INTRODUCTION

Organic chemists are continuously searching for the chemical reaction in non-hazardous conditions to minimize the generation of hazardous substances in the environment [1]. Water is the ideal solvent for chemical reaction as it is safe and environmental friendly [1,2]. But, in general, its use is limited in chemical reactions because most of the organic compounds are either insoluble or unstable [3]. Herein we report synthesis of imidazo[1,2-a]pyridine derivatives in water with high yields.

Imidazo[1,2-a]pyridine derivatives are an important class of molecules and have wide variety of biological activities such as anti-inflammatory, antiviral, antibacterial, antifungal, antiprotozoal, immunomodulatory, gastrointestinal, anxiolytic, hypnotic and antiulcer activities [4,5].

Imidazo[1,2-a]pyridine moieties also known in certain drug molecules such as zolpidem (I, treatment of insomnia), alpidem (II, an anxiolytic agent), minodronic acid (III, use for osteoporosis treatment) and zolimidine (IV, for peptic ulcer treatment) [6] (Fig. 1).

Three component coupling reaction are available using 2-amino pyridines, aldehyde/alkyl halide and alkynes/isocyanide [7,8]. Adib et al. [3] reports such reaction in a catalyst-free reaction in water at 70 °C.

Two component systems are also done with condensation of 2-aminopyridine with α-haloketones [4,5,9]. Most of the reactions uses polar organic solvent (particularly ethanol or methanol) in presence/absence of different bases (Scheme-I). The isolation and purification has been done by using column chromatography to obtained moderate to good yields [4,5,10].

Syntheses have also been carried out under microwave irradiation in the presence of Montmorillonite K10 [11], Sc(OTf)3 [12], etc. It has also been performed using a non-polar solvent [13], or in the presence of an ionic liquid [14].
In recent years several improved conditions have been reported [15]. Lei et al. [16] published the results on synthesis of imidazo[1,2-a]pyridines using silver carbonate in dioxane at 110 °C, with moderate yields [16] and Cai et al. [17] reported synthesis of imidazo[1,2-a]pyridines using Li/CuO in methanol. Though these methods are useful, but use of water as solvent for organic reactions is the most interesting and attracted step because of its economic and environmental friendly nature.

**EXPERIMENTAL**

Unless otherwise noted all reactions were carried out at room temperature. Solvents and reagents were purchased at the highest commercial quality and used without further drying and purification respectively. Reactions were monitored by thin-layer chromatography (TLC) analysis using TLC aluminum sheets silica gel 60 F254.

$^1$H NMR and $^{13}$C NMR spectra were recorded in CDCl$_3$ and DMSO-$d_6$ at 400 MHz. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for $^1$H NMR and $^{13}$C NMR. The water was prepared from tap water after sand filter-carbon filter-ionic exchange resin-reverse osmosis-UV-micro filter by passing through pre-packed cartridges.

**General procedure and representative analytical data of imidazo[1,2-][pyridines: A solution of 2-aminopyridine (1 eq) and α-bromoketone (1 eq) in water was stirred at room temperature for 8 h (Scheme-II). For some insoluble 2-aminopyridine, it was dissolved by heating up to 60-70 °C and then added α-bromoketones. The reactions were performed at room temperature for 8 h (Scheme-III). After completion of the reaction, the reaction mixture was basified (pH = 9) with 10% NaOH aqueous solution. In many cases product was precipitated out, so it was filtered to get pure compound. If product was not solid, it was extracted with pentane to get product in pure form.

**Synthesis of zolimidine:** The suspension of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (1 eq) and pyridin-2-amine (3 eq) in water was stirred at room temperature for 18 h (Scheme-IV). The heterogeneous reaction mixture was directly filtered and washed with water, followed by diethyl ether to get yellow solid zolimidine (91%).

**Scheme-II**

![Scheme-II](image)

**Scheme-III**

![Scheme-III](image)

**Scheme-IV**

![Scheme-IV](image)
RESULTS AND DISCUSSION

While pursuing synthesis of some specific imidazo[1,2-a]pyridines, we hypothesized this to be ideal reaction for trying in water as solvent. This has been further developed as reaction without use of any base/catalyst and isolating without any chromatography. The reaction produces good to excellent isolated yields at room temperature (Table-1). Three amino pyridines: no substitution, 4-methyl and 4-chloro have been selected to represent variety. These are made to react with α-bromoacyl derivatives with bulky group tert-butyl, ethyl, cyclohexyl and phenyl. All the 12 products are obtained in good to excellent yields (64-91%).

The isolation of the product needs basification of the reaction mixture withaq. sodium hydroxide to precipitate out required compounds or to extract the compounds in pentane.

Some of the substituted 2-amino pyridines (Scheme-III) showed insolubility in water, so were warmed up to 60-70 °C for making a clear solution. The reaction proceeded at room temperature and produced the required product in good yields (72-80 %), except for 6b (40 %). We believe the steric may not be the reason for such low yields. As the 3-chloro amino pyridine gave good yield (80 %), so the poor yield may be due to complication by participation of CN group during product formation (Table-2). All the compounds are purified without column chromatography.

The water plays a role of reaction medium only and does not play any role in the reaction mechanism. This was evident by performing a reaction in heavy water (example 3b). The reaction gave similar high yield as in water (91 %) vs. 88 %. This result is in contrast to the results obtained in literature [18]. The NMR data of the product 3b obtained in heavy water was same as the one obtained in water.

The developed reaction was applied to synthesize the zolimidine (IV) as per Scheme-IV. It gave the required product in good yields (91 %) and high purity (> 97 %) and was isolated with simple filtration. In recent paper, it has been synthesized over two steps (overall yield 40 %) [16]. The high yields and quick isolation makes it ideal route for scale up and manufacturing of zolimidine.

![Scheme-IV: Synthesis of zolimidine in water](image-url)

### Table-1

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Structure</th>
<th>Yield (%)</th>
<th>Compd. No.</th>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td><img src="image-url" alt="Structure" /></td>
<td>84</td>
<td>3g</td>
<td><img src="image-url" alt="Structure" /></td>
<td>78</td>
</tr>
<tr>
<td>3b</td>
<td><img src="image-url" alt="Structure" /></td>
<td>91</td>
<td>3h</td>
<td><img src="image-url" alt="Structure" /></td>
<td>67</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image-url" alt="Structure" /></td>
<td>90</td>
<td>3i</td>
<td><img src="image-url" alt="Structure" /></td>
<td>64</td>
</tr>
<tr>
<td>3d</td>
<td><img src="image-url" alt="Structure" /></td>
<td>84</td>
<td>3j</td>
<td><img src="image-url" alt="Structure" /></td>
<td>75</td>
</tr>
<tr>
<td>3e</td>
<td><img src="image-url" alt="Structure" /></td>
<td>86</td>
<td>3k</td>
<td><img src="image-url" alt="Structure" /></td>
<td>73</td>
</tr>
<tr>
<td>3f</td>
<td><img src="image-url" alt="Structure" /></td>
<td>75</td>
<td>3l</td>
<td><img src="image-url" alt="Structure" /></td>
<td>75</td>
</tr>
</tbody>
</table>
**TABLE-2**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td><img src="image" alt="Structure" /></td>
<td>72</td>
</tr>
<tr>
<td>6b</td>
<td><img src="image" alt="Structure" /></td>
<td>40</td>
</tr>
<tr>
<td>6c</td>
<td><img src="image" alt="Structure" /></td>
<td>80</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image" alt="Structure" /></td>
<td>77</td>
</tr>
<tr>
<td>6e</td>
<td><img src="image" alt="Structure" /></td>
<td>72</td>
</tr>
</tbody>
</table>

**Conclusion**

In summary, an easy, catalyst free, efficient and environmentally friendly synthesis of imidazo[1,2-a]pyridines from 2-amino-pyridines with α-bromo acyl derivatives is reported. The reactions are done in water as medium and at room temperature. Several products are isolated without any column chromatography with good to excellent yields. The drug like zolimidine has been synthesized using the developed procedure in high yield and purity using water as reaction medium.

**ACKNOWLEDGEMENTS**

Sincere thanks to Jubilant Chemsys Management in facilitating this research work and also to the analytical team for providing the spectral data.

**REFERENCES**

   (d) C.J. Li, *Chem. Rev.*, **105**, 3095 (2005); https://doi.org/10.1021/cr030009u.