SYNTHESIS AND SPECTRAL STUDY OF β-CARBONYLAMINES THROUGH THE USE OF THE MANNICH REACTION

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β-Carbonylamines were synthesized using the Mannich reaction. An aldehyde and an amine were condensed to form an imine compound, followed by the addition of concentrated sulphuric acid and acetophenone. The resulting compounds were characterised by IR, ^{1}H and ^{13}C NMR and mass spectroscopy.

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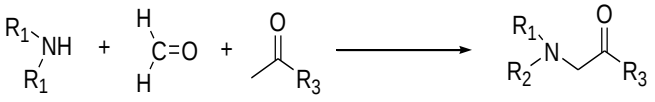
Introduction

There exists a definite need for the introduction of new drugs and drug delivery agents with enhanced efficacy and specific targets to counter the rise of multi-drug resistant (MDR) tumours and microbes.[1-5] The Mannich reaction can be a cost and time effective way of converting exsisting drugs into new bioactive molecules, having a greater efficacy than their precursors.[6] It also provides a suitable synthesis method to introduce aminoalkyl substituents into a molecule.[7] In many cases, derivatives from the Mannich reaction exhibit better activity than the analogous parent compound. Moreover, the existences of the Mannich side chain makes the product more soluble and consequently enhances the bioavailability of the drug molecule.[8] Mannich reactions play a vital role in the synthesis of anti-malarial, antitumor, antimicrobial, anti-tubercular, anti-inflammatory and anticonvulsant molecules.[9] The Mannich reaction is the reaction between formaldehyde and an amine to form an imine compound which is followed by adding a ketone-containing acid proton.[10]



Scheme 1. The preparation of β-carbonyl amines

The Mannich reaction is a very powerful reaction for building carbon-carbon bonds in synthetic organic chemistry. This reaction is particularly useful for the synthesis of β-carbonyl amine derivatives.[11] Due to the significance of the Mannich products in organic synthesis, several variations of this reaction have been developed. The products represent various pharmaceuticals, natural products, and versatile synthetic intermediates.[12] Straight protocols exist for three-component Mannich-type reactions of amines, aldehydes, and ketones in organic solvents. Many attempts have been carried out for the improvement of this type of reaction. Manabe and Kobayashi reported the use of DBSA- to catalyse the three-component Mannich-type reactions in colloidal systems.[1]

The Mannich reaction has many applications in the synthesis of natural products such as peptides, antibiotics and alkaloids.[13-15] The Mannich reaction is particularly useful for the synthesis of β-carbonyl amine derivatives.[11] The reaction is a versatile tool for one pot synthesis.[16,17] The reaction has been useful to synthesise various pharmaceuticals such as anti-malarial, antitumor, antimicrobial, anti-tubercular, anti-inflammatory and anticonvulsant molecules,[9] synthetic intermediates,[12] antibiotics and alkaloids.[13-15] The presence of the side chain on the products increases its solubility that augments the bioavailability of the drug molecules.[8] The reaction is effective to convert existing drugs into new bioactive molecules with greater efficacy than their precursors.[6] Similarly it is a suitable synthesis method to introduce aminoalkyl substituents into a molecule.[7] In many cases the derivatives from the Mannich reaction exhibit better activity than the analogous parent compounds. In this study, the Mannich reaction has been applied to the synthesis of secondary amines.

Experimental

All the chemicals were reagent grade unless stated otherwise and resourced from Sigma and Aldrich. Silica gel (Merck 7736), and silica gel plates for column and thin layer chromatography were Aldrich products, The separated components were detected using variously UV light and I_2. Anhydrous sodium sulfate was used to dry organic solutions. Infrared (IR) spectra were carried out on a Infrared Reflection Absorption Spectroscopy (IRRAS) (4000-400 cm^{-1}) and recorded using Perkin-Elmer tensor 27 as thin film. Melting points were measured using a SMP31melting point apparatus. ^{1}H NMR spectra were carried out on a VARIAN spectrophotometer (300 MHz). The ^{13}C-NMR spectra were recorded, using VARIAN spectrophotometer (75 MHz). HSQC 1H-13C-NMR spectra were recorded, using VARIAN spectrophotometer (600 MHz, 150 MHz).

General Procedure for the preparation of compound 1-3

A) 1,3-Diphenyl-3-(phenylamino)propan-1-one (1).

A mixture of absolute ethanol (40 mL), aniline (5 g, 53.7 mmol, 1 equiv.) and benzaldehyde (5.69 g, 53.7 mmol, 1 equiv) is refluxed for 2 hours in a round-bottomed flask . and monitored by TLC until disappearance of the starting material. The flaski is cooled and a mixture of acetophenone (6.45 g, 53.7 mmol), dissolved in ethanol (10 mL), and concentrated sulphuric acid (1 mL) is added, and this mixture is refluxed at 70 ˚C for 3 hours. The crude product is filtered and washed with ethanol and recrystallized from ethanol to give a white powder (12.89 gm, yield 87 %), m.p: 145-147 ºC; IR: 3385, 3025, 1671, 1600, 1510, 1437, 1417, 1311, 1221 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO), δ: 7.98-6.2 (15H, m, aromatic), 5.00 (1H, dd, J = 6, 12Hz), 3.64 (1H, dd, J = 9, 18 Hz), 3.34 (1H, s). ^{13}C NMR (75 MHz, d_6-DMSO) δ: 197.28, 147.79, 144.01, 136.77, 134.58, 133.13, 130.62, 130.58, 128.88, 128.78, 128.66, 128.50, 128.27, 128.01, 126.67, 126.61, 122.05, 115.77, 112.80, 52.84, and 46.43. [Found (M+H): Found: 302.1355; required: 302.1364 with existence of dimer at 625.2818.

B) 3-(4-Bromophenylamino)-1,3-diphenylpropan-1-one (2).

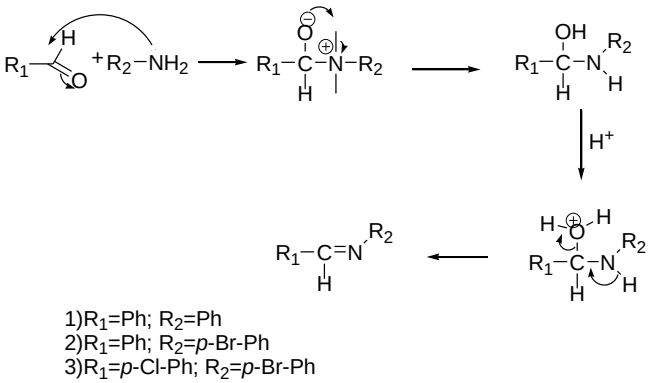
A mixture of absolute ethanol (40 mL), 4-bromo aniline (5 g, 53.7 mol) and benzaldehyde (3.1 g, 53.7 mmol, 1 equiv) round-bottomed flask is refluxed for 2 hours and monitored by TLC until disappearance of the starting material. The flask is cooled and a mixture of acetophenone (3.51 g, 53.7 mmol), dissolved in ethanol (10 mL), and concentrated sulphuric acid (1 mL) is added and this reaction mixture is refluxed at 70 ºC for 3 hours. The crude product is filtered and washed with ethanol and then recrystallized from ethanol to give a white powder (9.12 g, yield 82 %), 178-177 º C; IR: 3369, 3019, 1665, 1594, 1577, 1484, 1407, 1303, 1216, 1120 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ: 7.97-6.45 (14H, m, aromatic), 5.97 (1H, dd, J = 9, 12 Hz), 3.63 (1H, dd, J = 9, 18 Hz), 3.34 (1H, s). ^{13}C NMR (75 MHz, d_6-DMSO) δ: 197.07, 147.07, 143.48, 136.69, 133.11, 131.19, 128.66, 128.34, 138.00, 126.80, 126.57, 114.69, 106.44, 52.76, and 46.31. [Found (M+Na+K): Found: 442.9571; required: 442.3658 with existence of dimer without bromide at 602.2824.

C) 3-(4-Bromophenylamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one (4).

A mixture of absolute ethanol (40 mL), aniline (5 g, 53.7 mol) and 4-chlorobenzaldehyde (4.11 g, 53.7 mmol, 1 equiv) in round-bottomed flask is . refluxed for 2 hours and monitored by TLC until disappearance of the starting material. The flask ic cooled and a mixture of acetophenone (3.51 g, 53.7 mmol) dissolved in ethanol (10 mL) and concentrated sulphuric acid (1 mL) is added to it and this mixture is refluxed at 70 ºC for 3 hours. The crude product is filtered and washed with ethanol and then recrystallized from ethanol to give a white powder (10.21 g, yield 84 %), m.p: 92-94 ºC; IR: 3390, 1666, 1656, 1592, 1403, 1311, 1217, 1124 $cm^{-1;}$ ^1H NMR (300 MHz, d_6-DMSO) δ: 8.18-6.44 (13H, m, aromatic), 4.98 (1H, dd, J = 9, 20 Hz), 3.63 (1H, dd, J = 9, 18 Hz), 3.35 (1H, s). ^{13}C NMR (75 MHz, d_6-DMSO) δ: 196.83, 189.05, 146.85, 142.55, 142.50, 137.41, 136.60, 135.09, 133.62, 133.21, 131.29, 131.24, 130.57, 128.92, 128.77, 128.57, 128.54, 128.27, 128.00, 122.76, 114.74, 106.68, 52.12, 46.07. [Found (M): 413.0183; required: 413.0182 with existence of dimer without bromide at 671.1816.

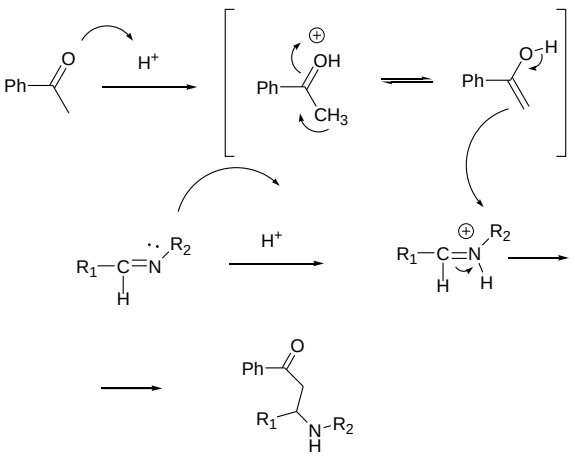
Results and Discussion

The Mannich reaction has many applications in the synthesis of natural products and is suitable for the production of secondary amines. [18—23] The preparation of 1,3-diphenyl-3-(phenylamino)propan-1-one is carried out into two steps. The first step of this reaction generates the imine by reacting the aldehyde with the amine. This step is carried under reflux for 1-2 hours whilst monitoring with TLC, Figure 1.[10]



Scheme 2. Formation of imine compounds

The formation of 1,3-diphenyl-3-(phenylamino)propan-1-one is accomplished in the second step by adding acetophenone with concentrated sulphuric acid. The acid attacks the oxygen of the carbonyl group leading to the formation of the enol form and simultaneously, the nitrogen atom of the imine is protonated with formation of ammonium-ion. The equivalent ratio of ketone to amine and aldehyde were 1 equivalent for each one of them.[16-18]



Scheme 3. Suggested mechanism of Mannich reaction using acid as catalyst

IR spectral analysis

All the prepared compounds **1a-1c** showed signals around 3369-3390 cm^{-1} belonging to the NH stretching. The signal which showed at 1665-1671 cm^{-1} belongs to the carbonyl group, while the aromatic C=C showed signals at 1510-1590 cm^{-1}. The C-H aromatic stretching showed absorbance at 3019-3025 cm^{-1}.

^{1}H-NMR analysis

Compound **1a** displayed multiplet signals for the aromatic compound protons between 6.45-7.98 ppm with an integration corresponding to 15 protons. The proton at the chiral centre resonated as a singlet at 3.34 ppm, while the protons of the CH_2 next to the carbonyl showed as a double doublet at 5.00 and 3.64 ppm (Figure 1). Compound **1b** showed a multiplet at 7.97-6.45 ppm for the aromatic protons. The chiral centre proton resonated at 3.34 ppm, while the two protons next to the carbonyl group resonated at 5.97 and 3.63 ppm respectively. Both of the protons showed as doublet of doublets. Compound (**1c**) showed multiplet signals at 8.18-6.44 ppm with an integration of 13 protons for the aromatic protons, while the CH_2 next to the carbonyl resonated at 4.98 and 3.63 ppm respectively. The chiral center proton resonated at 3.35 ppm.

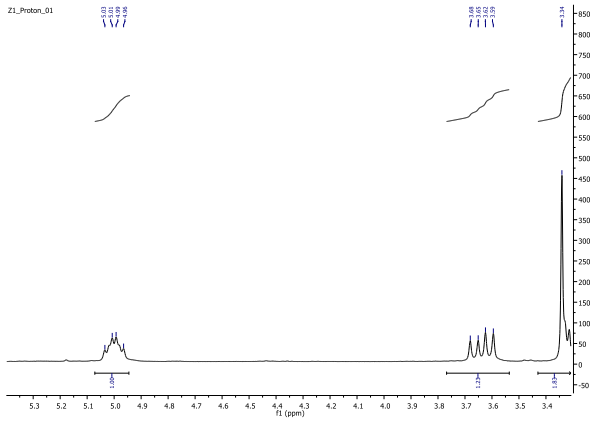
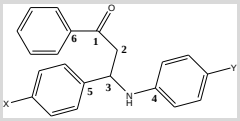


Figure 1. Proton NMR compound 1

^{13}C NMR analysis

Compound **1a** showed the carbonyl carbon signal at 197.28 and the CH_2 and the chiral centre carbon resonated at 46.43, 52.84 respectively. The quaternary carbons showed signals at 147.07, 143.48, 136.69 ppm. The other aromatic carbons resonated between 133 and 106 ppm. Compound **1b** showed a signal at 197.07 ppm for the carbon carbonyl group, while the CH_2 and the chiral center carbon showed 46.31 and 52.76 ppm respectively. The quaternary carbons resonated at 147.07, 143.48 and 136.69 ppm. Compound **1c** showed a signal at 196.83 for the carbon of the carbonyl group, while the CH_2 and the chiral center carbons resonated at 52.12 and 46.07 ppm, respectively. The quaternary carbons resonated at 142.55, 142.50 and 137.41 ppm (Table 1).

Table 1. Comparing between ^{13}C NMR of the prepared compounds



	Compound **1**	Compound **2**	Compound **3**
1	197.28	197.07	196.83
2	46.43	46.31	46.06
3	52.84	52.76	52.12
4	147.79	147.07	146.85
5	144.01	143.48	142.55
6	136.77	136.69	142.50

Mass spectrum analysis

The mass spectrum confirmed the successful preparation of the compounds **1a-1c**. All the prepared compounds showed the ability of forming a dimer Figure 2.

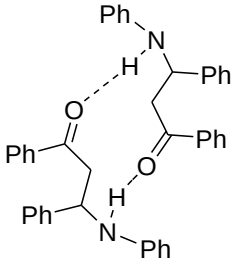


Figure 2. Dimer of the prepared compounds due to hydrogen bonding.

Compound **1a** showed a signal at 324.1355 and another signal at 324.1355. These belong to [M+H], while the signal belonging to the dimer [2M+Na] showed at 625.2818 (Figure 3).

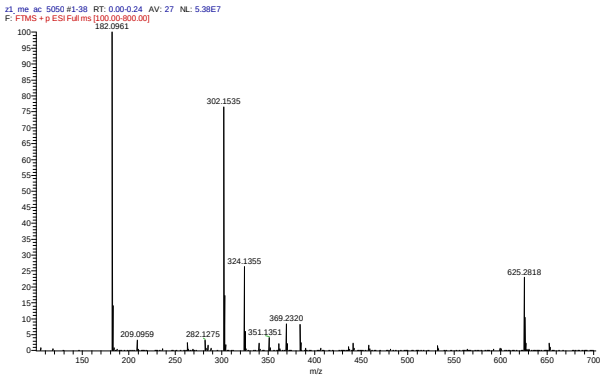


Figure 3. Mass spectra of compound 1a

Compound **1b** showed the existence of bromide since most of signals showed double peaks with gap of 2 Daltons between them. The signal at 380.0634 belongs to [M] while the signal at 442.9571 belongs to M+Na+K, while the signal at 602.2824 belongs to the dimer with the loss of the bromide ions.

The signal at 300.1382 belongs to the [M] without bromide (Figure 4). Compound **1c** showed the molecular ion at 413.0183 and the dimer signal at 671.1816 without bromide (Figure 5).

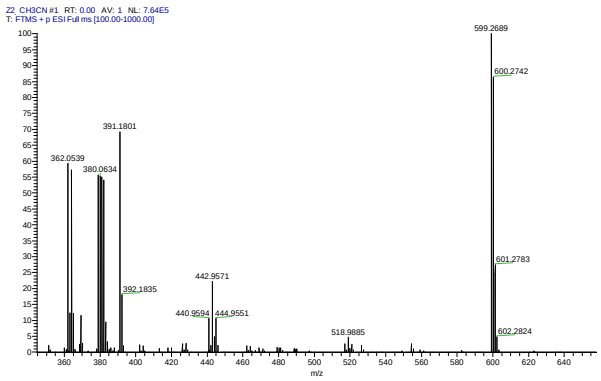


Figure 4. Mass spectra of compound **1b**

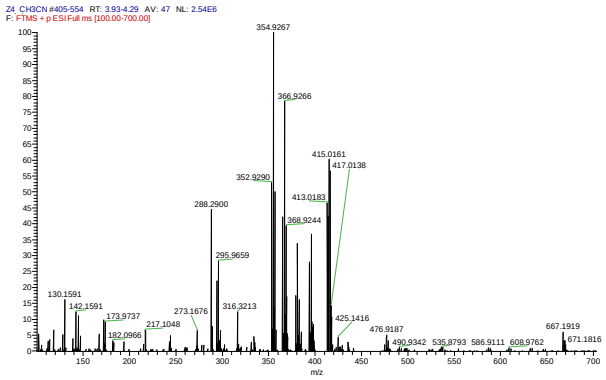


Figure 5. Mass spectra of compound **1b**

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