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Synthesis of Mono and Di-4′,4′-Dihydroxy-2,2-Diphenylpropane Mannich Side Chain

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Abstract: Four compounds of mono and di-4′,4′-dihydroxy-2,2-diphenylpropane mannich side chain were synthesized by three components Mannich reaction. These compounds (1-4) were synthesized by reaction of dialkylphenol (4′,4′-dihydroxy-2,2-diphenylpropane) with suitable secondary amines (dimethyl amine or pyrrolidine) and formaldehyde solution in methanol. The products were purified by thin layer chromatography and identified along with by NMR spectroscopic methods (^{1}HNMR, ^{13}CNMR, APT, COSY, HSQC, HMBC and NOSEY).
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Key word: Mannich reaction, three components reaction, alkyldiphenol

1-Introduction

The Mannich reaction is one of the most important C-C bond formation methods in organic synthesis (Sharifi, et al, 2001)**.** The Mannich reaction is employed in the organic synthesis of natural compounds like for instance Peptides-Nucleotides-Antibiotics and Alkaloids. Other applications are in agrochemicals such as plant growth regulators, paint and other polymer chemistry, catalysts and crosslinking. The Mannich reaction is also used to synthesized medicinal compounds. A large number of different bioactivities of Mannich bases, antimalarial (Nasr, et al 1978), (Li, et al 2003), (Raynes, et al 1999), anticancer (Dimmock, et al 1998), (Gul, et al 2002),analgesic (Janssen,et al 1959), anticonvulsant (Gul, et al 2002), (Janssen,et al 1959) and antimicrobial activity(Bayrak, et al 2008), (Bayrak, et al 2008) are known.

2-Materials and methods:

NMR spectroscopy was carried out using procker instrument model AVANCE II 600

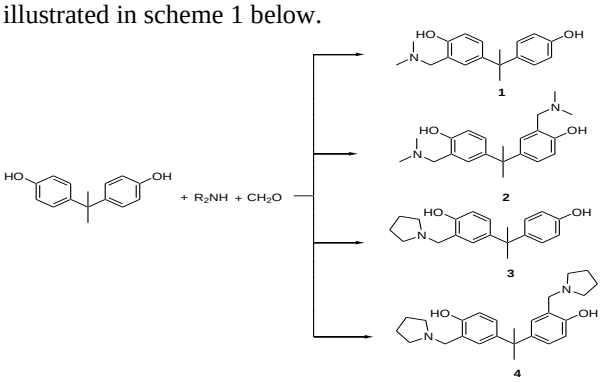
Synthesis of mono and di-4′,4′-dihydroxy-2,2-diphenylpropane mannich side chain

Formaldehyde solution (1 ml) was added dropwise to a mixture of 4′,4′-dihydroxy(2,2-diphenyl)propane (1.2g, 0.001 mol) and secondary amine (dimethylamine1ml or pyrrolidine 0.8 ml) in methanol (10 ml). The reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum and the product purified by TLC chromatography (hexane: ethyl acetate 7:3).

3. Results and discussion :

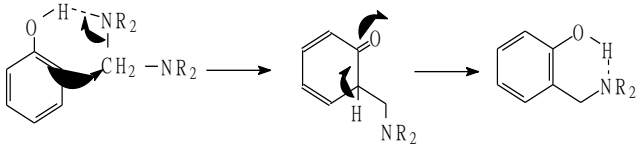
The aim of this work is to introduced mannich side chain of dialkylphenol which increase the hydrophilicity by amine group and increase the lipophilicity by methelene group.

We synthesized four compounds of mono and di-4′,4′-dihydroxy-2,2-diphenylpropane mannich side chain by reaction of dialkylphenol (4′,4′-dihydroxy-2,2-diphenyl
propane) with formaldehyde and secondary amine (dimethyl amine or pyrolidine). The reaction was illustrated in scheme 1 below.



Scheme 1: mono and di-4′,4′-dihydroxy-2,2-diphenylpropane mannich side

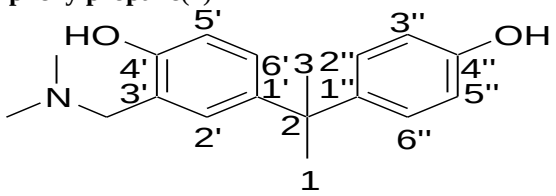
The reaction mechanism was suggested according to the observation for attack the alkylaminogroup at ortho position to hydroxyl group**.**Therefore the mechanism of mannich reaction involves hydrogen bonding of bis(dialkylamino) methane with phenolic group (scheme 2)



Scheme 2: reaction mechanism

When 4′,4′-dihydroxy-2,2-diphenylpropane was reacted with dimethylamine and formalin in methanol at room temperature mono-3′-dimethylaminomethyl-4′,4′-dihydroxy-2,2-diphenylpropane(1) and di-3′,3′-(dimethylaminomethyl)-4′,4′dihydroxy-2,2-diphenylpropane(2) were obtained (yield 65 % and 25% respectively).

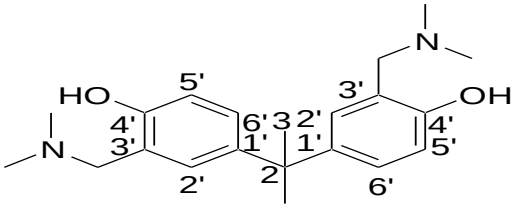
3′-dimethylaminomethyl-4′,4′-dihydroxy-2,2-diphenylpropane(1)



1

^{1}HNMR: δ (CD_3OD) 1.60 (s, 6H, H-1/3), 2.30 (s, 6H, $2CH_3N$-), 359 (s, 2H, -CH_2-N), 6.73 (d, 1H, J 7.8, H-5′), 6.75 (d, 2H, j 8.8, H-2,6), 6.81 (d, 1H, J 2.3, H-2′), 7.02 (dd, 1H, J 7.8, 2.3, H-6′), 7.05 (d, 2H, j 8.8, H-3,5). ^{13}CNMR: δ (CD_3OD) 31.1 (C-1/3), 44.40 (($CH_3)_2$-N-), 62.9 (-CH_2-N-), 114.7 (C-2"/6"), 115.4 (C-5′), 121.0 (C-1′), 126.6 (C-2′) 126.9 (C-6′), 127.7 (C-3"/5"), 141.7 (C-1") 142.6 (C-3') 153.9 (C-4'), 155.2 (C-4″).

3′,3′-(dimethylaminomethyl)-4′,4′-dihydroxy-2,2-diphenylpropane(2)



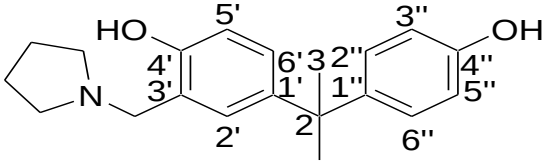
1

^{1}HNMR: δ (CD_3OD) 1.58 (s, 6H, H-1/3), 2.30 (s, 12H, $4CH_3N$-), 3.56 (s, 2H, -CH_2-N), 6.71 (d, 1H, J 8.4, H-5′), 6.76 (d, 1H, J 2.3, H-2′), 7.01 (dd, 1H, J 8.4, 2.3, H-6′). ^{13}CNMR: δ (CD_3OD) 31.0 (C-1/3), 44.6 (($CH_3)_2$-N-), 63.2 (-CH_2-N-), 115.2 (C-5'), 121.0 (C-1′), 126.7 (C-2′) 126.9 (C-6′), 141.6 (C-3'), 155.2 (C-4').

^{1}H-NMR spectrum showed singlet peaks at δ 1.60 (2H) and δ 1.58 (4H) were assigned tow methyl groups in compounds 1 and 2 respectively. the other six protons of compound 1 and twelve protons of compound 2 methyl groups of amino groups appeared at δ 2.30. The singlet's at δ 3.59 (2H) and δ 3.56 (4H) is characteristic of  of this two compounds 1 and 2 respectively. Compound 1 spectrum showed resonances as doublet at δ value 6.73 (H-5′), doublet at δ value 6.81 (H-2′), and doublet of doublet at δ value 7.02 (H-6′) is characteristic of ABX system. While the peaks as doublet at δ 6.75 and δ 7.05 indicated for AB system. The resonances peaks of compound 2 at δ values 6.71 (doublet), 6.76 (doublet) and 7.01 (doublet doublet) were characteristic of H-5′, H-2′ and H-6′ of ABX system respectively.

When 4′,4′-dihydroxy-2,2-diphenylpropane was reacted with pyrrolidine and formalin in methanol the mono-3′-(pyrroldinomethyl)-4′,4″-dihydroxy-2,2-diphenylpropane (3) and di-3′,3′-(pyrroldinomethyl)-4′,4′-dihydroxy-2,2-diphenylpropane(4) were obtained (yield 70% and 15 % respectively).

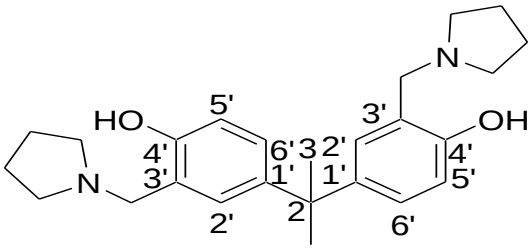
3′-(pyrroldinomethyl)-4′,4″-dihydroxy-2,2-diphenylpropane(3)



1

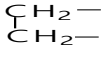
^{1}HNMR: δ (CD_3OD) 1.58 (s, 6H, H-1/3), 3.54 (br s, 4H, 2-CH_2-), 3.64 (s, 2H, -CH_2-N), 3.73 (br s, 4H, 2-CH_2-), 6.71 (d, 1H, J 8.6, H-5′), 6.73 (d, 2H, j 8.8, H-2″,6″), 6.82 (d, 1H, J 2.3, H-2′), 7.03 (dd, 1H, J 8.6, 2.3, H-6′), 7.05 (d, 2H, j 8.8, H-3″,5″). ^{13}CNMR: δ (CD_3OD) 31.1 (C-1/3), 41.5 (C-2), 52.8 (C-(-CH_2-)), 62.0 (C-CH_2), 66.7 (C-2CH_2), 114.7 (C-2″,6″), 115.3 (C-5′), 119.7 (C-1′),127.0 (C-2′), 127.2 (C-6′), 127.7 (C-3″,5″), 142.0 (C-3′) 142.5 (C-3″), 153.9 (C-4′), 154.8 (C-4″).

3′,3′-(pyrroldinomethyl)-4′,4′-dihydroxy-2,2-diphenylpropane(4)



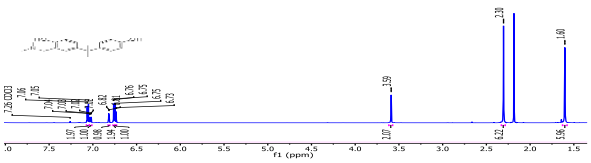
1

^{1}HNMR: δ (CD_3OD) 1.57 (s, 6H, H-1/3), 2.54 (br s, 8H, 2-CH_2-), 3.64 (s, 4H, -CH_2-N), 3.74 (br s, 8H, 2-CH_2-), 6.71 (d, 1H, J 8.6, H-5′), 6.80 (d, 1H, J 2.3, H-2′), 7.01 (dd, 1H, J 8.6, 2.3, H-6′). ^{13}CNMR: δ (CD_3OD) 31.3 (C-1/3), 41.56 (C-2), 44.5 (C-4NCH_3), 63.2 (C-CH_2), 115.2 (C-5′), 121.1 (C-1′), 126.7 (C-2′), 129.9 (C-6′), 141.6 (C-3′), 155.6 (C-4′).

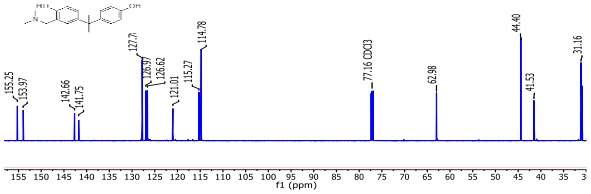
The 1H-NMR spectrum showed a brood singlet peak at δ 2.54 (4H of compound 3) and at δ 2.54 (8H of compound 4) characteristic of the four or eat methylene protons of  moiety

respectively. The brood resonance centered at δ 3.73 (4H in compound 3) and 3.74 (8H in compound 4) were assigned for four or eat protons methylene group $-CH_2>N-$ $-CH_2<$ of the pyrrolidine ring. The signal at δ 3.54 (s, 2H), ischaracteristic of two methylenes $>N-CH_2-$ in the Mannich side chain. The two methyl groupswere observed as a singlet at δ 1.58 (3) and 1.57 (4), while the other two or four of methyl protons of amino group appeared as singlet at δ 2.54 of compounds 3 and 4. The doublet at δ 6.71 in 3 and 4 spectra responding to $C_{5'}$-H, and the doublet at δ 6.82 and 6.80 (3 and 4 respectively) for $C_{2'}$-H, while the doublet of doublet at δ 7.03 and 7.01 (3 and 4 respectively) for $C_{6'}$-H were presenting ABX system. The signals at δ 6.73 (3) for $C_{2''}$– and $C_{6''}$-H and at δ 7.05 ($C_{3''}$– and $C_{5''}$-H) were assigned for AB system of compound (3). ^{1}H-^{1}H cosy NMR demonstrated a diagonal relationship between neighboring protons in synthesized compounds (1, 2, 3 and 4). The ^{13}CNMR spectrum showed a exact number of the carbons for all compounds (1, 2, 3 and 4). Apt experiments gave evidence for the types of the protons (negative and positive mode). HSQC and HMBC experiments showed full relationship for all types of protons with all types of carbons in structures of all compounds (1, 2, 3 and 4). The noesy experiments showed long range coupling between $>N-CH_2-$ and $C_{2'}$-H in all synthesized compounds (1, 2, 3 and 4). We introduced mono or di-alkylaminomethy groups to 4′,4′-dihydroxy-2,2-diphenylpropane as Mannich side chain and the final compounds were confirmed by NMR techniques

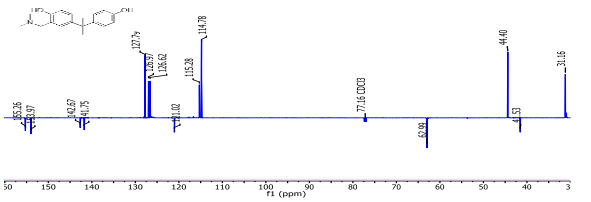
Conclusion



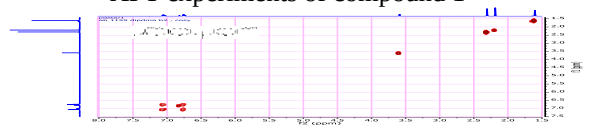
1HNMR of compound 1



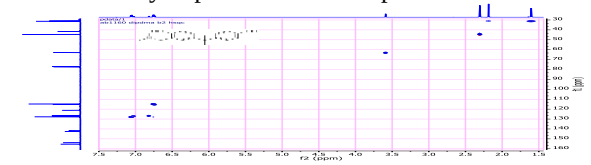
13CNMR of compound 1



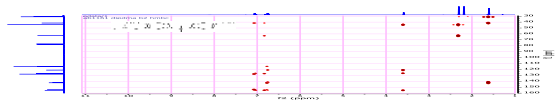
APT experiments of compound 1



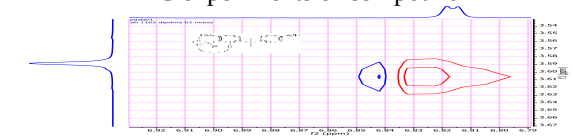
Cosy experiments of compound 1



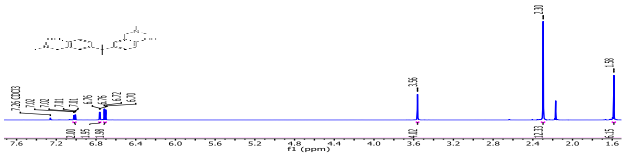
HSQC experiments of compound 1



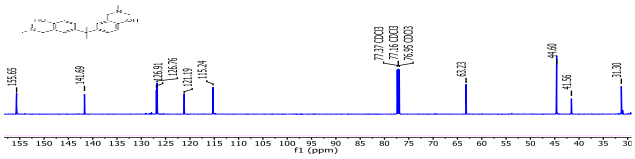
HMBC experiments of compound 1



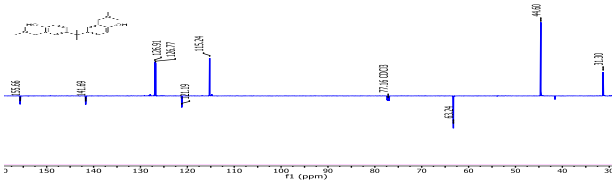
Noesy experiments of compound 1



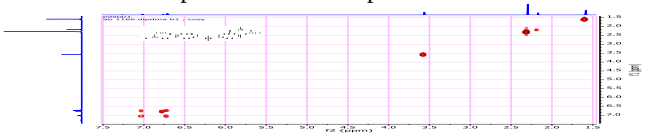
1HNMR of compound 2



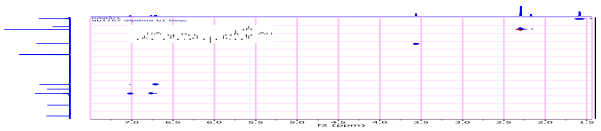
13CNMR of compound 1



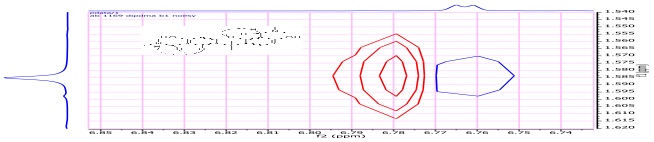
APT experiments of compound 2



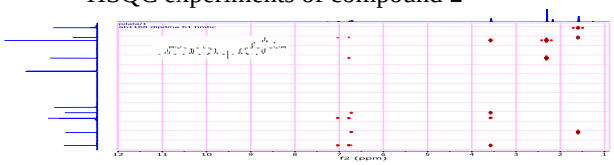
Cosy experiments of compound 2



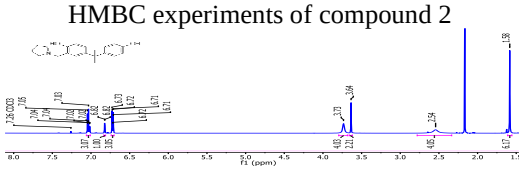
HSQC experiments of compound 2



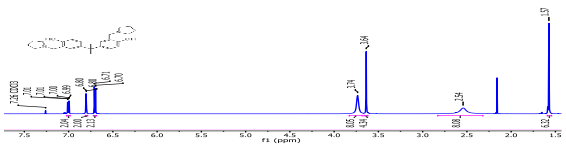
Noesy experiments of compound 2



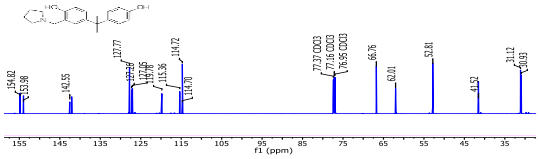
HMBC experiments of compound 2



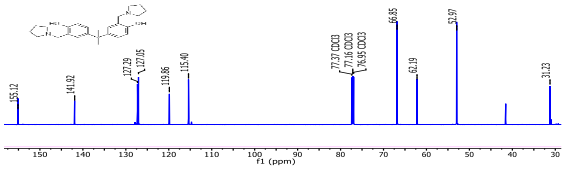
1HNMR of compound 3



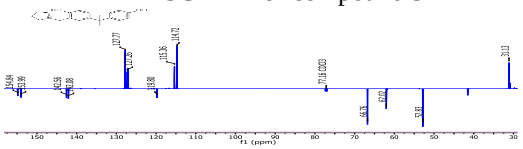
1HNMR of compound 4



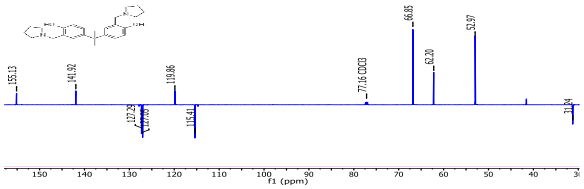
13CNMR of compound 3



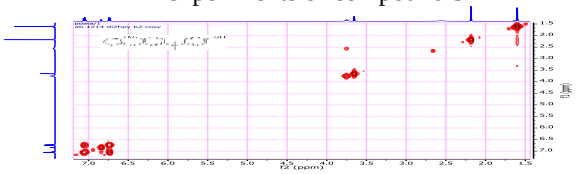
13CNMR of compound 4



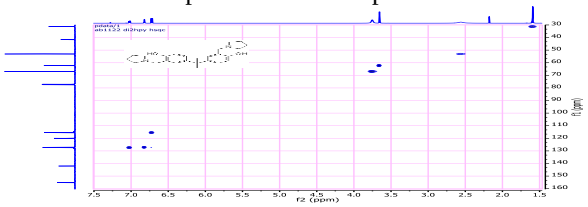
APT experiments of compound 3



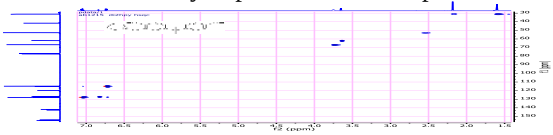
APT experiments of compound 4



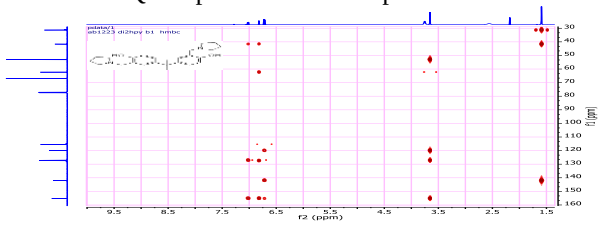
Cosy experiments of compound 3



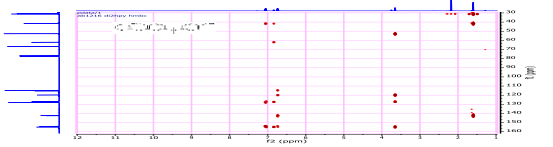
HSQC experiments of compound 4



HSQC experiments of compound 3



HMBC experiments of compound 4



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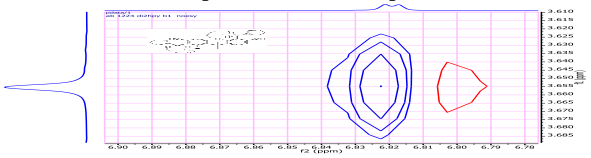
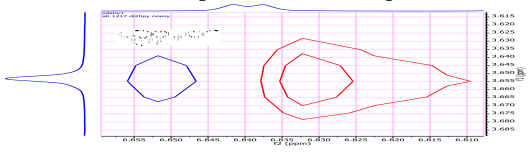


Noesy experiments of compound 4



Noesy experiments of compound 3

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4/22/2023