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ACETOPHENONE BASED MANNICH BASES: SYNTHESIS, CHARACTERIZATION AND THEIR ANTI-BACTERIAL ACTIVITY

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ABSTRACT

Five new Mannich bases, 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-methoxy-phenyl)-1-phenyl-propane-1-one (**4a**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one (**4b**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one (**4c**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-nitro-phenyl)-1-phenyl-propane-1-one (**4d**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(2-hydroxy-phenyl)-1-phenyl-1-propane-1-one (**4e**) have been synthesized and characterized by chemical and spectral analyses such as UV-Visible, FT-IR, ^{1}H NMR and ^{13}C NMR. All the synthesized compounds **4a-4e** was screened for their antibacterial activities against the Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus species)*, Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi)*. Compounds **4c** and **4d** of the series showed good activities against *Bacillus species*.

KEYWORDS: Mannich base, Acetophenone, Benzaldehyde derivatives, Cinnamaldehyde.

INTRODUCTION

Mannich reaction

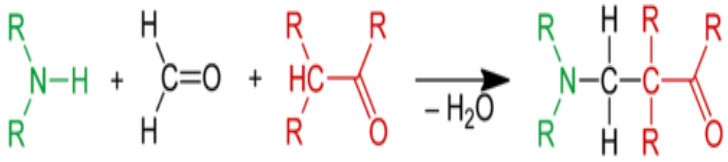
The first observation of a condensation of the Mannich reaction was made by Tollens.[1], who isolated the tertiary amine from ammonium chloride, formaldehyde and acetophenone. The first "Mannich reaction'' was serendipity in 1912, when Carl Mannich.[2], a young professor in the pharmaceutical laboratory at Gottingen University, was treating an acid solution of salicylantipyrine with hexamethylene tetramine (urotropine) for pharmaceutical preparation. He obtained a crystalline precipitate.

Having observed that the same condensation product was also formed by mixing antipyrine, formaldehyde and ammonium chloride, regardless of the order of addition, Mannich realized the great synthesis relevance of the reaction of which only a few examples were then known in literature. Mannich and Kather.[3] treated equivalent amounts of dimethylamine hydrochloride, formaldehyde and antipyrine and the base produced was 4-dimethylaminoantipyrine. Mannich observed that it allowed the linkage of two different chemical moieties in one step by means of a methylenic bridge. He then studies the reaction in considerable depth, assisted by a number of collaborators, and demonstrated products. Mannich bases have been the topic of growing interest as evidenced by the appearance of a reviews.[4-6], books.[7-8] and research papers.[9-12]

Mannich base

The Mannich reaction is the prototype of carbon-carbon bond forming reactions that involves the addition of resonance stabilized carbon nucleophiles to iminium salts and imines. In its original and most widely recognized form, Mannich reaction is a three component condensation of i) ammonia or primary amine or secondary amine.[13] of with amides.[14]; ii) a non-enolisable aldehyde, usually formaldehyde; and iii) a compound containing an active hydrogen.[15] atom (substrate). These three compounds condense with concomitant release of water to produce a new base known as a Mannich base, in which the active hydrogen is replaced by an aminomethyl group.

The formation of both carbon-carbon and carbon-nitrogen bond in this aminomethylation process makes the Mannich reaction an extremely useful synthetic transformation and it can be illustrated in the following scheme.



Scheme 1: Synthesis of Mannich bases

The Mannich base can react further in three ways. If it is a secondary or primary amine, it may condense respectively with one or two additional molecules of aldehyde and the compounds containing active hydrogen. If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine.

The Mannich reaction is an important biosynthetic route to natural products, mainly alkaloids. Che et-al.[16] has reported the aminoalkylation of aromatic substrates by the Mannich reaction which is considerable importance for the synthesis and modification of biologically active compounds. It also provides a convenient access to many useful synthetic building blocks because the amino group can be easily converted into a variety of other functionalities.[17]

Mannich bases were found to possess potent activities such as antibacterial.[18], antifungal.[19], anti-HIV.[20], antiviral.[21,22] anticancer.[23], antimicrobial.[24,25] They are also used in polymer industry as paints and surface active agents. Mannich bases demonstrated anticonvulsant activities and have been reported as potential biological agents. They also find application as antitubercular.[26], antimalarial.[27], vasorelaxing.[28], analgesic.[29], anti-convulsant.[30,31] drugs, biological.[32,33] and pharmacological.[34,35] activity.

In the context to the above principle, the present research work was aimed at to synthesize and characterize a series of five new Mannich bases, 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-methoxy-phenyl)-1-phenyl-propane-1-one (**4a**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one (**4b**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one (**4c**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-nitro-phenyl)-1-phenyl-propane-1-one (**4d**), 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(2-hydroxy-phenyl)-1-phenyl-1-propane-1-one (**4e**) have been synthesized from acetophenone, 2,4-dinitrophenylhydrazine and substituted benzaldehydes / cinnamaldehyde. All synthesized Mannich bases have been characterized by chemical and spectral analyses such as UV-Visible, FT-IR, ^{1}H NMR and ^{13}C NMR. All the compounds **4a-4e** was screened for their antibacterial activities against the Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus species)*, Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi)*.

MATERIALS AND METHODS

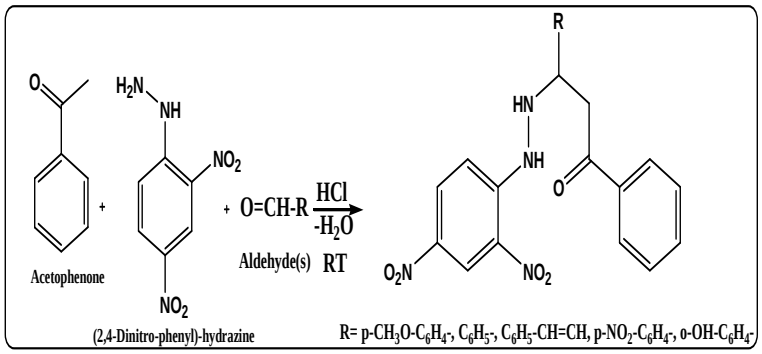
Chemicals: All chemicals and solvents were of reagent grade and were used as commercially purchased without further purification.

Methods: Melting points and were determined by open capillary tubes method purity and homogeneity of the compounds was routinely determined by thin layer chromatography on glass plates using silica gel-G as absorbent and solvent system. Benzene: Ethyl acetate: Methanol (8.5: 1.4: 0.1). Spots were visualized by iodine vapor by irradiation with UV light.

Infrared spectra of the compounds were recorded on KBr pellets using a Perkin Elmer RX1-FTIR Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz) at 298 K in $CDCl_3$. Chemical shifts δ in ppm were referenced to the solvent residual peak as an internal standard. ^{13}C NMR was recorded on a Bruker Avance spectrometer (500 MHz) at 298K in $CDCl_3$ and spectra was referenced to the solvent residual peak.

Synthesis of 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-methoxy-phenyl)-1-phenyl-propane-1-one (4a)

Ethanolic solution of 2,4-dinitrophenyl hydrazine (1.98 g, 0.01 mole) was added to hydrochloric acid (2.0 ml) in a round bottom flask, stirred for 10 minutes and then added minimum amount of ethanolic solution of acetophenone (1.2 ml, 0.01 mole). 0.01 mole of ethnolic solution of 4-methoxy benzaldehyde (1.10 ml, 0.01 mole) was added slowly to the reaction mixture with constant stirring. The reaction mixture was stirred at room temperature for two hours (**Scheme 2**). The obtained precipitate was washed with diethyl ether and dried in *vacuo*. The product was recrystallized from DMSO. Thin layer chromatography was used to check the purity of the compounds. Brown crystal, yield 84.78% (3.7006g), $R_f = 0.65$.



Scheme 2: Synthesis of some new acetophenone based Mannich bases

Synthesis of 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,3-diphenyl-propane-1-one (4b)

3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,3-diphenyl-propane-1-one were synthesized from 1:1:1 ratio of 2,4-dinitrophenylhydrazine (1.98g, 0.01 mole), acetophenone (1.2 ml, 0.01 mole) and benzaldehyde (1.05 ml, 0.01 mole) by above mentioned similar manner. Yellow crystal, yield 93.65% (3.8064g), $R_f = 0.74$.

Synthesis of 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one (4c)

E-3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-1,5-diphenyl-pent-4-en-1-one were synthesized from 1:1:1 ratio of 2,4-dinitrophenylhydrazine (1.98g, 0.01 mole), acetophenone (1.2 ml, 0.01 mole) and cinnamaldehyde (1.05 ml, 0.01 mole) by above mentioned similar manner. Reddish orange crystal, yield 83.47% (3.6099g), R_f = 0.69.

Synthesis of 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-nitro-phenyl)-1-phenyl-propane-1-one (4d)

3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(4-nitro-phenyl)-1-phenyl-propane-1-one were synthesized from 1:1:1 ratio of 2,4-dinitrophenylhydrazine (1.98g, 0.01 mole), acetophenone (1.2 ml, 0.01 mole) and 4-nitrobenzaldehyde (1.51g, 0.01 mole) by above mentioned similar manner. Orange crystal, yield 96.56% (4.3583g), R_f = 0.76.

Synthesis of 3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(2-hydroxy-phenyl)-1-phenyl-1-propane-1-one (4e)

3-[N'-(2,4-Dinitro-phenyl)-hydrazino]-3-(2-hydroxy-phenyl)-1-phenyl-1-propane-1-one were synthesized from 1:1:1 ratio of 2,4-dinitrophenylhydrazine (1.98g, 0.01 mole), acetophenone (1.2 ml, 0.01 mole) and salicylaldehyde (1.15 ml, 0.01 mole) by above mentioned similar manner. Yellow crystal, yield 80.39% (3.3959g), R_f = 0.62.

RESULTS AND DISCUSSION

The synthesized Mannich bases were checked by comparing the TLC with the starting materials, which resulted in a single spot different from the starting materials. The synthesis achieved in high yields**.** The structure of synthesized compounds was confirmed on the basis of analytical studies, UV-Vis., FT-IR, ^{1}H NMR and ^{13}C NMR spectral data. The physical properties, yield, R_f value and solubility are summarized in the **Table 1**.

UV – Visible and FT-IR spectral data

UV-Visible and FT-IR spectrum of synthesized **4a-e** are presented in the **Table 2**. The UV – Visible spectrum of newly synthesized compounds showed at 282-292 nm. This may be due to π-π * and n-π* transitions of C=C bond and C=O bond in aromatic keto group. A band appeared at 3426 cm^{-1} may be attributed to the ν(OH) group in **4e** only. The IR spectrum of all the synthesized compounds showed characteristic band in the region of 3360-3211 cm^{-1} may be attributed to the νNH stretching frequency. The aromatic stretching frequency is appeared at 3060-2941 cm^{-1}. Mannich bases exhibits the aliphatic C-H stretching frequency is

shown in the range of 2932-2837 cm^{-1}. The carbonyl stretching frequency is ν(C=O) appeared in the region of 1714-1647cm^{-1}. All the compounds exhibit nitro group within the range of expected values at 1592-1514 cm^{-1}.

Table 1: The physical properties, yield, R_f value and solubility of Mannich bases

Mannich bases	Molecular formula	Mol. Weight (g/mole)	Color	Melting Point (°C)	Yield (%)	R_f	Solubility
4a	$C_{22}H_{20}N_4O_6$	436.50	Brown	172-174	84.78 (3.7006g)	0.65	$CHCl_3$, THF, EtOAc, DMSO
4b	$C_{21}H_{18}N_4O_5$	406.45	Yellow	146-148	93.65 (3.8064g)	0.74	Acetone, $CHCl_3$, Benzene, EtOAc, DMSO
4c	$C_{23}H_{20}N_4O_5$	432.48	Reddish Orange	164-166	83.47 (3.6099g)	0.69	$CHCl_3$, Benzene, DMSO
4d	$C_{21}H_{17}N_5O_7$	451.36	Orange	157-159	96.56 (4.3583g)	0.76	$CHCl_3$, THF, EtOAc, DMSO
4e	$C_{21}H_{18}N_4O_6$	422.44	Yellow	224-226	80.39 (3.3959g)	0.62	Acetone, $CHCl_3$, Benzene, THF, DMSO

^{1}H NMR and ^{13}C NMR spectroscopy

The ^{1}H NMR data of Mannich bases **4a-e** are summarized in **Table 3** and ^{13}C NMR data in the T**able 4.**

Table 2: UV-Visible and FT-IR Spectral data of Mannich bases

Mannich bases	λ_{max} (nm)	λ_{max} (cm)	νOH	νNH	νAr-CH	νAli-CH	νC=O	νNO_2
4a	284	35211	-	3328	2941	2838	1714	1590
4b	292	34200	-	3228	2982	2932	1709	1592
4c	284	35211	-	3360	2970	2932	1701	1514
4d	282	35461	-	3330	2942	2837	1708	1591
4e	291	34364	3426	3311	3060	2851	1647	1543

^{1}H NMR and ^{13}C NMR spectrum of 4a

The Mannich base showed a multiplet at δ 9.44-6.97 (12 H), which is due to phenyl protons. The quartet at δ 4.00 (1H) which is assigned to N-**CH**-CH_2 proton. A singlet at δ 3.89 (3H) is assigned to O-**CH_3** protons. The doublet at δ 2.47 (1H), is assigned to NH-**NH**-Ph proton. The doublet at δ 2.18 (2H), is assigned CH-**CH_2**-CO protons. The triplet at δ 1.59 (1H), is assigned to CH-**NH**-NH proton. The ^{13}C NMR spectrum showed the peak at δ 201.5 was assigned to carbonyl group (**C=O**). The peak obtained in the region δ 155.22 showed the presence of –**C-O**-CH_3 group. The phenyl ring carbons show its range δ 114.5 – 152.35. The peak obtained in the region δ 76.77 shows the presence of aliphatic –**CH** group. The peak

obtained in the region δ 55.51 showed the presence of aliphatic –**CH$_2$**group. The peak obtained in the region δ 77.28 shows the presence of aliphatic O–**CH$_3$** group.

^{1}H NMR and ^{13}C NMR spectrum of 4b

The Mannich base observed a multiplet at δ 7.26-9.17 (13H). This may be due to phenyl protons. The quartet at δ 2.48 (1H), which is assigned to N-**CH**-CH$_2$ proton. The doublet at δ 2.43 (1H), is assigned to NH-**NH**-Ph proton. The doublet at δ 1.62 (2 H), is assigned CH-**CH$_2$**-CO protons. The triplet at δ 1.24 (1H), is assigned to CH-**NH**-NH proton. The ^{13}C NMR spectrum showed the peak at δ 207.22 was assigned to carbonyl group (**C=O**). The phenyl ring carbons show its range δ 108.00 – 147.89. The peak obtained in the region δ 91.54 showed the presence of aliphatic –**CH** group. The peak obtained in the region δ 77.02 shows the presence of aliphatic –**CH$_2$** group.

^{1}H NMR and ^{13}C NMR spectrum of 4c

The peak observed a multiplet at δ 7.26-9.17 (13H), which is due to phenyl protons. The doublet at δ 7.06 (1H), is assigned to CH-**CH**=CH proton. The doublet at δ 6.98 (1H), is assigned to CH-CH=**CH** proton. The multiplet at δ 5.37 (1H), is assigned to N-**CH**-CH$_2$ proton. The doublet at δ 2.47 (1H), is assigned to NH-**NH**-Ph proton. The doublet atδ 1.57 (2H), is assigned CH-**CH$_2$**-CO protons. The triplet atδ 1.25 (1H), is assigned to CH-**NH**-NH proton. The ^{13}C NMR spectrum showed the peak at δ 166.46 was assigned to carbonyl group (**C=O**). The phenyl ring carbons showed its range δ 116.72 – 152.34. The peak obtained in the region δ 123.49 and 126.52 are shows the presence of aliphatic alkene protons (**CH=CH**). The peak obtained in the region δ 77.27 showed the presence of aliphatic –**CH** group. The peak obtained in the region δ 66.70 showed the presence of aliphatic –**CH$_2$** group.

Table 3: ^{1}H NMR spectral data of Mannich bases

^{1}H NMR(ppm in CDCl$_3$, type of proton, multiplicity)					**Assignments**
4a	**4b**	**4c**	**4d**	**4e**	
1.59(1H, t)	1.24(1H, t)	1.25(1H, t)	1.60(1H, t)	1.25(1H, t)	-CH–**NH**-NH
2.47(1H, d)	2.43(1H, d)	2.47(1H, d)	2.48(1H, d)	2.44(1H, d)	-NH–**NH**-Ar
4.00(1H, q)	2.48(1H, q)	-	2.30(1H, q)	2.48(1H, q)	NH-**CH**(Ph)-CH$_2$
6.97–9.44 (12H, m)	7.26-9.17 (13H, m)	7.26-9.17 (13H, m)	7.26-9.17 (12H, m)	7.06-9.19 (12H, m)	Aromatic protons
2.18(1H, d)	1.62(1H, d)	1.57(1H, d)	2.69(1H, d)	1.58(1H, d)	CH-**CH$_2$**-C=O
-	-	6.98(1H, t)	-	-	-CH-**CH**=CH
-	-	7.06(1H, d)	-	-	-CH=**CH**-Ar
-	-	5.37(1H,q)	-	-	CH**CH**(NH)CH$_2$
-	-	-	-	-	-O**CH$_3$**
-	-	-	-	2.17(1H, s)	-O**H**

^{1}H NMR and ^{13}C NMR spectrum of 4d

The peak observed a multiplet at δ 7.26-9.17 (12H). This may be due to phenyl protons. The quartet at δ 2.30 (1H), is assigned to N-**CH**-CH_2 proton. The doublet at δ 2.48 (1H), is assigned to NH-**NH**-Ph proton. The doublet atδ 2.69 (2H), is assigned CH-**CH_2**-CO protons. The triplet atδ 1.60 (1H), is assigned to CH-**NH**-NH proton. The spectrum observed the peak at δ 190.26 was assigned to carbonyl group (**C=O**). The phenyl ring carbons show its range δ 116.78 – 140.05. The peak obtained in the region δ 77.25 showed the presence of aliphatic –**CH** group. The peak obtained in the region δ 76.75 showed the presence of aliphatic –**CH_2** group.

Table 4: ^{13}C NMR spectral data of Mannich bases

^{13}C NMR(ppm in $CDCl_3$, multiplicity)					Assignments
4a	**4b**	**4c**	**4d**	**4e**	
201.5 (s)	207.2 (s)	166.4 (s)	190.2 (s)	181.4 (s)	-**C**=O
114.5-152.35(d)	108.0-147.8 (d)	116.7-152.3(d)	116.7-140.0(d)	113.9-133.0(d)	Aromatic Carbons
76.77 (d)	91.5 (d)	77.27 (d)	77.25 (d)	75.81 (d)	HN**CH**(Ph)CH_2
55.51 (t)	77.02 (t)	66.70 (t)	76.75 (t)	57.95 (t)	CH**CH_2**CO
77.28 (q)	-	-	-	-	Ph-O**CH_3**
-	-	123.49 (d)	-	-	HNC**H**=CH
-	-	126.52 (d)	-	-	CH=**CH**-Ph
-	-	-	-	154.4 (s)	-**C**-**O**H
155.22 (s)	-	-	-	-	-**C**-**O**-CH_3

^{1}H NMR and ^{13}C NMR spectrum of 4e

The peak observed a multiplet at δ 7.06-9.19 (12H), which is due to phenyl protons. The quartet at δ 2.48 (1H), is assigned to N-**CH**-CH_2 proton. The doublet at δ 2.44 (1H), is assigned to NH-**NH**-Ph proton. The doublet atδ 1.58 (2H), is assigned CH-**CH_2**-CO protons. The triplet atδ 1.25 (1H), is assigned to CH-**NH**-NH proton. A singlet at δ 2.17 (1H), is assigned to Ph-**OH** proton. The ^{13}C NMR spectrum observed the peak at δ 181.40 was assigned to carbonyl group (**C=O**). The peak obtained in the region δ 154.42 shows the presence of –**C-OH** group. The phenyl ring carbons showed its range δ 113.97 – 133.01. The peak obtained in the region δ 75.81 shows the presence of aliphatic –**CH** group. The peak obtained in the region δ 57.95 shows the presence of aliphatic –**CH_2** group.

Anti – bacterial screening

Prepare nutrient broth, sterilize it and inoculate the test organisms (pathogens) and incubate it at 37°C for 24 hours. Prepare Mueller Hinton agar plates and swab the test organisms as a

lawn culture. Prepare the disc and impregnate with the compounds with desired quantity. For well diffusion method, cut the well with 6mm and add the compound solution of desired quantity (50µg). For disc diffusion method, add the compound solution to the sterile disc and make them to dry. After swabbing, place the disc and also add the compound solution in well. Incubate it at 37°C for 24 hours. After incubation, observe the plates for zone of inhibition (**Table 5**).

Table 5: Anti-bacterial activity of Mannich bases 4a-e

Mannich base[a]	Method	Inhibition zone (mm)			
		B. species	***E. coli***	***S. aureus***	***S. typhi***
4a	Disc	–	–	–	–
	Well	–	–	–	–
4b	Disc	–	–	–	–
	Well	–	–	–	–
4c	Disc	15	11	11	8
	Well	23	11	11	9
4d	Disc	20	13	–	–
	Well	25	18	–	–
4e	Disc	–	–	–	–
	Well	–	–	–	–
Vancomycin[b]	Well	21	16	18	20

a -50 µg/ml, *b* – 30 mg/ml

B. species - Bacillus species, E. coli - Escherichia coli, S. aureus - Staphylococcus aureus and *S. typhi – Salmonella typhi.*

CONCLUSION

Five new acetophenone based Mannich bases were synthesized in very good yields. All compounds were characterized by analytical and spectroscopic methods. The compounds **4c** and **4d** were found to possess very good anti-bacterial activity against *Bacillus species* compared than vancomycin as standard drug. Compound **4d** were found to possess very good anti-bacterial activity against *Escherichia coli.*

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