# Design a New and Efficient Approach Towards The Synthesis Mannich Bases of 2-arylimidazo[1,2-a]pyridines.

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**Abstract**

*6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine has been successfully synthesized from 4-chloroacetophenone and 5-methyl, 2-aminopyridine in one step. Iodine in present of $NH_4OAc$ reports 100% conversion with good yield of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine in short time period. This synthesized compound were used for mannich bases preparations which gives good yield of target molecule. Series of mannich bases of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine with aryl/alkyl amines were prepared in good and efficient yield. Present approach having significances with faster reaction, excellent and clean yield of mannich bases derivatives, mild reaction condition, easy work-up procedure, use of non-toxic, and inexpensive catalyst.*

**Keywords:** Imidazo-pyridine, Mannich bases, $I_2$, $NH_4OAc$, Efficient approach etc.

## Introduction

Mannich bases containing bridged N-atom exhibit pronounced biological activities. The study of mannich reaction attracted a great deal of attention to the chemists because it plays a vital role owing to their wide range of pharmacological and industrial applications. Mannich bases are also employed as intermediate in chemical synthesis [1-3]. Mannich base derivatives with bridge N-atom have been found to be potent drug in medicinal science and possess wide range of biological activities like anticancer, antibacterial, antimalarial, analgesic etc. Mannich bases have gained important because of their technological applications in polymer chemistry [4], especially as paints and surface-active agents and exhibits complexation characteristic with many transition metal ions. Over the years, there has been much contraversy about the mechanism of the Mannich reaction. Studies of the reaction kinetics have led to the following mechanistic proposals.

Imidazo[1,2-a]pyridines are indispensable biologically active nitrogen containing heterocyclic scaffolds and exhibit a wide range of biological activities [5]. These are broadly investigated in materials science and organometallics [6]. Imidazo[1,2-a]pyridines are recognized as a 'privileged scaffold' because these have significant importance in pharmaceutical industry owing to their interesting biological activities such as anti-cancer [7], anti-viral [8], anti-inflammatory [9], analgesic, anti-pyretic [10], anti-ulcer [11] and anti-bacterial [12]. Prospective radio ligands for positron emission tomography (PET) for b-amyloid in Alzheimer's disease based on imidazo[1,2-a] derivatives have been widely reported [13]. They also act as GABA and benzodiazepine receptor agonists [14] and cardiotonic agents [15]. These structures are also found in clinical drugs such as alpidem [16], zolpidem [14], olprinone [17], zolimidine

[10] and anti-HIV drug (GSK812397) [18], (Fig. 1). Furthermore, 2-(2-hydroxy phenyl)imidazo[1,2-a]pyridines exhibit excellent excited state intramolecular proton transfer (ESIPT) [19] thereby embracing significance in the field of optoelectronics. Prevalence of these skeletons in biologically active compounds continues to give chemists a momentum to develop novel methods for their synthesis.

Owing to the attractive properties of imidazo[1,2-a]pyridines, various methods to synthesize this core have been developed and reviewed [20 a-c]. Initial coupling reaction of endocyclic nitrogen of 2-aminopyridine with various reagents such as acetophenones [20-d] a-haloketones [20-e] nitroalkenes [20 f], a diazoketones [20-g], alkynes derivatives [20-h] etc followed by cyclization via exocyclic amino group generates a variety of imidazo[1,2-a]pyridines. These reactions occur in the presence of various Bronsted or Lewis acids [21,22] metal catalysts (Cu [23], Fe [24], Zn [25]) and a carbocatalyst graphene oxide [26]. Few literature reports are available for the synthesis of 2-arylimidazo[1,2-a]pyridines from 2-aminopyridine and aryl methyl ketones

In the present report we have synthesis mannich bases of imidazo pyridine derivatives. At first our work start with synthesis of imidazo-pyridine from 2-amino, 5-methyl pyridine and 4-chloro acetophenone. After words, this can be used for synthesis of mannich bases reacting with various secondary amines and formaldehyde. We have following the efficient and an eco-friendly procedure which reports good yield of product in short time. All synthesized compounds conformed through spectral analysis.

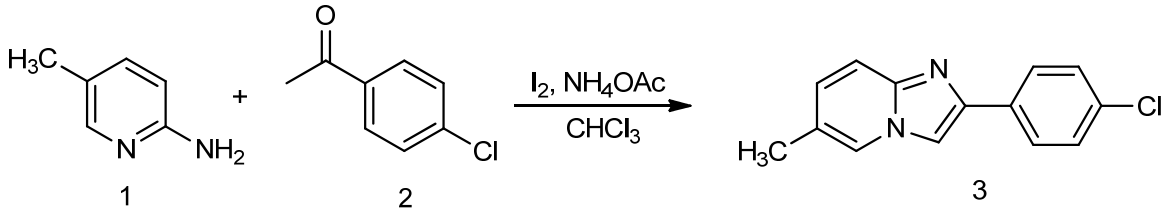
**Experimental Work**

All the chemicals used for synthesis were of LR (Laboratory Reagent) grade and used after further purification. All solvents were obtained from commercial sources and were distilled from appropriate agents prior to use it. All the melting points of prepared compounds were determined in open capillary tubes and are uncorrected. The IR spectra (in $cm^{-1}$) were recorded on a perkin-Elmer spectrophotometer in KBr pellets. $^{1}$HMR spectra were recorded on Varian Gemini (200 MHz) spectrometer using DMSO-$d_6$ as solvent and TMS as internal standard.$^{13}$C-NMR spectra recorded on 50 MHz in DMSO-$d_6$ solvent, in δ ppm. All chemical shifts values are reported in δ scale downfield from TMS. Homogeneity of the compound was checked by TLC on silica gel plates.

**General procedure for the synthesis of Mannich bases of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine with aryl/alkyl amines.**

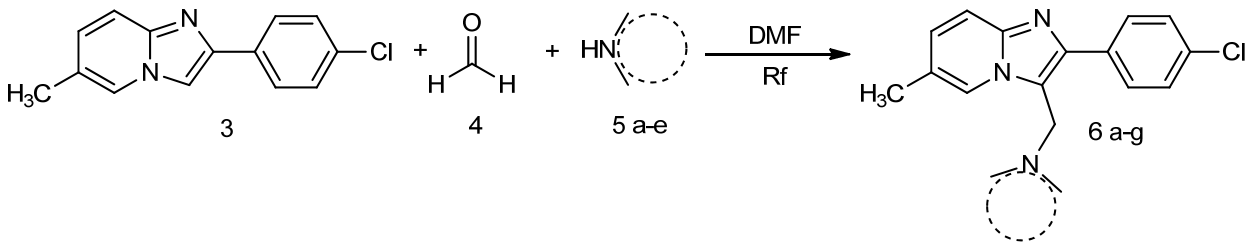
***Step I: Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine.***

Make a mixture of 5-methyl 2-aminopyridine **1** (1.2 mmol) and 4-chloroacetophenone **2** (1.0 mmol) in a 100ml RB. Add $I_2$ (1.0 mmol) and $NH_4OAc$ (2.0 mmol) in 15 ml $CHCl_3$. Resulting mixture was stirred at room temperature for appropriate time, after the completion of reaction (monitored on TLC) near about 1.30 h reaction mass was poured on ice cold water, which led to the formation ppt of the desired product 2-phenylimidazo[1,2-a]pyridine **3**. Filter the product wash it with water at several times and recrystallized from acetic acid. Product obtained in good yield as 85%.




***Step II: Synthesis of imidazo [1,2-a]pyridine nucleus, the preparation of 2 -(4'chlorophenyl)-6-methyl-(3-N, N'-diaryl/dialkyl amino methyl)-imidazo [1, 2-a]pyridines.***

To a solution of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine **3** (0.1 mole) in DMF, formaldehyde (0.1 mole) **4** was added under stirring. The reaction-mixture was stirred at RT for 0.5 hr to complete the reaction of formaldehyde and to yield methylol derivative of **3**. To this, solution of secondary amines **5a-g** (0.1 mole) in DMF was added drop wise and refluxed for reported time. Completion of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured into ice cold water and filtered off and washed with hot water. Finally, it was dried and purified by recrystallization from hexane to give **6a-g**.




**Spectral analysis of *6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine 3***

*IR (KBr, cm-1):* 2958 ( C-H str, sym); 1466 ( C-H def, asym.); 1368 ( C-H def, asym.); 3650 ( C-H Str. Aromatic ); 801 ( C- H, str., o.p.p. def. ) ; 1488 ( C=C str. ) ; 1350 ( C-N str. ); 760 ( C-Cl Str.) : 1648 ( C=N Str.). *1H-NMR* ( DMSO-d6, d ppm); 2.3 (s, 3H, –CH3 ); 7.02-7.94 ( m, 8H,Ar-H ). m/z: 44, 65, 77, 92, 110, 219, 242. *Anal. Calcd*. For C14H11ClN2 Require : C, 69.28, H, 4.53, N, 11.54 %; Found: C, 69.26, H, 4.52, N, 11.50 %.

***Spectral analysis of 2 -(4'chlorophenyl)-6-methyl- (3-N, N'-methyll amino methyl)-imidazo [1, 2-a]pyridines 6a***

*IR ( KBr, cm-1 ):* 2881 ( C-H, str., sym ); 1361 ( C-H, def, sym.); 1442 ( C-H def, asym.); 3090 ( C-H, str., aromatic ); 1487 ( C=C, str. ) ; 1174 ( C-N, str. ); 1633 ( C=N ); 796 (C-Cl). *1H-NMR* ( CDCl3, d ppm) ; 2.24 (s, 6H, –CH3 ); 7.05-8.10 ( m, 8H, Ar-H ); 3.8 ( s, 2H, Ar-CH2 ). m/z:44,65, 77, 92, 110, 114, 128, 149, 165, 178, 192, 205, 219, 232, 239, 255, 267, 282, 299. *Ana. cacd*. for C17H18ClN3: Required : C, 68.11; H, 6.05; N, 14.02%; found : C, 68.10; H,6.03; N, 14.00%.

**Result and Discussion**

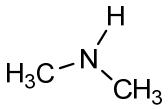
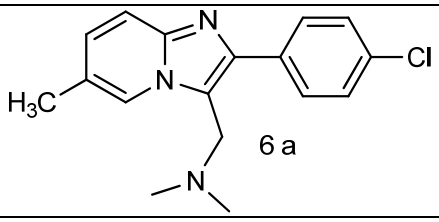
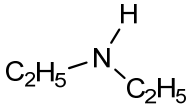
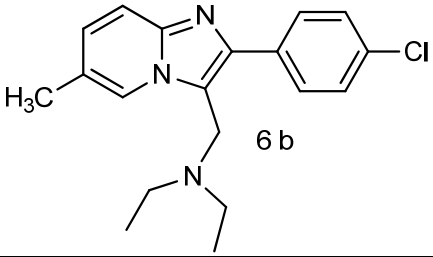
Mannich bases and imidazo-pyridine exhibits numerous pharmacological activities and its an important class of organic chemistry. Due to this we take attention to synthesis mannich bases of imidazo-pyrimide derivative. In the first step we have synthesized *6-methyl-2-(4' chlorophenyl)imidazo[1,2-a]pyridine* from 4-chloro acetophenone and 5-methyl,2-amino pyridine. This transformation done through

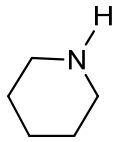
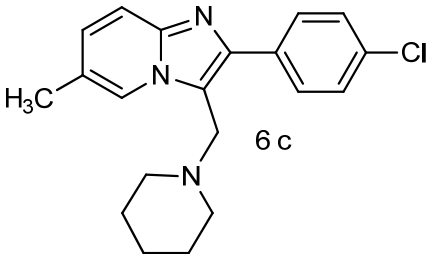
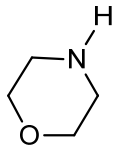
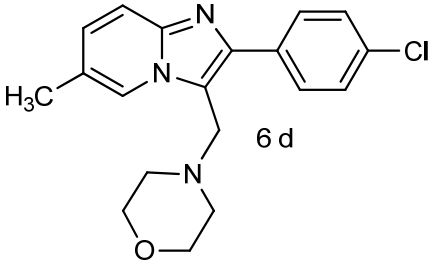
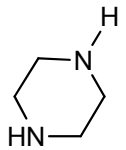
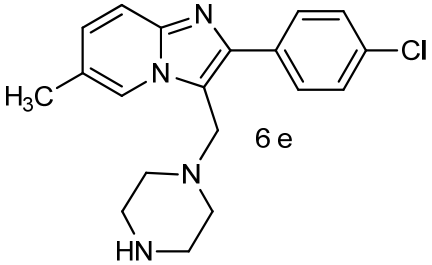
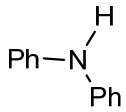
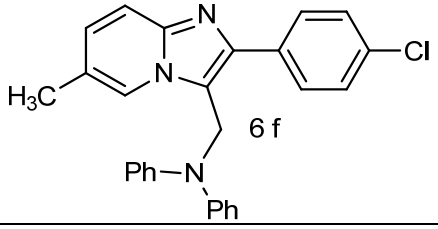
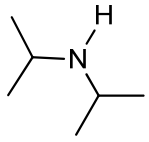
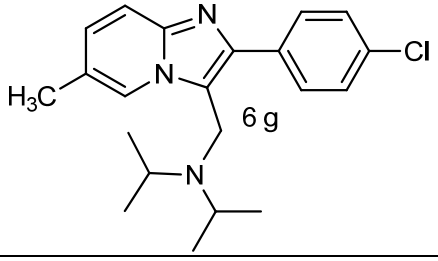
using iodine and $NH_4OAc$, this is eco-friendly and efficient process than other reported methods in literature. It gave 100% conversion with 86% of yield. Structure of synthesized *6-methyl-2-(4' chlorophenyl)imidazo[1,2-a]pyridine* ***3*** conformed by comparing spectral data and analytical data with literature. This prepared compound used for next step to synthesis mannich bases, by means reacting with various secondary amines and formaldehyde in DMF solvent. Conversion of reactant in to product can done through stir at 80°C. Under the optimized reaction conditions, we have synthesis serious of mannich bases (6a-g) from imidazo-pyridine.

Our work start with synthesis of mannich bases of imidazo-pyridine (1mmole) from dimethyl amine (1 mmole) and formaldehyde (1 mmole) in DMF solvent, it gave 100% conversion with 70% yield of respective product (Entry 1). Furthermore, under the same reaction conditions dietyh amine and pipyridine reports successful conversion with 68% & 80% yield respectively (Entry 2 & 3), diethyl amine shows somewhat minute yield that may be due to free motion of diethyl group which produce steric hindrance. Additionally, we also reports efficient yield of mannich bases from morphine and piprazine (Entry 4 & 5) as 70 and 82% yield respectively. Under the same reaction conditions reaction of diphenyl amine and di(isopropyl)amine with imidazo-pyridine (1 mmole) and formaldehyde (1 mmole) in DMF gave 72 and 75% of yield respectively (Entry 6 & 7). All synthesized compounds conformed through the comparing spectral and analytical data with data available in literature, from this in clearly conclude that the synthesized compounds were achieved the target.

From the result obtained in given work shows given process is an efficient, eco-friendly and rapid for the mannich bases of imidazo-pyridine. Present protocol is an easy and applicable to many more secondary amines without producing any side products. Additionally, result reveals that current process good for both aliphatic and aromatic amines, it also better in case of cyclic and acyclic amines. Analytical data of synthesized compounds were summarized in table given below.

**Table: Physical and Analytical data of synthesized compounds 6 a-g.**

| Entry | Secondary amines | Product | Mol. Formula | Melting point in °C (reported) | Yield (in %) |
|---|---|---|---|---|---|
| 1 |  5a |  6 a | C17H18ClN3 | 171 (170-172) | 70 |
| 2 |  5b |  6 b | C19H22ClN3 | 150 (150-151) | 68 |

| | | | | | |
|---|---|---|---|---|---|
| 3 |  5c |  6 c | C19H20ClN3 | 169 (168-170) | 80 |
| 4 |  5d |  6 d | C19H20ClN3 | 152 (150-152) | 70 |
| 5 |  5e |  6 e | C19H21ClN4 | 190 (189-191) | 82 |
| 6 |  5f |  6 f | C27H22ClN3 | 212 (210-212) | 72 |
| 7 |  5g |  6 g | C21H26ClN3 | 179 (180-182) | 75 |

**Conculsion**

In conclusion, we have developed a simple and efficient method for the synthesis of mannich bases from imidazo-pyridine. We have report conversion of acetophenone to imidazo-pyridine by reacting it with 2-aminopyridine which successful prepared in one step. For the given transformation we have used iodine and $NH_4OAc$ which is key of our work. The advantages of the present technique are the operational simplicity, high efficiency, no side products formation, easy of workup procedure, less reaction time, thus suitable for large-scale production of mannich bases derivatives. Various synthesized moieties are important pharmacophores in several pharmaceutically important compounds and useful intermediate for synthesis of a wide variety of bioactive natural products. We present our protocol as an

efficient and simplest alternative to the current methods of mannich bases derivative of imidazo-pyridine preparations.

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