Citric acid catalysed Beckmann rearrangement, under solvent free conditions

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Citric acid is reported to be a highly efficient and eco-friendly catalyst for the Beckmann rearrangement under solvent free conditions.

Keywords: amides, Beckmann rearrangement, citric acid, eco-friendly catalyst, solvent free conditions

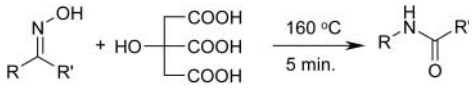
Green chemistry has attracted an increasing interest in recent years[1–4] due to the growing concern over environmental pollution; arising from the use of toxic solvents. The problem may be addressed by recycling the solvents or using environmentally benign solvents. However, the most promising approach is to perform organic reactions under solvent-free conditions. Solvent-free reactions have received considerable attention in recent years, not only for ecological and economical reasons, but also for simplicity in procedures, high yields of products and short reaction times. A number of organic reactions require acid catalyst which generate toxic waste that is harmful to the environment. The development of cheap, naturally occurring, green acid catalyst could change the traditional procedures into green ones, thus minimising chemical waste further.

As a part of ongoing program related to the development of a clean and eco-friendly acid catalyst, citric acid was considered as a possible candidate. It is widely distributed in nature, and is readily and cheaply available. Beckmann rearrangement is a powerful tool in organic synthesis[5,6] and is also a topic of current interest. Several acids such as trifluromethanesulfonic acid,[7] chlorosulfonic acid,[8] sulfamic acid,[9] anhydrous oxalic acid,[10] p-toluenesulfonic acid[11] have been employed for this reaction. However, these methods suffers from certain drawbacks such as use of toxic/costly solvents, expensive reagents, co-catalysts, production of considerable amount of by-products, long reaction time and low yields. Therefore, the development of a simple, inexpensive, highly efficient yet eco-friendly catalyst for Beckmann rearrangement is worthwhile. We report here a simple and highly efficient protocol for Beckmann rearrangement using citric acid as a green catalyst under solvent free conditions.

Results and discussion

Initially, acetophenone oxime (1.00 g) (Table 1, Entry 1) and anhydrous citric acid **2** (1.20 equiv.), were heated at 160 °C in preheated oil bath for five minutes to afford acetanilide (0.930 g, 93 % yield). In order to establish the optimum reaction conditions, we examined the effect of the amount of citric acid on the Beckmann rearrangement of acetophenone oxime. It was found that 0.33 equivalent citric acid was sufficient to afford similar results. However, the use of less than 0.33 equivalents of citric acid resulted in low yield of the product along with the recovery of the starting material. This result showed that 0.33 equivalent of citric acid was enough for the complete conversion of the starting material. To check the generality and scope of this reaction, various ketoximes were subjected to the Beckmann rearrangement under the above conditions. Result showed that the Beckmann rearrangement of various ketoximes proceeded smoothly to completion within five minutes to give the corresponding amides in good to excellent yield (Table 1).

Table 1 Citric acid catalysed Beckmann rearrangement of ketoximes under solvent free condition



33 mol. %

1 **2** **3**

Entry	R	R′	3 % yield[a, b]
1	Ph	Me	93
2	4-Me-C_6H_4	Me	92
3	4-OMe-C_6H_4	Me	93
4	4-Br-C_6H_4	Me	72
5	2-OH-C_6H_4	Me	88
6	2-OMe-C_6H_4	Me	95
7	3-NH_2-C_6H_4	Me	90
8	3-NO_2-C_6H_4	Me	90
9	Ph	Et	84
10	Ph	n-Propyl	85
11	4-OMe-C_6H_4	n-Propyl	92
12	Naphth-1-yl	Me	94
13	Naphth-2-yl	Me	90
14	Thiophene-2-yl	Me	70
15	t-Butyl	Me	68
16	Ph	Ph	97
17	4-Me-C_6H_4	4-Me-C_6H_4	89

[a] Isolated yield

[b] All the products were identified spectroscopically (IR, ^{1}H, ^{13}C NMR and GCMS)

Conclusion

In conclusion, we have shown that citric acid can be used as an environment-friendly acid catalyst. It efficiently catalyses the Beckmann rearrangement of a variety of ketoximes into corresponding amides under solvent free condition in short time. The operational simplicity, use of commercially available natural catalyst, solvent free reaction condition, short reaction time, easy work up and high yield makes this catalyst a more convenient alternative to the reported catalysts. Further studies are in progress to expand the scope of this catalyst in organic synthesis.

Experimental

Reactions were performed in oven-dried glassware under a N_2 atmosphere and were monitored by TLC silica gel plates (60 F_{254}) which were visualised by UV and $KMnO_4$ solution. All solvents and reagents were used as obtained from commercial source. The oximes were prepared by standard methods and their purities were established before utilisation by melting point. Standard ^{1}H NMR and ^{13}C NMR were recorded on a Varian Mercury spectrometer at 300 and 75 MHz respectively in $CDCl_3$ solution and with TMS as an internal standard. IR spectra were recorded on Perkin Elmer Model 1600 series FTIR instrument. Low resolution mass spectra were recorded on Shimadzu GC-MS - Q 5050A, connected to GC-17A, at an ionisation potential 70 eV and the fragmentation pattern is given after the corresponding *m/z* value.

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General procedure: The mixture of ketoxime (1.00 g) and anhydrous citric acid (33 mol %) was heated in an oil bath, preheated at 160 °C under nitrogen atmosphere. The reaction commenced with effervescence and was completed in 5 minutes (TLC check). The brownish black molten mass was cooled to room temperature, water (10.00 mL) and ethyl acetate (10.00 mL) were added. Reaction mixture was neutralised by addition of solid $NaHCO_3$. Organic layer was separated and the aqueous layer was extracted in ethyl acetate (2 × 10.00 mL). Combined organic extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane-ethyl acetate solvent system to give the corresponding amide in high yield.

Acetanilide (entry 1): M.p. 113–114 °C (lit.[12,13] m.p. 114 °C); IR $\tilde{\nu}$: 3295, 2856, 1663, 1599, 1500, 909, 848, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.14 (3H, s), 7.09 (1H, t, *J* = 7.5 Hz), 7.28 (2H, m), 7.53 (2H, m), 8.34 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2 (CH_3), 120.1 (2 × CH), 124.1 (CH), 128.7 (2 x CH), 137.9 (C), 169.0 (–CONH–); GC-MS (%): 135 (M^+, 28), 93 (100), 77 (5), 66 (20), 43 (24).

N-(4-Methylphenyl)acetamide (entry 2): M.p. 145–146 °C (lit.[14] m.p. 149–150 °C); IR $\tilde{\nu}$: 3293, 3122, 2944, 1666, 1604, 1454, 821, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.28 (3H, s), 7.06 (2H, d, *J* = 8.4 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 8.21 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (CH_3), 24.2 (CH_3), 120.1 (2 x CH), 129.3 (2 × CH), 133.7 (CH), 135.3 (CH), 168.7 (–CONH–); GC-MS (%): 149 (M^+, 40), 107 (100), 91 (6), 77 (22), 65 (5), 43 (24).

N-(4-Methoxyphenyl)acetamide (entry 3): M.p. 130 °C (lit.[12] m.p. 130 °C); IR $\tilde{\nu}$: 3243, 2836, 1648, 1514, 1369, 1247, 1031, 839, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (3H, s), 3.75 (3H, s), 6.79 (2H, d, *J* = 6.8 Hz), 7.39 (2H, d, *J* = 6.8 Hz), 8.28 (1H, s); ^{13}C NMR (75MHz, CDCl3): δ 23.9 (CH_3), 55.3 (O-CH_3), 113.8 (2 x CH), 122.0 (2 x CH), 131.1 (C), 156.2 (C), 168.8 (–CONH–); GC-MS (%): 165 (M^+, 45), 123 (58), 108 (100), 95 (10), 80 (15), 65 (5), 43 (24).

N-(4-Bromophenyl)acetamide (entry 4): M.p. 165–167 °C (lit.[12] m. p. 167 °C); IR $\tilde{\nu}$: 3300, 3115, 1667, 1600, 1530, 831, 741, 504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71 (1H, s), 2.17 (3H, s), 7.38–7.44 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5 (CH_3), 116.8 (C), 121.3 (2 x CH), 131.9 (2 x CH), 136.9 (C), 168.3 (–CONH–); GC-MS (%): 213, 215 (M^+, M^++2, 1:1, 29), 169, 171 (1:1, 100), 92 (55), 65 (35), 63 (24).

N-(2-Hydroxyphenyl)acetamide (entry 5): M.p. 209–210 °C (lit.[12,13] m.p. 209 °C); ^1H NMR (300 MHz, DMSO): δ 2.10 (3H, s), 6.75 (1H, m), 6.95 (2H, m), 7.67 (1H, d, *J* = 7.7 Hz), 9.33 (1H, s), 9.76 (1H, s); ^{13}C NMR (75 MHz, DMSO): δ 23.5 (CH_3), 115.9 (CH), 118.9 (CH), 122.4 (C), 124.6 (CH), 126.3 (C), 147.9 (CH), 169.0 (–CONH–).

N-(2-methoxyphenyl)acetamide.(entry 6): M.p. 87–88 °C (lit.[12] m. p. 88 °C); ^1H NMR (300 MHz, $CDCl_3$): δ 2.17 (3H, s), 3.84 (3H, s), 6.83–7.04 (3H, m), 7.81 (1H, s), 8.38 (1H, d, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7 (CH_3), 55.4 (O-CH_3), 109.7 (CH), 119.6 (CH), 120.8 (CH), 123.4 (CH), 127.5 (C), 141.5 (C), 168.1 (–CONH–).

Propionanilide (entry 9): M.p. 106–107 °C (lit.[12] m.p. 106 °C); IR $\tilde{\nu}$: 3262, 2978, 2934, 1668, 1602, 1546, 1496, 1440, 927, 751, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, t, *J* = 7.5 Hz), 2.36 (2H, q, *J* = 7.5 Hz), 7.07 (1H, t, *J* = 7.5 Hz), 7.27 (2H, t, *J* = 8.2 Hz), 7.52 (2H, d, *J* = 7.5 Hz), 7.98 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.6 (CH_3), 30.4 (CH_2), 119.9 (2 × CH), 124.0 (CH), 128.7 (2 × CH), 138.0 (C), 172.5 (–CONH–). GC-MS (%): 149 (M^+, 20), 77 (8), 93 (100), 57 (12), 51 (5).

Butyranilide (entry 10): M.p. 94–96 °C (lit.[12] m.p. 96 °C); IR $\tilde{\nu}$: 3274, 2961, 2868, 1659, 1599, 1500, 900, 760, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.2 Hz), 1.75 (2H, m), 2.31 (2H, t, *J* = 7.5 Hz), 7.07 (1H, m), 7.27 (2H, t, *J* = 7.2 Hz), 7.52 (2H, d, *J* = 7.2 Hz), 7.90 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.0 (CH_2), 39.4 (CH_2), 119.9 (2 x CH), 124.0 (CH), 128.7 (2 x CH), 138.0 (C), 171.8 (–CONH–); GC-MS (%): 163 (M^+, 15), 93 (100), 77 (9), 65 (10), 43 (22).

N-(4-Methoxyphenyl)butyramide (entry 11): M.p. 78–80 °C; IR $\tilde{\nu}$: 3283, 2965, 1647, 1606, 1537, 1522, 1242, 826, 781, 785, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.5 Hz), 1.72 (2H, m), 2.28 (2H, t, *J* = 7.5 Hz), 3.75 (3H, s), 6.80 (2H, d, *J* = 8.1 Hz), 7.40 (2H, *J* = 8.1 Hz), 7.85 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.0 (CH_2), 39.2 (CH_2), 55.3 (O–CH_3), 113.8 (2 x CH), 121.8 (2 x CH), 131.1 (C), 156.1 (C), 171.5 (–CONH–).

N-(1-Naphthyl)acetamide (entry 12): M.p. 162–163 °C (lit.[12] m.p. 163 °C); IR $\tilde{\nu}$: 3271, 3051, 1655, 1551, 1505, 1280, 792, 774, 721, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (3H, s), 7.34–7.82 (7H, m), 7.90 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 (CH_3), 121.0 (CH), 121.6 (CH), 125.5 (CH), 125.8 (CH), 125.9 (CH), 126.0 (CH), 127.5 (C), 128.5 (CH), 132.2 (C), 133.9 (C), 169.3 (–CONH–).

N-(2-Naphthyl)acetamide (entry 13): M.p. 170–171 °C (lit.[12] m.p. 171 °C); IR $\tilde{\nu}$: 3285, 3209, 1667, 1589, 1560, 1354, 1283, 885, 858, 817, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (3H, s), 7.39 (3H, m), 7.70 (3H, m), 8.15 (1H, s), 8.24 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4 (CH_3), 116.8 (CH), 120.0 (CH), 124.9 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 128.5 (CH), 130.5 (C), 133.6 (C), 135.3 (C), 169.1 (–CONH–).

N-(2-Thiophenyl)acetamide (entry 14): M.p. 150–152 °C. ^1H NMR (300 MHz, $CDCl_3$ /DMSO): δ 2.14 (3H, s), 6.73 (1H, m), 6.79 (2H, m), 10.69 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO): δ 22.2 (CH_3), 110.4 (CH), 116.1 (CH), 123.2 (CH), 139.4 (C), 166.4 (–CONH–).

2,2-Dimethyl-N-acetylethylamine (entry 15): M.p. 95–97 °C; IR $\tilde{\nu}$: 3285, 3208, 3082, 2966, 1639, 1557, 1225, 1038, 721, 611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 1.91(3H, s), 5.57 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3 (CH_3), 28.6 (3 x CH_3), 51.0 (C), 169.5 (–CONH–); GC-MS (%): 115 (M^+, 10), 71 (15), 58 (100), 42 (20), 27 (10).

Benzanilide (entry 16): M.p. 161–162 °C (lit.[12] m.p. 162 °C); IR: $\tilde{\nu}$: 3344, 3051, 1656, 1600, 1529, 1524, 1442, 1323, 925, 790, 725, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.10–7.20 (1H, m), 7.32–7.40 (2H, m), 7.41–7.58 (3H, m), 7.60–7.70 (2H, m), 7.60–7.92 (2H, m), 7.97 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.2 (2 x CH_3), 124.5 (CH), 126.9 (2 x CH), 128.7 (2 x CH_3), 129.0 (2 x CH_3), 131.7 (CH), 134.9 (C), 137.8 (C), 165.7 (–CONH–) ; GC-MS (%): 197 (M^+, 25), 105 (100), 77 (80), 65 (10), 51 (15).

N-(4-Methylphenyl)p-methylbenzanilide (entry 17): M.p. 158–160 °C (lit.[12] m.p. 160 °C); IR $\tilde{\nu}$: 3349, 3038, 1649, 1599, 1522, 814, 750, 704, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (3H, s), 2.36 (3H, s), 7.09 (2H, d, *J* = 7.6 Hz), 7.16 (2H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 7.6 Hz), 7.71 (2H, d, *J* = 7.6 Hz), 8.13 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (CH_3), 21.3 (CH_3), 120.3 (2 x CH), 127.0 (2 x CH), 129.1 (2 x CH), 129.3 (2 x CH), 132.0 (C), 133.8 (C), 135.4 (C), 141.9 (C), 165.8 (–CONH–).

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