***Original Research Article***

# Synthesis of Nitrogen-Containing Chalcone via One-Pot Three-Component Reaction: part iv

Anwar, E. M. Nor ELjaleel[1], Himat, M. A. Fadul[1], Saad, M. H. Ayuob[2], M, Abdel Karim[3], Jan, H. van der Westhuizen[4], M. J. A. Abualreish[1,5](*)

[1] *Department of Chemistry, Omdorman Islamic University, Faculty of Science, Khartoum- Sudan.*

[2] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, El-Neeilain University , Khartoum-Sudan,*

[3] *Department of Chemistry* , Sudan University of Science and Technology, Faculty of Science, Khartoum-*Sudan.*

[4] *Department of Chemistry, Faculty of Agriculture, University of Free state, Bloemfontein-South Africa*

[5] *Department of Chemistry, Faculty of Science, Northern Border University, Arar, Kingdom of Saudi Arabia*

**Abstract :**

The Mannich reaction is one of the most important C-C bond formation methods in organic synthesis**.** The Mannich-Reaction is employed in the organic synthesis of natural compounds like for instance Peptides-Nucleotides-Antibiotics and Alkaloids. Other application are in agrochemicals such as plant growth regulators, paint and other polymer chemistry, catalysts and cross linking. The Mannich Reaction is also used in synthesis of medicinal compounds.

The compound 4-Hydroxy-4'-methoxychalcone was prepared by reacting 4-hydroxybenzaldehyde with 4-methoxyacetophenone .The aminomethylation of this chalcone was accomplished by reaction with formaldehyde and suitable amine in acetonitrile to obtain

4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone(2) 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone(3)and4-hydroxy-4'-methoxy-3,5-bis-piperdinomethylchalcone(4). The products were purified by column and thin layer chromatography and were identified along with their intermediates by spectroscopic methods: UV, IR, and NMR and mass spectrometry.

**Key Words:** Chalcones, Mannich bases, Aminoalkylation, Three components reaction

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(*)Corresponding author : *mustjeed_2008@hotmail.com*

## Introduction

The aim of this study to increase the bioactivity of the chalcones by introducing alkylamino group. Its increase the lipophilicity and hydrophilicity of chalchones by methylene and teretary amino group respectively.

The Mannich reaction is a three-component single pot reaction in which a secondary amine reacts with an aldehyde and an active hydrogen compound to afforded compounds known as

Mannich bases. Sometimes the secondary amine is replaced by a primary amine or ammonia.

Studies on the chemistry of Mannich bases are of interest in various areas of applications. A large number of aminoalkyl derivatives have been synthesized in order to correlate their structure and reactivity with their pharmacological potential. Also Mannich bases represent easily obtainable intermediates for the synthesis of other compounds such as heterocycles , aminoalcohols …*etc.*

Mannich bases are known for their biological potential. Some Mannich bases possess anticonvulsant activity[1,2], others exhibit analgesic potency[3], some Mannich bases were reported[13] as potential chemo preventive agents. Mannich bases with putative cytotoxic activity were reported [4,5,6]. Stephen *et-al.*[7] claimed antimalarial activity for some

aminomethylated phenols. Tomas *et.al*[8] described the antibacterial potential of some fused Mannich ketones. Afaf *et.al* [9]. Reported some aminomethylated benzimidazoles with potent antimicrobial activity. The anticancer potential of some Mannich bases was outlined [10,11].

Chalcones are valuable intermediates in organic synthesis because of their ability to act as activated unsaturated systems in addition reactions of carbanions. They react with active methylene compounds of some phytochemicals to offered synthetics of pharmacy potential[12,13,14,15].

Chalcones exhibits diverse pharmacological activities, including antileshmania[l7], anti-inflammatory[16], antimitotic[17], antiinvasive[18], antitubercolosis[19], antifungal[20], antimalarial[21], antiplasmodial[21], antitumor[22], antioxidant[23], immunosuppressive[24], and cytotoxic[25] properties.

Bearing such interesting properties of Mannich bases and chalcones in mind it, was decided to join Mannich bases and chalcones in one molecule probably which potential pharmacological activities. The target molecule is approached via effective and facile strategy involving synthesis of chalcones and subsequent aminomethylation.

## Materials and methods :

**Instruments**

IR spectroscopy was carried out using Spectrum BX instrument model L1050033,

UV/Vis spectroscopy was carried out using BECKMAN COULTER instrument model DU 800 SPECTROPHOTOMETER,

NMR spectroscopy was carried out using procker instrument model AVANCE II 600 and using procker instrumen AVANCE II 300 and MS spectroscopy carried out using MDS SCIEX instrument modelAPI 2000 LC/ MS/MS System.

**Synthesis of 4-hydroxy-4'-methoxychalcone (1):**

The solution of sodium hydroxide (10 ml of 10%) was added to a solution of the 4-methoxyacetophenone (0.02 mol) and 4-hydrxybenzaldehyde (0.02 mol) in ethanol (6 ml).The mixture was stirred at room temperature for 24 h and pourred into water (100 ml). After neutralization with 10% hydrochloric acid a yellow solid was obtained. m.p 152-154 °C (yield 85%) (Fig 1).

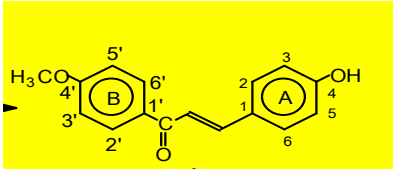



Figure 1: 4-hydroxy-4'-methoxychalcone (1)

**Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone(2):**

A mixture of 4-hydroxy-4'-methoxychalcone **(1)** (0.005 mol), formalin (0.01 mol) and dimethylamine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the precipitate was formed. This crude product was fractionated on silica gel G using the solvent (hexane/ethylacetate/methanol/isopropylamine 7.5:1:1:0.5), 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone **(2)** was obtained as pale yellow crystals, m.p 112-116 °C (yield 41%) Fig 2.

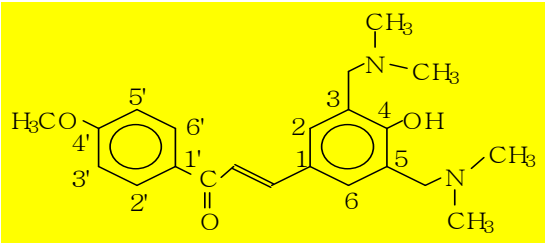



Figure 2: 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone(2)

**Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3):**

A mixture of 4-hydroxy-4'-methoxychalcone **(1)** (0.005 mol), formalin (0.01 mol) and pyrrolidine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the

precipitate was formed. This crude product was fractionated on silica gel G using the solvent (hexane/ethylacetate/methanol/isopropylamine 7.5:1:1:0.5), 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone **(2)** was obtained as pale yellow crystals, m.p 122-124 °C (yield 50%)

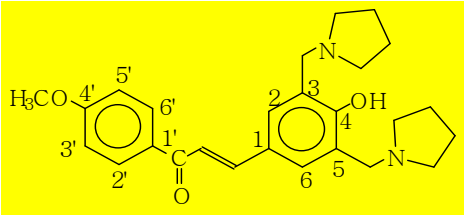



Figure 3: 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

**Synthesis of 4-hydroxy-4'-methoxy-3,5-bis-piperdinomethylchalcone (4):**

A mixture of 4-hydroxy-4'-methoxychalcone **(1)** (0.005 mol), formalin (0.01 mol) and piperidine (0.01 mol) were reacted in refluxing acetonitrile (50 ml) for 36 h. On cooling the precipitate was formed. This crude product was fractionated on silica gel G using the solvent system: hexane / ethyl acetate/ isopropyl amine (6:3.1) where 3-hydroxy-4'-methoxy-4-piperidinochacone **(4)** was obtained as pale yellow crystals, m.p 124-125 °C (yield 42%) Fig 4.

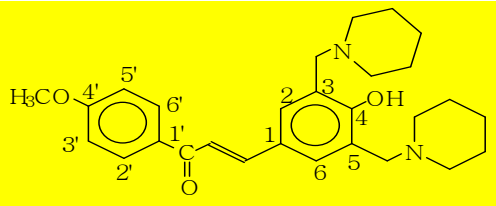



Figure 4: 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone (3)

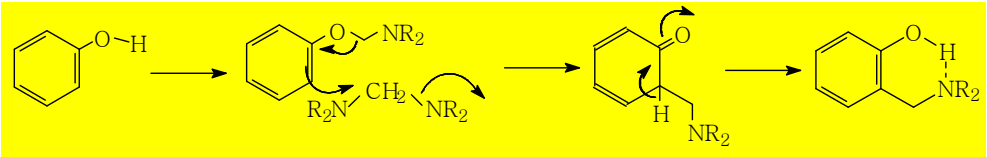
## Results and discussion

The new chalcones with Mannich side chain presented in this work were synthesized by recting the chlcone 4-Hydroxy-4'-methoxychalcone with formaldehyde and suitable amine

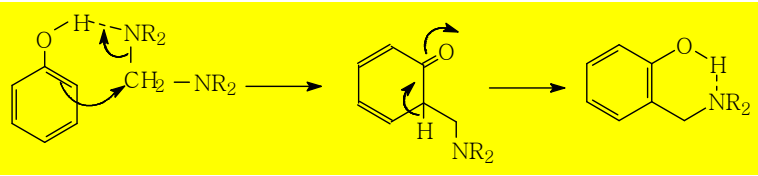
(dimethylamine, pyrroline and piperdine) in acetonitrile to obtain 4-hydroxy-4'-methoxy-3,5-bis-dialkylaminomethylchalcone

In the reaction mechanism all this groups ($R\text{-}CH_2\text{-}OH$, $R_2N\text{-}CH_2\text{-}NR_2$ and $R_2N^+{=}CH_2 \rightleftharpoons R_2N{=}CH_2^+$) were formed during the Mannich reaction , but the bis(dialkylamino)methane (aminal) is eligible to function as intermediate . Its eligibility was established by successful use of bis(dialkylamino)methane in abbreviated Mannich reaction

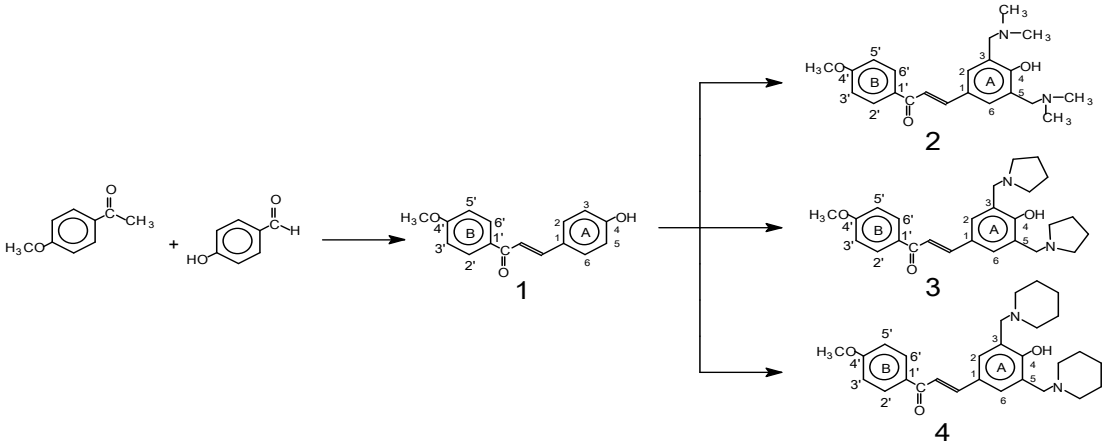
in aqueous media bis(dialkylamino)methane (aminal) and alkoxydialky aminomethane (aminol) should take part in Mannich reactin like claisen rearrangement rather than elctrophelic aromatic substitution because the reaction occur in ortho position of phenolic group, and the intermediate is considered to be in enolic form or in an analogous tautomeric form.




Also the observed preference for attack ortho to hydroxyl group has result suggestion that the mechanism of mannich reaction involves hydrogen bonding of bis(dialkylamino)methane with phenolic group



Three chalcones with Mannich side chain **(2)**, **(3)** and **(4)** were prepared together with their intermediate.




4-Hydroxy-4'-methoxychalcone was obtained by reaction of 4-methoxyacetophenone and 4-hydroxybenzaldehyde in alkaline ethanol solution m.p 152-154 °C (yield 85%) The **UV$_\lambda$** spectrum **$\lambda_{max}$** (ethanol), 250, 316 and 324 and 372 nm due to the benzoyl and cinnamoyl chromophores. The IR spectrum showed **ν(KBr)** 829 (C-H, Ar, bending), 1226.6 (C-O), 1554, 1581, 1600 (C=C, Ar, st,vib), 1643 (C=O. st, vib), 3000 and 2800 and 3080 (C-H Ar) and 3182 cm$^{-1}$ (OH). The $^1$H-NMR spectrum showed signal at δ 3.95 (s, 3H) assigned for methoxyl group. The α and β protons resonate at δ 7.58 (d, J = 15.1 Hz, 1H) and δ 7.7 (d, J = 15.1 Hz, 1H). The signal at 7.71 (d, J = 9.0 Hz, 2H) was assigned for $C_3$ and $C_5$-H, while the signal at δ 7.06 (d, J = 9.0 Hz, 2H) is due to $C_2$, and $C_6$-H of ring B. The doublet at δ 8.33 (J = 8.5 Hz, 2H) was assigned for $C_{3'}$ and $C_{5'}$-H, while the signal at δ 7.70 (d, J = 8.5 Hz, 2H), is characteristic of $C_{2',6'}$-H of ring A. $^1$H-$^1$H cosy NMR demonstrated a diagonal relationship between α- and β-H of the chalcone moiety. Also coupling

between $C_3$ and $C_5$-H $C_2$, of ring B and $C_6$-H of ring A. The $^{13}$CNMR spectrum showed a pattern characteristic of a $C_{16}$ system. Apt experiments showed 11 carbons in positive mode (one $–OCH_3$, one Me, nine =CH-), and five types are in negative mode (quaternary carbons).

When 4-hydroxy-4'-methoxychalcone (**1**) was reacted with dimethylamine and formalin in dry acetonitrile under reflux the 4-hydroxy-4'-methoxy-3,5-bis-dimethylaminomethylchalcone **(2)** was obtained. m.p 112-116 (yield 41%) The $^1$H-NMR spectrum showed a singlet at δ 2.40 (12H) assigned for four methyl groups. The signal at δ 3.70 (s, 2H), is characteristic of . The methoxy groups . The resonance at δ 7.73 (d, 1H, J = 15.5) is characteristic of β –H , while the singlet at δ 7.45 (2H) was assigned $C_2$ and $C_6$-H. The signal at δ 6.98 (J 8.2 Hz, 2H) was assigned for $C_{3'}$ - and $C_{5'}$-H, while the signal at δ 8.07 (d, J 8.2 Hz, 2H) is characteristic of $C_{2'}$ and $C_{6'}$-H. $^{13}$C NMR spectrum showed a pattern characteristic of a $C_{22}$ system. Apt experiments showed 13 carbons in negative mode (one $–OCH_3$, four Me, eight =CH-), and 9 carbons in positive (two $CH_2$-, and seven quaternary carbons). The mass spectrum gave m/z 369.2 (42%) for the molecular ion. Other fragment at m/z 324.2 (100%) (base peak) is due to loss of amino group.

When 4-hydroxy-4'-methoxychalcone **(1)** was reacted with pyrrolidine and formalin in dry acetonitrile under reflux the 4-hydroxy-4'-methoxy-3,5-bis-pyrrolidinomethylchalcone **(2)** was obtained. m.p 122-124, (yield 50%) In

the IR showed **ν(KBr**) 808 (C-H, Ar, bending), 1022 (C-N), 1163, 1253 (C-O), 1586 (C=C, Ar, st,vib), 1652 (C=O. st, vib), 2830 (C-H, aliphatic) 2930 (C-H and 2962 (OH) $cm^{-1}$. The $^{1}$H-NMR spectrum showed a multiplet at δ 1.82-1.88 (8H) characteristic of the four methylene groups of $\begin{matrix}CH_2-\\CH_2-\end{matrix}$ moiety. The resonance centered at δ 2.05-3.25 (8H) was assigned for four methylenes of $\begin{matrix}-CH_2\\-CH_2\end{matrix}\!\!>N-$ of the pyrrolidine ring. signal at δ 3.98 (s, 4H), is characteristic of two methylenes $>N-CH_2-$ in the Mannich side chain. The methoxy groups were observed as a singlet at δ 3.78. The resonance at δ 7.43 (s, 1 H) was assigned for β–H while the signal at δ 7.73 (d, 1H, J = 15.5 Hz) was assigned for α–H The singlet at δ 7.40 (2H) was assigned $C_2$-H and $C_6$-H. The signal at δ 6.06 (J 9.0 Hz, 2H) was assigned for $C_{3'}$ – and $C_{5'}$-H, while the signal δ 8.05 (d, J 9.0 Hz, 2H) assigned for $C_{2'}$ – and $C_{6'}$-H. $^{1}$H-$^{1}$H cosy NMR demonstrated a diagonal relationship between 8 protons of $\begin{matrix}CH_2-\\CH_2-\end{matrix}$ (δ 1.82-1.88) and 8 protons of $\begin{matrix}-CH_2\\-CH_2\end{matrix}\!\!>N-$ ( δ 2.05-3.25). The $^{13}$CNMR spectrum showed a pattern characteristic of a $C_{25}$ system. Apt experiments showed 9 carbons in negative mode (one –$OCH_3$, eight =CH-), and 17 carbons in positive (ten $CH_2$-, and seven quaternary carbons). The noesy experiments showed long range coupling between $C_2$-H and $C_6$-H. The mass spectrum gave m/z 350 (100%) (base peak) for the molecular ion. Other fragment at m/z 279 (99%) are due to loss of amino group.

When 4-hydroxy-4-methylchalcone was reacted with piperdine and formaldehyde in dry acetonitrile under reflux . The 4-hydroxy-4'-methoxy-3,5-bis-piperlidinomethylchalcone **(4)** was obtained, m.p 124-125 $^{0}$C (42%). The UV spectrum gave **λmax** (ethanol) 252, and 354 nm due to the benzoyl and cinnamoyl chromophores. The IR showed **ν(KBr)** 829 (C-H, Ar, bending), 1149 (C-N), 1255 (C-O), 1471 and 1598 (C=C, Ar, st,vib), 1652 (C=O. st, vib), , 2796 (C-H, aliphatic) 2848 (C-H Ar) and 3933 (OH) cm$^{-1}$ . The $^{1}$H-NMR spectrum showed a multiplet at δ 2.40-260 (2H) characteristic of $\overset{\frown}{CH_2}$ of the piperidine moiety, while the multiplet at δ 1.70-1.90 (4H) was assigned for the $<^{CH_2-}_{CH_2-}$ protons .The resonance at δ 1.53-173 (4H) was assigned for $^{-CH_2>}_{-CH_2>}N-$ of the piperdine ring. The methoxyl protons resonate at δ 3.90 (s, 3H). The signal at δ 3.64 (s, 2H), is characteristic of $>N-CH_2-$ . The resonance at δ 7.40 (s, 2H) was assigned for β–H and the signal at δ 7.74 (d, 1H, J =15.5 Hz) was assigned for α–H The singlet at δ 7.39 (2H) was assigned $C_2$- and $C_6$-H. The signal at δ 6.98 (J 9.0 Hz, 2H) is characteristic of $C_{3'}$- and $C_{,5'}$-H, while the signal δ 8.05 (d, J 9.0 Hz, 2H) was assigned for $C_{2'}$- and $C_{6'}$-H. $^{1}$H-$^{1}$H cosy NMR demonstrated a diagonal relationship between the α and β protons of the chalcone moiety which resonate at δ 7.74 and δ 7.40 respectively, also demonstrated a diagonal relationship between all protons at piperdine moiety. The $^{13}$CNMR spectrum showed a pattern characteristic of a $C_{28}$ system. Apt experiments showed 9 carbons in negative mode (one –$OCH_{3,}$

eight =CH-), and 19 in positive mode (twelve $CH_2$-, and seven quaternary carbons). The mass spectrum gave m/z 449.5 (3%) for the molecular ion. The most important fragments are at m/z 364.4 (100%) (base peak) due to loss of amino group, and m/z . 279.3 (80%) due to lost of two amino groups.

Two possible routes for target molecules (chalcones with Mannich side chains) are done during this work. The first route the dialkylaminomethyl group was introduced to aldehyde and then the chalcone was prepared (part i and ii). In the second route the chalcone was prepared and then dialkylaminomethyl group was introduced (part iii and iv)

The Mannich bases are important synthetic products used in different fields of applied sciences, and due to this application the present work was designed to synthesize a number of Mannich bases of chalcones that could further be assessed for their different biological activites.

**Conclusion**

The aminomethylation of chalcone by reaction with formaldehyde and suitable amine in acetonitrile was achieved and characterization of the products and their intermediates by spectroscopic methods: UV, IR, and NMR and mass spectrometry was disucussed.

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