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Yttrium (III) chloride catalyzed Mannich reaction: An efficient procedure for the synthesis of β-amino carbonyl compounds

Venkateswarlu Yekkirala, Ramesh Kumar Sudhagani and Leelavathi Panuganti*

Department of Chemistry, Osmania University, Hyderabad-500007, A. P., India

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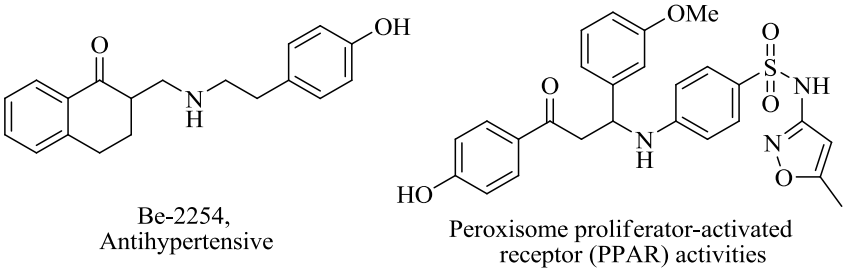
Abstract: Yttrium (III) chloride catalyzed Mannich reaction of aldehydes with ketones and amines in acetonitrile at reflux temperature to give various β-amino carbonyl compounds in very good yields.

Keywords: β-Amino carbonyl compounds; YCl_3; aromatic aldehyde; ketone and amines.

1. Introduction

Mannich reaction is one of the most important carbon-carbon bond forming reactions and a classical routes to prepare of β-amino ketone compounds and their derivatives which are versatile synthetic intermediates for the synthesis of biologically active compounds. In addition, chiral β-amino carbonyl compounds exhibit high potential as ligands in asymmetric catalysis[1-18]. Some of the β-amino ketone compounds having antihypertensive peroxisome proliferator activated receptor activity properties have shown in **Figure 1**. Because of the ubiquitous nature of nitrogen containg compounds, there is an increasing interest for Mannich products and the preferable route is one pot three component condensation of aldehyde, ketone and amine using an appropriate catalysts such as $Cu(OTf)_2$[19], $NaBAr^F{}_4$[20], $NbCl_5$[21], Re $(PFO)_3$[22], $ZrOCl_2 \cdot 8H_2O$ [23], $H_3PW_{12}O_{40}$[24], SiO_2-$OAlCl_2$ [25], BDMS [26], $Fe(HSO_4)_3$ [27], CBSA [28], TBAAMPS [29], amino acids [30] have also been found to be catalyze this reaction. They often suffer the drawbacks of long reaction times, harsh reaction conditions, toxicity and difficulty in product isolation. While searching for better catalyst, therefore, it is still desirable to develop highly efficient catalysts for this reaction. As part of our research program in developing synthetic methodologies.[31-35] Herein, we report, the synthesis of β-amino carbonyl compounds using yttrium chloride. The catalyst is known in the literature for various organic transformations.[36]



Be-2254, Antihypertensive

Peroxisome proliferator-activated receptor (PPAR) activities

Figure 1. Biologically active β-amino ketones

* Corresponding author: E-Mail: yekkiralavenkat@gmail.com

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2. Results and discussion

In a typical experiment, benzaldehyde, aniline and acetophenone were reacted in presence of a catalytic amount of yttrium chloride at acetonitrile reflux. The reaction was completed within 3.hours to afford the corresponding product of 1,3-diphenyl-3-(phenyl amino)-propan-1-one **(4a)** in good yields. As shown in the **Figure 2**.

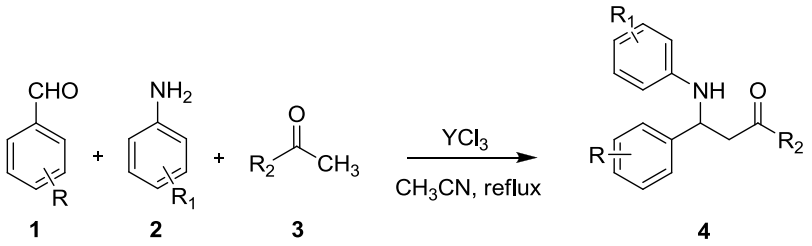


Figure 2. Mannich reaction catalyzed by YCl_3

Herein we report a method for synthesis of β-amino ketones. Initially we have examined the several catalysts and the then amount of catalyst used in the reaction. The results were summarized in the **Table 1**. There was no product formation without catalyst at room temperature and at reflux conditions even after 24 hours. The product formation was observed in presence of different catalysts at room temperature after 24 hours. It was found that the ideal reaction conditions were at acetonitrile reflux and using the catalyst YCl_3 in 10 mole %.

Table 1. Optimization of various catalysts for the Mannich reaction

Entry	Catalyst	Amount of catalysts (mol %)	Time (h)	Yield (%)
1	no cat	-	24	NR
2	DABCO	1.0	24	20
3	I_2	1.0	24	30
3	$LaCl_3$	1.0	24	40
4	$CuSO_4$	1.0	24	75
5	$Cu(NO)_3$	1.0	24	80
6	YCl_3	0.1	3	91

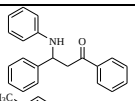
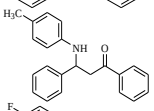
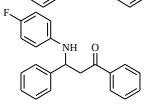
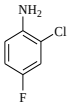
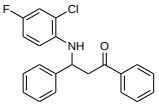
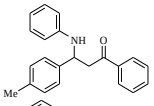
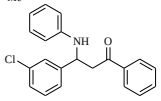
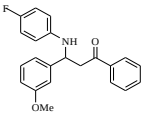
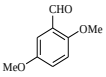
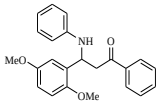
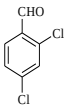
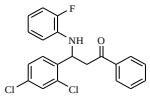
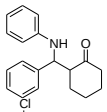
In a similar manner, a comparative study on the role and requirement of the solvent was studied. The solvents also played an important role in the Mannich reaction catalyzed by yttrium chloride. The different solvents tested for the reaction are water, Toluene, DCM and CH_3CN. The reaction hardly proceeded in water, toluene or DCM. However, the reaction in CH_3CN afforded product with nearly complete conversion. Therefore CH_3CN was selected as the reaction solvent in the following investigation **Table 2**.

Table 2. Yttrium chloride catalyzed Mannich reaction in different solvents

Entry	Solvent	Yield (%)
1	None	0
2	Water	10
3	Toluene	20
3	CH_2Cl_2	30
4	CH_3CN	91

Encouraged by these results, we examined the scope of this protocol by using a various aromatic aldehydes, amines and ketones at established reaction conditions as shown in the **Table 3**.

Table 3. YCl_3 catalyzed by synthesis of β-amino carbonyl compounds **(4a-n)**

S. No	Aldehyde	Aniline	Acetophenone	Product	Time (h)	Yield (%)
a					3.0	91
b					4.0	90
c					3.5	87
d					3.5	85
e					3.0	89
f					3.5	86
g					3.5	87
h					4.0	85
i					3.0	88
j					3.5	83
k					3.5	86
l					4.0	84
m					4.0	82
n					4.0	87

Aromatic aldehydes gave good yields. The annotations indicate that both electron donating and electron withdrawing substitution on aldehydes and amines undergo the reaction with good yields. Finally the scope of the reaction was studied using cyclohexanone, substituted benzaldehyde and amines. The cyclohexanone was observed to be less reactive than acetophenone. In the optimized reaction conditions, the synthesis of β-amino ketones **1a-n** were successfully obtained in good yields; it is worth mentioning that the aliphatic aldehydes and amines were inactive and failed to furnish the desired products with this protocol. In general, all the reactions were completed within 3 to 4 hours at

reflux temperature and the products, β-amino carbonyl derivatives were obtained in 82-91% yields. All the products were confirmed by their ^{1}H NMR, IR and mass spectral data.

3. Experimental Section

All commercial reagents were used without purification and all solvents were reagent grade. All the reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel $60F_{254}$ precoated glass plates, which were visualized with UV light. Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT/IR-240 C spectrophotometer with KBr optics. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer recorded in $CDCl_3$ using TMS as an internal standard. MAT1020 Mass spectrum operating at 70eV. Mass spectra were recorded on a VG 7070 H Micromass spectrometer.

3.1. General procedure for the synthesis of β-aminocarbonylcompounds (4a-n):

To a mixture of aromatic aldehyde, (106 mg, 1.0 mmol), ketone (120 mg, 1.0 mmol) and amine (93 mg, 1.1 mmol) in acetonitrile (5.0 mL) was added the catalyst Yttrium chloride (10 mol %) and refluxed. The resulting reaction mixture was stirred at reflux condition for a period of 3.0 to 4.0 hours (as mentioned in the **Table 3**). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, as indicated by TLC, the solvent was removed from the reaction mixture under reduced pressure. The residue was extracted with ethyl acetate (2x10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude products, which were purified by column chromatography using silica gel (60-120 mesh) eluted with hexane and ethyl acetate to afford the product. All the pure products were identified by their IR, ^{1}H NMR and mass spectral data.

3.1.1. 1,3-Diphenyl-3-(phenylamino) propan-1-one (4a): White solid; mp. 143-144 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3384, 3030, 2850, 1670, 1597, 1510, 1493, 1448, 1369, 1311, 1290, 1221, 1117, 1077, 1068, 1002, 991, 919, 861, 768 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.35 (dd, J_1 = 7.5 & J_2 = 16.0 Hz, 1H), 3.50 (dd, J_1 = 5.5 & J_2 = 16.0 Hz, 1H), 4.55 (br, NH), 4.90-4.98 (m, 1H), 6.50 (d, J = 7.5 Hz, 2H), 6.60 (t, J = 7.9 Hz, 1H), 7.05 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.25-7.35 (m, 4H), 7.40-7.45 (m, 2H), 7.55 (t, 1H), 7.90 (d, J = 8.0 Hz, 2H); MS (ESI) *m/z*: 302 $(M+1)^+$, 100), 263 (05), 209 (05), 182 (07).

3.1.2. 1,3-Diphenyl-3-(p-tolylamino) propan-1-one (4b): White solid; mp. 170-171 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3394, 3030, 2921, 1668, 1600, 1520, 1350, 860; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.40 (dd, J_1 = 7.6 & J_2 = 16.0 Hz, 1H), 3.45 (dd, J_1 = 5.2 & J_2 = 16.0 Hz, 1H), 4.45 (br, NH), 4.90 (t, J = 6.4 Hz, 1H), 6.40 (d, 2H), 6.85 (d, 2H), 7.15-7.25 (m, 1H), 7.26-7.33 (m, 4H), 7.35-7.45 (m, 2H), 7.50-7.55 (m, 1H), 7.90 (d, J = 7.5 Hz, 2H); MS (ESI) *m/z*: 316 $(M+1)^+$, 100), 285 (40).

3.1.3. 1,3-Diphenyl-3-(4-flurophenylamino) propan-1-one (4c): Brown solid; mp. 149-150 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3385, 3062, 3029, 2917, 2875, 1871, 1855, 1671, 1595, 1513, 1450, 1412, 1370, 1289, 1252, 1220, 1192, 1115, 1056, 997, 918, 815, 767, 746; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.35 (dd, J_1 = 7.1 & J_2 = 15.5 Hz, 1H), 3.55 (dd, J_1 = 5.5 & J_2 = 15.5 Hz, 1H), 4.50 (br, NH), 4.95-5.05 (m, 1H), 6.40-6.55 (m, 2H), 6.75 (t, 2H), 7.15-7.30 (m, 5H), 7.40-7.65 (m, 3H), 7.95 (d, J = 8.1 Hz, 2H); MS (ESI) *m/z*: 320 $(M+1)^+$, 100), 200 (35).

3.1.4. 1,3-Diphenyl-3-(2-chloro-4-fluorophenylamino)-propan-1-one (4d): White solid; mp. 163-165 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3394, 3060, 3028, 2927, 1661, 1617, 1559, 1517, 1473, 1449, 1415, 1373, 1331, 1304, 1263, 1219, 1190, 1130, 1073, 995, 896, 866, 842, 796, 760, 740, 702, 662, 612, 555; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.40 (dd, J_1 = 7.1 & J_2 = 16.3 Hz, 1H), 3.60 (dd, J_1 = 5.8 & J_2 = 16.3 Hz, 1H), 4.50 (br, 1H), 4.90-5.00 (m, 1H), 6.35-6.45 (m, 1H), 6.75 (d, 1H), 6.95 (d, 1H), 7.20-7.33 (m, 4H), 7.46-7.70 (m, 3H), 7.56-7.60 (m, 1H), 7.90 (d, J = 7.5 Hz, 2H); MS (ESI) *m/z*: 354 $(M+1)^+$, 100), 334 (85), 317 (30), 276 (20), 274 (45), 214 (05).

3.1.5. 1-Phenyl-3-(phenyl amino)-3-(p-tolyl) propan-1-one (4e): Brown solid; mp. 134-135 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3385, 3021, 2922, 2854, 1742, 1670, 1596, 1509, 1448, 1411, 1368, 1312, 1288, 1215, 1178, 1115, 1068, 1027, 994, 918, 857, 810, 753; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.35 (dd, J_1 = 7.2 & J_2 = 16.0 Hz, 1H), 3.45 (dd, J_1 = 5.9 & J_2 = 16.0 Hz, 1H), 4.50 (br, 1H), 4.88-4.95 (m, 1H), 6.55 (d, J = 7.5 Hz, 2H), 6.65 (t, 1H), 7.00-7.15 (m, 4H), 7.25-7.35 (m, 2H), 7.42 (t, 2H), 7.55 (t, 1H), 7.90 (d, J = 8.0 Hz, 2H); MS (ESI) *m/z*: 316 (M+1)$^+$, 100), 255 (20), 184 (55), 170 (20), 167 (30), 145 (50), 134 (10).

3.1.6. 3-(3-Chlorophenyl)-1-phenyl-3-(phenyl amino) propan-1-one (4f): White solid; mp. 140-141 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3395, 2360, 1669, 1592, 1578, 1513, 1485, 1448, 1401, 1365, 1314, 1298, 1254, 1219, 1196, 1152, 1124, 1102, 1074, 1012, 983, 921, 844, 782, 752, 718; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.33 (dd, J_1 = 7.1 & J_2 = 15.5 Hz, 1H), 3.60 (dd, J_1 = 5.5 & J_2 = 15.5 Hz, 1H), 4.43 (br, 1NH), 4.95-5.05 (m, 1H), 6.60-6.70 (m, 3H), 7.10-7.15 (m, 2H), 7.20-7.30 (m, 3H), 7.40 (s, 1H), 7.50-7.65 (m, 3H), 7.90 (d, J = 7.6 Hz, 2H); MS (ESI) *m/z*: 336 (M+1)$^+$, 100), 319 (5), 302 (5), 282 (5), 243 (5), 229 (5), 216 (30).

3.1.7. 3-(4-Fluorophenylamino)-3-(3-methoxyphenyl)-1-phenylpropan-1-one (4g): Solid; mp. 100-104 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3369, 3060, 1666, 1583, 1509, 1487, 1447, 1434, 1280, 1259, 1213, 1189, 1156, 1146, 1042, 1000, 816, 767, 752, 730, 705; ^{1}H NMR (DMSO-d_6): δ 3.33 (dd, J_1 = 7.2 & J_2 = 16.4 Hz, 1H) 3.56 (dd, J_1 = 4.8 & J_2 = 16.4 Hz, 1H), 3.75 (s, 3H), 4.95 (br, 1H), 5.20-5.30 (m, 1H), 6.50 (d, 2H), 6.80 (d, 2H), 7.00 (t, 2H), 7.35 (d, 2H), 7.41-7.60 (m, 3H), 7.90 (d, J = 8.1 Hz, 2H); MS (ESI) *m/z*: 350 (M+1)$^+$, 100), 326 (5), 293 (5), 261 (5), 230 (20), 212 (5).

3.1.8. 3-(2,5-Dimethoxyphenyl)-1-phenyl-3-(phenylamino) propan-1-one (4h): White solid, mp. 166-167 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3390, 3347, 2915, 1675, 1640, 1493, 1340, 1217, 1050, 860, 751, 690; ^{1}H NMR (DMSO-d_6): δ 3.25, (dd, J_1 = 7.6 & J_2 = 16.3 Hz, 1H), 3.55 (dd, J_1 = 5.2 & J_2 =16.3 Hz, 1H), 3.81 (s, 3H), 390 (s, 3H), 4.95-5.05 (m, 1H), 6.40-6.60 (m, 5H), 7.90 (s, 1H), 7.10-7.20 (m, 2H), 7.35-7.60 (m, 3H), 7.85 (d, J = 7.6 Hz, 2H); MS (ESI) *m/z*: 362 (M+1)$^+$, 100), 342 (10), 269 (5), 242 (15).

3.1.9. 3-(2,4-Dichlorophenyl)-3-(2-fluorophenylamino)-1-phenylpropan-1-one (4i): Solid; mp. 118-120 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3417, 3060, 2913, 2362, 1681, 1618, 1587, 1515, 1466, 1446, 1412, 1385, 1355, 1332, 1305, 1260, 1232, 1203, 1183, 1141, 1096, 1064, 1039, 983, 941, 910, 865, 821, 794, 750, 737; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.30 (dd, J_1 = 7.7 & J_2 = 16.0 Hz, 1H), 3.60 (dd, J_1 = 5.2 & J_2 = 16.0 Hz, 1H), 4.80 (br, 1H), 5.15-5.25 (m, 1H), 6.50 (d, 2H), 6.90-7.00 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.40-7.60 (m, 3H), 7.70 (s, 1H), 8.00 (d, J = 7.6 Hz, 2H); MS (ESI) *m/z*: 388 (M+1)$^+$, 100), 279 (10).

3.1.10. 2-(Phenyl (phenylamino) methyl) cyclohexanone (4j): White solid; mp. 137-138 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3328, 3028, 2935, 2865, 1700, 1600, 1525, 1451, 1310; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-2.00 (m, 6H), 2.20-2.50 (m, 2H), 2.65-2.85 (m, 1H), 4.20 (br, 1H), 4.60 (d, J = 4.8 Hz, 1H), 6.55-6.70 (m, 3H), 6.95-7.10 (m, 2H), 7.15-7.45 (m, 5H); MS (ESI) *m/z*: 280 (M+1)$^+$, 30), 204 (10), 187 (40), 181 (100), 169 (40).

3.1.11. 2-[(3-Chlorophenylamino)(phenyl)methyl]cyclohexanone (4k): Yellowish solid; mp. 122-123 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3388, 3051, 2936, 2860, 1706, 1578, 1600, 1494, 1311, 1142, 829, 750; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-2.10 (m, 6H), 2.30-2.45 (m, 2H), 2.85-3.00 (m, 1H), 4.55 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 7.3 Hz, 2H), 6.60-6.80 (m, 1H), 7.05-7.75 (m, 6H); MS (ESI) *m/z*: 314 (M+1)$^+$, 100).

3.1.12. 2-[(4-Nitrophenyl) (phenyl amino) methyl] cyclohexanone (4l): Solid; mp. 264-265 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3404, 3053, 2948, 2936, 2882, 1706, 1601, 1516, 1345, 1317, 1260, 1108, 854, 751, 595, 511; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-2.25 (m, 6H), 2.20-2.50 (m, 2H), 2.75-2.90 (m, 1H),

4.55 (br, NH), 4.75 (d, 1H), 6.50 (d, *J* = 7.5 Hz, 2H), 6.60-6.70 (m, 1H), 6.95-7.15 (m. 2H), 7.45-7.60 (m, 2H), 8.20 (d, *J* = 7.7 Hz, 2H); MS (ESI) *m/z*: 325 $(M+1)^+$,100), 316 (20), 289 (30), 221 (100), 174 (20).

3.1.13. 2-((2-Chlorophenyl) (2-fluorophenylamino)methyl)cyclohexanone (4m): IR (KBr, cm^{-1}) υ_{max}: 3420, 3025, 2945, 2860, 1680, 1618, 1594, 1579, 1520, 1509, 1468, 1447, 1409, 1358, 1333, 1304, 1261, 1232, 1203, 1180, 1127, 1109, 1092, 1062, 1035, 1015, 986, 944, 910, 857, 7842, 791, 773, 754, 736, 725, 704; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-2.15 (m, 6H), 2.30-2.45 (m, 2H), 2.90-3.05 (m, 1H), 5.00 (br,1H), 5.55 (d, 1H), 6.30-6.65 (m, 1H), 6.80-7.00 (m, 1H), 7.10-7.30 (m, 2H), 7.35-7.45 (m, 2H) 7.55 (d, 2H); MS (ESI) *m/z*: 331 $(M+1)^+$, 100).

3.1.14. 2-((Furan-2-yl)(phenyl amino) methyl) cyclohexanone (4n): Solid; mp. 194-195 ^{0}C; IR (KBr, cm^{-1}) υ_{max}: 3358, 3026, 2942, 2858, 1706, 1602, 1500, 1313; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-2.10 (m, 6H), 2.35-2.55 (m, 2H), 2.90-3.10 (m, 1H), 4.60 (br, NH), 4.81 (d, *J* = 5.3 Hz, 1H), 6.20 (d, 1H), 6.30 (s, 1H), 6.61-6.75 (m, 3H), 7.10-7.20 (m, 2H), 7.80 (d, *J* = 7.7 Hz, 1H); MS (ESI) *m/z*: 270 $(M+H)^+$, 100).

4. Conclusions

In conclusion, we have demonstrated a simple and efficient three-component process for the synthesis of β-amino carbonyl compounds by the condensation of aldehyde, ketone and aniline using yttrium chloride as the catalyst. The notable features of this protocol are mild reaction conditions, simplicity in operation, improved yields and cleaner reaction profiles.

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