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Beckmann Rearrangement of Oximes Using Doped Silica Gel Complex

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A new complex of perchloric acid absorbed on silica gel (doped silica gel) and dichloromethane was found to be very effective for converting ketoximes into their corresponding amides or lactams with excellent conversion *via* the Beckmann rearrangement. This method offers significant advantages such as efficiency and mild reaction conditions with shorter reaction time.

Keywords: Doped silica gel/dichloromethane, Beckmann rearrangement, Ketoximes, Amides.

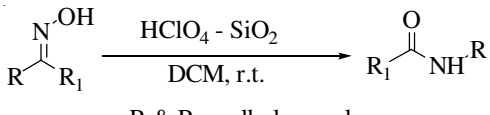
INTRODUCTION

The conversion of ketoxime into corresponding amide, known as the Beckmann rearrangement, is a common method used in organic chemistry and is also a topic of current interest. It accomplishes both the cleavage of C-C bond and the formation of a C-N bond and represents a powerful method particularly for manufacture ε-caprolactam in chemical industry[1-2].

The Beckmann rearrangement of oximes to lactams is a very important commercial process for the production of raw material of polyamides such as nylon-6 and nylon-12[3]. Currently, the Beckmann rearrangement is carried out using oleum as a catalyst, which results in undesired sulfates as by-products and requires a large amount of a strong acid such as sulfuric acid[4]. Until now the mild conditions were related to the formation of activation of oxime derivatives followed by rearrangement, for example, using chloral[5], anhydrous oxalic acid[6], sulfamic acid[7], chlorosulfonic acid[8], cyanuric chloride/DMF[9], ethyl chloroformate/boron trifluoride etherate[10], *etc*. Although various protocols have been reported[11], they have their own drawbacks such as the use of toxic solvents, expensive reagents, formation of undesired by products, prolonged reaction timings, tedious workup procedures and low yields[12].

Nevertheless, until now the occurrence of mild conditions was only related to the use of rather toxic and expensive reagents and homogeneous catalyst system. On the other hand, the problem, which is almost common to homogeneous catalyst system, is that it is very difficult to separate the product from the resulting mixtures, in order to obtain a neat desired product large amounts of basic neutralization agent has to be used, which lead to the large amounts of byproducts. Therefore, it is necessary to develop a green, simple and low-cost catalyst system for Beckmann rearrangement of ketoxime.

Therefore, the development of a sulfate-free, green and simple system for Beckmann rearrangement of ketoximes, has been of interest to organic chemists. The search for improved conditions for the rearrangement of ketoximes to the corresponding amides essentially involves a search for an efficient mild electrophilic reagent and herein we wish to report a simple and efficient protocol for the Beckmann rearrangement using perchloric acid adsorbed on silica gel and DCM complex (**Scheme-I**).



R & R_1 = alkyl or aryl

Scheme-I: General scheme

The search for improved conditions for the Beckmann reaction essentially involves a search for new electrophilic reagents with the desired characteristics of mildness, *etc*. (The reaction occurs under conditions of electrophilic activation of the oxime hydroxyl group[1]) Generally, a variety of Brønsted and strong Lewis acids have been employed as reagents, *e.g*., *p*-toluenesulphonic acid, $SnCl_4$, PCl_5, *etc*. However, mild Lewis acids have hardly ever been reported to the best of our knowledge. It was of interest to investigate the possible use of pivaloyal chloride in view of its ready availability and known Lewis acidic properties.

EXPERIMENTAL

All the reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before being used. Melting points were determined using a Buchi melting point apparatus and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) performed on silica gel G (Merck) and spots were exposed to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^{1}H NMR spectra were recorded on Brucker DPX-400 at 400 MHz (chemical shifts in d, ppm) and Mass spectra on an Agilent LC-MS instrument giving only M^+ values in Q + 1 mode.

General procedure for conversion of ketoximes to acetamides with doped silica gel and DCM complex: To the mixture of $HClO_4$-SiO_2 (doped silica gel) (1.3 mmol) and DCM (5 mL) added the solution of ketoxime (0.1 g, 0.66 mmol) in DCM (5 mL) at room temperature. The reaction was monitored (TLC) until the complete disappearance of starting material. Water (10 mL) was added and then the organic phase was washed with 2.5 mL of a saturated solution of $NaHCO_3$, followed by 1 N HCl and brine. The organic layers were dried over Na_2SO_4 and the solvent evaporated to yield acetamide.

***N*-(4-Hydroxyphenyl)acetamide (1):** m.p. 167-168 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.39 (bs, 1H), 8.92 (s, 1H), 7.55 (d, 2H), 6.95 (d, 2H), 2.04 (s, 3H); ^{13}C NMR: 168.4, 153, 130.1, 121.7, 115.4, 24.2. MS (CI): *m/z* 152 [M^+ + 1] [Found: C, 63.98; H, 5.99; N, 9.03; $C_8H_9NO_2$ requires C, 63.56; H, 6.00; N, 9.27].

***N*-(3-Hydroxyphenyl)acetamide (2):** m.p. 147-149 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (bs, 1H), 8.94 (s, 1H), 7.33 (m, 1H), 7.05 (t, 1H), 6.89 (d, 1H), 6.54 (d, 1H), 2.08 (s, 3H); ^{13}C NMR: 169.1, 157.5, 139.6, 129.3, 113, 110.7, 107.2, 24.2. MS (CI): *m/z* 152 [M^+ + 1] [Found: C, 63.52; H, 6.17; N, 9.09; $C_8H_9NO_2$ requires C, 63.56; H, 6; N, 9.27.

***N*-(2-Hydroxyphenyl)acetamide (3):** m.p. 208-209 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (bs, 1H), 8.69 (s, 1H), 7.48 (d, 1H), 7.02 (t, 2H), 6.85 (d, 1H), 2.24 (s, 3H); ^{13}C NMR: 169.5, 147.5, 126.9, 125.6, 123.1, 121.2, 116.6, 22.8. MS (CI): *m/z* 152 [M^+ + 1] [Found: C, 63.27; H, 6.13; N, 9.11; $C_8H_9NO_2$ requires C, 63.56; H, 6; N, 9.27].

***N*-(4-Methylphenyl)acetamide (4):** m.p. 148-150 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (bs, 1H), 7.48 (d, 2H), 7.01 (d, 2H), 2.24 (s, 3H), 2.09 (s, 3H); ^{13}C NMR: 169.5, 134.5, 133.1, 128.6, 128.2,121.2, 120.9, 23.8,22.6. MS (CI): *m/z* 150 [M^+ + 1] [Found: C, 72.55; H, 7.25; N, 9.54; $C_9H_{11}NO$ requires C, 72.46; H, 7.43; N, 9.39].

***N*-(4-Chlorophenyl)acetamide (5):** m.p. 175-176 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.58 (bs, 1H), 7.48 (d, 2H), 7.12 (d, 2H), 2.09 (s, 3H); ^{13}C NMR: 168.7, 134.5, 130.1, 128.6, 128.2,121.2, 120.9, 23.8. MS (CI): *m/z* 170 [M^+ + 1] [Found: C, 56.72; H, 4.86; Cl, 20.88; N, 8.14, C_8H_8NOCl requires C, 56.65; H, 4.75; Cl, 20.90; N, 8.26].

***N*-(4-Bromophenyl)acetamide (6):** m.p. 165-168 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.68 (bs, 1H), 7.51 (d, 2H), 7.32 (d, 2H), 2.07 (s, 3H); 13C NMR: 169.7, 137.5, 131.7, 131.2, 123.4,123.2, 119.2, 23.8. MS (CI): *m/z* 215 [M^+ + 1] [Found: C, 44.55; H, 3.81; Br, 37.12; N, 6.67, C_8H_8NOBr requires C, 44.89; H, 3.77; Br, 37.33; N, 6.54].

***N*-(4-Methoxyphenyl)acetamide (7):** m.p. 128-129 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (bs, 1H), 7.48 (d, 2H), 6.69 (d, 2H), 3.54 (s, 3H), 2.07 (s, 3H); ^{13}C NMR: 169.3, 154.5, 133.1, 122.4, 122.2,113.9, 113.5, 53.8,22.7. MS (CI): *m/z* 166 [M^+ + 1] [Found: C, 65.55; H, 6.65; N, 8.52, $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48].

***N*-(2-Nitrophenyl)acetamide (8):** m.p. 92-94 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.94 (bs, 1H), 8.14 (d, 1H), 7.72 (d, 1H), 7.63 (t, 1H), 7.38 (t, 1H), 2.16 (s, 3H); ^{13}C NMR: 169.1, 141.3, 135.6, 134.9, 126.5, 124.2, 121.4, 23.2. MS (CI): *m/z* 181 [M^+ + 1] [Found: C, 53.29; H, 4.50; N, 15.62; $C_8H_8N_2O_3$ requires C, 53.33; H, 4.48; N, 15.55].

***N*-(3-Nitrophenyl)acetamide (9):** m.p. 155-156 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (bs, 1H), 8.20 (s, 1H), 8.04 (d, 1H), 7.94 (d, 1H), 7.52 (t, 1H), 2.09 (s, 3H); ^{13}C NMR: 170.1, 148.3, 138.5, 128.9, 126.5, 116.2, 115.4, 22.7. MS (CI): *m/z* 181 [M^+ + 1] [Found: C, 53.35; H, 4.49; N, 15.56, $C_8H_8N_2O_3$ requires C, 53.33; H, 4.48; N, 15.55].

3,4-Dihydro-2(1*H*)-quinolone (10): m.p. 165-166 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (bs, 1H), 7.53 (d, 1H), 7.09 (d, 1H), 7.07 (t, 1H), 6.91 (t, 1H), 2.90 (t, 2H), 2.51 (t, 2H); ^{13}C NMR: 170.1, 137.3, 131.5, 128.9, 126.5, 124.2, 121.4, 29.7, 26.3. MS (CI): *m/z* 148 [M^+ + 1] [Found: C, 73.39; H, 6.09; N, 9.66; C_9H_9NO requires C, 73.45; H, 6.16; N, 9.52].

RESULTS AND DISCUSSION

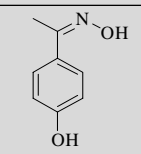
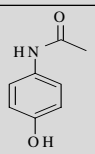
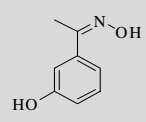
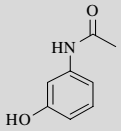
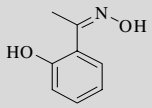
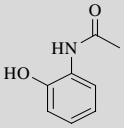
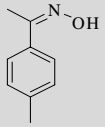
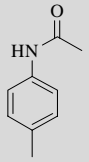
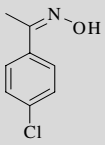
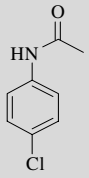
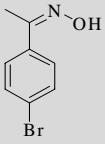
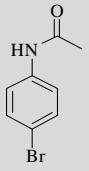
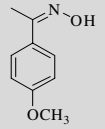
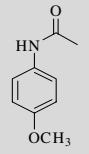
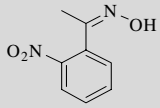
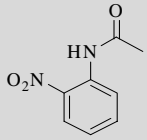
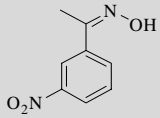
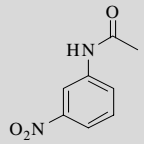
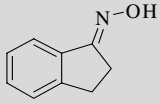
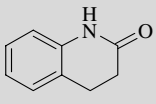
Herein we wish to present our results for a very mild and efficient conversion of ketoxime into corresponding amide. In a typical experimental procedure doped silica gel and DCM are mixed together to form a complex which is found to be reactive, leading to Beckmann rearrangement when treated with ketoximes. Classical Beckmann rearrangement generally requires high reaction temperatures and strongly acidic and dehydrating media[13]. But what we observed is that when we use doped silica gel and DCM complex reaction proceeds in room temperature without need of strong acids and dehydrating conditions.

The doped silica gel complex[14] added to stirring solution of ketoxime in DCM at room temperature. Reaction was monitored by TLC, water was added and then the organic phase was washed with saturated solution of sodium carbonate followed by 1 N HCl solution and brine. The corresponding amides were recovered chemically pure in high yields.

To understand the scope and applicability of this reagent for Beckmann rearrangement, various substrates were scanned (Table-1) and observed that when electron releasing or withdrawing group is in *ortho* or *para* position of aromatic ring reaction proceeds for longer time (6-12 h).

A possible explanation for reaction mechanism is discussed in **Scheme-II**. Addition of proton from perchloric acid to oxime followed by removal of water. In the transition state leading to the iminium ion (σ-complex), the methyl group migrates to the nitrogen atom in a concerted reaction and the hydroxyl group is expulsed. In the next step the electrophilic carbon atom in the nitrilium ion is attacked by water and the proton is donated back to perchloric acid. In the transition state leading to the N-methyl acetimidic acid, the water oxygen

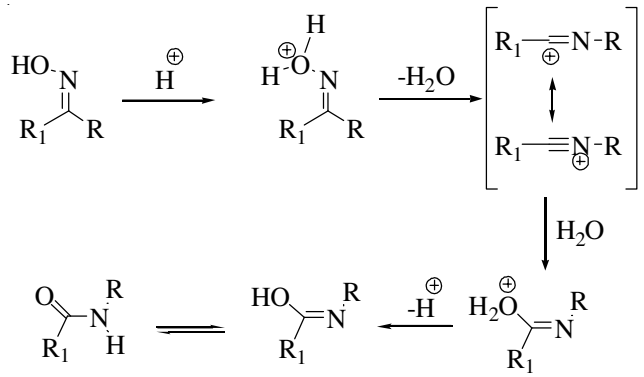
TABLE-1
CONVERSION OF KETOXIMES TO AMIDES

Entry	Oximes	Amides	Reaction time (h)	Conversion (%)
1			12	98
2			6	98
3			11	90
4			9	90
5			8	90
6			9	85
7			9	81
8			8	81
9			6	85
10			8	78

atom is coordinated to 4 other atoms. In the third step, an isomerization step protonates the nitrogen atom leading to the amide.

Conclusion

In conclusion, a mild, general and efficient conversion of oximes to corresponding amides has been developed. The key feature of this method is that use of perchloric acid adsorbed silica gel/DCM as a mild, non-toxic and inexpensive reagent. This method seems to be convenient with respect to other existing reports and can be used as an alternative, which will avoid tedious purifications or the use of toxic or expensive reagents.



Scheme-II: Proposed mechanism

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