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Synthesis of Mannich bases of 4-hydroxyacetophenone

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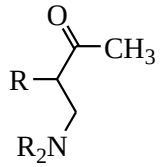
GRAPHICAL ABSTRACT



Mannich Base

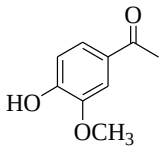
ABSTRACT

Mannich bases are the products of Mannich reactions which involve aldehyde, ketone and primary or secondary amine. Mannich bases are widely studied as they possess important diverse activities such as antibacterial, anticancer and analgesics. Apart from that, they are also being used in detergent additives, resins and polymers. In this study, a series of Mannich bases were synthesized by using 4-hydroxyacetophenone as the precursor. The initial step in the synthesis was to prepare 4-methoxyacetophenone by methylation of phenolic hydroxyl group of 4-hydroxyacetophenone. Both 4-hydroxyacetophenone and 4-methoxyacetophenone were refluxed separately with piperidine and formaldehyde by using absolute ethanol as the solvent to produce 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone and 4-methoxy-3-(piperidin-1-ylmethyl)acetophenone respectively. The reactions were monitored by using thin layer chromatography and purified by column chromatography. The structures of the final compounds obtained were elucidated by using several spectroscopic techniques which were IR, ^{1}H NMR and ^{13}C NMR. Both reactions produced Mannich bases as yellowish brown liquid.

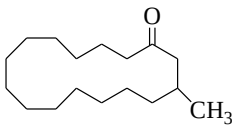
Keywords: Mannich bases, methylation, 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone, 4-methoxy-3-(piperidin-1-ylmethyl)acetophenone

1. INTRODUCTION

Ketone is an organic compound that contains a carbonyl group [1]. It is easily found in nature and often combined with other functional groups. It is also known for its sweet and sometimes pungent odor. The vanillin **(1)** molecule produces the odor of vanilla extract contrast to the (R)-Muscone **(2)** which give the musky smell from Himalayan musk deer. Ketones have high molecular dipole moments. The polarity of the carbonyl group has an effect on its chemical reactivity [2]. Some examples of ketone are vanilin **(1)**, (R)-Muscone **(2)** and cyclohexanone **(3)**.



(1)



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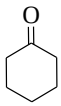
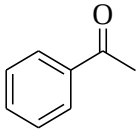


(3)

Acetophenone **(4)** is the simplest aromatic ketone and it has a pleasant odor and taste like an orange. Its molecular formula is $C_6H_5C(O)CH_3$ and often be used as precursor, solvent for plastics and resins and as flavoring of foods. It can also be found naturally in food such as banana, apple and beef [3]. Direct contact to the acetophenone **(4)** can cause chemical poisoning such as headaches, eye irritation, dry skin and nausea. It is being used as additive in cigarettes and in synthesis of pharmaceutical materials. It is currently being used as the substance to make fragrances that smell like cherry, almond, strawberry or other fruits [3].

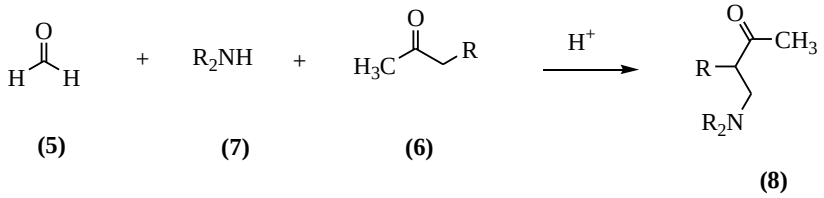


(4)

Mannich reaction involves the reaction of an enolizable aldehyde **(5)** or ketone **(6)**, a secondary amine **(7)** and HCl which acts as catalyst. This reaction will produce Mannich base **(8)**. The product is an amino-ketone from the addition of one

molecule each of formaldehyde and the amine to the ketone [3]. Mannich bases **(8)** are known to play an important role in the development of synthetic pharmaceutical chemistry. Some example of Mannich bases that are being used clinically which consist of aminoalkyl chain are cocaine, fluoxetine and atropine [4]. Mannich base are known for their highly reactive and easily converted to other compounds for example, it can reduce to form physiologically active amino alcohols. Mannich bases are known to possess anticancer, antibacterial and analgesic [4].

The general structure of Mannich reaction [5] is represented in the schematic representation given in **Scheme 1.1**.



(5) **(7)** **(6)** **(8)**

Scheme 1.1: General Mannich Reaction

2. EXPERIMENTAL

2.1 Methylation of 4-hydroxyacetophenone

To a solution of 4-hydroxyacetophenone **(9)** (1.00 g, 7.3 mmol), dry acetone (10 mL) was added K_2CO_3 (1.00 g, 7.3 mmol) and CH_3I (1.03 g, 7.3 mmol). The mixture was refluxed for 4 hours and monitored by TLC. The reaction mixture is poured into distilled water (50 mL) and extracted with ethyl acetate (3 x 20 mL) followed by drying with anhydrous $MgSO_4$ and evaporated under reduced pressure. Evaporation of the residue gave 4-methoxyacetophenone **(12)** (0.2381 g, 47.3%) as a white solid with melting point 40.1 ºC (lit 38.5 ºC. IR (υ_{max} cm^{-1}) **(a):** 2917 (sp^3 C-H), 1665 (C=O), 1596 (C=C), 1019 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) **(b)**: δ 2.58 (3H, s, H-1), 3.89 (3H, s, H-9), 6.95 (2H, d, *J*=8.8 Hz, H-5/H-7) and δ 7.96 (2H, d, *J*=8.8 Hz, H-4/H-8).

2.2 Formation of Mannich base from 4-hydroxyacetophenone

The 4-hydroxyacetophenone **(9)** (2.7237 g, 0.02 mol) was added to piperidine (2 mL, 0.02 mol) and formaldehyde (1.7 mL, 0.02 mol) in ethanol at room temperature. The mixture was refluxed for 30 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by CC and VLC using $CHCl_3$/ EtOAc to give 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone **(41)** as a yellowish brown liquid (1.2132 g, 44.6%). IR (υ_{max} cm^{-1}) **(c):** 3501 (O-H), 3002 (sp^2 C-H), 2964 (sp^3 C-H), 1666 (C=O), 1598 (C=C), 1357 (C-N), 1254 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) **(d)**: δ 1.42 (4H, m, H-12/H-12'), 1.64 (8H, m, H-11/H-13 & H-11'/H-13'), 2.51 (8H, s, H-10/H-14 & H-10'/H-14'), 2.56 (4H, s, H-9/H-9), 6.43 (1H, s, OH), 7.73 (2H, s, H-4/H-8).

2.3 Formation of Mannich base from 4-methoxyacetophenone

The 4-methoxyacetophenone **(12)** (0.723 g, 0.005 mol) was added to piperidine (0.5 mL, 0.005 mol) and formaldehyde (0.15 mL, 0.005 mol) in ethanol **(18)** at room temperature. The mixture was refluxed for 30 hours. The reaction mixture was concentrated under reduced pressure. The crude product was purified using CC with $CHCl_3$/ EtOAc in gradient polarity as the eluent. Purification gave 4-methoxy-3-(dipiperidin-1-ylmethyl)acetophenone **(42)** as a yellowish brown liquid (0.2211 g, 30.6 %). IR (υ_{max} cm^{-1}) **(e):** 2930 (sp^3 C-H), 1671 (C=O), 1596 (C=C), 1355 (C-N), 1300 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) **(f)**: δ 25.6 (C-1), 25.8 (C-11/C-13 & C-11'/C-13'), 53.8 (C-10/C-14 & C-10'/C-14'), 61.6 (C-9/C-9') 26.7 (C-12/C-12'), 115.9 (C-5/C-7), 130.3 (C-4 & C-8), 121.1 (C-3), 163.3 (C-6), 196.8 (C-2).

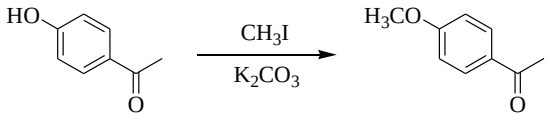
3. RESULTS AND DISCUSSION

3.1. Synthesis of Precursors

The Mannich base **(8)** derivatives were prepared through Mannich reaction by reacting substituted acetophenone namely 4-hydroxyacetophenone **(9)** and 4-methoxyacetophenone **(10)**. The reactions involved heating under reflux method as a way to prevent evaporation process that may cause loss of solvent. The heating process was used to increase the rate of reaction.

3.2 Synthesis of 4-Methoxyacetophenone (10)

Methylation is a common procedure in organic synthesis. The most used methylating agent is methyl iodide because the iodo ion is a good leaving group that can easily be displaced since is the weakest base of halide ions. Another method of methylation reaction involves the use of sulfonate agent. It will form a weak conjugate base which acts as a good leaving group. In this study, methylation of 4-hydroxyacetophenone **(4)** was done by reacting it with methyl iodide and freshly ignited K_2CO_3 in dry acetone at 50ºC. The product obtained was 4-methoxyacetophenone **(10)** as a yellowish brown liquid in 47.3% yield. The reaction equation is depicted in **Scheme 3.1**.



(9) **(10)**

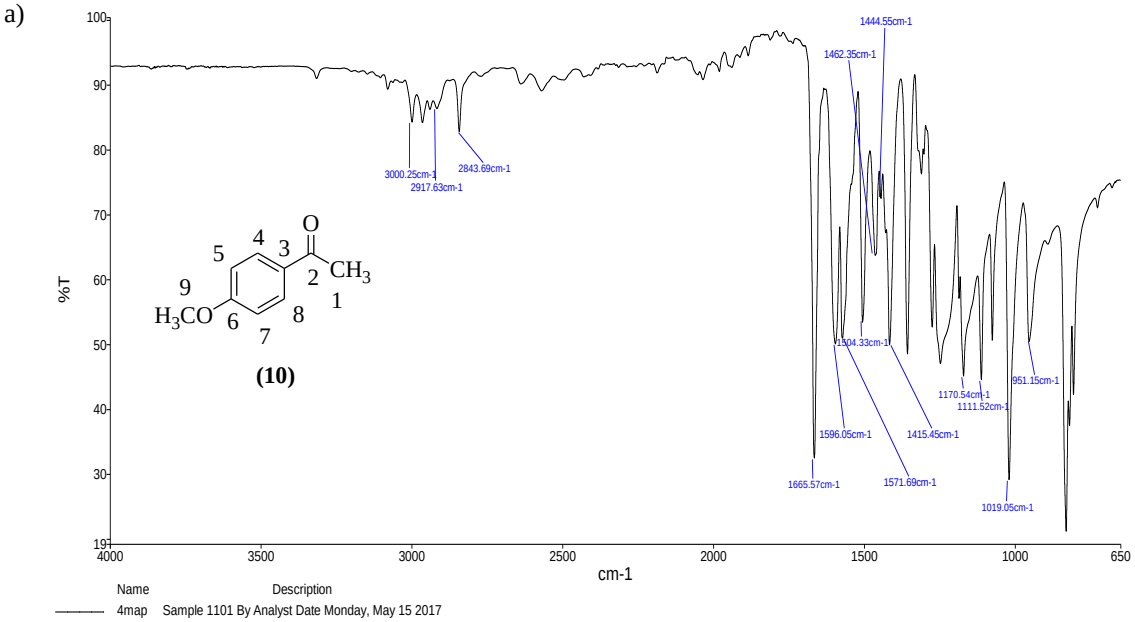
Scheme 3.1: Methylation of Starting Material

The methylation of methyl iodide requires strong basic condition where alcohol is first protonated by activated K_2CO_3 in order to facilitate the reaction. The reaction is S_N2 nucleophilic substitution where carbonate ion abstract a proton from hydroxyl group at *para* position of the starting material. Then, the phenoxide ion acts as strong nucleophile attacks the electron deficient carbon of methyl iodide and displaced the iodo ion. The reaction transforms the hydroxyl into methoxyl group.

The IR spectrum **(Appendix 1)** of compound **(1)** showed C-O stretching at 1019 cm^{-1}. There were also absorption bands at 1665 cm^{-1} which indicated C=O (ketone) and 1596 cm^{-1} for C=C aromatic. The frequency for the C=O (ketone) was low due to the conjugation effect with adjacent aromatic ring. The ^1H NMR spectrum **(Appendix 2)** of 4-methoxyacetophenone **(12)** showed two singlets at δ 2.58 (3H, s, H-1), 3.89 (3H, s, H-9) each was assigned to the acyl group and methoxyl group. Two doublet signals were observed at 6.95 (2H, d, J = 8.8 Hz) and δ 7.96 (2H, d, J = 8.8Hz) which were assigned for aromatic protons H-5/H-7 and H-4/H-8 respectively.

3.3 Synthesis of 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone (11)

The Mannich base reaction involved 4-hydroxyacetophenone **(9)** with formaldehyde and piperidine dissolved in absolute ethanol. Refluxing method was used to speed up the reaction. The ethanol served as acidic medium and source of protons since it acted as polar protic solvent. The product obtained was 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone **(11)** as a yellowish brown liquid (1.2132 g, 27.56%).



(10)

Figure 1 IR spectrum of **(10)**

b)

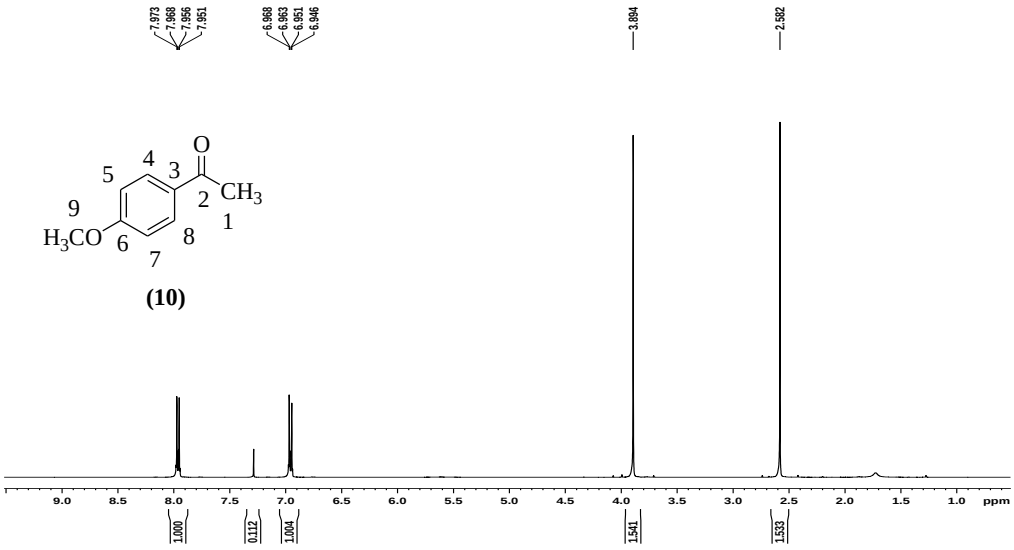
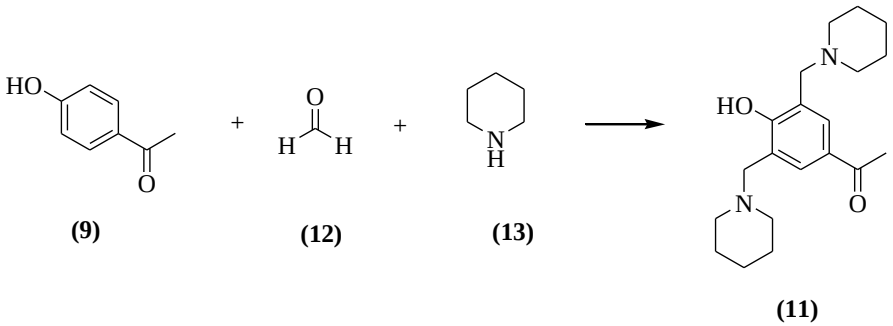


Figure 2 ^{1}H-NMR spectrum of **(10)**



Scheme 4.3: Formation of 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone **(11)**

c)

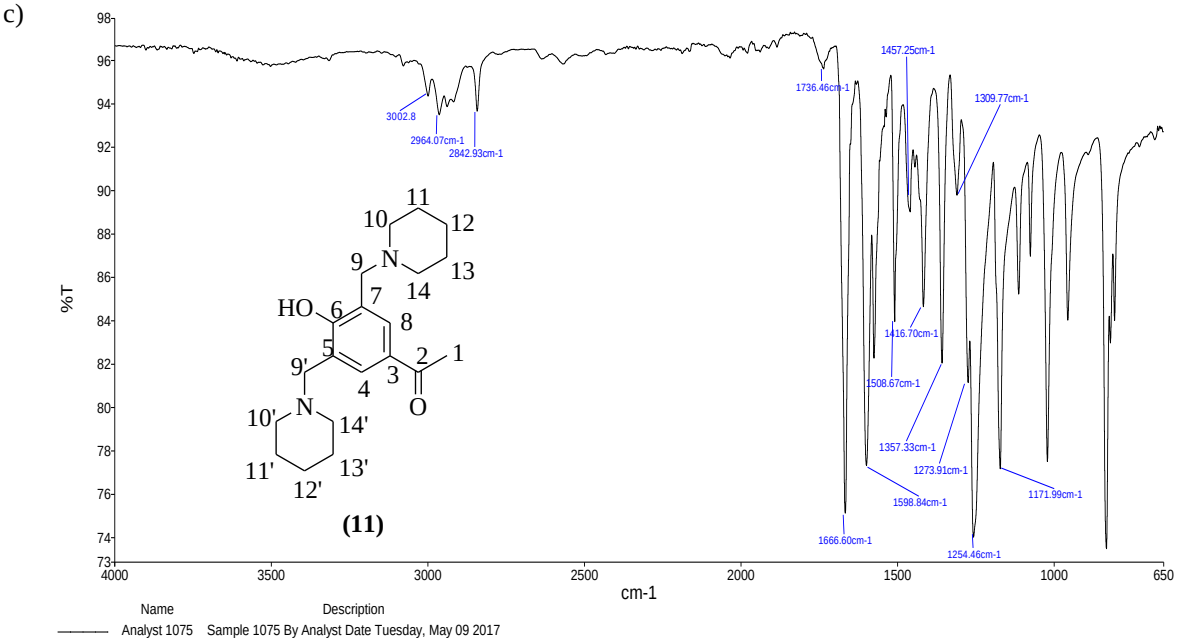


Figure 3 IR spectrum of Mannich Base **(11)**

d)

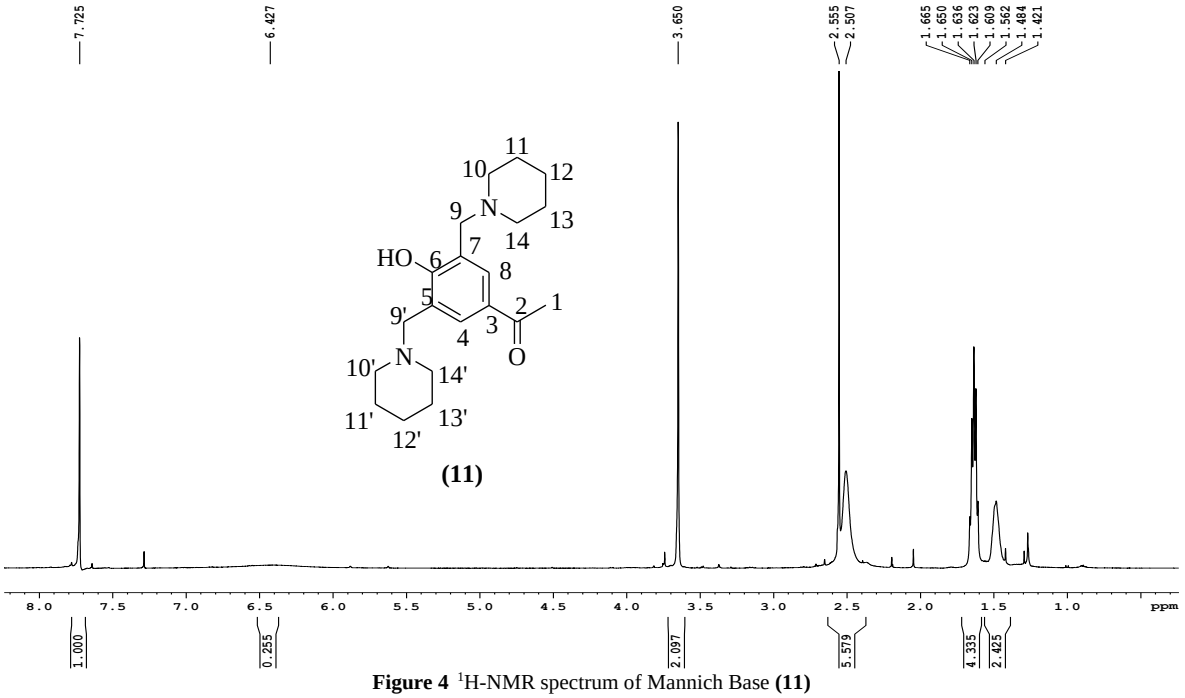
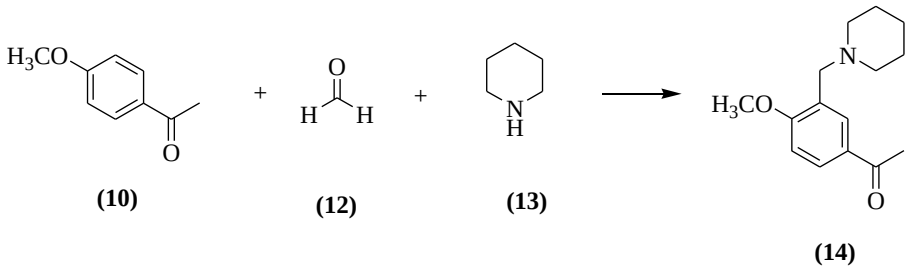


Figure 4 ^{1}H-NMR spectrum of Mannich Base **(11)**



Scheme 4.5: Formation of Mannich base **(14)**

The reaction equation is shown in **Scheme 4.3** above. The reaction was an electrophilic aromatic substitution and did not involve any acid as the catalyst. The existence of hydrogen group in compound **(9)** will direct the substitution at *ortho* and *para* position from it since it is a strong activator. The reaction occurred between the aromatic system with secondary amine and formaldehyde. The Mannich reaction is initiated by the attacked of piperidine on the carbonyl group of formaldeyde to form an intermediate consisted of an electron deficient carbon. The hydroxyl group of acetophenone **(9)** activated both *ortho* and *para* position to form intermediate. The reaction gave C-3 and C-5 disubtituted aminomethyl on the aromatic substrate.

The IR spectrum **(Appendix 4)** of Mannich base **(11)** showed a broad O-H stretching frequency at 3501 cm^{-1}, sp^2 C-H at 3002 cm^{-1} and sp^3 C-H stretch at 2964 cm^{-1}. The IR spectra also displayed C=O stretching frequency at 1666 cm^{-1} while adsorption bands at1598 cm^{-1}, 1357 cm^{-1} and 1254 cm^{-1} were corresponding to C=C aromatic, C-N and C-O, respectively.

The ^{1}H NMR spectrum **(Appendix 5)** of Mannich base **(11)** displayed a broad singlet signal at δ 6.43 referred to hydroxyl proton. Another singlet signals at δ 3.65 and δ 2.56 were assigned for protons of H-9 / H-9' and acetyl proton H-1, respectively. A multiplet signal appeared at δ 2.51 was attributed to methylene protons of H-10 & H-14 / H-10' & H-14'. Two multiplets at δ 1.64 and δ 1.49 each were corresponding to H-11 & H-13 / H-11' & H-13' and H-12/H-12' of the piperidine ring, respectively. A singlet signal at δ 7.73 attributed to aromatic protons of H-4 and and H-8 which have similar chemical environment proved that the reactions took place at both ortho position of the aromatic 4-hydroxyacetophenone **(9)**.

3.3 **Synthesis of 4-methoxy-3-(piperidin-1-ylmethyl)acetophenone (14)**

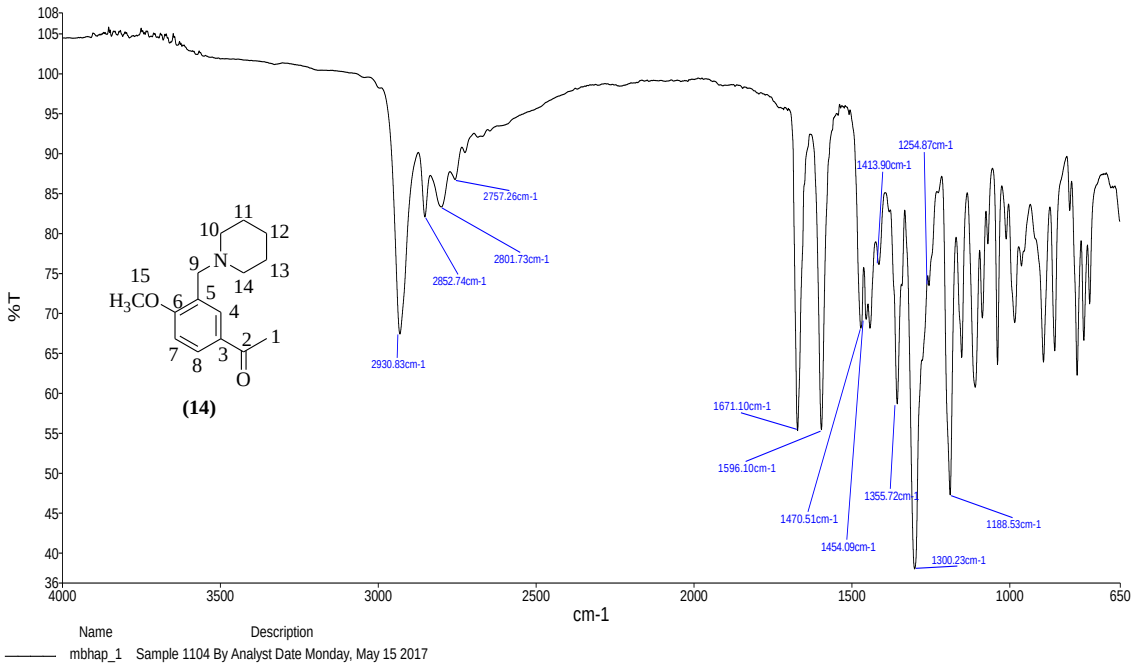
4-hydroxyacetophenone **(9)** was used to form Mannich base **(14)**. Refluxing of 4-methoxyacetophenone **(10)** with piperidine and formaldehyde was refluxed using absolute ethanol **(18)** as the solvent. The reaction has formed compound **(14)** in 30.6 %. The product was obtained as a yellowish brown liquid from CC with $CDCl_3$/EtOAC as eluents. The reaction equation for formation of 4-hydroxy-3-(piperidin-1-ylmethyl)acetophenone is depicted in the **Scheme 4.5**.

Methoxyl group is a strong electron donating group (EDG), thus having it in the aromatic ring gave monosubtituted Mannich base. The presence of EDG increased the nucleophilicity of aromatic compound. The methoxyl group donated its electron density into the conjugated π system via resonance and making the compound more nucleophilic. The methoxyl group is an *ortho* director thus the methylation process occurred at *ortho* position C-3 of the methoxyl group. The C=O group attached at C-1 of the aromatic ring is an EWG. It will remove the electron density from the π aromatic system. Since C=O is a *meta* director, thus the methylation process occurred at *meta* position of the C=O.

The IR spectrum **(Appendix 7)** of Mannich base **(14)** gave sp^3 C-H frequency at 2930 cm^{-1}, C=O stretching frequency 1671 cm^{-1} with a lowered value due to the conjugation effect with the neighbouring aromatic ring. In addition, bands at 1596 cm^{-1} attributed to and a band at C=C aromatic and also at 1355 cm^{-1} for C-N were also observed. The IR spectrum was also displayed a band attributed to C-O group at 1254 cm^{-1}.

The ^{1}H NMR spectrum **(Appendix 8)** of Mannich base **(14)** displayed a signal at δ 1.54 assigned for protons of H-12. Two multiplets at δ 1.73 and δ 2.60 were corresponding to H-11 & H-13 and protons of H-10 & H-14. Another singlet signals at δ 2.66 and δ 3.74 were assigned for protons of acetyl proton H-1 and H-9, respectively. A singlet signal at δ 7.90 attributed to aromatic protons of H-4.

e)



(14)

Figure 5 IR spectrum of Mannich Base **(14)**

f)

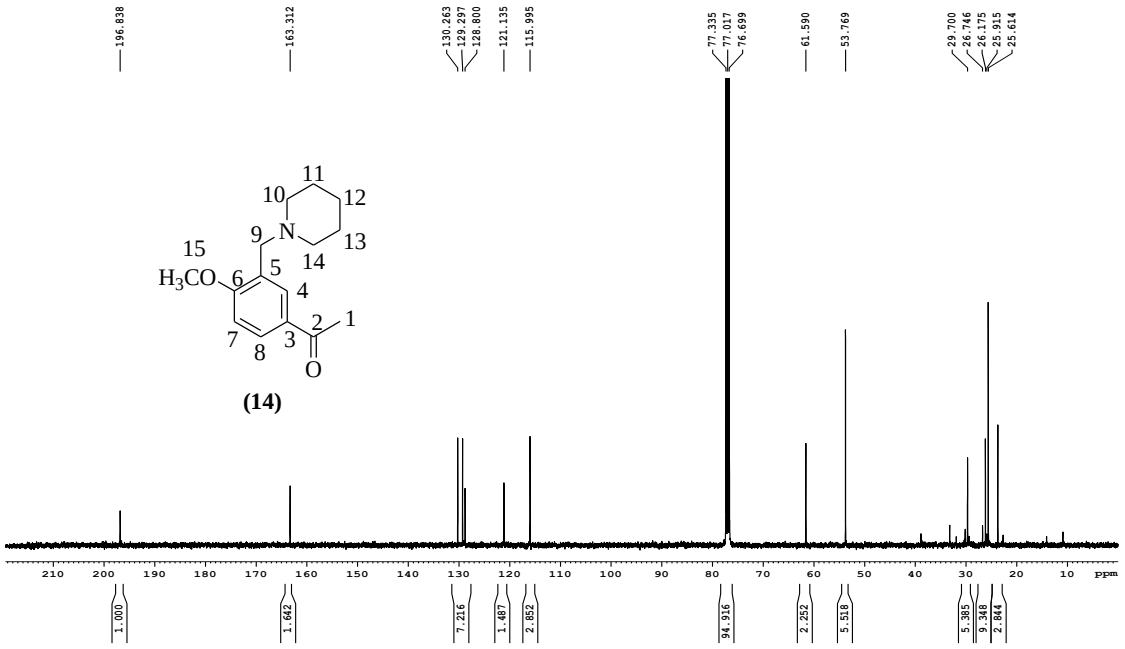


Figure 6 ^{13}C-NMR spectrum of Mannich Base **(14)**

4. CONCLUSION

The synthesis of 4-methoxyacetophenone **(10)** from the methylation of 4-hydroxyacetophenone **(9)** was successfully synthesized. The Mannich base for both reactions from the 4-hydroxyacetophenone **(9)** and 4-methoxyacetophenone also were successfully been produced and identified as 4-hydroxy-3,5-(dipiperidin-1-ylmethyl)acetophenone **(11)** and 4-methoxy-3-(piperidin-1-ylmethyl)acetophenone **(14)**. The compounds were characterized by using spectroscopic techniques such as IR, ^{1}H NMR and ^{13}C NMR.

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