Zinc Acetate Catalysed Mannich Reaction: An Efficient Procedure for the Synthesis of β-amino Carbonyl Compounds.

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ABSTRACT

An efficient and new protocol for the synthesis of β-amino carbonyl compounds 4(a-m) has been developed by using Zn $(OAc)_2$ as a catalyst. This is one of the useful new catalyst that can be easily separated and is not ruined by products. This method offers several advantages including high yields, short reaction times, simple work up procedure and easy isolation.

Keywords: Benzaldehyde, Acetophenone, Aniline, Acetonitrile, β-amino carbonyl compounds and Zinc acetate

INTRODUCTION

Synthetic organic chemistry has seen enormous growth not only in terms of development of new methodologies for construction of C-C and carbon hetero atom bonds but also in terms of development of new strategies, reagents, catalysts, transformations and technologies.[1-7] The Mannich reaction is a classical tool for the synthesis of β-amino ketones, which may be achieved via a number of other protocols. Mannich reaction involves the sequential formation of C-N, C-C bonds and is one of the most useful MCR. [8-10]

The Mannich reaction is a classical tool for the synthesis of β-amino ketones, which may be achieved via a number of other protocols, as illustrated in (scheme-1).[11]

Mannich reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics and alkaloids. The Mannich reaction is also utilized in agrochemicals, paint, polymer chemistry[12,13] and also the synthesis of medicinal compounds like rolitetracycline, fluoxetine (antidepressant) and tolmetin (anti-inflammatory drug).

Literature survey reveals that some Mannich bases of substituted aminophenol and acetophenone those possess broad spectrum biological activities, which include antineoplastic, [14] antibacterial, [15] antifungal, [16] antiHIV, [17] anticancer, [18] versorelaxant, [19] antiinflammatory, [20] antimalarial,[21] antimicrobial,[22] antituberculosis[23] and anticonvulsant.[24]

EXPERIMENTAL SECTION

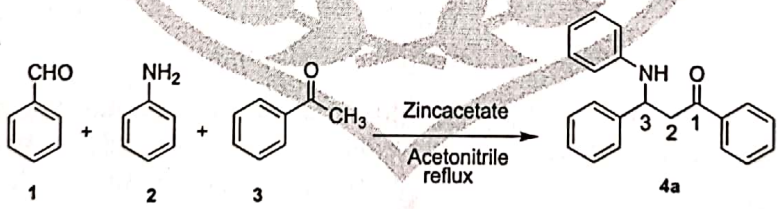
To a mixture of aromatic aldehyde, (1.0 mmole), ketone (1.0 mmole) and aromatic aniline (1 mmole) in acetonitrile (5.0 ml) was added the catalyst Zinc acetate (10 mol %) and refluxed for a period of 3.0 to 4.0 hours (as mentioned in the Table-3). The progress of the reaction was monitored by thin layer 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). All the pure products were identified by their ^1H NMR, IR and mass spectral data.

RESULTS AND DISCUSSION

It was observed that with the presence of Zn $(OAc)_2$ it took very less time for the product formation, where as 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 Zn $(OAc)_2$ in 0.1 mole%. The solvents also played an important role in the Mannich reaction catalyzed by Zinc acetate. 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-1: Optimization of various catalysts for the Mannich reaction

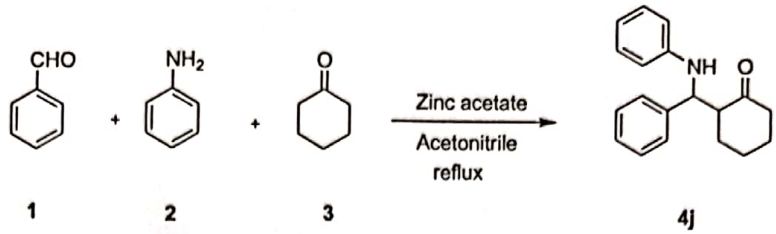
Entry	Catalyst	Amount of catalysts (mol %)	Time (h)	Yield (%)
1	no cat	-	24	NR
2	DABCO	1.0	24	20
3	$LaCl_3$	1.0	24	40
4	$CuSO_4$	1.0	24	75
5	Cu $(NO_3)_2$	1.0	24	80
6	**Zn $(OAc)_2$**	**0.1**	**3**	**91**



Scheme-1

The product was identified by the spectral data. The ^1H NMR spectrum for this compound showed two double doublets at δ 3.35 and 3.50 integrating for 1 proton each assigned to CH_2 at C-2, a broad singlet at δ 4.55 integrating for 1 proton assigned to NH, a multiplet at δ 4.90-4.98 integrating for 1 proton assigned to CH at C-3,a doublet at δ 6.50 integrating for 2 protons assigned to Ar-H ortho to NH,two triplets at δ 6.60 and 7.05 integrating for 1 and 2 protons respectively assigned to Ar-H para and meta to NH, a triplet at δ 7.20 integrating for 1 proton assigned aromatic proton, a multiplet at δ 7.25-7.35 integrating for 4 protons assigned to aromatic protons, a multiplet at δ 7.40-7.45 integrating for 2 protons assigned to Ar-H meta to carbonyl group,a triplet at δ 7.55 integrating for 1 proton assigned Ar-H para to carbonyl group, a doublet at δ 7.90 integrating for 2 protons assigned to Ar-H ortho to carbonyl group.

The another experiment was carried out by refluxing benzaldehyde, aniline and cyclohexanone in the presence of the catalyst Zinc acetate in acetonitrile for 3.5 hours to afford the corresponding product, 2-(phenyl(phenylamino) methyl) cyclohexanone**(4j)**, in 83% yield, as shown in the scheme-2



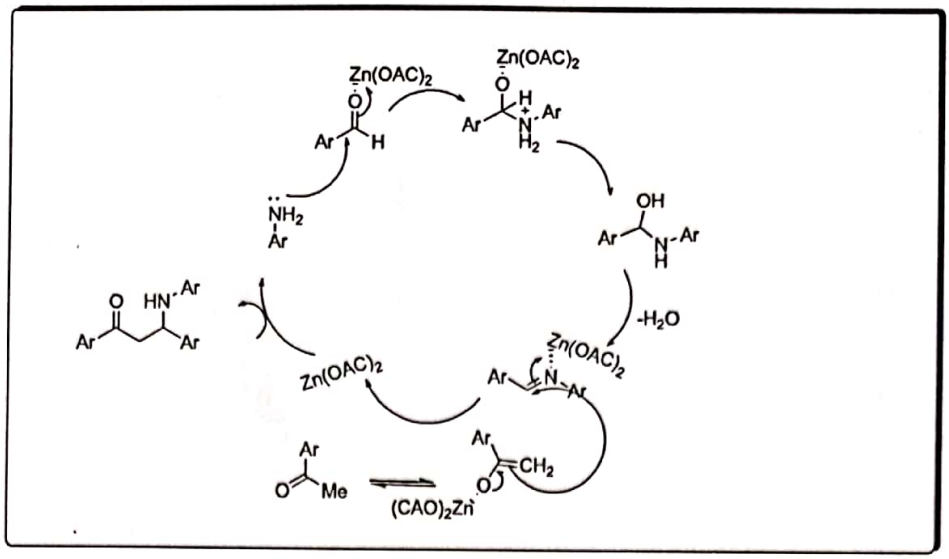
Scheme-2

The product was identified by its spectral data. The ^{1}H NMR spectrum of this compound showed multiplets at δ 1.55-2.00 and δ 2.20-2.50 integrating for 6 and 2 protons respectively assigned to CH_2 of cyclohexanone, a multiplet at δ 2.65-2.85 integrating for 1 proton assigned to CH of cyclohexanone, a broad singlet at δ 4.20 integrating for 1 proton assigned to NH, a doublet at δ 4.60 integrating for 1 proton assigned to CH attached to NH, a doublet at δ 6.45 integrating for 2 protons assigned to Ar-H ortho to NH, a multiplet at δ 6.55-6.70 integrating for 1 proton assigned to Ar-H para to NH, a multiplet at δ 6.95-7.10 integrating for 2 protons assigned to Ar-H meta to NH, a multiplet at δ 7.15-7.45 integrating for 5 protons was due to phenyl ring.

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-2. 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 **(a-n)** were successfully obtained in good yields.

A PLAUSIBLE MECHANISM

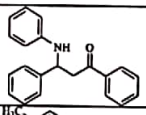
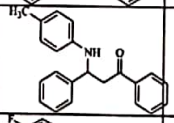
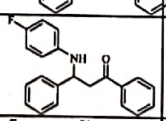
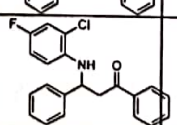
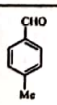
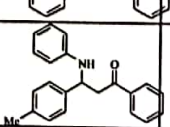
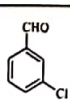
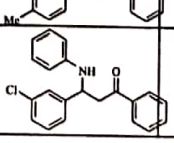
The first step in Mannich reaction is nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in a nucleophilic addition with a compound containing an acidic proton.

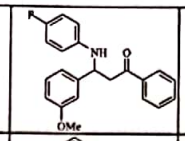
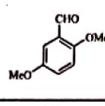
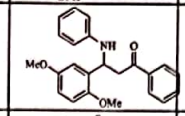
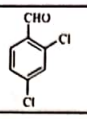
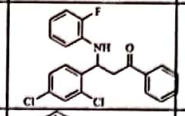
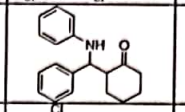
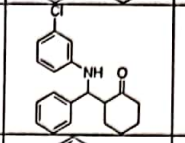
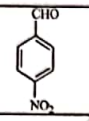
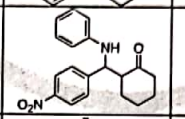
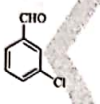
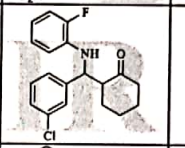
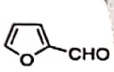
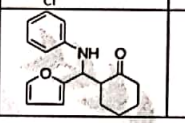


Scheme-3

A plausible mechanism of $Zn(OAc)_2$ catalyzed Mannich reaction is shown in scheme-3. First it coordinates with the carbonyl oxygen of aldehyde and activates nucleophilic attack of amine followed by dehydration gives imine. The intermediate imine again activated by the catalyst through coordination by $Zn(OAc)_2$ and then the attack by enol on imine gives the desired product.

Table-2: Zn $(OAc)_2$ Catalyzed By Synthesis Of β-Amino Carbonyl Compound

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

GENERAL PROCEDURE:

To a mixture of benzaldehyde, acetophenone and aniline in acetonitrile was added the catalyst Zinc acetate and refluxed. 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. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography using silica gel (60-120 mesh). The pure product 1,3-diphenyl-3-(phenylamino) propan-1-one **(4a)** obtained in 90% yield as shown in scheme-1 and the another product 2-(phenyl(phenylamino) methyl) cyclohexanone**(4j)** got 83% yield as shown in scheme -2.

SPECTRAL DATA :

1,3-Diphenyl-3-(phenylamino)propan-1-one (4a): White solid, mp, 143-144 ^{0}C.; IR (KBr): υ 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 ($CDCl_3$): δ 3.35 (dd, 1H, J_1= 7.5 & J_2= 16.0 Hz), 3.50 (dd, 1H, J_1= 5.5 & J_2= 16.0 Hz), 4.55 (br, 1H, NH), 4.90-4.98 (m, 1H), 6.50 (d, 2H, J = 7.5 Hz), 6.60 (t, 1H, J = 7.9 Hz), 7.05 (t, 2H, J = 7.7 Hz), 7.20 (t, 1H, J = 7.8 Hz), 7.25-7.35 (m, 4H), 7.40-7.45 (m, 2H), 7.55 (t, 1H), 7.90 (d, 2H, J = 8.0 Hz).; ESI-MS *m/z* (%): 302([M+H]$^+$, 100), 263 (05), 209 (05), 182 (07).

1,3-Diphenyl-3-(*p*-tolylamino)propan-1-one (4b):White solid, mp, 170-171 ^{0}C.; IR (KBr): υ 3394, 3030, 2921, 1668, 1600, 1520, 1350, 860 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H), 3.40 (dd, 1H, J_1= 7.6 &J_2= 16.0 Hz), 3.45 (dd, 1H, J_1= 5.2 &J_2= 16.0 Hz), 4.45 (br, 1H, NH), 4.90 (t, 1H, J = 6.4 Hz), 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, 2H, J = 7.5 Hz).; ESI-MS *m/z* (%): 316 ([M+H]$^+$, 100), 285 (40).

1,3-Diphenyl-3-(4-flurophenylamino)propan-1-one (4c):Brown solid,mp, 149-150 ^{0}C.; IR (KBr): υ 3385, 3062, 3029, 2917, 2875, 1871, 1855, 1671, 1595, 1513, 1450, 1412, 1370, 1289, 1252, 1220, 1192, 1115, 1056, 997, 918, 815, 767, 746 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 3.35 (dd, 1H, J_1= 7.1 &J_2= 15.5 Hz), 3.55 (dd, 1H, J_1= 5.5 &J_2= 15.5 Hz), 4.50 (br, 1H, 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, 2H, J = 8.1 Hz).; ESI-MS *m/z* (%): 320 ([M+H]$^+$, 100), 200 (35).

1,3-Diphenyl-3-(2-chloro-4-fluorophenylamino)-propan-1-one (4d):White solid, mp, 163-165 ^{0}C.; IR (KBr): υ 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 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$):δ 3.35 (dd, 1H, J_1= 7.1 &J_2= 16.3 Hz), 3.55 (dd, 1H, J_1= 5.8 &J_2= 16.3 Hz),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, 2H, J = 7.5 Hz).; ESI-MS *m/z* (%): 354 ([M+H]$^+$, 100), 334 (85), 317 (30), 276 (20), 274 (45), 214 (05).

1-Phenyl-3-(phenylamino)-3-(*p*-tolyl)propan-1-one(4e): Brown solid, mp, 134-135 ^{0}C.; IR (KBr): υ 3385, 3021, 2922, 2854, 1742, 1670, 1596, 1509, 1448, 1411, 1368, 1312, 1288, 1215, 1178, 1115, 1068, 1027, 994, 918, 857, 810, 753 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 3.35 (dd, 1H, J_1= 7.2 &J_2= 16.0 Hz), 3.45 (dd, 1H, J_1= 5.9 &J_2= 16.00 Hz), 4.50 (br, 1H), 4.88-4.95 (m, 1H), 6.55 (d, 2H, J = 7.5 Hz), 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, 2H, J = 8.0 Hz).; ESI-MS *m/z* (%): 316 ([M+H]$^+$,100), 255 (20), 184 (55), 170 (20), 167 (30), 145 (50), 134 (10).

3-(3-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4f):White solid, mp, 140-141 ^{0}C.; IR (KBr): υ 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 cm.$^{-1}$; ^{1}H NMR (DMSO-d_6): δ 3.35 (dd, 1H, J_1= 7.1 &J_2= 15.5 Hz), 3.60 (dd, 1H, J_1= 5.5 &J_2= 15.5 Hz), 4.45 (br, 1NH), 4.96-5.03 (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, 2H, J = 7.6 Hz).; ESI-MS *m/z* (%): 336 ([M+H]$^+$, 100), 319 (5), 302 (5), 282 (5), 243 (5), 229 (5), 216 (30).

3-(4-Fluorophenylamino)-3-(3-methoxyphenyl)-1-phenylpropan-1-one (4g):Solid, mp, 100-104 ^{0}C.; IR (KBr): υ 3369, 3060, 1666, 1583, 1509, 1487, 1447, 1434, 1280, 1259, 1213, 1189, 1156, 1146, 1042, 1000, 816, 767, 752, 730, 705 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 3.33 (dd,1H, J_1= 7.2 &J_2= 16.4 Hz) 3.50 (dd, 1H, J_1= 4.8 &J_2= 16.4 Hz), 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, 2H, J = 8.1 Hz).; ESI-MS *m/z* (%): 350 ([M+H]$^+$,100), 326 (5), 293 (5), 261 (5), 230 (20), 212 (5).

3-(2,5-Dimethoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (4h): White solid, mp, 166-167 ^{0}C.; IR (KBr): υ3390, 3347, 2915, 1675, 1640, 1493, 1340, 1217, 1050, 860, 751, 690 cm.$^{-1}$; ^{1}H NMR (DMSO-d_6): δ 3.25, (dd, 1H, J_1= 7.6 &J_2= 16.3 Hz), 3.55 (dd, 1H, J_1= 5.2 &J_2= 16.3 Hz), 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, 2H, J = 7.6 Hz).; ESI-MS m/z (%): 362 ([M+H]$^+$, 100), 342 (10), 269 (5), 242 (15).

3-(2,4-Dichlorophenyl)-3-(2-fluorophenylamino)-1-phenylpropan-1-one(4i):Solid, mp, 118-120 ^{0}C.; IR (KBr): υ 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 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 3.39 (dd, 1H, J_1 = 7.7 &J_2 = 16.0 Hz), 3.60 (dd, 1H, J_1 = 5.2 &J_2 = 16.0 Hz),4.80 (br, 1H), 5.20 (m, 1H),6.50 (d, 2H),6.90-7.00 (m, 3H),7.20 (d, 1H, J = 7.5 Hz), 7.40-7.60 (m, 3H), 7.70 (s, 1H), 8.00 (d, 2H, J = 7.6 Hz).;ESI-MS m/z (%): 388 ([M+H]$^+$,100), 279 (10).

2-(Phenyl(phenylamino)methyl)cyclohexanone (4j): White solid, mp, 137-138 ^{0}C.; IR (KBr): υ 3328, 3028, 2935, 2865, 1700, 1600, 1525, 1451, 1310 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ1.55-2.00 (m, 6H), 2.20-2.50 (m, 2H), 2.65-2.85 (m, 1H), 4.20 (br,1H), 4.60 (d, 1H, *J* = 4.8 Hz), 6.55-6.70 (m, 3H), 6.95-7.10 (m, 2H), 7.15-7.45 (m, 5H).; ESI-MS *m/z* (%): 280 ([M+H]$^+$, 30), 204 (10), 187 (40), 181 (100), 169 (40).

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

2-[(4-Nitrophenyl) (phenylamino)methyl] cyclohexanone (4l): Solid, mp, 264-265 ^{0}C.; IR (KBr): υ 3404, 3053, 2948, 2936, 2882, 1706, 1601, 1516, 1345, 1317, 1260, 1108, 854, 751, 595, 511 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): 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, 2H, *J* = 7.5 Hz), 6.60-6.70 (m, 1H), 6.95-7.15 (m. 2H), 7.45-7.60 (m, 2H), 8.20 (d, 2H, *J* = 7.7 Hz).; ESI-MS *m/z* (%): 325 ([M+H]$^+$,100), 316 (20), 289 (30), 221 (100), 174 (20).

2-((2-Chlorophenyl) (2-fluorophenylamino)methyl)cyclohexanone (4m):IR (KBr): υ 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, 784, 791, 773, 754, 736, 725, 704 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): 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).; ESI-MS: *m/z* (%): 331 ([M+H]$^+$,100).

2-(Furan-2-yl-(phenylamino)methyl) cyclohexanone (4n):Solid, mp, 194-195 ^{0}C.; IR (KBr): υ 3358, 3026, 2942, 2858, 1706, 1602, 1500, 1313 ^{1}H NMR ($CDCl_3$): 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, 1H, *J* = 5.3 Hz), 6.20 (d, 1H), 6.30 (s, 1H), 6.61-6.75 (m, 3H), 7.10-7.20 (m, 2H), 7.80 (d, 1H, *J* = 7.7 Hz,).; ESI-MS *m/z* (%): 270 ([M+H]$^+$, 100).

CONCLUSION

The objective of the present research work is to develop various new synthetic methodologies, Here we have developed a simple and efficient methodology for the synthesis of β-amino ketones derivatives. We reported Zn $(OAc)_2$ as a new catalyst for the aboveβ-amino ketones(Mannich Reaction) derivatives, The new catalyst reduced the reaction time and the yields were very good. In conclusion, this method is very easy to handle, environmentally benign and the recovery of the products is easy. The products obtained were characterized by ^{1}H NMR, IR and Mass Spectra.

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