

SYNTHESIS, CHARACTERIZATION AND CHEMOSENSING STUDIES OF MANNICH BASE DERIVATIVES

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ABSTRACT

New Mannich Derivatives have been synthesized using Indole substituted derivatives with formaldehyde and acetophenone derivatives through condensation reaction. Reaction progress has been monitored using TLC in solvent system i.e. ethyl acetate and hexane (1:1 Ratio). The synthesized product has been characterized by IR, UV-Visible and NMR spectroscopy. The sensing properties have also been in various solvents like ethanol, methanol, acetic acid, dichloromethane and dimethylsulfoxide. Results revealed that The relative absorption intensity increases or decreases depending on solvent polarity, suggesting the ligand would be able to act as solvent polarity sensor

KEYWORDS: Mannich Base; Formaldehyde; Sensing; indole.

INTRODUCTION

Coordination complexes are so widespread that their structures and reactions are described in many ways. The central atom or ions, together with all ligands comprise the coordination sphere. The coordination chemistry of transition metal complexes is a very extensive area in the field of inorganic chemistry [1]. Mannich reaction is an important tool for synthesis of novel compounds which consists of nucleophilic addition reaction of a non enolizable aldehyde and any primary or secondary amine to produce resonance stabilized imine (iminium ion or imine salt). It is a one pot three-component condensation reaction involving active hydrogen containing compound and a secondary amine for the synthesis of β -amino carbonyl derivatives. Mannich reaction is of great importance in the amino alkylation of aromatic substrates for the synthesis and modification of biologically active compounds [2,3]. Mannich reaction depends on the nucleophilicity of substrate and the pH of reaction medium. The substituted phenols are most commonly used in the Mannich reaction; it has been difficult to undergo amino-methylation of different phenols with sterically hindered amines. Instead of direct amino-methylation the bulky aza-crown ethers were treated with the methanol solution of

formaldehyde to give N-methoxymethyl substituted aza crown ether which gave the Mannich base by the reaction. A method has been developed by Chi and co-workers using 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, para-formaldehyde and phenolic derivatives in benzene to produce double-armed diaza-crown ether in good yields without the isolation of intermediates [4]. In past decades, many new ways have been developed to synthesize highly diastereoselective and enantioselective mannich reactions. These bases have excellent characteristics and structural similarities with many of the naturally occurring biological substances. Mannich base ligands have been widely studied due to their sensitivity, selectivity and synthetic flexibility towards metal ions to form transition metal complexes. They are used as catalysts in medicines like antibiotics and anti-inflammatory agents. The presence of more electronegative nitrogen, oxygen or sulphur atoms in the ligand enhances the coordinating possibilities to form metal complexes. Transition metal complexes of Mannich bases have been used in many reactions like carbonylation, hydroformylation, reduction, oxidation, epoxidation, hydrolysis etc.

The flexibility of disposition of different donor sites is the secret behind their successful performance in mimicking

peculiar geometries around the metal centre, leading to very interesting spectroscopic properties. Optically active Mannich base complexes are especially important in enzyme catalysis. In Mannich base metal complexes, the environment at the coordination centre provides a useful range of steric and electronic properties which are essential for tuning the structure and reactivity [5, 6]. The Mannich base metal complexes containing hetero atoms like O, N, S and P have been used as effective adsorbents and corrosion inhibitors [7, 8]. The Mannich reaction has been involved in various synthetic procedures such as preparation of peptides, nucleotides, antibiotics, alkaloids, agro-chemicals, paints, resins and surface coatings and various additives and catalysts [9]. The aromatic substrates of Mannich bases can undergo amino alkylation which is of great interest for the synthesis and modification of biologically active compound owing to the amino group which can be easily converted into a variety of other functionalities [10]. The Mannich base derivatives have been used as target for the synthesis of hypnotic, anti-inflammatory, antibacterial and anticonvulsant molecules. These bases are commonly used as pharmacophores in the design development and synthesis of potent anticancer, anti HIV and chemotherapeutic drugs. It was also

observed that some drugs show enhanced activity when administered in the form of metal complexes because metal complexes have good tendency to form DNA adducts and are effective as anti-cancer agents [11-14]. Mannich base also act as important pharmacophores or bioactive leads which are further used for synthesis of various potential agents of high medicinal value which possess amino alky chain. The example of clinically useful Mannich base which consist of amino alkyl chain are cocaine, fluoxetine, atropine and biperiden. Mannich base are known to play a vital role in the development of synthetic pharmaceutical chemistry. The literature studies revealed that Mannich base are very reactive and can be easily converted to other compound for ex-reduced to from physiologically active amino alcohols. Along with biological activities Mannich base are also known for their uses in detergent, additives, polymers, surface active agents [15-18].

Chemical sensors are miniaturized devices that can deliver real time and online information on the presence of specific compounds or ions and closely associated with a molecular event. Sensor is a system that on stimulation by any form of energy undergoes change in its own state and some of its characteristics that is why it is used to analyze the stimulant [19, 20]. The optical and photo-physical changes in a molecule are

found more valuable in this regard. The techniques used most widely in chemical sensor are optical absorption, luminescence, redox potential etc. These receptor molecules exhibit selective response to specific ions or neutral species to be used as chemosensors. Various neutral and ionic species or transition metals widespread used in physiology, medical diagnostics, catalysis and in environmental chemistry. In past few years, many of the sensors for transition metal ions were developed due to the better understanding in biological systems. The transition metal ions in heavy industries are prime target for the development of metal sensor [21, 22]. As cations and anions are prevalent in chemosensors are beginning to find many applications. Ag^+ is useful in radio-immunotherapy and photographic technology and reduces the bacterial and fungal infection by inhibiting the growth of bacteria and fungi. Ag^+ ion has been used in cancer treatment, deodorizing clothes and as an agricultural sterilizing agent. Hg^{2+} cause health problems like digestive, kidney and especially neurological diseases. Co^{2+} is an essential element required for the coenzyme vitamin B_{12} , Cu^{2+} is necessary for the growth, development, and maintenance of bones and connective tissues. It is noteworthy that detection of ions is vital as many industrial and agricultural processes can lead to the release of ions to the environment, which causes devastating effects. Efforts have been

made towards finding inexpensive, reliable and simple ways of detecting ions in solution. Therefore, finding new selective ion receptor systems is an important goal which involves sensor [23].

EXPERIMENTAL WORK

Chemicals

Isatin and Acetophenone were purchased from Lobachemie, Formaldehyde (SDFCL). All the solvents were of AR and LR grade which were used without further purification. Precoated aluminium sheets (silica gel 60 F254, Merck Germany) were used for thin layer chromatography (TLC) and spots were visualized under UV light.

Instruments/Equipment

The reactions were monitored by TLC using UV cabinet for visualization. Melting point was recorded using an electro-thermal melting point apparatus and were uncorrected. Electronic spectra were achieved with T80+ UV-visible spectrophotometer. IR spectra were recorded in the range of $4000\text{-}400\text{ cm}^{-1}$ on Agilent technologies instrument as neat compound. ^1H NMR spectra were recorded on Bruker DPX-300 NMR.

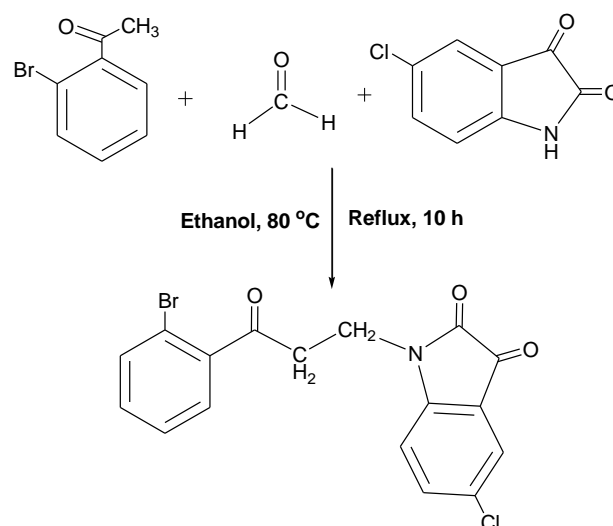
Synthesis of Mannich Base (M_1)

To the solution of chloro-isatin (0.180 g) in 15 ml ethanol in 250 ml two necked round

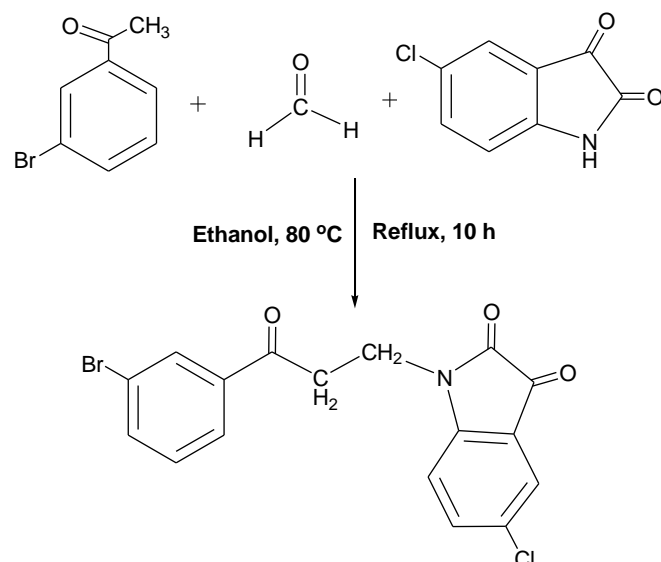
bottom a solution of formaldehyde (0.03g) was added drop-wise and the mixture was refluxed. After few minutes a solution of 2-bromoacetophenone (0.197 g) in ethanol was added to the above solution with continuous stirring and refluxed for 10 h. The progress of the reaction was monitored by using TLC (ethyl acetate: hexane, 1:1). The solution was allowed to stand at room temperature overnight. The orange precipitate was subsequently filtered and washed thoroughly with ethyle acetate. The synthesis of Mannich base ligand (**M₁**) is represented in **Scheme 1**.

Synthesis of Mannich Base (**M₂**)

0.180 g of isatin in 15 ml ethanol was added to a solution of formaldehyde (0.03 g) in 250 ml two necked round bottom flask in 5 ml ethanol and the mixture was refluxed. After few minutes a solution of 3-bromoacetophenone (0.197 g) in ethanol was added drop wise to the above solution with continuous stirring and refluxed for 10 h. The progress of the reaction was monitored by using TLC (methanol: chloroform, 1:1). The solution was allowed to stand at room temperature. The orange precipitate was subsequently filtered and washed thoroughly with ethyl acetate. The synthesis of Mannich base ligand (**M₂**) is represented in **Scheme II**.



Scheme I. Synthesis of Mannich Base (**M₁**)



Scheme II. Synthesis of Mannich Base (**M₂**)

RESULTS AND DISCUSSION

All the synthesized Mannich Base (**M₁** and **M₂**) are stable in air. All the compounds are soluble in Methanol, Ethanol and acetic acid. The solubility of the compounds in different solvents is given in **Table 1**. The reaction was monitored by thin layer chromatography (TLC) in solvent system in ethyl acetate:

hexane (1:1) for ligand. The molecular weight, analytical data, molar conductance, colour, % yield and melting point are presented in **Table 2**.

Table 1. Solubility of the Mannich Base (**M₁** and **M₂**)

Solvents	Mannich Base (M₁)	Mannich Base (M₂)
Methanol	√	√
Water	√	X
DCM	X	X
Ethanol	√	√
Petroleum Ether	X	√
Chloroform	√	√
Hexane	X	X
Acetic acid	√	√

Infrared Spectra

The relevant IR spectral bands of Mannich base ligand shown in **figure 1**. The stretching frequency appears at 1680 cm^{-1} and 1687 cm^{-1} corresponds to $\nu(\text{C}=\text{O})$ for ligand (**M₁**) and ligand (**M₂**), respectively [24-25].

¹H NMR Spectra

The ¹H NMR spectra of ligands was exhibited resolved signals. A Signal appears in the range of 2.51-2.76 ppm for the ligand (**M₁**) and (**M₂**) in the form of multiplet corresponds to methylene group ($-\text{CH}_2$) protons. The appearance of signal in the range of 3.81-3.94

ppm for ligand (**M₁**) and (**M₂**) also attribute to methylene proton as multiplet. The aromatic protons appeared as multiple signals for both the ligands (**M₁**) and (**M₂**) between 7.61 and 8.51 ppm. [26-28].

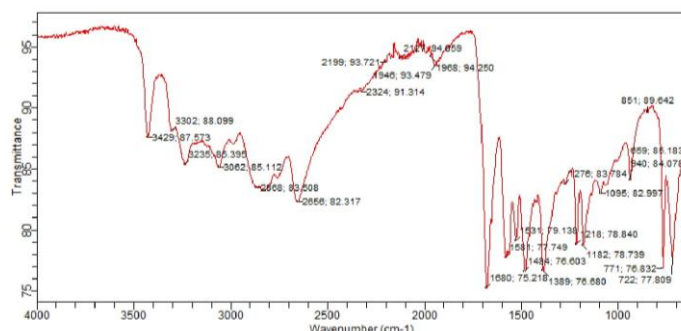
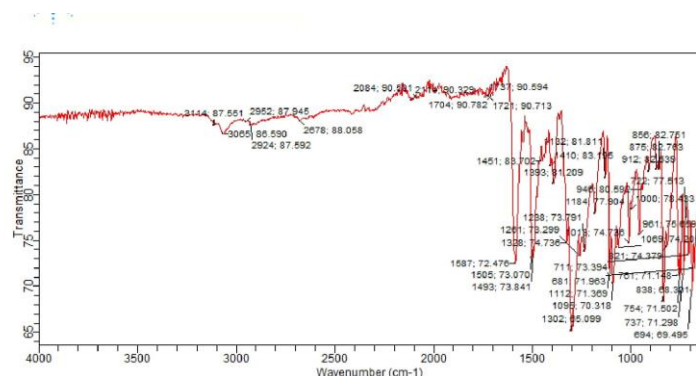


Figure 1. IR spectra of Mannich Base (**M₁** and **M₂**)

CHEMOSENSING PROPERTIES

The photophysical sensitivity of Mannich base ligand (**M₂**) was studied towards various solvents of different polarity in order to find out its spectral properties in organic solvents (**Figure 2 and Table 3**).

Table 2: Molecular weight, analytical data, colour, % yield and melting point.

Compounds (Mol. Wt.)	Yield (%)	Colour	M.P. (°C)	Analytical data (% Calcd).			
				C	H	N	O
[C ₁₇ H ₁₁ BrClNO ₃], M ₁ (392.63)	89	Orange	195	52.00	2.82	3.57	
[C ₁₇ H ₁₁ BrClNO ₃], M ₂ ,(392.63))	86	Yellow	132	80.7	4.76	13.33	

Result showed that with increasing the polarity of solvent there was a red-shift or bathochromic shift in absorbance maxima of ligand. The absorbance maxima in dimethyl sulfoxide and acetic acid were located at 394.29 and 377.52 nm where as in less-polar solvents such as acetonitrile and chloroform, there was a hypochromism was observed and located at 393.84 and 371.07 nm. However on increasing the polarity of solvent bathochromic shift was observed which indicate that the ground state is less polar than the singlet excited state. Since dipole moment of the molecule increased upon excitation, the excited molecule is better stabilized in polar solvent, due to large dipole-dipole interactions and intermolecular hydrogen bonds between compound and solvent molecules [29].

Table 3. Photophysical data of the Mannich base ligand (M_2)

Solvent	λ_{max}	Absorbance
Methanol	394.84	0.595
DMSO	394.29	0.377
Acetic acid	377.52	0.978
Acetonitrile	393.84	0.272
Ethanol	395.84	0.435
Chloroform	371.07	0.142

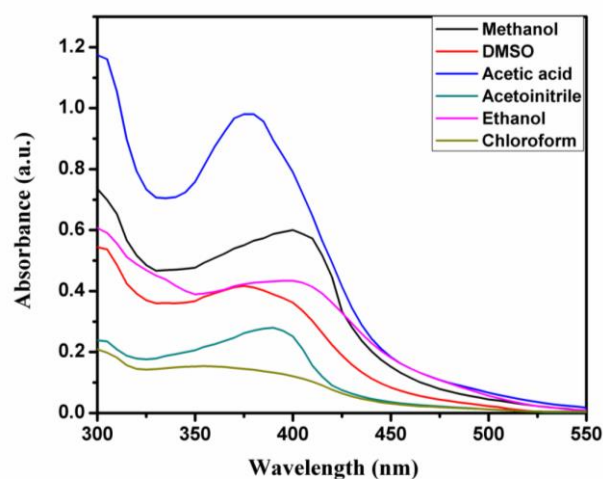


Figure 2. Absorbance spectra of Mannich Base ligand (M_1) in different solvent.

CONCLUSIONS

In this project report, we have developed a novel Mannich base chemosensor sensitive to solvent polarity, pH and selective to Fe^{2+} ion. The two ligands (M_1) of Mannich base were synthesized. These compounds were characterized by UV-VIS, IR and 1H NMR spectral analysis. The Chemosensing property of the ligand was investigated by UV-Visible measurement. The relative absorption intensity increases or decreases depending on solvent polarity, suggesting the ligand would be able to act as solvent polarity sensor.

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