



## Ionic liquid mediated synthesis of Schiff bases under reflux condition

Ganesh S. Kulkarni, Priyanka L. Anandgaonker, Sidharth D. Janrao, Digambar D. Gaikwad and D. M. Janrao\*

Department of Chemistry, Govt. College of Arts & Science, Aurangabad(MS), India

\*Department of Chemistry, JES College Jalna, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad(MS), India

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### ABSTRACT

Imidazolium based ionic liquid catalyzed an efficient synthesis of  $N^2$ -arylbenzylidenyl isonicotinic acid hydrazide derivatives under reflux condition. This protocol offers several advantages including high yields of pure Schiff base products in short reaction time and easy experimental work-up procedure. Ionic liquid can be recovered and reused up to four cycles without loss of catalytic activity.

**Key words:** Synthesis of Schiff bases derivatives, dicationic ionic liquid, reflux condition, reusability of catalyst.

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### INTRODUCTION

Owing to the importance of Schiff bases ligands and its metal complexes in many application including biological [1], clinical [2], analytical [3], catalytical [4] as well as their wide spread use as model compounds for the study of active site of metallo-enzymes [5], solid phase extraction of metal ions [6] to various types of polymerization [7], preparation of ion selective electrode [8] etc., each year many literature have been published for the synthesis of these compounds through two component reactions to their applications in different fields.

Tuberculosis is still a serious health problem that causes the death of about three million world people every year. It is an infection bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs. It can be treated with Anti-TB drugs which are classified in to first and second line drugs classes. Isonicotinylhydrazine is an organic compound that is the first line medication in prevention and treatment of tuberculosis. Isonicotinylhydrazine has also an antidepressive effect, being one of the first antidepressive drugs discovered. It is also used in a wide range of bacterial disease [9-12]. Isoniazid develops resistance quickly due to which it is never used on its own to treat active tuberculosis. Increasing the resistance of *Mycobacterium tuberculosis* strain against anti-mycobacterial drugs indicates the needs for new effective anti-tuberculosis drugs. Structural modification of the isonicotinic acid hydrazide provides lipophilic adaptations of the drugs in which the hydrazine moiety of the parent compound has been chemically blocked from the deactivating process of  $N^2$ -acetylation by N-arylaminoacetyl transferases [13]. Hydrazones derived from condensation of isoniazid with pyridine aldehydes and ketones have been found to show better anti-tubercular activity rather than INH. This was proved by its ability to form stable complexes with *d* and *f* block metal ions [14-16].

In the recent years, the use of ionic liquid as a recyclable reaction medium in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, high

thermal stability and rate enhancer [17-20]. Ionic liquid also called “the designer of solvent” has been extensively employed for various organic transformations including Diels-Alder [21], aldol condensation [22], Hantzsch condensation [23], Mannich reaction [24]. Moreover an ionic liquid with the acidic counter ions is also found to be an efficient medium in synthetic organic chemistry [25, 26].

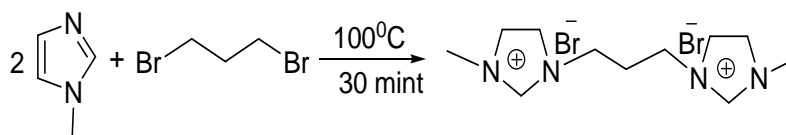
In view of the previous trend towards the development of clean and environmental friendly green chemical process and in conjunction with ongoing work in our laboratory on the preparation of new Schiff bases and their metal complexes, here we report the new methodology with prepared ionic liquid 3-methyl-1-[3-(methyl-1H-imidazolium-1-yl) propyl]-1H-imidazolium dibromide ionic liquid catalyzed synthesis of Schiff bases by one pot condensation of isonicotinyldiazine with aromatic aldehydes under reflux condition.

### EXPERIMENTAL SECTION

All used chemicals were purchased from Merck or S.D. Fine chemicals. Melting points were determined on an electrochemical digital melting point apparatus. The formation of the product was determined by thin layer chromatography. Products were characterized by comparison of spectroscopic data (UV-Visible, FT-IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR spectrum) and melting points with authentic samples. The wavelength of absorbance was determined by UV-Visible spectrophotometer [JASCO 503] using a quartz cuvette and ethanol as reference. The IR spectra were recorded on FT-IR spectrophotometer [JASCO, FT-IR/4100] Japan using dry KBr as standard reference. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a 400 MHz FT-NMR spectrometer in CDCl<sub>3</sub>/DMSO as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me<sub>4</sub>Si) as an internal standard. Elemental analyses were done using Perkin Elmer 2400CHN analyzer.

#### Synthesis of ionic liquid:

A mixture of 1, 3-dibromopropane (10 mmol) and N-methyl imidazole (20 mmol) was stirred at room temperature in 15 minutes (scheme1). Further the mixture was heated up to 100°C for 30 minutes, keeping a guard tube at mouth of round bottom flask. The progress of reaction was monitored by TLC. A clear colorless viscous liquid was formed. It was cooled and washed with ether to remove unreacted bromide. The viscous liquid was dried using vacuum pump.

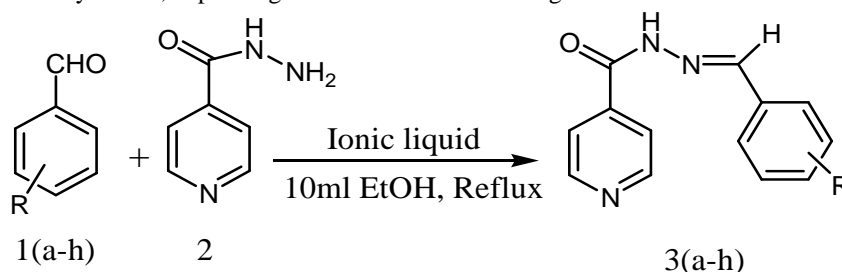


Scheme1: Synthesis of 3-methyl-1-[3-(methyl-1H-imidazolium-1-yl) propyl]-1H-imidazolium dibromide

The <sup>1</sup>H-NMR spectrum of above ionic liquid sharp singlets at 3.86 & 3.98 δ for methyl group and three different protons in imidazole moiety such as 9.45, 7.65 and 7.72 respectively.

#### General procedure for the synthesis of Schiff base derivatives:

Eight Schiff base were synthesis, depending on the chemical reaction given in scheme2.



Scheme2: Synthesis of Schiff bases using ionic liquid under reflux condition

INH(10.0 mmol) and ionic liquid (1.0 mmol) was dissolved in 10 ml of ethanol stir for some time to give a clear solution to this aromatic aldehydes (10.0 mmol) was added drop wise over 5 min. The resulting reaction mixture

was refluxed for an appropriate time as indicated in Table 2. After completion of the reaction it was allowed to cool slowly and stand overnight. Obtain crystalline solid was filtered off. Finally washed with hot water, dried and recrystallized to afford pure crystals. The products were confirmed by comparisons with authentic samples, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and melting points.

Spectral data of representative compounds:-

**(3a)**:- IR (KBr disk,  $\nu_{\text{max}}$ ): 3431.4 (CO-NH-), 2946.0 (C-H, aromatic), 1727.5 (C=O), 1688.4 (C=N), 1599.2-1619.6 (C=C), 1227.2 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR(DMSO-400MHz)  $\delta$ =11.81 (s,2H,CO-NH-), 8.71 (s,2H,CH=N), 7.55-7.83 (m,8H,Ar), 3.49 (s, 5H), 2.95-2.91 (s, 2-CH<sub>3</sub>);  $^{13}\text{C}$  NMR (DMSO-400MHz)  $\delta$ = 163.09, 151.65, 150.20, 149.90, 140.78, 128.66, 128.51, 123.20, 121.13, 111.71, 56.05, 40.03, 39.82, 38.99; UV/Vis(DMSO)nm: 410, 370nm, Anal Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O: C, 67.16. H, 5.97. N, 20.89%. Found: C, 67.21. H, 5.89. N, 20.81%.

**(3d)**:- IR (KBr disk,  $\nu_{\text{max}}$ ): 3435.2(CO-NH-), 3209.5 (-NH), 3035.9 & 2950.1 (C-H, aromatic), 1673.6 (C=O), 1602.8 (C=N), 1550.7 (C=C), 1295.0 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR(DMSO-400MHz)  $\delta$ =12.32 (s,2H,CO-NH-), 8.81 (s,2H,CH=N), 7.16-8.04 (m,8H,Ar), 3.41 (s, 5H);  $^{13}\text{C}$  NMR (DMSO-400MHz)  $\delta$ = 161.71, 150.30, 147.71, 140.31, 139.85, 132.98, 128.90, 128.87, 121.50, 40.02, 39.01, 39.60, 39.39; UV/Vis(DMSO)nm: 362nm, Anal Calcd for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: C, 61.39. H, 4.18. N, 19.53%. Found: C, 61.43. H, 4.16. N, 19.49%

**(3e)**:- IR (KBr disk,  $\nu_{\text{max}}$ ): 3421.3 (CO-NH-), 3250.4 (-NH), 3009.8 & 2953.5 (C-H, aromatic), 1680.2 (C=O), 1624.3 (C=N), 1546.2 (C=C), 1274.4 (C-O) $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR(DMSO-400MHz)  $\delta$ =12.321 (s,2H,CO-NH-), 8.813 (s,2H,CH=N), 7.165-8.043 (m,8H,Ar), 5.121 (s, aromatic C-OH);  $^{13}\text{C}$  NMR (DMSO-400MHz)  $\delta$ = 163.21, 140.23, 149.52, 149.23, 122.33, 123.50, 115.98, 150.21, 143.13, 131.20, 122.5, 161.56, UV/Vis(DMSO)nm: 374nm, Anal Calcd for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 64.73. H, 4.56. N, 17.42%. Found: C, 64.52. H, 4.59. N, 17.39%

**(3f)**:- IR (KBr disk,  $\nu_{\text{max}}$ ): 3446.7 (CO-NH-), 3207.76 (-NH), 3039.8 & 2993.5 (C-H, aromatic), 1689.5 (C=O), 1649.4 (C=N), 1599.2 (C=C), 1227.2 (C-O) $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR(DMSO-400MHz)  $\delta$ =12.321 (s,2H,CO-NH-), 8.813 (s,2H,CH=N), 7.165-8.043 (m,8H,Ar);  $^{13}\text{C}$  NMR (DMSO-400MHz)  $\delta$ = 163.23, 160.32, 149.72, 149.84, 143.51, 141.11, 132.23, 130.26, 122.89, 122.87, 121.72, 116.13, 114.58, 55.92; UV/Vis(DMSO)nm: 374nm, Anal Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 65.88. H, 5.09. N, 16.47%. Found: C, 65.83. H, 5.12. N, 16.44%

## RESULTS AND DISCUSSION

Here we present our results for the synthesis of Schiff base derivatives with ionic liquid as the catalyst under a variety of reaction conditions. The reaction between isoniazide and 4-Chloro benzaldehyde was used as a model reaction to afford the Schiff base (3b). The results are recorded in Table 1.

**Table 1: The synthesis of Schiff bases under various reaction conditions**

Sr. No.	Catalyst/solvent Reaction conditions	Time	Yield <sup>a</sup> (%)
1	5 mL of MeOH + no catalyst RT	6h	10
2	5ml of EtOH+ no catalyst RT	6h	15
3	10ml of EtOH +no catalyst under reflux condition	5h	53
4	10ml of EtOH +acetic acid under reflux condition	2.5h	81
5	10ml of EtOH +IL100mg under reflux condition	1h	85
6	10ml of EtOH +IL150mg under reflux condition	30min	94
7	10ml of EtOH +IL200mg under reflux condition	25min	94

<sup>a</sup>Isolated yield

When we carried out reaction in 5ml methanol at room temperature very less amount of product was obtained then we replace solvent by ethanol at similar reaction condition we obtained 15% yield of product. In contrast, when we carried out reaction at reflux condition product yield was increased to 53%. It was clear from Table1; the best results were obtained using 150mg of ionic liquid in 10ml ethanol at reflux condition. With increase the concentration of ionic liquid the yield of the desired product was found to be constant. Using these optimized conditions the condensation reaction between aldehydes and isoniazide preceded well (scheme1) and the desired product were obtained in good to excellent yield.

Scope and general applicability of the present methodology were demonstrated by subjecting a broad range of structurally diverse aromatic aldehydes, having electron withdrawing and electron donating groups as well as hetero

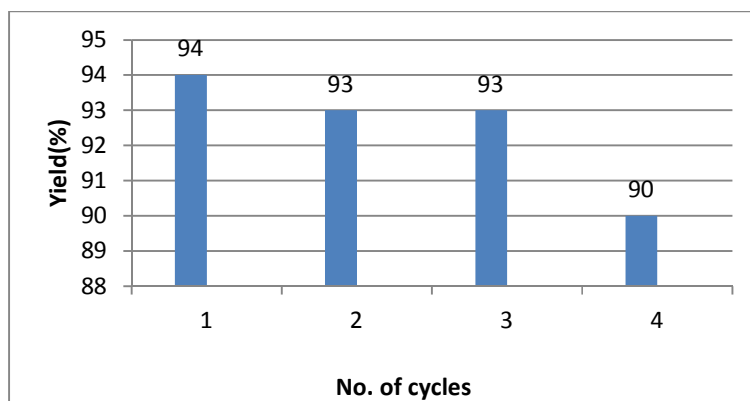
aromatic aldehydes, with INH under the reflux condition in the presence of 150 mg IL. All the reactions were monitored by TLC and taken to completion. The time taken for the completion of each conversion, aldehyde employed, isolated yields and melting points of products are summarized in Table 2. It can be observed that all the aldehydes have reacted in short reaction times (30–40 min) under these conditions to afford Schiff bases in very good to excellent yields. The process was tolerated well by all the aldehydes irrespective of the nature of substituent present in them.

**Table 2: Synthesis of Schiff bases under reflux conditions in IL using variously substituted aromatic aldehydes**

Compound	RCHO	Time <sup>a</sup> (min)	Yield <sup>b</sup> (%)	M.P.(°C)	
				Found	Reported
3a	4-ClC <sub>6</sub> H <sub>4</sub>	30	94	215-217	212-215[27]
3b	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	37	90	185-187	182-186[27]
3c	2-furfural	40	89	225-227	-
3d	4-FC <sub>6</sub> H <sub>4</sub>	28	91	214-216	216-220[27]
3e	2-ClC <sub>6</sub> H <sub>4</sub>	40	92	210-212	206-210[27]
3f	2-OHC <sub>6</sub> H <sub>4</sub>	34	90	196-198	192-196[27]
3g	4-OMeC <sub>6</sub> H <sub>4</sub>	30	93	148-150	154-157[27]
3h	3-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	42	91	218-220	-

<sup>a</sup>Reactions were run till the completion as indicated by TLC, <sup>b</sup>Yield after crystallization.

The reusability of the ionic liquid in a model reaction was also investigated. After reaction, the products were isolated from the catalytic system by extraction with ethyl acetate. The combined aqueous extract (aqueous media containing the catalyst) was reused in subsequent runs without further purification. As shown in Figure 1, the catalyst can be reused at least four times without any noticeable decrease in yield or reaction rate. The yields ranged from 94% to 90%.



**Figure 1: Reusability of the catalyst in model reaction. Reaction conditions: 4-Cl benzaldehyde (10.0 mmol), INH (10.0 mmol), IL (150mg) under reflux condition**

## CONCLUSION

We have demonstrated the IL catalyst was proved to be highly efficient in present reaction of aldehydes and INH. Furthermore, the catalyst can be easily separated and recovered from the reaction mixture by extraction and reused for up to four runs without noticeable loss in catalytical activities.

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