A Mild and Highly Efficient Catalyst for Beckmann Rearrangement, BF_3•OEt_2

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BF_3•OEt_2 (Boron trifluoride etherate), an inexpensive and commercially easily available Lewis acid stoichiometrically employed for Beckamann rearrangement in general, was now found to efficiently catalyze Beckmann rearrangement of ketoximes into their corresponding amides (up to 99% yield) in anhydrous acetonitrile under reflux temperature.

Keywords Beckmann rearrangement, BF_3•OEt_2, catalyst, amide

Introduction

Beckmann rearrangement, as one of the fundamental tools in organic chemistry, has carried out the transformation of aldoximes or ketoximes into amides/lactams.[1] The Rearrangement requires harsh conditions such as a large amount of oleum and high reaction temperature. Besides, it also suffers from a considerable large amount of ammonium sulfate byproduct.[2] Hence, extensive efforts have been devoted to the development of an effective and mild catalytic system. Many catalytic systems, such as liquid phase system,[3] vapor phase system,[4] supercritical water system,[5] and ionic liquids system[6] even microwave technique[7] have thus been developed. And liquid phase catalytic Beckmann rearrangement under mild conditions has become a topic of current interest. As a consequence, many Lewis acids instead of Brönsted acids have been reported to carry out Beckmann rearrangement with good to excellent catalytic activities, such as Me_3OBF_4/$CF_3SO_3CH_3$,[8] P_2O_5,[9] BPO_4,[10] $AlCl_3$,[11] $[RhCl(cod)]_2$,[12] $Yb(OTf)_3$,[13] $Y(OTf)_3$,[14] $Ga(OTf)_3$,[15] $Nd(OTf)_3$,[16] $RuCl_3$,[17] $HgCl_2$[18] and $SbCl_5$/$AgSbF_6$.[19] However, due to drawbacks such as toxicity, high cost and relatively low catalytic activities (10—50 mol% catalyst loading), these catalysts have not yet been industrially utilized.

Interestingly, BF_3•OEt_2, as a cheap and commercially available reagent, has been often employed as a highly active promotor for Beckmann rearrangement in organic synthesis,[20-23] but in stoichiometric amount. In the case of Beckmann rearrangement of ketoxime ethyl carbonates described by Chandrasekhar,[23] an attempt to employ the catalytic amount of BF_3•OEt_2 turned out failed presumably due to its complexation with the immediate product of the rearrangement. Recently, we found that the catalytic amount of catalysts, such as TsCl,[24] BOPCl[25] and TAPC,[26] were highly active for Beckmann rearrangement. Herein we would like to report the first example of the BF_3•OEt_2-catalyzed Beckmann rearrangement of ketoximes to produce corresponding amides using only 10 mol% of the catalyst.

Results and discussion

Initially, 20 mol% of BF_3•OEt_2 was tested for Beckmann rearrangement of acetophenone oxime in anhydrous CH_3CN at refluxing temperature. To our delight, it did transform acetophenone oxime into *N*-acetyl aniline smoothly in 84% yield. Further screening of the catalyst loading turned out that 10 mol% of BF_3•OEt_2 was optimal considering the balance between the yield of product and the catalyst loading (Table 1). And then the solvent screening suggested that polar solvent anhydrous acetonitrile gave the best result (Entry 5, Table 2).

Next, the generality and scope of the boron trifluoride etherate (10 mol%) catalyzed Beckmann rearrangement in anhydrous acetonitrile were also investigated using the optimal reaction condition. As summarized in Table 2, Beckmann rearrangement of various representative ketoximes proceeded smoothly to give the corresponding amides in good to excellent yields under the same condition. It is clear that excellent yields were obtained for the rearrangement of diarylketone oximes into corresponding amides. For the substituted acetophenone oximes, the rearrangement was generally effective, however it was found that only the oxime with electron-withdrawing

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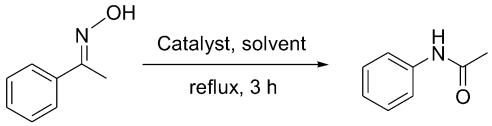
Received September 5, 2010; revised December 28, 2010; accepted January 21, 2011.
Project supported by the National Natural Science Foundation of China (No. 20602011), New Century Excellent Talents in University, the Ministry of Education, China (No. NCET-07-0283), and '111' Project (No. B07023).

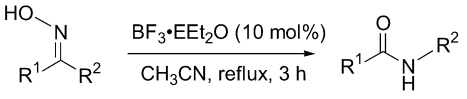
Table 1 Effect of amount of catalyst and solvents effect on Beckmann rearrangement of acetophenone oxime



Entry	Catalyst (mol%)	Solvent	Yield/%
1	BF_3•OEt_2 (5)	CH_3CN	56
2	BF_3•OEt_2 (10)	CH_3CN	76
3	BF_3•OEt_2 (20)	CH_3CN	84
4	BF_3•OEt_2 (10)	THF	Trace
5	BF_3•OEt_2 (10)	Toluene	23
6	BF_3•OEt_2 (10)	Dioxane	Trace
7	BF_3•OEt_2 (10)	Dioxane	Trace
8	BF_3•OEt_2 (10)	CH_3CN	76

para-chloro group gave low reaction activity (60% yield, Entry 12). Beckmann rearrangement of cyclododecanone oxime using the same condition gave the laurolactam in good yield (71% yield, Entry 13). Unfortunately, the rearrangement of cyclohexanone oxime gave only trace amount of ε-caprolactam (Entry 14).

Table 2 The generality and scope of BF_3•Et_2O-catalyzed Beckmann rearrangement of ketoximes into corresponding amides



1a – 1n **2a – 2n**

Entry	R^1	R^2	Yield/%
1 (**2a**)	Ph	Me	76
2 (**2b**)	Ph	Ph	99
3 (**2c**)	*p*-(Me)C_6H_4	Ph	92[a]
4 (**2d**)	*p*-(Me)C_6H_4	*p*-(Cl)C_6H_4	98[b]
5 (**2e**)	*p*-(Me)C_6H_4	*p*-(MeO)C_6H_4	98[c]
6 (**2f**)	*p*-(Cl)C_6H_4	*p*-(MeO)C_6H_4	97[d]
7 (**2g**)	*p*-(Me)C_6H_4	Me	95
8 (**2h**)	*p*-(MeO)C_6H_4	Me	91
9 (**2i**)	*o*-(MeO)C_6H_4	Me	99
10 (**2j**)	*m*-(MeO)C_6H_4	Me	76
11 (**2k**)	pH	Et	81
12 (**2l**)	*p*-(Cl)C_6H_4	Me	60
13 (**2m**)	$(CH_2)_{11}$		71
14 (**2n**)	$(CH_2)_5$		Trace

[a] Overall yield of isomeric mixtures; [b] Overall yield of isomeric mixtures; [c] Overall yield of isomeric mixtures; [d] Overall yield of isomeric mixtures.

Conclusions

In summary, we have developed BF_3•OEt_2/CH_3CN as new catalytic system for Beckmann rearrangement of aromatic and alkyl ketoximes with good to excellent yields under reflux condition. This highly active catalytic system would provide an alternative way for Beckmann rearrangement involved organic synthesis. Further studies are in progress in our laboratory to focus on clarifying the catalytic mechanism and further exploring the synthetic utility of this BF_3•OEt_2-catalyzed Beckmann rearrangement system.

Experimental

All solvents were distilled under standard procedures prior to use under nitrogen atmosphere (For example: CH_3CN distilled from CaH_2; THF, dioxane, toluene distilled from sodium). ^1H (400 MHz) chemical shifts are reported in $CDCl_3$ (δ 7.27) for ^1H NMR, as standards and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

General procedure of BF_3•OEt_2-promoted catalytic Beckmann rearrangement of ketoximes

To a solution of ketoxime (2.0 mmol) in anhydrous CH_3CN (2 mL), 1 mL of BF_3•OEt_2 in CH_3CN (boron trifluoride etherate in CH_3CN solvent, 0.2 mol/L) was added. The mixture was refluxed for 3 h under a nitrogen atmosphere. After the reaction had been completed, the organic layer was diluted with 10 mL of ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (using different ratios of ethyl acetate and *n*-hexane as eluent according to different products)

All known compounds gave NMR spectra that matched data reported in the cited references[18,25]

***N*-Phenylacetamide (2a)** m.p. 114—115 ℃ (Lit[18] 114—116 ℃); ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.59 (brs, 1H), 7.53 (d, J=8.0 Hz, 2H), 7.28 (t, J=7.7 Hz, 2H), 7.09 (t, J=7.4 Hz, 1H), 2.13 (s, 3H).

***N*-Phenylbenzamide (2b)** m.p. 164—165 ℃ (Lit[18] 164—165 ℃); ^1H NMR ($CDCl_3$, 400 MHz): δ: 8.03 (brs, 1H), 7.87 (d, J=7.3 Hz, 2H), 7.66 (d, J=7.9 Hz, 2H), 7.54 (t, J=7.3 Hz, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.37 (t, J=7.9 Hz, 2H), 7.16 (t, J=7.4 Hz, 1H).

***N*-*p*-Tolylbenzamide and 4-methyl-*N*-phenylbenzamide (2c)** ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.92—7.73 (m, 6H), 7.65 (d, J=7.9 Hz, 2H), 7.55—7.49 (m, 3H), 7.38 (t, J=7.8 Hz, 2H), 7.32—7.26 (m, 3H), 7.19—7.14 (m, 2H), 2.44 (s, 3H), 2.35 (s, 3H).

4-Chloro-*N*-*p*-tolylbenzamide and *N*-(4-chlorophenyl)-4-methylbenzamide (2d) ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.27 (brs, 1H), 10.21 (brs, 1H), 7.98 (d, J=8.4 Hz, 2H), 7.87 (d, J=8.0 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H), 7.64 (d, J=8.2 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H), 7.33 (d, J=7.9 Hz, 2H),

7.15 (d, *J*=8.2 Hz, 2H), 2.38 (s, 3H), 2.27 (s, 3H).

4-Methoxy-*N*-*p*-tolylbenzamide and *N*-(4-methoxyphenyl)-4-methylbenzamide (2e) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17 (brs, 1H), 8.16 (brs, 1H), 7.80 (d, *J*=8.4 Hz, 2H), 7.74 (d, *J*=7.7 Hz, 2H), 7.53 (d, *J*=6.3 Hz, 2H), 7.51 (d, *J*=5.1 Hz, 2H), 7.19 (d, *J*=7.7 Hz, 2H), 7.11 (d, *J*=7.9 Hz, 2H), 6.86 (d, *J*=9.6 Hz, 2H), 6.84 (d, *J*=9.2 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H).

***N*-(4-Chlorophenyl)-4-methoxybenzamide and 4-chloro-*N*-(4-methoxyphenyl)benzamide (2f)** ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.22 (brs, 1H), 10.20 (brs, 1H), 7.98 (d, *J*=6.9 Hz, 2H), 7.96 (d, *J*=6.7 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 7.68 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=8.4 Hz, 2H), 6.92 (d, *J*=8.6 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H).

***N*-*p*-Tolylacetamide (2g)** m.p. 149—150 ℃ (Lit[18] 149—151 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.28 (brs, 1H), 7.40 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.1 Hz, 2H), 2.30 (s, 3H), 2.12 (s, 3H).

***N*-(4-Methoxyphenyl)acetamide (2h)** m.p. 128—129 ℃ (Lit[18] 129—130 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09 (brs, 1H), 7.38 (d, *J*=8.8 Hz, 2H), 6.81 (d, *J*=8.5 Hz, 2H), 3.76 (s, 3H), 2.10 (s, 3H).

***N*-(2-Methoxyphenyl)acetamide (2i)** m.p. 85—86 ℃ (Lit[18] 85—86 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.35 (d, *J*=7.8 Hz, 1H), 7.79 (brs, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 6.94 (t, *J*=7.4 Hz, 1H), 6.86 (d, *J*=8.0 Hz, 1H), 3.86 (s, 3H), 2.18 (s, 3H).

***N*-(3-Methoxyphenyl)acetamide (2j)** m.p. 81—82 ℃ (Lit[18] 87—88 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.58 (brs, 1H), 7.28 (s, 1H), 7.16 (t, *J*=8.1 Hz, 1H), 7.04 (d, *J*=7.9 Hz, 1H), 6.64 (d, *J*=8.0 Hz, 1H), 3.73 (s, 3H), 2.13 (s, 3H).

***N*-Phenylpropionamide (2k)** m.p. 106—107 ℃ (Lit[18] 103—104 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.30 (brs, 1H), 7.55 (d, *J*=7.9 Hz, 2H), 7.27 (t, *J*=7.7 Hz, 2H), 7.08 (t, *J*=7.3 Hz, 1H), 2.37 (q, *J*=7.5 Hz, 2H), 1.21 (t, *J*=7.6 Hz, 3H).

***N*-(4-Chlorophenyl)acetamide (2l)** m.p. 180—181 ℃ (Lit[27] 180 ℃); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.05 (brs, 1H), 7.60 (d, *J*=8.5 Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 2.04 (s, 3H).

Azacyclotridecan-2-one (2m) m.p. 150—151 ℃ (Lit[28] 143—145 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.07 (brs, 1H), 3.26 (dd, *J*=5.7, 10.5 Hz, 2H), 2.19—2.16 (m, 2H), 1.68—1.62 (m, 2H), 1.55—1.45 (m, 2H), 1.34—1.27 (m, 14H).

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