Heterocyclic Letters
Vol. 10| No.4|609-617|Aug-Oct |2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND BIOLOGICAL STUDIES OF CINNAMALDEHYDE BASED MANNICH BASE

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ABSTRACT

A convenient and efficient synthesis of mannich base by one-pot reaction of cinnamaldehyde, various anilines and ammonium acetate using ethanol as solvent at room temperature. Synthesized compounds have been characterized by FT-IR, 1H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. The anti bacteral activity of newly synthesized compounds were evaluated against four bacterial strains *Staphylococcusaureus*, *Bacillussubtilis*, *Salmonella typhi*, *Micrococcus luteus* and *Bacillus licheniformis.* These compounds were also tested for their anti parkinson's activity against S. aureus biofilm.

KEYWORDS: Phenylpropanoid, cinnamaldehyde, aniline, mannich bases etc.

INTRODUCTION

The mannich reaction is one of the most powerful tools for the synthesis of heterocyclic compound, which are crucial building blocks for the synthesis of a wide variety of nitrogen-containing drugs and natural products.[i] These are also used in polymer industry as paints and surface active agents.[ii] Mannich bases are a class of heterocyclic compounds that are obtained through the introduction of an aminoalkyl moiety in substrates having diverse structures.[iii] Medicinal chemistry is one of most important fields of application for these compounds. A large number of studies have been reporting various biological activities for mannich base such as anticancer,[iv]antimicrobial[v] anti-HIV[vi] and antimalarial activity .[vii]

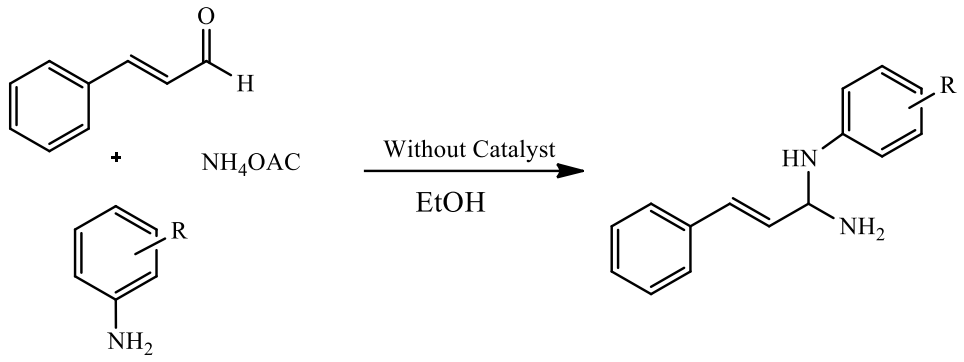
Cinnamaldehyde is used in the mannich base reaction is a flavouring phenylpropanoid compound.[viii] Cinnamaldehyde is an organic molecule having an aryl moiety, a propene chain having an aldehyde group. This has been widely used as spice and flavoring agent in foods items.[ix] Cinnamaldehyde has many biological activities like antibacterial[x,xi]antioxidant,[xii,xiii]antifungal[xiv,xv]antidiabetic,[xvi,] [xvii]antiprolifereative [xviii],[ix]and antiinflamatory.[xx,xxi]

A number of methodologies have been reported for the synthesis of mannich derivatives reactions catalyzed by various catalysts such as ceric ammonium nitrate,[xxii] rare earth perfluorooctanoate,[xxiii] silicasupported aluminum chloride[xxiv,] $BiCl_3$,[xxv] brønsted acid-surfactant-combined,[xxvi] triethylamine,[xxvii] ionic liquid triethanolammonium chloroacetate [xxviii,] solid-catalyst,[xxix]acid-ionic polymer bearing imidazolium trifluoromethanesulfonate, [PS-Im]

[OT_f],[xxx] carbon-based solid acid (CBSA),[xxxi] sodium dodecylbenzene sulfonate (DBSNa), [xxxii] CuI-catalyzed, xxxii and sulfamic acid under ultrasound irradiation.[xxxiv]

All of these methods involve various catalyst system, multistep synthesis, low yield, use of toxic reagents, excess solvent and long reaction time. Therefore, there is a strong demand for a greener, more effective, environmentally friendly and simple approach process for the synthesis of these heterocyclic derivatives.

Considering the significance of our research interest to explore novel synthesis of heterocyclic derivatives, recently herein we investigated new methodology for the synthesis of cinnamaldehyde based mannich base *viz* one-pot reaction of cinnamaldehyde, various aniline and ammonium acetate at room temperature in ethanol without using any catalyst (**Scheme 1**).



(Scheme 1)

Results and discussion

Initially, we studied the one-pot reaction of cinnamaldehyde (1 mmol), anilines (1 mmol), and ammonium acetate (1 mmol) in ethanol in the presence L-proline of as a catalyst.No product was obtained at 80 ºC temperature after 10 h (Table 1, entry 7). When the same reaction was carried out under solvent-free conditions, no product was obtained after 24 h at room temperature (Table 1, entry 12). Since the solvent has important role for progress of the reaction. Further, we have studied the selection of catalyst. Various catalysts have been used and results are summarized in **Table 1**. It has been observed that no effect on the yield of the product. Now the same reaction was carried out in ethanol in the absence of catalyst, product was obtained in 30 % yield at room temperature after 24 h (**Table 1**, entry 11). The best yield (95%) was obtained when the reaction was carried out in the absence of catalyst in ethanol at room temperature after 1 h (Table 1, entry 8). Therefore ethanol is a good solvent for the synthesis of cinnamaldehyde based mannich base.

Table 1 Effects of various parameters on the model reaction

Entry	Catalyst	Solvent	Time (h)	Temp. (°C)	Yield (%)
1	$TfOH–SiO_2$	Ethanol	24	r.t.	No product
2	CTAB	Water	24	120	30
3	DCC	THF		60	30
4	HSO_4	Ethanol	24	100	No product
5	Et_3NH	Ethanol	14	60	No product
6	SiO_2	Ethanol	10	70	trace

7	L-proline	Ethanol	24	80	No product
8	Without catalyst	Ethanol	1	r.t.	95
9	Twine-20	Water	10	90	No product
10	SLS	Water	10	100	30
11	Without catalyst	Water	24	r.t.	30
12	SLS	Without Solvent	24	r.t.	No product

After screening the parameters, the scope of the present methodology has been investigated in the synthesis of various substituted anilines. Variety of electron-donating and electron-withdrawing substituents on anilines have been used and results have been highlighted in Table 2.

Table -2. Synthesis of cinnamaldehyde mannich bases.

Entry	-R	Product	Time(h)	Yield(%)	M.P(°C)
1	H	1a	1	95	95
2	4-Cl	1b	2	80	100
3	3-Cl	1c	2	82	115
4	3-CH_3	1d	1	80	65
5	4-CH_3	1e	1	9	50
6	3-NO_2	1f	2	80	40
7	2-F	1g	1	75	65
8	3-F	1h	2	75	55
9	4-F	1i	2	80	97
10	3-Br	1j	1	68	90

We tried the same reaction in different solvent system other than ethanol like methanol chloroform, acetone and water, but low yields were obtained. Therefore ethanol is the best solvent system for the chemical reaction and gave better result with cost affected and safe for the environment. We also tried this reaction to have result in short time carried out in refluxing condition but it is not possible. On heating reagents were degrade and product was not formed.

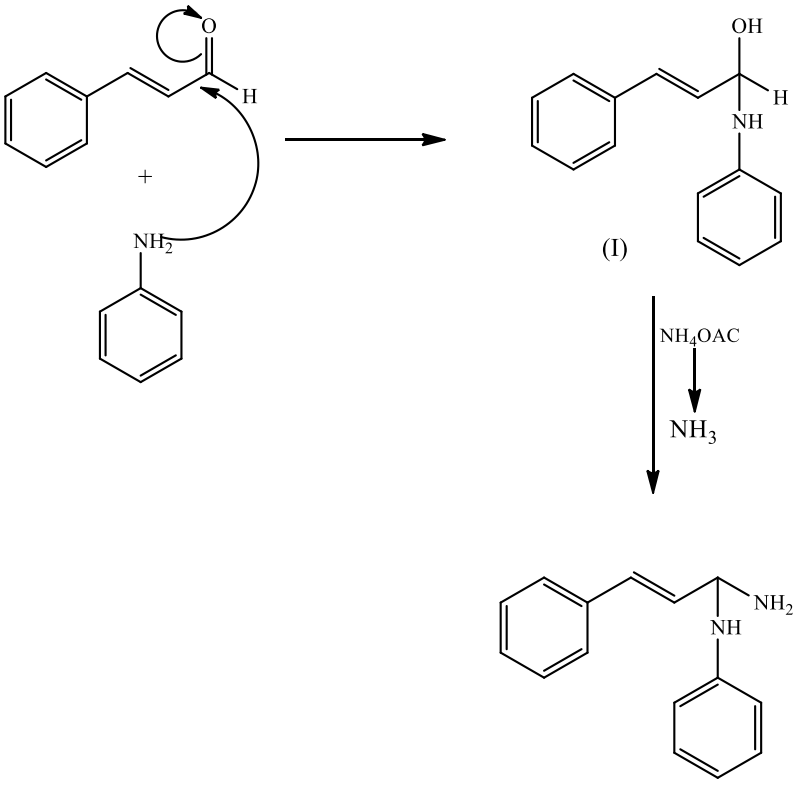
The effect of the various solvent on present methodology were also studies. When polar aprotic solvents such as acetonitrile, and were used for the reaction the desired product obtained in lesser yield (**Table 3,** entries 1 to 4), polar protic solvents such as methanol, CH_3COOH, Ethanol and H_2O, ethanol were used in the reaction then product obtained in moderate yield (Table 3, entries 5–8). We found that the maximum yield (95%) of desired product was obtained by employing ethanol as a solvent for the reaction at room temperatures (**Table 3,** entry 7). The results are shown in table 3.

Table 3. Solvent optimization

Entry	**Solvent[a]**	**Time(h)[b]**	**Yield(%)[c]**
1	THF,	1	40
2	DCM	1	30
3	1,4-dioxane	1	50
4	DMSO	1	40
5	Methanol	1	50
6	CH_3COOH	1	65
7	Ethanol	1	95
8	H_2O	1	30

a. Reaction was performed with cinnamaldehyde (1.0 mmol), anilines (1.0mmol) with ammonium acetate in different solvents.
b. Reaction time monitored by TLC.
c. Isolated yield

The plausible mechanism for the synthesis of mannich bases is shown in **Scheme 2**. In the beginning, coordinates with the carbonyl group of benzaldehyde causing its electrophonic activation, which facilitates nucleophilic attack of the amino group from aniline leading to formation of the intermediate (I) which loses a water molecule and undergoes reaction with ammonium acetate to form the desired product.



Scheme 2 Plausible mechanism for the synthesis of mannich bases.

Anti Parkinson's activity

The synthesized mannich bases were evaluated for *in-vivo* anti parkinson's activity by free radical scavenging assay and *in vivo* screening for their anti parkinson's activity by using the L-DOPA model. The synthesized mannich bases were evaluated for *in vitro* anti parkinson's activity by *In-silico* analysis method. Mice were pretreated with vehicle, a-1 (50mg/kg, i.p.), ac-1 (50mg/kg, i.p.), ap-1 (50mg/kg, i.p) and L-DOPA (30 mg/kg, i.p.) 30 min before haloperidol (1 mg/kg, i.p.). The duration of catalepsy was measured at 0, 30, 60, 90, 120, and 150 min after haloperidol administration using bar test. Both the forepaws of the animals were placed on a wooden bar elevated 3 cm above the ground. The cutoff time (time for which animal was placed on elevated bar) was 300 seconds.The results are presented in Table 4. Based on *In-vivo* study by *In-silico* analysis method, These derivatives were subjected to *in vivo* screening for their anti parkinson's activity. (mannichbases) by using *vitro In-silico* analysis method. Based on the results of *In-vivo, In-silico* analysis method, Compound 1c has shown maximum anti parkinson's activity. The estimated parameters were closely relevant to clinical parkinsonism and the drug treatment protected the diseased brain of rat. We appreciate further detailed studies with these drugs in anti parkinson's pharmacology and toxicology. From these findings, we suggest that these drug molecules can be future drugs of choice for the treatment of clinical parkinsonism.

Table 4Result of *in-vivo* anti parkinson's activity of cinnamaldehyde based mannich base

Group (n=6)	**Treatment**	**0 min**	**30 min**	**60 min**	**90 min**	**120 min**
Control	Saline + Haloperidol	1.16±0.752	65.66±8.936*	86.33±7.20*	115.33±11.00*	101.0±7.509*
Standard	L-Dopa + Haloperidol	1.33±0.516	25.0±4.857*	35.16±5.87*	28.5±5.787*	16.5±2.810*
Test 1	A1 + Haloperidol	1.83±0.752	39.0±6.449*	67.66±4.27*	86.83±8.109*	75.166±6.853*
Test 2	AC1 + Haloperidol	2.0±0.632	54.0±5.692*	73.5±8.619*	94±8.508*	87.83±9.196*
Test 3	AP1 + Haloperidol	1.5±0.547	31.16±4.956*	49.16±6.67*	73.5±8.408*	49.166±6.306*

Anti bacterial activity

Antibacterial sensitivity profile of selected compounds among the synthesized derivatives, were screened against selected strains *viz*. *Staphylococcusaureus, Bacillussubtilis,Salmonella typhi, Micrococcus luteus* and *Bacillus licheniformis* using standard drug *chloramphenicol* respectively, to compare relative activity of compounds. Zone of inhibition around the disc against the test bacterial were determined at 300µ and 600µ (1ml) concentration by disc diffusion assay as indicative of the antibacterial activity. The results are shown in Table 5.

Table 5.Result of *in-vitro* antibacterial activity ofcinnamaldehyde based mannich bases

S.No.	Compounds	**Diameter of zone of inhibition in mm**									
		S. aureus		*B. subtilis*		*S. typhi*		*M. luteus*		*B. licheniformis*	
		300 µg/mL	**600 µg/mL**	**300 µg/mL**	**600 µg/mL**	**300 µg/mL**	**600 µg/mL**	**300 µg/mL**	**600 µg/mL**	**300 µg/mL**	**600 µg/mL**
1.	1a	10	15	15	25	17	20	15	20	14	20
2.	1c	15	22	23	30	18	23	18	25	17	23
3.	1d	15	22	24	30	21	26	23	30	21	29
4.	1h	17	24	30	40	26	38	27	34	20	28
5.	Chloramphenicol	28	36	30	38	28	32	30	42	26	37
6.	DMF	--	--	--	--	--	--	--	--	--	--

Experimental

All the chemicals and solvents were purchased from Sigma-Aldrich. Melting points of the newly synthesized compounds were observed using an open capillary tube melting point apparatus. IR spectral studies have done by using FT-IR spectra in the range 400-4000 cm^{-1} of samples as KBr pellets with a Perkin Elmer FTIR spectrophotometer. Mass spectra were observed in the range 40-800 amu on a Shimadzu Japan GCMS-QP2010 Ultra apparatus. NMR spectra was recorded with a Bruker AV III spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as internal standard.

Typical Procedure for the Synthesis of Cinnamaldehyde Mannich base.

The reaction was carried out in a round bottom flask having a mixture of aniline and ammonium acetate in ethanol as a solvent. After the complete dissolution of the reactants the solution of cinnamaldehyde was added on continuous stirring resulting the product. Stirring was continued at room temperature till the reaction gets completed. Progress of the reaction was checked by TLC (Thin layer chromatography) in a 1% solvent system of hexane: ethyl acetate (9:1).
After completion of the reaction, the reaction mixture was work up by pouring it in ice a white precipitate was formed instantly then left the reaction mixture overnight for slow precipitate of the product. After that filter the reaction mixture by washing with distilled water several times removing extra ammonium acetate left in the reaction. The resulting solid was crystallizing by ethanol.

CONCLUSION

We have successfully developed a clean, safe, mild and metal-free protocol for the synthesis of the cinnamaldehyde based mannich bases using ethanol as a solvent with excellent yield. Purifications achieved with the simple procedure of filtration method by pouring reaction mixture into water. Our method has many advantages such as simple set of workup, single shot purification, clean synthesis, and approachable yield. All the synthesized compounds were investigated for their antibacterial and anti parkinson'sactivites. Importantly, the results demonstrate that the compounds are effective against various gram-negative and gram-positive

bacterial strains. We hope that the projected methodology would help for the development of more advanced antimicrobial and anti parkinson's agents in future at an alarming pace.

ACKNOWLEDGEMENTS

The authors would like to appreciate the School of Studies in Chemistry, Jiwaji University, Gwalior and the Central Library Jiwaji University Gwalior for their support.

Spectral data of synthesized compounds

3-phenyl-N-(p-tolyl)prop-2-ene-1,1-diamine (1A):- Yield = 90, Yellow solid, Melting point = 65 ºC, **Elemental Analysis Data for:** $C_{16}H_{18}N_2$, found (required %) C = 80.53 (80.63), H = 7.50 (7.61), N = 11.65 (11.75). **FT-IR (KBr):** 3405.61 (N-H), 2922.72 (C-H), 1448.74 (C=C) cm-1. **^{1} H NMR (400 MHz, $CDCl_3$)ppm:** 7.11-7.38 (J = 7.2 Hz, m, 6H), 7.39-7.60 (J = 7.6 Hz, m, 4H), 8.30 (t, J = 8.4 Hz, 1H), 11.11 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$) ppm:** 21.18, 121.03, 127.62, 128.86, 128.91, 129.08, 129.47, 129.65, 129.98, 135.87, 136.22, 143.63, 149.27, 160.91.

***N*-(4-chlorophenyl)-3-phenylprop-2-ene-1,1-diamine (1B)** Yield = 90, Light Brown, Melting point = 100 ºC, **Elemental Analysis Data for:** $C_{15}H_{15}ClN_2$, found (required %) C = 69.53 (69.63), H = 5.74 (5.84), Cl=13.60 (13.70), N = 10.73 (10.83). **FT-IR (KBr):** 3403.88 (N-H), 2923.03 (C-H), 1574.03 (C=C) cm-1. **^{1} H NMR (400 MHz, $CDCl_3$)ppm:** 6.68-7.23 (J = 7.2 Hz, m, 6H), 7.28-7.58 (J = 7.6 Hz, m, 4H), 8.6-8.25 (q, J = 8.4 Hz, 1H), 11.72 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$) ppm:** 119.74, 120.97, 126.09, 127.78, 128.02, 128.36, 128.65, 129.05, 129.12, 130.00, 130.33,134.91,135.54,145.15,153.24, 162.75.

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Received on February 29, 2020.