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Synthesis of β-amino carbonyl compounds by using Aza- Michael reaction

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ABSTRACT:

Objectives:

The Aza Michael reaction is widely recognized as one of the most important carbon- nitrogen bond forming reactions in organic synthesis [2.] In general this transformation is a heteroatom (Nitrogen) nucleophilic (donor addition to a β-carbon of electro poor alkenes accepter) giving a stabilized carbanion intermediate, which after protonation with another electrophile furnishes the final addition product. The obtained β-amino ketones owing to their wide range of biological activities[7] and pharmacological properties[3-4].

The synthesis of β-amino carbonyl compounds has become a field of increasing interest in organic synthesis during the past few decades.[4]

Carbonyl compounds (aza- Michael addition) are one of the simplest and most effective methods for preparing β-amino carbonyl compound. In recent years a number of catalysts such as SmI_2 CuO_7f_2, Bi (NO_3), Bi $(OTF)_2$, $LiClO_4$, $FeCl_3$-$6H_2O$. TMSCI, boric acid and clay have been developed for this reaction

Material and Methods:

To a mixture of α, β-unsaturated compound (2 m mol) and amine (2 m mol) in CH_2Cl_2 (10 ml) was added AgOTf (0.2 mol %) at room temperature. The resulting mixture was stirred at the same temperature for a specified period. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O and brine, and the organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Thus obtained crude products were purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 2:8).

Result:

Most effective methods for preparing β- amino carbonyl compound. In recent years a number of catalysts such as SmI_2 CuO_7f_2, Bi (NO_3), Bi $(OTF)_2$, $LiClO_4$, $FeCl_3$-$6H_2O$. TMSCI, boric acid and clay have been developed for this reaction. B-amino carbonyl compounds are useful building blocks for the molecules with applications in pharmaceuticals and fine chemicals[5-10].

They are versatile intermediates for the synthesis of biologically important natural products and antibiotics.

β- Amino carbonyl ingredients have attracted great attention for their use as key intermediates of anticancer agents, antibiotics and other drugs[15] β-amino carbonyl compounds used as essential intermediates in the synthesis of β- amino acid and β- lactam antibiotic[12].

Conclusion

In conclusion, the present procedure provides an efficient methodology for the synthesis of β-amino carbonyl compounds via aza- Michael reaction. The notable advantages offered by this method are simple operation, mild (room temperature) and environment friendly reaction conditions, much faster (20-50 min) reaction, high yields of products and cost effectiveness.

Key words:

Synthesis of β- amino carbonyl compound, catalysts such as SmI_2 CuO_7f_2, Bi (NO_3), Bi $(OTF)_2$, $LiClO_4$, $FeCl_3$-$6H_2O$. TMSCI, boric acid and clay. Use as key intermediates of anticancer agents, antibiotics and other drugs[11].

INTRODUCTION:

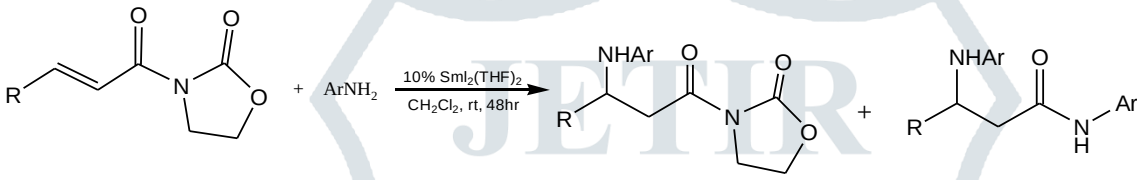
The Aza Michael reaction is widely recognized as one of the most important carbon- nitrogen bond forming reactions in organic synthesis[1]. The synthesis of β-amino carbonyl compounds has become a field of increasing interest in organic synthesis during the past few decades.[4] Carbonyl compounds (aza- Michael addition) is one of the simplest and most effective methods for preparing β- amino carbonyl compound. In recent years a number of catalysts such as SmI_2 CuO_7f_2, Bi (NO_3), Bi $(OTF)_2$, $LiClO_4$, $FeCl_3$-$6H_2O$. TMSCI, boric acid and clay have been developed for this reaction. However, most of these catalytic systems are restricted to only aliphatic amines since aromatic amines are poor nucleophiles. Authors have established general protocol using Ytterbium trifoliate as a catalyst which is relatively expensive compared to other lanthanide triplets. The method was further extended to yield optically active B-lactum.

Synthesis of β-amino carbonyl compounds via aza- Michael reaction

A) Procedure

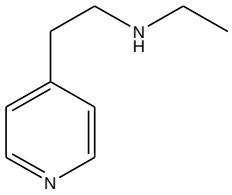
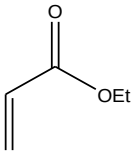
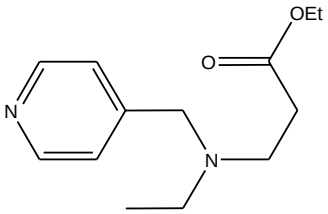
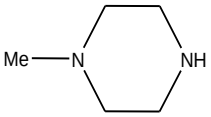
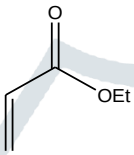
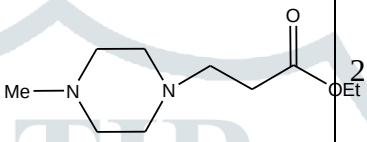
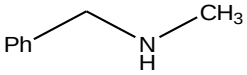
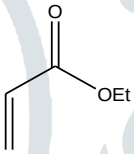
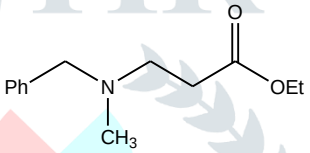
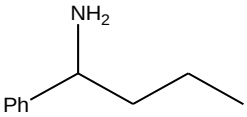
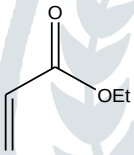
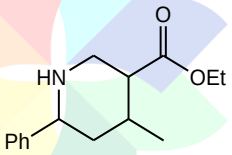
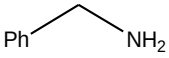
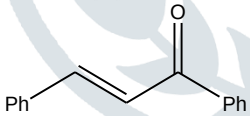
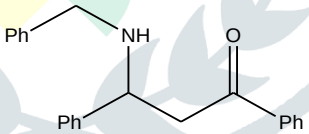
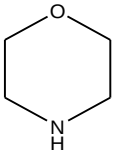
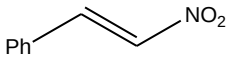
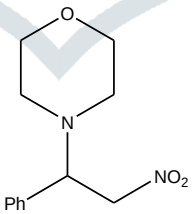
To a mixture of α-β-unsaturated compound (2 m mol) and amine (2 m mol) in CH_2Cl_2 (10 ml) was added AgOTf (0.2 mol %) at room temperature. The resulting mixture was stirred at the same temperature for a specified period. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O and brine, and the organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Thus obtained crude products were purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 2:8).

B) Reaction



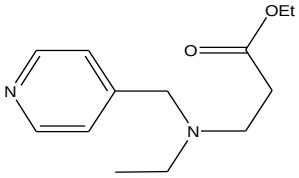
Result and Discussion:

Melting points were recorded on Buch R-533 apparatus and uncorrected.IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. 1H NMR and 13C spectra were recorded onGemini-200 MHz, Bruker Avance 300M Hz and Unity-400M Hz spectrometer in CDCL3 using TMS as internal standard. Mass spectra were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70eV.Column chromatography was performed using E. Merck 60-120, mesh silica gel. All the solvent were distilled, dried and stored under nitrogen prior to use.

Entry	Nucleophile	Olefin	Product	Reaction Time (h)	Yield (%)
H a				2.5	88
I b				2.6	90
J e				3.0	92
K c				2.8	89
L d				3.2	85
M e				2.8	86

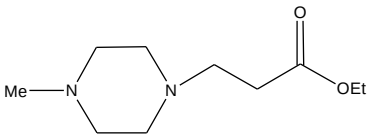
Spectral Data:

A] Ethyl 3-((N-ethyl-N-(pyridine-4-yl) methyl) amino) propanoate (3h):



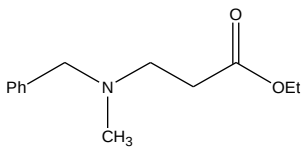
Sr. No.		
1	State	Brown liquid
2	M.P.	
3	IR	V 3440, 3051, 2943, 2837, 1728, 1645, 1605, 1573, 1461, 1339, 1258, 1169, 1108, 1071, 968, 842, 741 cm^{-1}
4	^1H NMR (200 MHz, $CDCl_3$)	□ 1.08 (t, 3H, J = 6.5 Hz), 1.26 (t, 3H, J = 6.5 Hz), 2.40 – 2.60 (m, 4H), 2.81 (t, 2H, J = 6.0 Hz), 3.60 (s, 2H), 4.15 (q, 2H, J = 6.5 Hz), 7.24 (d, 2H, J = 6.0 Hz), 8.58 (d, 2H, J = 6.0 Hz)
5	EIMS (m / z) %	236 (M^+ 15), 207 (18), 163 (100), 135 (32), 134 (20), 106 (45), 78 (25), 53 (15), 40 (10)

B] Ethyl 3-(4-methyliperazin-1-yl) propanoate (3i):



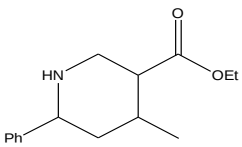
Sr. No.		
1	State	Light yellow liquid
2	M.P.	
3	IR	V 3418, 2936, 2800, 1735, 1508, 1459, 1410, 1372, 1206, 1183, 1115, 1088, 1010, 961, 836, 795, 742 cm^{-1}
4	^1H NMR (200 MHz, $CDCl_3$)	□ 1.25 (t, 3H, J = 6.5 Hz), 2.23 (s, 3H), 2.38 – 2.55 (m, 10H), 2.68 (t, 2H, J = 6.0 Hz), 4.15 (q, 2H, J = 6.5 Hz)
5	EIMS (m / z) %	200 (M^+ 100), 171 (12), 127 (40), 99 (0), 84 (10), 56 (10)

C] Ethyl 3-(N-benzyl-N-methylamino) propanoate (3j):



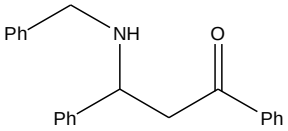
Sr. No.		
1	State	Colorless liquid
2	M.P.	
3	IR	V 3424, 3052, 2926, 2843, 1735, 1587, 1458, 1386, 1212, 1123, 1029, 745, 700, 604 cm^{-1}
4	^1H NMR (200 MHz, $CDCl_3$)	□ 1.27 (t, 3H, J = 7.5 Hz), 2.18 (s, 3H), 2.50 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 7.5 Hz), 3.50 (s, 2H), 4.12 (q, 2H, J = 7.5 Hz), 7.15 – 7.30 (m, 5H)
5	EIMS (m / z) %	222 (M^+ 100), 216 (20), 194 (12), 149 (10), 134 (20), 121 (12), 92 (15), 77 (15), 66 (10), 51 (35)

D] Ethyl 3-(N-phenyl-N-propylamino) propanoate (3k):



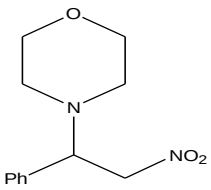
Sr. No.		
1	State	Colourless liquid
2	M.P.	
3	IR	V 3432, 3051, 2942, 2839, 1730, 1605, 1570, 1462, 1378, 1259, 1170, 1125, 1034, 952, 840, 739 cm^{-1}
4	^1H NMR (200 MHz, $CDCl_3$)	□ 0.88 (t, 3H, J = 7.0 Hz), 1.35 (t, 3H, J = 7.0 Hz), 1.50 – 1.70 (m, 2H), 2.36 – 2.42 (m, 2H), 2.60 – 2.70(m, 2H), 3.55 (t, 1H, J = 6.0 Hz), 4.10 (q, 2H, J = 7.0 Hz), 7.20 – 7.35 (m, 5H)
5	EIMS (m / z) %	249 (M^+ 100), 220 (22), 176 (45), 148 (24), 119 (15), 104 (10), 77 (62), 61 (20)

E] 3-(Benzylamino)-1, 3-diphenylpropan-1-one (3l):



Sr. No.		
1	State	Colorless liquid
2	M.P.	
3	IR	V 3338, 3060, 3028, 2924, 2853, 1682, 1643, 1603, 1493, 1450, 1336, 1283, 1214, 1178, 1022, 981, 855, 750 cm^{-1}
4	^1H NMR (200 MHz, $CDCl_3$)	□ 3.25 – 3.35 (m, 1H), 3.55 – 3.70 (m, 1H), 4.25 – 4.35 (m, 1H), 4.70 (s, 2H), 7.20 – 7.50 (m, 10H), 7.55 – 8.05 (m, 5H)
5	EIMS (m / z) %	317 (15), 316 (40), 315 (M^+ 10), 308 (15), 299 (32), 298 (100), 224 (18), 210 (15), 147 (15), 119 (25), 77 (18), 51 (20)

F] 4-(2-Nitro-1-phenylethyl) morpholine (3m):



Sr. No.		
1	State	Light red solid
2	M.P.	51 – 52^{0}C
3	IR (KBr)	V 3426, 3032, 2922, 2854, 1634, 1560, 1493, 1452, 1366, 1276, 1227, 1112, 1035, 1002, 868, 741 cm^{-1}
4	^{1}H NMR (200 MHz, $CDCl_3$)	□ 2.30 – 2.55 (m, 4H), 3.50 – 3.70 (4H), 4.30 (dd, 1H, J = 6.5, 2.0 Hz), 4.50 (dd, 1H, J = 6.5, 2.0 Hz), 4.95 (t, 1H, J = 7.5 Hz), 7.20 – 7.60 (m, 5H)
5	EIMS (m / z) %	237 (60), 236 (M^+ 20), 235 (10), 197 (35), 177 (10), 176 (90), 169 (12), 161 (10), 132 (15), 131 (100), 90 (15), 77 (12), 65 (18), 51 (20)

All the above synthesized β-amino carbonyl compounds are useful building blocks for the molecules with applications in pharmaceuticals and fine chemicals[5-10]. They are versatile intermediates for the synthesis of biologically important natural products and antibiotics and chiral auxiliaries and other nitrogen containing molecules.

CONCLUSION:

the synthesis of β-amino carbonyl compounds via aza- Michael reaction is the notable advantages offered by this method are simple operation, mild (room temperature) and environment friendly reaction conditions, much faster (20-50min) reaction, high yields of products

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