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Ammonium Chloride Promoted One-Pot, Three-Component Mannich Reaction: An Efficient Synthesis of β-Amino Ketones and β-Amino Esters

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Ammonium chloride was found to efficiently reagent for the one pot-three component Mannich reaction between aromatic aldehyde, ketone and amine in ethanol at room temperature to furnish β-amino ketones in good to excellent yields. The said protocol was further applied for the direct synthesis of β-amino esters, which are important precursors for the synthesis of β-amino acids. This protocol is potentially applicable for the development of a clean and environment-friendly strategy for the synthesis of β-amino ketones and found applications in the synthesis of potent biologically active molecules due to its simple experimental conditions, inexpensive reagents and straight forward product isolation procedure.

Keywords: Ammonium chloride, Mannich reaction, β-Amino ketones, β-Amino esters.

INTRODUCTION

Multicomponent reactions (MCRs) have attracted a great deal of interest in organic syntheses due to its utility in the synthesis of complex compounds [1]. MCRs are time efficient, easy to operate and furnish products without need of isolation of intermediates. As a result, it reduces environmental loading, making it an acceptable form of green chemistry [2]. Mannich reaction is one of the classical examples of MCRs which is an important biosynthetic/synthetic route to many natural products, mainly alkaloids [3]. Mannich bases are very reactive and have showed diverse biolgical activities such as anti-inflammatory, anticancer, anti-filarial, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, antiviral, *etc.* [4].

In particular, Mannich reaction has been widely used for the synthesis of β-amino carbonyl compounds owing to their importance as valuable building blocks for the preparation of 1,3-amino alcohols [5,6], β-amino acids [7] and esters as well as for the synthesis of bioactive molecules such as antibiotics nikkomycins and neopolyoxines [8,9]. Although, numerous methods have been reported in the literature for the synthesis of β-amino carbonyl compounds,but β-amino ketones are not investigated extensively. Few methods for direct synthesis of β-amino ketones have been reported that involved Mannich reactions catalyzed using cobalt(III)-catalyzed and dimethyl sulfoxide-involved cross-coupling reaction [10], $CeCl_3 \cdot 7H_2O$ catalyzed [11], iodine [12], Amberlyst-15 [13], Fe_3O_4 magnetite nanoparticles [14], bismuth(III) triflate [15], bismuth nitrate [16], (bromodimethyl)sulfonium bromide [17], conc. HCl [18], *etc.* However, most of the methods have certain drawbacks such as moisture sensitive reaction conditions, longer reaction times, catalyst loading and availability, high temperature, low yields, tedious work-up procedures, toxic solvents, *etc.*

Ammonium chloride is a versatile reagent and has been used in various organic transformations such as Ugi reaction [19], Biginelli reaction [20], Claisen rearrangement [21], isocyanide based MCRs for the synthesis of 4-imino-4*H*-3,1-benzoxazines [22], *etc*. It is also used as promoter in the oxidation or reduction reactions of organic compounds [23]. MCRs involving ammonium chloride are very much common and have been successfully used in synthesis of imidazo[1,2-*a*]-pyridines [24], dihydropyrimidinones [25], imidazo[1,2*a*]-pyrimidines [26], tetrahydrobenzo[*a*]xanthene-11-ones [27], imino-oxazolines, spirochromenes, spiroacridines [28], *etc.* (Fig. 1). With our ongoing research toward Mannich reactions, ammonium chloride promoted synthesis of β-amino carbonyl coumpounds in ethanol were carried out. The said method-

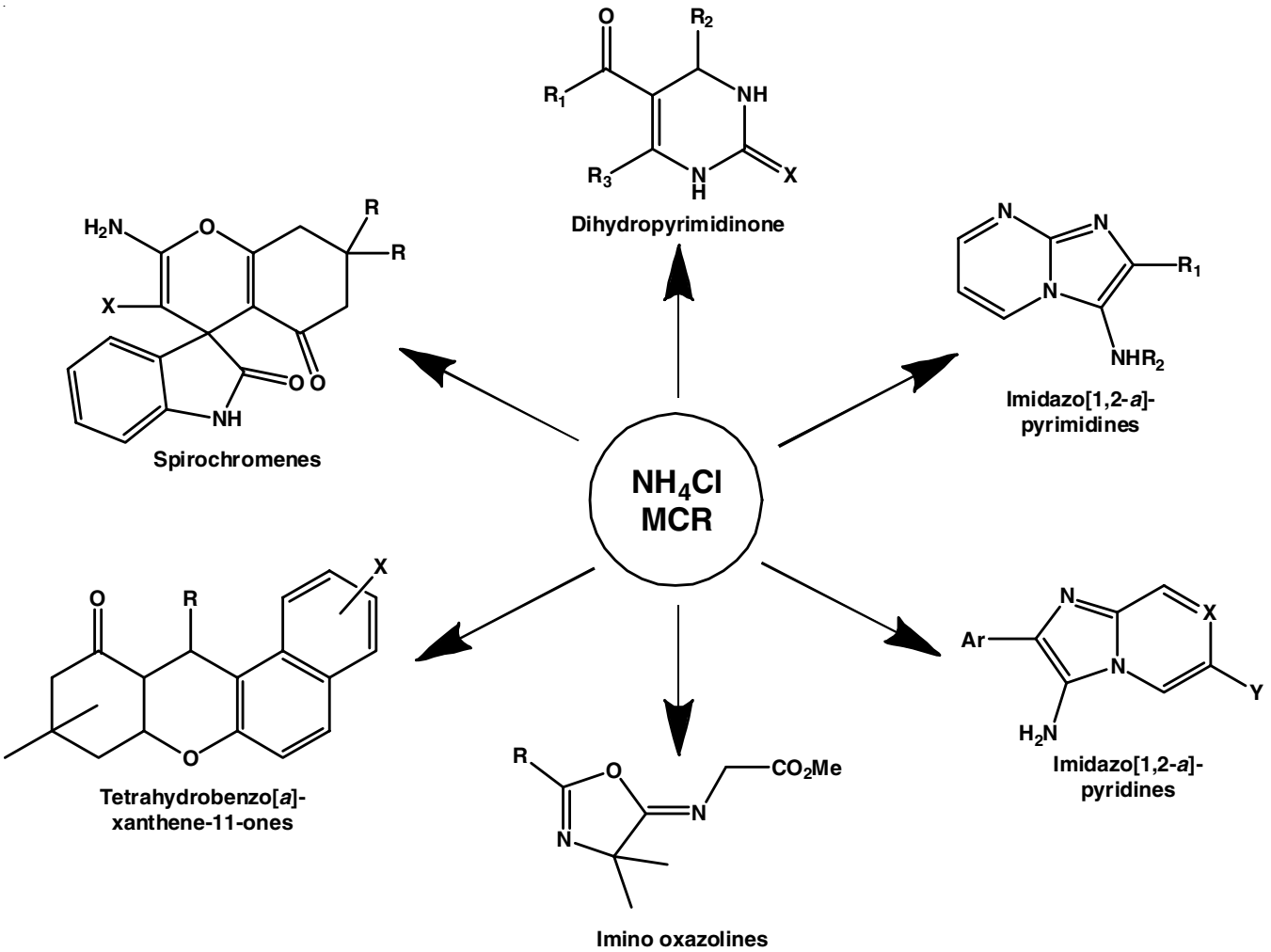


Fig. 1. Various heterocycles synthesis through MCR catalyzed by ammonium chloride

ology has been successfully applied for the synthesis of β-amino esters as well as benzylamino coumarins

EXPERIMENTAL

Melting points determined are uncorrected. All solvents used were of reagent grade and when necessary, were purified and dried by standard methods. Reactions and products were routinely monitored by thin layer chromatography (TLC) on silica gel (Kiesel gel 60 F_{254}, Merck). Column chromatographic purifications were performed using 100-200 mesh silica gel. IR spectra were recorded on Nicolet 5700 instrument. The ^1H & ^{13}C NMR spectra were recorded on Varian and Bruker spectrometer. The HRMS spectra were obtained on a Micromass Q-TOF apparatus.

General procedure for the synthesis of Mannich bases (4a-w): A mixture of aromatic ketone (1 mmol), aromatic aldehyde (1 mmol), aromatic amine (1 mmol) and ammonium chloride (0.5 mmol) in ethanol was stirred at room temperature for 15-24 h. When reaction was completed as indicated by TLC, precipitated the product, filtered off and then dissolved in hot ethanol. The filtrate was kept at room temperature and the resulting crystallized product was collected by filtration. The product were characterized by IR, ^1H NMR, ^{13}C NMR and LCMS techniques.

1,3-Diphenyl-3-(phenyl amino)propan-1-one (4a): White solid; Yield: 96%; m.p.: 169-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 3386, 1680, 1597, 1510, 1289, 860, 768; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.46 (dd, *J* = 8 and 8 Hz, 1H), 3.55 (dd, *J* = 4 and 4 Hz, 1H), 4.59 (s, 1H,-NH), 5.05 (t, *J* = 8 Hz, 1H), 6.60 (d, *J* = 8 Hz, 2H), 6.70 (t, *J* = 8 Hz, 1H), 7.08-7.14 (m, 2H), 7.24-7.30 (m, 1H), 7.36 (t, *J* = 8 Hz, 2H), 7.45-7.50 (m, 4H), 7.59-7.61 (m, 1H), 7.97-7.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.3, 54.8, 113.8, 117.8, 126.4, 127.4, 128.2, 128.7, 128.8, 129.1, 133.4, 136.7, 143.0, 147.0, 198.2; *m/z*: 306 (M^+).

3-(3-Chlorophenylamino)-1,3-diphenylpropan-1-one (4b): White solid; Yield: 85%; m.p.: 134-136 ºC; IR (KBr, ν_{max}, cm^{-1}): 1289, 860, 710; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.44 (dd, *J* = 8 and 8 Hz, 1H), 3.53 (dd, *J* = 4 and 4 Hz, 1H), 4.72 (s, 1H,-NH), 5.01 (t, *J* = 8 Hz, 1H), 6.45 (dd, *J* = 4 and 2 Hz, 1H), 6.57 (t, *J* = 4 Hz, 1H), 6.65 (dd, *J* = 1.2 and 1.2 Hz, 1H) 7.01 (t, *J* = 4 Hz, 1H), 7.27-7.30 (m, 1H), 7.34-7.39 (m, 2H),7.43-7.51 (m, 4H), 7.57-7.62 (m, 1H), 7.90-7.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.1, 54.7, 111.9, 113.6, 117.7, 126.2, 127.5, 128.2, 128.7, 128.8, 130.0, 133.5, 134.8, 136.6, 142.3, 148.2, 198.0; *m/z*: 335.21 (M^+).

3-(4-Chlorophenylamino)-1,3-diphenylpropan-1-one (4c): White solid; Yield: 82%; m.p.: 171-172 ºC; IR (KBr, ν_{max}, cm^{-1}): 3371, 1663, 1598, 1488, 1307, 743, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.44 (dd, *J* = 8 and 8 Hz, 1H), 3.52 (dd, *J* = 4 and 4 Hz, 1H), 4.66 (s, 1H,-NH), 4.98 (t, *J* = 8 Hz, 1H), 6.51 (d, *J* = 8 Hz, 2H), 7.05 (d, *J* = 8 Hz, 2H), 7.28 (t, *J* = 4 Hz, 1H), 7.36-7.40 (m, 2H), 7. 42-7.51 (m, 4H), 7.60 (t, *J* = 4 Hz, 1H), 7.93 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.2, 54.9, 114.9, 122.4, 126.3, 127.5, 128.2, 128.4, 128.7, 128.9, 133.5, 136.6, 142.5, 145.6, 198.1; *m/z*: 335.9 (M^+).

3-(*p*-Tolylamino)-1,3-diphenylpropan-1-one (4d): White solid; Yield: 96%; m.p. 165-166 ºC; IR (KBr, ν_{max}, cm^{-1}): 3402, 1679, 1595, 1525, 1291, 744, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.24 (s, 3H), 3.46 (dd, *J* = 8 and 8 Hz, 1H), 3.52 (dd, *J* = 4 and 4 Hz, 1H), 4.50 (s, 1H,-NH), 5.05 (t, *J* = 8 Hz, 1H), 6.56 (d, *J* = 4 Hz, 2H), 6.96 (d, *J* = 8 Hz, 2H), 7.29 (t, *J* = 8 Hz, 1H), 7.38-7.40 (m, 2H), 7. 45-7.53 (m, 4H), 7.61 (t, *J* = 8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 20.4, 46.2, 55.1, 114.0, 126.4, 127.0, 127.3, 128.2, 128.7, 128.8, 129.6, 133.4, 136.8, 143.2, 144.7, 198.3; *m/z*: 316(M^+).

3-(4-Methoxyphenylamino)-1,3-diphenylpropan-1-one (4e): White solid; Yield: 95%; m.p.: 124-126 ºC; IR (KBr, ν_{max}, cm^{-1}): 3376, 1679, 1595, 1520, 1291, 744, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.46 (dd, *J* = 8 and 8 Hz, 1H), 3.53 (dd, *J* = 4 and 4 Hz, 1H), 3.81 (s, 3H), 4.50 (s, 1H,-NH), 5.04 (t, *J* = 8 Hz, 1H), 6.63 (d, *J* = 8 Hz, 2H), 6.72 (t, *J* = 8 Hz, 1H), 6.91 (d, *J* = 8 Hz, 2H), 7.13-7.18 (m, 2H), 7.41 (d, *J* = 8 Hz, 2H), 7. 46-7.52 (m, 4H), 7.60 (t, *J* = 4 Hz, 1H), 7.98 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.3, 54.2, 55.2, 113.8, 114.2, 117.7, 127.5, 128.2, 128.7, 129.1, 133.4, 135.0, 136.8, 147.1, 158.8, 198.4; *m/z:* 331.16 (M^+).

3-(4-Nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4f): White solid; Yield: 80%; m.p.: 148-150 ºC; IR (KBr, ν_{max}, cm^{-1}): 3376, 1665, 1600, 1510, 1291, 1219, 818, 749, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.49 (dd, *J* = 8 and 8 Hz, 1H), 3.54 (dd, *J* = 4 and 4 Hz, 1H), 4.75 (s, 1H,-NH), 5.14 (t, *J* = 8 Hz, 1H), 6.54 (d, *J* = 8 Hz, 2H), 6.72 (t, *J* = 8 Hz, 1H), 7.13 (t, *J* = 8 Hz, 2H), 7.48 (t, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H), 7.53-7.61 (m, 3H), 7.78-7.84 (m, 2H), 8.17 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.8, 54.2, 55.2, 114.2, 118.5, 124.0, 125.6, 128.8, 129.2, 133.7, 136.4, 146.3, 148.6, 150.7, 198.4; *m/z*: 346.13 (M^+).

3-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4g): White solid; Yield: 85%; m.p.: 131-133 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 1666, 1608, 1510, 1291, 711, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.45 (dd, *J* = 8 and 8 Hz, 1H), 3.52 (dd, *J* = 4 and 4 Hz, 1H), 4.62 (s, 1H,-NH), 5.03 (t, *J* = 8 Hz, 1H), 6.58 (d, *J* = 8 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 7.11-7.16 (m, 2H), 7.28-7.34 (m, 2H), 7.42-7.51 (m, 4H), 7.57-7.62 (m, 1H), 7.94 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.1, 54.1, 113.9, 118.0, 128.2, 128.4, 128.7, 128.9, 129.2, 132.9, 133.6, 136.6, 141.5, 146.7, 197.9; *m/z*: 335.83 (M^+).

3-(4-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4h): White solid; Yield: 89%; m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 1666, 1608, 1510, 1291, 711, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.42 (dd, *J* = 8 and 8 Hz, 1H), 3.51 (dd, *J* = 4 and 4 Hz, 1H), 4.60 (s, 1H,-NH), 5.00 (t, *J* = 8 Hz, 1H), 6.53 (d, *J* = 8 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 7.11 (t, *J* = 8 Hz, 1H), 7.28 (d, *J* = 8 Hz, 2H), 7.45-7.75 (m, 5H), 7.90 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.1, 54.2, 113.9, 118.1, 121.1, 127.9, 128.2, 128.4, 129.2, 131.9, 133.6, 136.6, 142.1, 146.7, 197.9; *m/z:* 380.28 (M^+).

3-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino)-propan-1-one (4i): White solid; Yield: 85%; m.p.: 148-150 ºC; IR (KBr, ν_{max}, cm^{-1}): 3376, 1665, 1600, 1510, 1291, 1219, 818, 749, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.46 (dd, *J* = 8 and 8 Hz, 1H), 3.53 (dd, *J* = 4 and 4 Hz, 1H), 3.81 (s, 3H), 4.50 (s, 1H,-NH) 5.04 (t, *J* = 8 Hz, 1H), 6.63 (d, *J* = 8 Hz, 2H), 6.72 (t, *J* = 8 Hz, 1H), 6.91 (d, *J* = 8 Hz, 2H), 7.13-7.18 (m, 2H), 7.41 (d, *J* = 8 Hz, 2H), 7. 46-7.52 (m, 4H), 7.60 (t, *J* = 4 Hz, 1H), 7.98 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.3, 54.2, 55.2, 113.8, 114.2, 117.7, 127.5, 128.2, 128.7, 129.1, 133.4, 135.0, 136.8, 147.1, 158.8, 198.4; *m/z*: 331.41 (M^+).

3-(3-Chlorophenylamino)-1-phenyl-3-(pyridin-2-yl)-propan-1-one (4j): White solid; Yield: 83%; m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3270, 1591, 1481, 1219, 749, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.63 (dd, *J* = 4 and 4 Hz, 1H), 3.70 (dd, *J* = 8 and 8 Hz, 1H), 5.09 (s, 1H,-NH), 5.19 (t, *J* = 4 Hz, 1H), 6.55 (dd, *J* = 8 and 1.2 Hz, 1H), 6.65-6.71 (m, 2H), 7.02-7.10 (m, 1H), 7.14-7.20 (m, 1H),7. 41-7.51 (m, 4H), 7.54-7.66 (m, 2H), 7.93 (t, *J* = 4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 43.8, 55.1, 111.9, 113.5, 117.7, 122.1, 122.4, 128.2, 128.6, 130.2, 133.4, 135.0, 136.6, 136.8, 147.9, 149.4, 160.6, 198.6; *m/z*: 331.41 (M^+).

3-(*p*-Tolylamino)-1-phenyl-3-*p*-tolylpropan-1-one (4k): White solid; Yield: 89%; m.p.: 136-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3398, 1678, 1656, 1575, 731, 622; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.35 (s, 6H), 3.44 (dd, *J* = 8 and 8 Hz, 1H), 3.52 (dd, *J* = 8 and 8 Hz, 1H), 4.62 (s, 1H,-NH), 4.99 (t, *J* = 8 Hz, 1H), 6.47 (d, *J* = 8 Hz, 1H), 6.59 (t, *J* = 8 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 7.01 (t, *J* = 8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 2H), 7.25-7.29 (m, 1H), 7. 34 (d, *J* = 8 Hz, 2H), 7.45-7.62 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 21.1, 21.5, 46.1, 54.4, 114.9, 126.2, 128.4, 128.6, 128.7, 129.2, 132.1, 133.6, 136.6, 137.2, 141.1, 145.0, 198.1; *m/z*: 329.43 (M^+).

3-(3-Chlorophenylamino)-1-phenyl-3-*p*-tolylpropan-1-one (4l): White solid; Yield: 85%; m.p.: 142-144 ºC; IR (KBr, ν_{max}, cm^{-1}): 3270, 1686, 1591, 1481, 1219, 749, 684; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.48 (dd, *J* = 8 and 8 Hz, 1H), 3.56 (dd, *J* = 8 and 8 Hz, 1H), 4.79 (s, 1H,-NH), 5.04 (t, *J* = 8 Hz, 1H), 6.47 (d, *J* = 8 Hz, 1H), 6.59 (t, *J* = 8 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 7.01 (t, *J* = 8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 2H), 7.25-7.29 (m, 1H), 7.34 (d, *J* = 8 Hz, 2H) 7.45-7.62 (m, 4H); ^{13}C NMR 101 MHz, $CDCl_3$) δ ppm: 21.1, 46.1, 54.4, 114.9, 126.2, 128.4, 128.6, 128.7, 129.2, 132.1, 133.6, 136.6, 137.2, 141.1, 145.0, 198.1; *m/z*: 349.12 (M^+).

3-(3-Chlorophenylamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one (4m): White solid; Yield: 80%; m.p.: 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3395, 1674, 1596, 1576, 1291, 830, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.42 (dd, *J* = 8 and 8

Hz, 1H), 3.55 (dd, *J* = 4 and 4 Hz, 1H), 5.02 (s, 1H,-NH), 5.32 (t, *J* = 8 Hz, 1H), 6.43 (d, *J* = 2 Hz, 1H), 6.58 (d, *J* = 2 Hz, 1H), 7.02 (t, *J* = 2 Hz, 2H), 7.28-7.32 (m, 2H), 7. 34-7.60 (m, 4H), 7.70-7.80 (m, 1H), 8.02 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 45.9, 54.0, 111.9, 113.6, 117.9, 127.7, 128.0, 128.7, 128.9, 129.9, 132.5, 133.2, 133.6, 136.4, 140.9, 147.9, 197.9; *m/z*: 370.27 (M^+).

3-(4-Chlorophenylamino)-3-(2-chlorophenyl)-1-phenylpropan-1-one (4n): White solid; Yield: 65%; m.p.: 142-143 ºC; IR (KBr, ν_{max}, cm^{-1}): 3395, 1674, 1596, 1576, 1291, 830, 687, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.34 (dd, *J* = 8 and 8 Hz, 1H), 3.62 (dd, *J* = 4 and 4 Hz, 1H), 4.99 (s, 1H,-NH), 5.29 (t, *J* = 4 Hz, 1H), 6.42 (d, *J* = 8 Hz, 2H), 7.04 (d, *J* = 8 Hz, 2H), 7.19-7.23 (m, 2H), 7.40-7.54 (m, 4H), 7.57-7.62 (m, 1H), 7.96-8.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 43.5, 52.1, 114.7, 122.5, 127.4, 128.0, 128.3, 128.7, 128.9, 129.6, 129.9, 132.3, 133.6, 136.4, 139.0, 145.0, 198.4; *m/z*: 370.27 (M^+).

3-(4-Chlorophenylamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one (4o): White solid; Yield: 82%; m.p.: 165-166 ºC; IR (KBr, ν_{max}, cm^{-1}): 3395, 1674, 1596, 1576, 1291, 830, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.42 (dd, *J* = 8 and 4 Hz, 1H), 3.48 (dd, *J* = 8 and 4 Hz, 1H), 4.66 (s, 1H,-NH), 4.95 (t, *J* = 8 Hz, 1H), 6.37 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.16-7.24 (m, 2H), 7.28-7.50 (m, 4H), 7.55-7.62 (m, 1H), 8.00 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.1, 54.1, 118.0, 123.8, 128.2, 128.4, 128.7, 128.9, 129.2, 132.5, 133.6, 136.8, 141.5, 146.7, 197.9; *m/z*: 370.27 (M^+).

3-(3-Chlorophenylamino)-3-(2,4-dichlorophenyl)-1-phenylpropan-1-one (4p): White solid; Yield: 75%; m.p.: 125-128 ºC; IR (KBr, ν_{max}, cm^{-1}): 3303, 1600, 1589, 1576, 1511, 889, 615; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.44 (dd, *J* = 8 and 8 Hz, 1H), 3.50 (dd, *J* = 4 and 4 Hz, 1H), 4.61 (s, 1H,-NH), 5.08 (t, *J* = 8 Hz, 1H), 6.35 (d, *J* = 8 Hz, 1H), 6.49 (d, *J* = 2 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 7.01 (t, *J* = 8 Hz,1H), 7.16 (d, *J* = 8 Hz, 1H), 7.22 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 2 Hz, 1H), 7.40-7.62 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.3, 53.0, 113.8, 116.8, 117.8, 126.4, 128.0, 128.6, 129.7, 130.0, 130.8, 131.9, 132.6, 133.4, 134.7, 136.6, 141.5, 146.7, 198.0; *m/z*: 404.72 (M^+).

3-Phenyl-3-(phenylamino)-1-*p*-tolylpropan-1-one (4q): White solid; Yield: 86%; m.p.: 136-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 1715, 1654, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 3.42 (dd, *J* = 8 and 8 Hz, 1H), 3.52 (dd, *J* = 4 and 4 Hz, 1H), 4.62 (s, 1H,-NH), 5.02 (t, *J* = 8 Hz, 1H), 6.58 (d, *J* = 8 Hz, 2H), 6.73 (t, *J* = 8 Hz, 1H), 7.11-7.16 (m, 2H), 7.28-7.34 (m, 2H), 7.42-7.51 (m, 4H), 7.57-7.62 (m, 1H), 7.84 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 21.2, 46.2, 54.9, 113.8, 117.7, 126.3, 127.3, 128.2, 128.4, 128.6, 129.0, 129.3, 133.6, 141.5, 146.7, 197.9; *m/z*: 315.41 (M^+).

3-(*p*-Tolylamino)-3-phenyl-1-*p*-tolylpropan-1-one (4r): White solid; Yield: 90%; m.p.: m.p.136-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3350, 1715, 1654, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23 (s, 3H), 2.26(s, 3H), 3.22 (dd, *J* = 4 and 4 Hz, 1H), 3.52 (dd, *J* = 8 and 8 Hz, 1H), 4.71 (s, 1H,-NH), 4.93 (t, *J* = 4 Hz, 1H), 6.50 (d, *J* = 8 Hz, 2H), 6.72-7.10 (m, 2H), 7.28-7.34 (m, 2H), 7.36-7.51 (m, 5H), 7.80 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 21.2, 46.1, 53.9, 116.2, 118.9, 127.0, 127.6, 128.2, 128.4, 129.2, 129.6, 136.2, 141.4, 143.9, 146.7, 197.4; *m/z:* 329.18(M^+).

3-(4-Chlorophenylamino)-3-phenyl-1-*p*-tolylpropan-1-one (4s): White solid; Yield: 82%; m.p.: 140-142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3348, 1720, 1680, 1210, 815, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 3.24 (dd, *J* = 8 and 8Hz, 1H), 3.52 (dd, *J* = 4 and 4Hz, 1H), 4.70 (s, 1H,-NH), 5.07 (t, *J* = 4 Hz, 1H), 6.52 (d, *J* = 2 Hz, 2H), 6.70 (d, *J* = 2 Hz, 1H), 7.18-7.30 (m, 2H),7.36-7.51 (m, 6H), 7.89 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 21.6, 46.2, 54.9, 113.8, 117.7, 126.3, 127.3, 128.7, 128.9, 129.0, 129.3, 134.2, 143.1, 144.3, 147.7, 197.9; *m/z*: 349.12 (M^+).

3-(4-Methoxyphenyl)-3-(phenylamino)-1-*p*-tolylpropan-1-one (4t): White solid; Yield: 85%; m.p.: . 122-125 ºC; IR (KBr, ν_{max}, cm^{-1}): 3348, 1720, 1680, 815, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.24 (s, 3H), 3.35 (dd, *J* = 8 and 8Hz, 1H), 3.52 (dd, *J* = 4 and 4Hz, 1H), 3.80 (s, 3H), 4.70 (s, 1H, -NH), 4.98 (t, *J* = 8 Hz, 1H), 6.55 (m, 3H), 6.88 (d, *J* = 8 Hz, 2H), 7.01 (t, *J* = 8 Hz, 2H), 7.28-7.40 (m, 4H), 7.86 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 21.6, 46.8, 54.1, 56.0, 113.3, 114.1, 117.0, 128.2, 128.6, 129.1,1 29.7, 134.8, 136.3, 143.9, 148.3, 158.4, 197.9; *m/z*: 345.17 (M^+).

3-(Phenylamino)-1,3-dip-tolylpropan-1-one (4u): White solid; Yield: 86%; m.p.: 122-125 ºC; IR (KBr, ν_{max}, cm^{-1}): 3392, 1666, 1601, 1510, 986, 683; ^{1}H NMR (400 MHz, DMSO) δ ppm: 2.23 (s, 3H), 2.26 (s, 3H), 3.22 (dd, *J* = 4 and 4 Hz, 1H), 3.52 (dd, *J* = 8 and 8 Hz, 1H), 4.71 (s, 1H,-NH), 4.93 (t, *J* = 4 Hz, 1H), 6.50 (d, *J* = 8 Hz, 2H), 6.72-7.10 (m, 2H), 7.28-7.34 (m, 2H), 7.36-7.51 (m, 5H), 7.80 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 21.2, 46.1, 53.9, 116.2, 118.9, 127.0, 127.6, 128.2, 128.4, 129.2, 129.6, 136.2, 141.4, 143.9, 146.7, 197.4; *m/z:* 329.18 (M^+).

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-3-(phenylamino)propan-1-one (4v): White solid; Yield: 80%; m.p.: 135-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3303, 1600, 1576, 1511, 889, 615; ^{1}H NMR (400 MHz, DMSO) δ ppm: 3.24 (dd, *J* = 8 and 8Hz, 1H), 3.63 (dd, *J* = 8 and 8 Hz, 1H), 3.75 (s, 3H), 4.60 (s, 1H, -NH), 4.91 (t, *J* = 4 Hz, 1H), 6.25 (d, *J* = 8 Hz, 1H), 6.50 (d, *J* = 8 Hz, 2H), 6.83 (d, *J* = 8 Hz, 2H), 6.96 (t, *J* = 8 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.57 (d, *J* = 8 Hz, 2H), 7.96 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ ppm: 46.9, 54.8, 55.4, 117.9, 119.6, 128.2, 128.6, 129.1, 129.2, 129.3, 131.4, 136.1, 138.5, 148.3, 158.5, 197.1; *m/z*: 365.12 (M^+).

3-(2-Chlorophenyl)-1-(4-chlorophenyl)-3-(2-chlorophenylamino)propan-1-one(*E*) (4w): White solid; Yield: 70%; m.p.: 90-91 ºC; IR (KBr, ν_{max}, cm^{-1}): 3406, 1682, 1597, 1477, 1095, 984, 822, 767, 721, 687, 525, 470, 459, 414; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.42 (dd, *J* = 8 and 8 Hz, 1H), 3.54 (dd, *J* = 4 and 4 Hz, 1H), 4.72 (s, 1H,-NH), 5.02 (t, *J* = 8 Hz, 1H), 6.62 (dd, *J* = 8 and 2 Hz, 1H), 6.76 (m, 1H), 7.08 (m, 1H), 7.10-7.32 (m, 5H), 7.37 (d, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 46.1, 54.1, 118.0, 120.4, 125.2, 126.4, 126.9, 127.2, 128.4, 128.7, 128.9, 129.2, 130.6, 133.6, 136.0, 138.9, 141.5, 142.6, 197.2; *m/z:* 403.03 (M^+).

General procedure for the synthesis of Mannich bases (6a-e): A mixture of diethyl malonate (1 mmol), aromatic

aldehyde (1 mmol), aromatic amine (1 mmol) and ammonium chloride (0.5 mmol) in ethanol was stirred at room temperature for 15-24 h. When reaction was completed as indicated by TLC, then the product was precipitated from reaction mixture. The precipitate was filtered off, dissolved in hot ethanol. The filtrate was kept at room temperature and the resulting crystallized product was collected by filtration. The product were characterized by IR, ^{1}H NMR, ^{13}C NMR, LCMS techniques.

Diethyl 2-(phenyl(phenylamino)methyl)malonate (6a): White solid; Yield: 92%; m.p.: 92-93 ºC; IR (KBr, ν_{max}, cm^{-1}): 3375, 1728; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.20 (t, *J* = 4 Hz, 6H), 3.93 (d, *J* = 8 Hz, 1H), 4.10 (m, 4H), 5.26 (d, *J* = 8 Hz, 1H), 5.34 (s, 1H,-NH), 6.61-6.72 (m, 3H), 7.12 (t, *J* = 8 Hz, 2H), 7.22-7.28 (m, 1H), 7. 30-7.35 (m, 2H), 7.39 (d, *J* = 4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.1, 53.8, 56.3, 61.9, 114.3, 117.9, 127.4, 127.7, 128.7, 129.3, 141.9, 147.7, 167.5; *m/z*: 341.16 (M^+).

Diethyl 2-((phenylamino)(4-chlorophenyl) methyl) Malonate (6b): White solid; Yield: 75%; m.p.: 76-78 ºC; IR (KBr, ν_{max}, cm^{-1}): 3374, 1744; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.25 (t, *J* = 4 Hz, 6H), 3.95 (d, *J* = 4 Hz, 1H), 4.15- 4.30 (m, 4H), 5.28 (d, *J* = 4 Hz, 1H), 5.40 (s, 1H,-NH), 6.42 (d, *J* = 4 Hz, 1H), 6.52-6.70 (m, 2H), 7.0 (d, *J* = 4 Hz, 1H), 7.28-7.50 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.9, 53.2, 58.2, 61.8, 117.8, 123.8, 126.8, 127.6, 128.6, 129.1, 139.7, 146.6, 167.2; *m/z*: 375.12 (M^+).

Diethyl 2-((4-methylphenylamino)methyl) malonate (6c): White solid; Yield: 82%; m.p.: 78-90 ºC; IR (KBr, ν_{max}, cm^{-1}): 3368, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.36 (dd, *J* = 13.4 and 7.0 Hz, 6H), 2.29 (s, 3H), 3.54 (d, *J* = 5.6 Hz, 1H), 4.05-4.16 (m, 4H), 5.16 (d, *J* = 5.5 Hz, 1H), 5.38 (s, 1H), 6.57-6.72 (m, 2H), 7.05-7.11 (m, 2H), 7.15-7.23 (m, 1H), 7.27 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.8, 21.13, 53.1, 57.9, 61.5, 114.7, 126.6, 127.75, 127.9, 128.4, 130.35, 140.2, 143.2, 167.45; *m/z*: 355.18 (M^+).

iethyl 2-((3-methylphenylamino)methyl) malonate (6d): White solid; Yield: 95%; m.p.: 76-78 ºC; IR (KBr, ν_{max}, cm^{-1}): 3315, 1750; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30 (t, *J* = 4Hz, 6H), 2.33 (s, 3H), 3.54 (d, *J* = 8 Hz, 1H), 4.15-4.30 (m, 4H), 5.40 (s, 1H,-NH), 5.44 (d, *J* = 8 Hz, 1H), 6.55 (dd, *J* = 8 and 2 Hz, 2H), 6.68-7.02 (m, 1H), 7.15-7.20 (m, 2H), 7. 22 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.9, 21.2, 53.2, 59.1, 61.8, 116.8, 119.6, 127.6, 128.9, 129.3, 136.3, 139.2, 146.1, 167.4; *m/z*: 355.18 (M+).

Diethyl 2-(phenyl(4-methoxyphenylamino)methyl)-malonate (6e): White solid; Yield: 90%; m.p.: 70-72 ºC; IR (KBr, ν_{max}, cm^{-1}): 3360, 1750; ^{1}H NMR (400MHz, $CDCl_3$) δ ppm: 1.35 (t, *J* = 4 Hz, 6H), 3.81 (s, 3H), 3.95 (d, *J* = 4 Hz, 1H), 4.15-4.30 (m, 4H), 5.35 (d, *J* = 4 Hz, 1H), 5.40 (s, 1H, -NH), 6.72 (dd, *J* = 8 and 2 Hz, 2H), 6.80-6.86 (m, 1H), 7.15-7.25 (m, 2H), 7.02 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 13.9, 53.2, 56.0, 58.8, 61.8, 113.1, 116.4, 119.6, 128.1, 129.2, 132.9, 146.2, 158.2, 167.2; *m/z*: 371.43 (M^+).

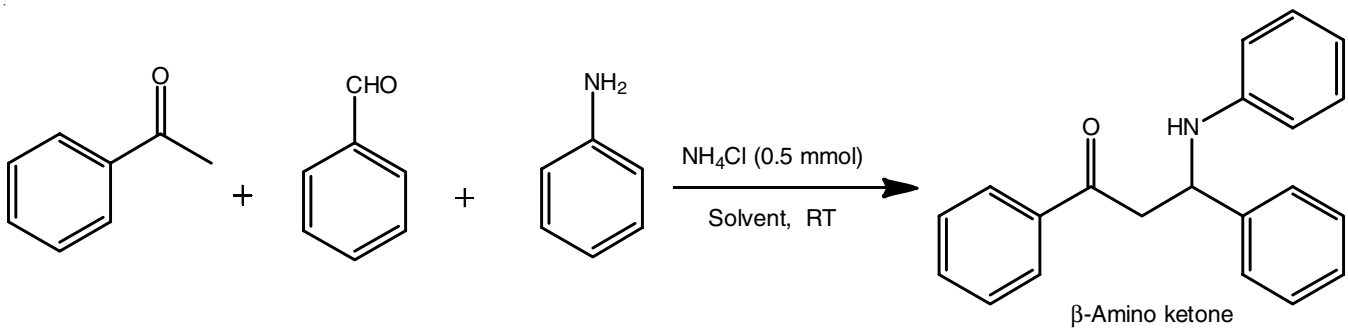
RESULTS AND DISCUSSION

In primary investigation, model reaction between benzaldehyde, acetophenone and aniline in presence of ammonium chloride (0.5 mmol) with ethanol as a solvent was performed at room temperature. The clean reaction conversion with 96% yield was observed in 15 h without any side products to furnish the desired β-amino ketone (**Scheme-I**).

Inspired with the initial findings of the reaction, it is decided to test the scope of reaction using various solvents, other ammonium salts as well as the reaction temperature. The model reaction was tested in various solvents such as tetrahydrofuran, ethanol, dichloromethane, acetonitrile, benzene, polyethylene glycol using ammonium chloride at room temperature. In absence of the solvent, reaction did not proceed indicating the reaction needs to be run in presence of solvent. Ethanol was found to be the ideal solvent for the reaction with highest yield of 96%, while polyethylene glycol was found to be the moderate one with 70% yield. Surprisingly reaction did not worked with dichloromethane and tetrahydrofuran as well as only traces of product were observed with acetonitrile after 48 h. While in benzene reaction furnished only 25% yield after 24 h. Ultimately, ethanol was the choice of solvent for better results (Table-1).

TABLE-1
SCREENING OF THE SOLVENTS IN MANNICH REACTION

Entry	Solvent	Time (h)	Isolated yield (%)
1	No solvent	24	Nil
2	Acetonitrile	48	Trace
3	Ethanol	15	96
4	Benzene	24	25
5	Polyethylene glycol	24	70
6	Dichloromethane	24	Nil
7	Tetrahydrofuran	24	Nil



Scheme-I: One-pot, three-component Mannich-type reaction between acetophenone, benzaldehyde and aniline

To order to find the effect of ammonium salts, a reaction was carried out in absence of reagent, where desired product was not observed even after 24 h. In next set of experiment, the effect of different ammonium salts such as $(NH_4)_2CO_3$, NH_4Br, NH_4OH, NH_4HCOOH, NH_4COOCH_3 on progress of reaction were examined. Among the studied ammonium salts, NH_4OH showed lowest reactivity in the reaction with lowest yield of only 25% after 48 h. Other ammonium salts were moderately reactive with yields 50-70%, whereas NH_4Cl was found to be the most efficient, which gave the highest yield (96%) within 15 h (Table-2).

TABLE-2
SCREENING OF THE CATALYST FOR MANNICH REACTION

Entry	Catalyst	Time (h)	Isolated yield (%)
1	No catalyst	24	Nil
2	$(NH_4)_2CO_3$	48	50
3	NH_4Br	20	65
4	NH_4Cl	15	96
5	NH_4OH	48	25
6	NH_4HCOOH	48	70
7	NH_4COOCH_3	48	55

Further screening was done on sub-stoichiometric loading of ammonium chloride. Ammoium chloride concentration was found to play an important role in driving the reaction by optimizing the rate and the yield of the reaction. Various concentrations of ammonium chlorides were tried from 0.1 to 0.8 mmol. It was observed that the reactions with lower concentration of ammonium chloride gave lower yield even after prolonged reaction times. The concentration between 0.5 to 0.8 mmol, no significant effect on reaction rate as well as yield was observed (Table-3). So, the optimum concentration of 0.5 mmol was found to be sufficient to furnish the desired product in 15 h. With addition of stoichiometric quantity of ammonium chloride (1mmol) and prolonged reaction time of 48 h, formation of elimination product *i.e.* chalcone was observed. Thus, chalcone formation can be controlled taking advantage of ammonium chloride concentration.

TABLE-3
EFFECT OF CATALYST CONCENTRATION ON REACTION

S. No.	NH_4Cl (mmol)	Time (h)	Isolated yield (%)
1	0.1	48	25
2	0.2	36	40
3	0.3	30	55
4	0.4	24	70
5	0.5	15	96
6	0.8	24	92
7	1.0	48	–[a]

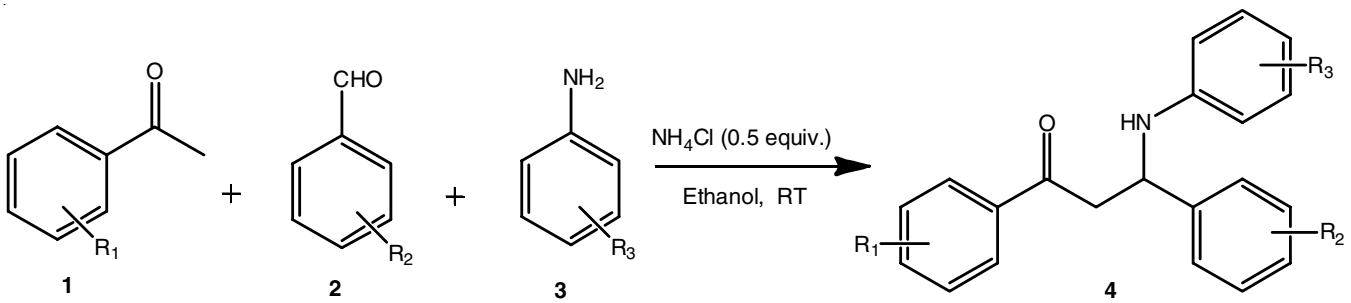
[a]Chalcone formation was observed.

Next factor to optimize was the reaction temperature. The reaction could proceed smoothly at room temperature. However, increasing the temperature from room temperature to 40, 60 and 80 ºC significantly reduced the conversion of β-amino ketone and formation of side products was found to be substantial.

Optimistic by these results, next attention turned to explore the scope and generality of the present method with variety of aromatic aldehydes, aromatic ketones and amines. Various aromatic aldehydes, ketones and amines having electron withdrawing group *viz.*, NO_2, Cl, Br as well as electron donating groups like OMe, Me were chosen for screening (**Scheme-II**). In each case, good to excellent yields were observed. As can also be seen from Table-4, the substitutional group of reactant was crucial in determining the yield of β-amino ketone. So, as far as aromatic amines were concerned, the existence of electron donating group could be favourable to increase its nucleophilic ability which determined the reaction speed and excellent yields (Table-4; entries 4 and 5).

However, when *ortho* substituted benzaldehydes were used, yield of product was reduced as a result of steric hindrance (Table-4; entries 14 & 16). Presence of Cl group on either aldehyde/ketone or amine always took more than 20 h for completion of reaction irrespective of its position on the aryl ring in reactant (Table-4; entries 12-16), whereas Br group found to accelerate the reaction compare to chloro derivatives (Table-4; entry 8). This behaviour is attributed to the fact that the reactivity of haloarenes is controlled by electron donating resonance effect and electron withdrawing inductive effect. Chlorine is more electronegative than bromine and hence, electron withdrawing inductive effect is also less when Br is present on ring this leads to facilitate the reaction. Surprisingly reaction of 4-nitroanilne gave better yields in short reaction time (Table-4; entry 6). Another notable observation was found, when methyl group was present on the ring at *para* position, reaction rate was much faster compare to other substrates (Table-4; entries 4, 11, 17, 19).

As an application of the present investigation, the scope of findings beyond aromatic ketones was extended. β-Amino esters are the precursors for β-amino acids, which are synthetically important building blocks. Several reactions were tried



Scheme-II: Mannich reaction between substituted aromatic aldehydes, ketones and anilines

TABLE-4
AMMONIUM CHLORIDE CATALYZED ONE POT MANNICH REACTION BETWEEN VARIOUS AROMATIC KETONES, AROMATIC ALDEHYDES AND AROMATIC AMINES

Entry	R_1	R_2	R_3	Product	Time (h)	Isolated yield (%)
1	H	H	H	**4a**	15	96
2	H	H	3-Cl	**4b**	20	85
3	H	H	4-Cl	**4c**	20	82
4	H	H	4-Me	**4d**	12	96
5	H	H	4-OMe	**4e**	15	95
6	H	H	4-NO_2	**4f**	20	80
7	H	4-Cl	H	**4g**	18	85
8	H	4-Br	H	**4h**	16	89
9	H	4-OMe	H	**4i**	15	85
10	H	Pyridine	3-Cl	**4j**	24	83
11	H	4-Me	4-Me	**4k**	12	90
12	H	4-Me	4-Cl	**4l**	20	89
13	H	4-Cl	3-Cl	**4m**	24	80
14	H	2-Cl	4-Cl	**4n**	24	75
15	H	4-Cl	4-Cl	**4o**	24	82
16	H	2,4-dichloro	3-Cl	**4p**	24	65
17	4-Me	H	H	**4q**	12	86
18	4-Me	H	4-Me	**4r**	15	90
19	4-Me	H	4-Cl	**4s**	12	82
20	4-Me	4-OMe	H	**4t**	20	85
21	4-Me	4-Me	H	**4u**	20	86
22	4-Cl	4-OMe	H	**4v**	15	80
23	4-Cl	2-Cl	2-Cl	**4w**	20	70

between various aromatic aldehaydes, amines and ethyl malonate in order to synthesize β-amino esters (**Scheme-III**). The reactions were found to furnish good to excellent yields in overnight reaction conditions (Table-5). The synthesized β-amino esters on furhther hydrolysis followed by decarboxylation could furnish the desired β-amino acids.

Conclusion

In conclusion, an efficient methodology for the synthesis of β-amino ketones through one-pot, three-component Mannich type reaction using ammonium chloride in ethanol at room temperature was developed. The said methodology has been successfully applied for the synthesis of β-amino esters as well as benzylamino coumarins, which are synthetically important building blocks for the synthesis of natural products as well as pharmaceutically demanding scaffolds.

TABLE-5
SYNTHESIS OF β-AMINO ESTERS THROUGH MANNICH REACTION

Entry	R_1	R_2	R	Product	Time (h)	Yield (%)
1	H	H	CH_2CH_3	**6a**	15	92
2	Cl	H	CH_2CH_3	**6b**	20	75
3	CH_3	H	CH_2CH_3	**6c**	18	82
4	H	CH_3	CH_2CH_3	**6d**	12	95
5	H	OCH_3	CH_2CH_3	**6e**	15	90

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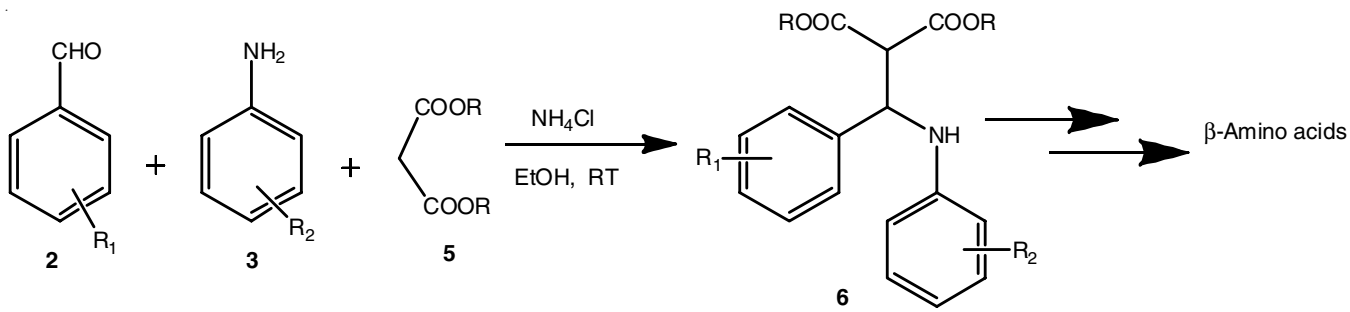
CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.



Scheme-III: Synthesis of β-amino esters through Mannich reaction

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