.48-2.45 (m, 2H, CH_2), 1.77-1.62 (m, 6H, CH_2 CH_2 CH_2)。

3. RESULTS AND DISCUSSION

Several Lewis acids as cocatalysts for cyanuric chloride were examined for Beckmann rearrangement of benzophenone oxime in acetonitrile under reflux condition for 2 h (Table 1). All Lewis acids except CuCl obtained high catalytic effect by comparing with the reported $ZnCl_2$. It is speculated that CuCl is not soluble in solution and cannot play an auxiliary catalytic role (entry 7). Unlike using anhydrous Lewis acid and anhydrous acetonitrile in reference,[5] the Lewis acid containing crystalline water represented by $MnCl_2{\cdot}4H_2O$ also has good auxiliary catalytic effect, which indicated that the reaction was not necessary to carry out under anhydrous conditions (entry 4). Therefore, less-expensive $MnCl_2{\cdot}4H_2O$ was the best choice as a cocatalyst for cyanuric chloride. It is also showed that the catalytic effect is poor when using cyanuric chloride or $MnCl_2{\cdot}4H_2O$ alone (entry 9 and 11), which determined $MnCl_2{\cdot}4H_2O$ as the cocatalysts in the rearrangement. Thus, the rearrangement gave *N*-phenylbenzamide in 96% yield within 2 h in the presence of cyanuric chloride (2 mol%) and $MnCl_2{\cdot}4H_2O$ (2 mol%).

Table 1 Screening of Auxiliary Catalysts for Beckmann Rearrangement Catalyzed by Cyanuric Chloride



Entry	Cyanuric chloride (mol%)	Lewis acids (mol%)	Yield (%)[a]
1	2	$ZnCl_2$ (2)	95
2	2	$SnCl_2{\cdot}2H_2O$ (2)	90
3	2	$CdCl_2$ (2)	95
4	2	$MnCl_2{\cdot}4H_2O$ (2)	96
5	2	$SrCl_2{\cdot}6H_2O$ (2)	95
6	2	$SbCl_3$ (2)	94
7	2	CuCl (2)	NA[b]
8	2	$La(NO_3)_3{\cdot}6H_2O$ (2)	80
9	0	$MnCl_2{\cdot}4H_2O$ (2)	15
10	1	$MnCl_2{\cdot}4H_2O$ (2)	85
11	2	$MnCl_2{\cdot}4H_2O$ (0)	60

[a] *Isolated yield.*

The solvent effect was also investigated (Table 2). Polar solvent, such as *N, N*-dimethylformamide (DMF), *N*-methyl pyrrolidone (NMP), acetone and toluene, were not suitable for this catalysis (entry 2-4). Although cyanuric chloride in DMF have afforded good catalytic activity in previous report,[4] it is concluded that the addition of $MnCl_2{\cdot}4H_2O$ inhibited the formation of corresponding Vilsmeier-Haack complexes between cyanuric chloride and DMF.

Table 2 Effect of Solvent on the Reaction

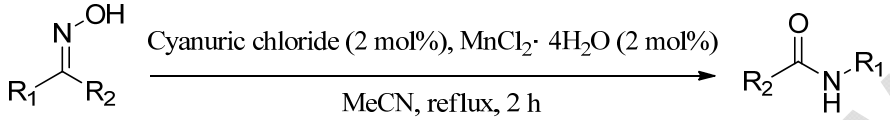
Entry [a]	Solvent	Temperature (℃)	Yield (%)
1	MeCN	Reflux	96
2	DMF	Reflux	NA [b]
3	NMP	Reflux	NA
4	Acetone	Reflux	38
5	Toluene	Reflux	45

[a] *Benzophenone oxime(4 mmol), solvent(8 mL), cyanuric chloride(2mol%)，$MnCl_2 \cdot 4H_2O$(2mol%), 2 h.*

[b] *not available*

To explore the generality and scope of the Beckmann rearrangement catalyzed by cyanuric chloride and $MnCl_2 \cdot 4H_2O$, representative ketoximes as substrates were examined under reflux conditions in acetonitrile (Table 3). Substituted acetophenone oximes (Entry 3-5) with electron donor group have higher yield than that with electron acceptor group (Entry 6-7), while the yield of 2-methylacetophenone oxime is lower than that of 4-methylacetophenone oxime. Consistent with the results reported in literature [5,8], the yield of cyclohexanone oxime (Entry 10) is low. Ronchin et al. [11] showed that cyclohexanone oxime was prone to Beckmann rearrangement only after protonation of strong acid (such as trifluoroacetic acid), so the reaction of cyclohexanone oxime was poor in cyanuric chloride /Lewis salt system.

Table 3 Scope of Different Ketoximes

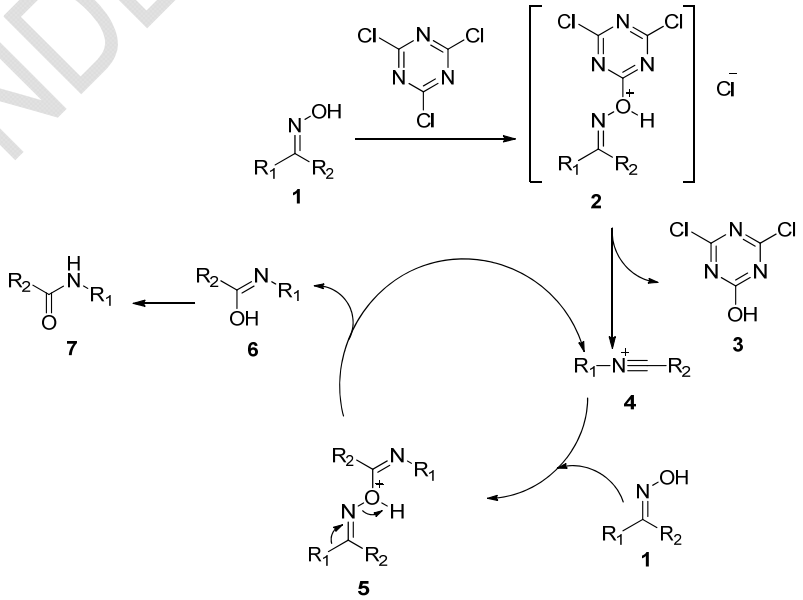


Entry [a]	R_1	R_2	Yield (%) [b]
1	Ph	Ph	96
2	Ph	Me	85
3	4-(HO)C_6H_4	Me	86
4	4-Me C_6H_4	Me	90
5	4-(MeO) C_6H_4	Me	80
6	4-F C_6H_4	Me	75
7	4-Cl C_6H_4	Me	70
8	2-CH_3 C_6H_4	Me	70
9	4-Me C_6H_4	4-Me C_6H_4	85
10	$(CH_2)_5$		50

[a] *Ketoximes(4 mmol), acetonitrile(8 mL), cyanuric chloride(2mol%), $MnCl_2 \cdot 4H_2O$(2mol%), 2 h.*

[b] *Isolated yield.*

According to references reported by Deng et al. [12-13], the Beckmann rearrangement promoted by cyanuric chloride undergoes a self-propagating mechanism, rather than a catalytic process proposed by Yamamoto et al. [5] Therefore, the reaction mechanism is inferred as shown in Scheme 1. Ketoximes react with cyanuric chloride to form complex 2, and then compound 3 is removed to obtain active intermediate 4. Intermediate 4 can easily react with ketoximes to form cationic intermediate 5. The formation of oxygen cation reduces the energy barrier of Beckmann rearrangement reaction. It is speculated that Lewis acid can chelate with nitrogen atom in intermediate 5 and accelerate Beckmann rearrangement reaction.



Scheme 1 Proposed mechanism

4. CONCLUSION

A new catalytic system for Beckman rearrangement method for ketoximes was reported. The method used cyanuric chloride and $MnCl_2 \cdot 4H_2O$ as catalysts, refluxed in acetonitrile for 2 hours at low catalyst usage (2 mol%) with good catalytic effect on Beckmann rearrangement of ketoximes. The reaction does not need to be carried out under anhydrous conditions and the catalyst is cheap and easy to obtain.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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