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Gallium (III) triflate catalyzed Beckmann rearrangement

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☆Dedicated to Professor Gabor Somorjai on the occasion of his 70th birthday with admiration and friendship.

Gallium triflate catalyzed Beckmann rearrangement is described. Various aliphatic or aromatic amides are obtained from the corresponding ketoximes in good yields. Gallium triflate exhibits high catalytic activity for a wide variety of substrates.

KEY WORDS: gallium triflate; Beckmann rearrangement; homogeneous catalysis; ketoximes; amides.

1. Introduction

The Beckmann rearrangement [1] is a classic transformation to synthesisze amides from ketoximes. Beckmann rearrangement is industrially important for the manufacture of Nylon-6 precursor, ε-caprolactam, from cyclohexanone oxime. Furthermore, Beckmann rearrangement provides a facile route for the incorporation of nitrogen into polycyclic structures for the synthesis of important pharmaceuticals or natural products. This reaction usually takes place in strongly acidic and dehydrating media, such as sulfuric acid, polyphosphoric acid, PCl_5, $SOCl_2$, etc., thus preventing its application to sensitive substrates. Cosequently, research is being pursued to make the process mild and catalytic. Although numerous reagents have been introduced so far for the Beckmann rearrangement, they suffer from various economic and environmental problems [2g]. Recent reports include the applications of chloral [2a], PPh_3/chlorosuccinimide [2b], $Yb(OTf)_3$ [2c], $In(OTf)_3$ [2d], $Rh/CF_3SO_3H/(p\text{-toly})_3P$ [2e], 2,4,6-trichloro[1,3,5]triazine[2f] and $AlCl_3{\cdot}6H_2O/KI/H_2O/CH_3CN$ [2g] as catalysts in Beckmann rearrangement. Reactions adapted to vapor-phase [3], ionic liquid phase [4], solid phase [5] and hydrated media [6] are also reported. As an extension of our ongoing efforts in the use of $Ga(OTf)_3$ as a water tolerant strong Lewis acid catalyst in organic transformations [7,8], we examined the Beckmann rearrangement of ketoximes.

2. Experimental

2-Butanone oxime (99%) and cyclohexanone oxime were purchased from Aldrich. Acetophenone oxime (98%) was obtained from Lancaster Chemicals. Benzophenone oxime, pivalophenone oxime, 1-tetralone oxime, 2-methylcyclohexanone oxime, *p*-methoxyacetophenone oxime and *m*-nitroacetophenone oxime were prepared from the corresponding ketones and hydroxylamine hydrochloride ($NH_2OH{\cdot}HC1$). Gallium triflate was prepared as described earlier [8]. ^1H and ^{13}C NMR spectra were obtained on a 360 MHz superconducting NMR spectrometer. Chemical shifts were referenced to tetramethylsilane.

A typical reaction was carried out in a closed glass tube. The oxime (1 mmol) was weighed into the tube and dissolved in 2 mL dry CH_3CN. Subsequently, 26 mg (0.05 mmol) of gallium triflate was added to give a homogeneous reaction mixture. In the cases of less reactive substrates, larger amounts of catalysts (up to 50 mol%) were used (Table 1). The tube was heated to the desired temperature and the reaction mixture was periodically monitored by TLC (silica gel, CH_2Cl_2/CH_3OH mixtures) for completion of the reaction. The mixture was cooled at the end of the reaction. In some cases, the product precipitated and was easily separated by filtration followed by washing with a small amount of acetonitrile. Otherwise, the reaction mixture was quenched with water and extracted using diethyl ether (three to five times). The combined organics were dried over anhydrous magnesium sulfate and then solvents were removed at reduced pressure to give the crude product. In most cases, product was almost pure and directly characterized by GC-MS and NMR. Otherwise, the products were purified by column chromatography (silica gel, CH_2Cl_2/CH_3OH mixtures) before analysis. The spectral data of the known compounds are consistent with those reported, and the NMR data of the new compounds are listed below.

2.1. *N-(p-methoxyphenyl)acetamide*

NMR ^1H (360 MHz, $CDCl_3$): δ2.15 (s, 3H), 3.80 (s, 3H), 6.86 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.88 (br s, NH). ^{13}C (90 MHz, $CDCl_3$): δ24.1, 55.4, 114.0, 122.1, 131.2, 156.4, 168.8.

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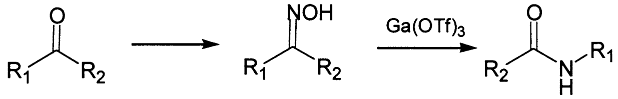
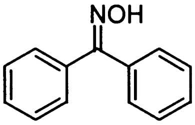
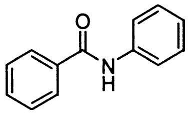
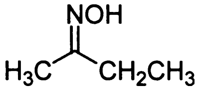
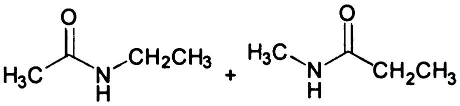
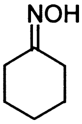
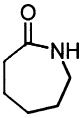
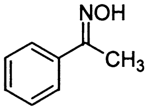
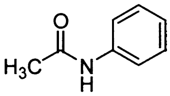
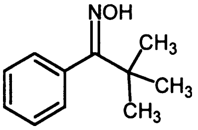
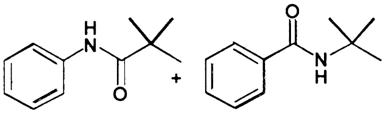
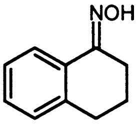
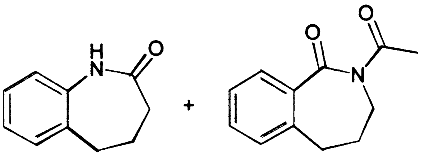
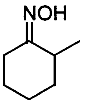
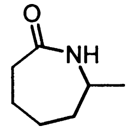
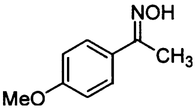
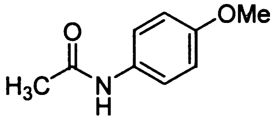
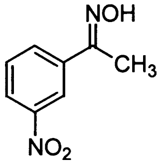
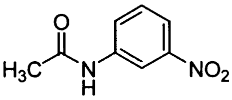
Table 1

Beckmann rearrangement of ketoxime in CH_3CN by $Ga(OTf)_3$



	Ketoxime	Product	Temp (°C)	Time	Catalyst (mol%)	Yield (%)
1			40	20 min	5	93
2		 10 : 1	85	2 h	5	90
3			85	1 h	50	92
4			85	2 h	5	96
5		 5.3 : 1	85	16 h	10	68
6		 1.3 : 1	120	4 h	50	75
7			85	3 h	25	94
8			85	3 h	5	98
9			85	15 h	10	78

2.2. *N-(m-nitrophenyl)acetamide*

NMR ^{1}H (360 MHz, acetone-d^6): δ2.02 (s, 3H), 7.41 (t, 1H), 7.76 (m, 2H), 8.56 (s, 1H), 9.70 (br s, NH). ^{13}C (90 MHz, acetone-d^6): δ24.2, 114.2, 118.4, 125.5, 130.6, 141.4, 149.3, 169.9.

2.3. *1,3,4,5-Tetrahydro-1H-benzo[b]azepin-2-one*

NMR ^{1}H (360 MHz, $CDCl_3$): δ 2.17–2.42 (m, 4H), 2.80 (t, 2H, J = 7.0 Hz), 6.99–7.29 (m, 4H), 8.73 (br s). ^{13}C (90 MHz, $CDCl_3$): δ28.6, 30.3, 32.8, 121.9, 125.6, 127.5, 129.7, 134.3, 138.0, 175.8.

2.4. *N-acetyl-2,3,4,5-Tetrahydro-1H-benzo[c]azepin-l-one*

NMR ^{1}H (360 MHz, $CDCl_3$): δ1.99 (quintet, J = 6.8 Hz, 2H), 2.63 (s, 3H), 2.81 (t, J = 6.8 Hz, 2H), 3.77 (t, J = 6.8 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.38 (t, 1H), 7.48 (t, 1H), 7.78 (d, J = 7.3 Hz, 1H). ^{13}C (90 MHz, $CDCl_3$): δ26.7, 26.8, 30.1, 41.4, 127.3, 129.0, 129.7, 132.8, 138.1, 172.4, 172.9.

3. Results and discussion

Benzophenone oxime was used as a substrate to optimize the conditions for the $Ga(OTf)_3$ catalyzed Beckmann rearrangement. Diethylether, dimethoxyethane and CH_2Cl_2 were not suitable as solvents due to their poor solubility of the ketoxime or the catalyst. Although polar solvents deactivate the catalyst to some extent, we discovered that the reaction in acetonitrile is very effective in the presence of only 5 mol% catalyst. At room temperature, we observed precipitation of products and obtained 50% conversion in 2 h. However, raising temperature to 40 °C gives complete conversion in only 20 min (entry 1, Table 1).

Applying similar reaction conditions to other substrates, we also obtained excellent yields of Beckmann rearrangement products using 5–50 mol% catalyst between 85 and 120 °C. In the course of optimization of the reaction conditions, we found that in the cases of low yields, main reaction involved was the regeneration of the corresponding ketone through hydrolysis. As shown in the table, under $Ga(OTf)_3$ catalysis, both aromatic and aliphatic ketoximes are able to rearrange to give the corresponding amides in good to excellent yields.

Usual migratory aptitude of Beckmann rearrangement is followed with the listed substrates. For example, in all cases of substituted acetophenone oximes (entries 4, 8 and 9), only migration of the aryl group is observed without any product from migration of the methyl group. However, if the migratory aptitudes of the two substituents are close, mixture of products was obtained. Pivalophenone oxime (entry 5) as anticipated produces both N-*tert*-butylbenzamide and pivalanilide, but the migration of phenyl group is still favored over that of the *tert*-butyl group by a factor of 4. As is customary in Beckmann rearrangements, electron-donating groups on the aromatic ring facilitate the reaction, and electron-withdrawing groups retard it. Thus, *m*-nitroacetophenone oxime (entry 9) requires prolonged reaction times than acetophenone oxime (entry 4). Nevertheless, the yield of the product is satisfactory.

Larger amounts of catalysts are required for cyclic ketoximes (entries 3, 6 and 7) due to the ring strain present in the seven membered lactam rings. Specifically, α-tetralone oxime (entry 6) also needs higher temperature (120 °C) and proceeds with 50 mol% catalyst. Two products are obtained involving migration of both carbons adjacent to the oxime carbon. At such higher temperature, the solvent CH_3CN itself is activated to react further with the Beckmann rearrangement product to give the N-acetyl amide **3** (figure 1). Because access to the nitrogen atom in product **1** is sterically unfavorable, only product **2** undergoes the acetylation by acetonitrile.

It has been recognized that Beckmann rearrangement is stereospecific and generally the group *anti* to the hydroxyl group on the ketoxime will selectively migrate. This behavior has also been used to assign *syn* or *anti* configuration of oximes. The starting oximes used in the present study are mixtures of *syn* and *anti* isomers (where applicable), but in most cases we obtained a

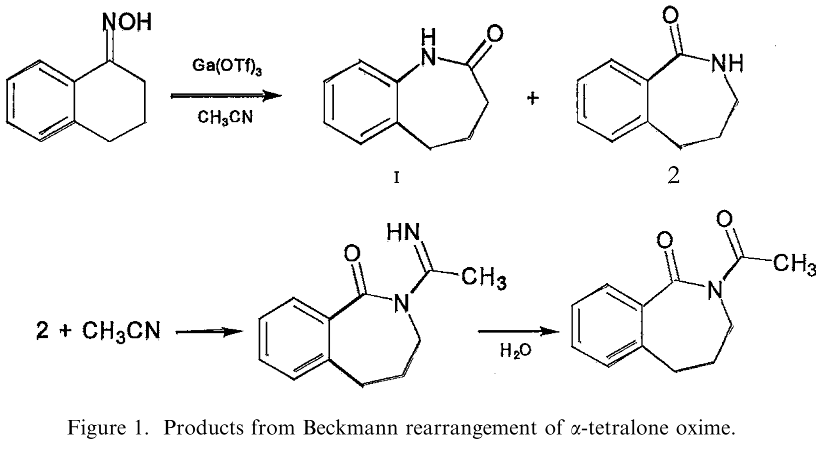


Figure 1. Products from Beckmann rearrangement of α-tetralone oxime.

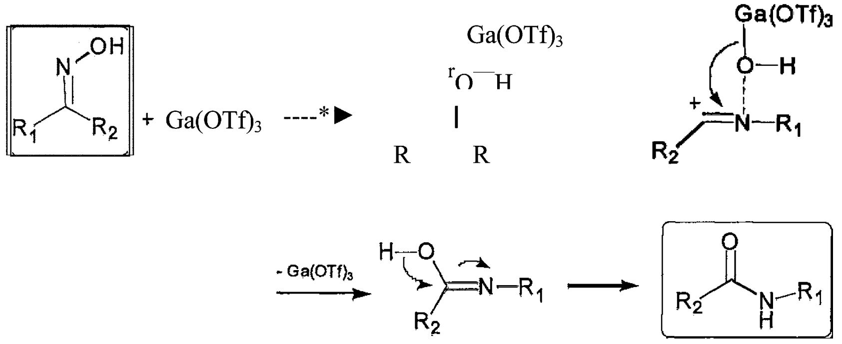


Figure 2. Mechanism of $Ga(OTf)_3$ catalyzed Beckmann rearrangement.

majority of a single amide isomer as the product, which is favored based on the migratory aptitude. This indicates that $Ga(OTf)_3$ is also capable of catalyzing the *syn–anti* isomerization of oximes under the conditions of Beckmann rearrangement. The equilibrium among involved isomers is faster than the rearrangement so that the product composition is determined by the relative rates of migration of the involved groups and is independent of the stereochemistry of the starting oximes.

The mechanism of $Ga(OTf)_3$ catalyzed Beckmann rearrangement is suggested in figure 2.

4. Conclusion

Gallium triflate was found to be an excellent homogeneous catalyst to promote the Beckmann rearrangement of a wide variety of a ketoximes into the corresponding amides in acetonitrile solution. Gallium triflate, a strong and potentially recyclable Lewis acid catalyst [7,8], not only extends the scope of Beckmann rearrangement, but also can be a viable substitute for corrosive acid catalysts presently used.

Acknowledgments

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