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## Environmentally Benign Synthesis of 2-aryl Benzimidazoles and their Antibacterial Screening

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### ABSTRACT

Ultrasound Promoted one pot synthesis of 2-aryl benzimidazoles, by the condensation of 1,2-phenylenediamine and benzoyl chloride in presence of ionic liquids, 1-butylimidazolium bisulphate [Hbim][HSO<sub>4</sub>] and 1,3-dibutylimidazolium bisulphate [bbim][HSO<sub>4</sub>]. There is no need of any additional catalyst. The products obtained in good to moderate yields with simple work up procedure. The compound 3d was investigated *in vitro* against Gram positive and Gram negative bacteria at different concentrations and compared with standard drug ciprofloxacin.

**Key words:** 2-aryl benzimidazoles, Ionic liquid, Ultrasound, Antibacterial

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### INTRODUCTION

Benzimidazole is an important pharmacophore in medicinal chemistry which is receiving considerable attention [1-4]. In nature, the benzimidazole nucleus constitutes an important part of the vitamin B<sub>12</sub> structure. Substituted benzimidazoles, especially at positions 1 and 2, are generally found to be more potent compared to benzimidazole [5]. Some widely used drugs such as rabeprazole (anti-ulcer) [6], pimozide (antipsychotic) [7] and telmisartan (antihypertension) [8-11] contain a benzimidazole group.

Usually benzimidazoles are synthesized by the condensation of 1,2-phenylenediamine with aldehydes, carboxylic acid, nitriles and orthoester [8-11] under very high temperature and strong acidic condition or under microwave irradiation [12-15]. However, most of these reported protocols suffer from one or more drawbacks such as drastic reaction conditions, long reaction time, poor yield, side product formation, use of expensive catalyst, use of toxic reagent and hazardous solvent, use of excessive oxidant, work-up difficulties, which makes them undesirable under the aspect of green chemistry, sustainable development, and industrial applications.

One-pot reaction and use of room temperature Ionic Liquids (ILs) as 'green' solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapour pressure, easy recyclability and reusability [16-19]. They have the potential to be highly polar yet non-coordinating solvents. Here we are interested to use ultrasound irradiation which has been established as an important technique in synthetic organic chemistry. It has been used as an efficient energy source for the organic reactions. Simple experimental procedure, very high yields, increased selectivity and clean reaction [20-23]. The reason may be the phenomenon of cavitation produced by ultrasound. Cavitation is the origin of sonochemistry, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer and allowing chemical reactions to occur. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances, these bubbles are small and rapidly collapse, they can be seen as microreactors that offer the opportunity of speeding up certain reactions and also allow mechanistically novel reactions to take place in an absolutely safe manner [24-26].

### EXPERIMENTAL SECTION

#### General considerations

All reagents and solvents purchased from commercial sources were used as received. The ionic liquids was prepared by reported procedure and used. All reactions were carried out in oven-dried glassware and were magnetically stirred.

Fourier Transform Infrared (FTIR) spectra were taken on FTIR Spectrophotometer Model RZX (Perkin Elmer) and  $^1\text{H}$  and  $^{13}\text{C}$  spectra were taken on Bruker Avance II 400 MHz spectrometer with Tetramethylsilane (TMS) as internal standard Deuterated Chloroform ( $\text{CDCl}_3$ )/Dimethyl Sulfoxide (DMSO) as solvent. Electrospray Ionisation (ESI)-mass spectral data were recorded on Q-TOF Micro Waters (ESI-MS) Spectrometer.

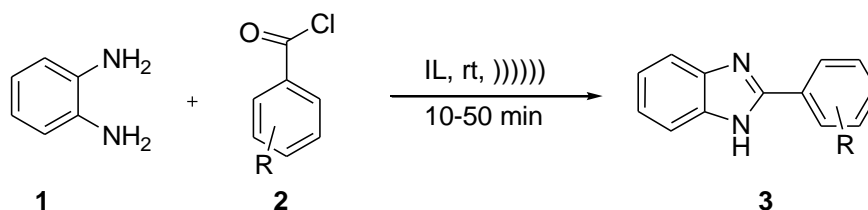
### General procedure for the screening of solvents

Screening of solvents for the synthesis of 2-aryl benzimidazoles, various reaction conditions have been investigated in the reaction of 1,2-phenyldiamine **1** and benzoyl chloride **2d** as a model reaction (Scheme 1). We examined the effect of different solvents such as Ethanol, Methanol, Tetrahydrofuran (THF), Dimethylformamide (DMF), Methyl Cyanide ( $\text{CH}_3\text{CN}$ ), Dichloromethane (DCM) and sets of ionic liquids N-butyl imidazolium [Hbim] and N,N-dibutyl imidazolium [bbim], the salts with varying basicity like [Hbim][HCOO], [Hbim][ $\text{CH}_3\text{COO}$ ], [Hbim][TOS], [Hbim][ $\text{HSO}_4$ ], [bbim][ $\text{HSO}_4$ ], [bbim][ $\text{CH}_3\text{COO}$ ], [bbim][TOS] and [bbim][HCOO] were synthesized and used on a model reaction under ultrasound irradiation (power intensity: 40%) at rt. The results were summarized in Table 1. The ionic liquids [Hbim][ $\text{HSO}_4$ ] and [bbim][ $\text{HSO}_4$ ] afforded the best yield for the reaction (Table 1, entry 10, 11). Therefore [Hbim][ $\text{HSO}_4$ ] and [bbim][ $\text{HSO}_4$ ] was chosen as solvent and catalyst for the reaction.

**Table 1: Screening of solvents effect on model reaction (3d)<sup>a</sup>**

| Entry | Solvent                           | Time (min) | Yield <sup>b</sup> (%) |
|-------|-----------------------------------|------------|------------------------|
| 1     | Methanol                          | 20         | 45                     |
| 2     | Ethanol                           | 20         | 38                     |
| 3     | Acetonitrile                      | 20         | 50                     |
| 4     | DMF                               | 20         | 48                     |
| 5     | THF                               | 20         | 40                     |
| 6     | DCM                               | 20         | 54                     |
| 7     | [Hbim][HCOO]                      | 20         | 85                     |
| 8     | [Hbim][ $\text{CH}_3\text{COO}$ ] | 20         | 78                     |
| 9     | [Hbim][TOS]                       | 20         | 70                     |
| 10    | [Hbim][ $\text{HSO}_4$ ]          | 20         | 90                     |
| 11    | [bbim][ $\text{HSO}_4$ ]          | 20         | 93                     |
| 12    | [bbim][ $\text{CH}_3\text{COO}$ ] | 20         | 80                     |
| 13    | [bbim][TOS]                       | 20         | 83                     |
| 14    | [bbim][HCOO]                      | 20         | 75                     |

<sup>a</sup>Reaction of 1,2-phenyldiamine **1** and benzoyl chloride **2d** in presence of solvents (entries 1-14) under ultrasonic irradiation with power intensity of 40% at rt; <sup>b</sup>Isolated yield



**Scheme 1: One pot synthesis of 2-aryl benzimidazoles catalyzed by [Hbim][ $\text{HSO}_4$ ] and [bbim][ $\text{HSO}_4$ ] under ultrasound irradiation at room temperature**

### General procedure for the synthesis of 2-aryl benzimidazoles (3a-3h) under ultrasonic irradiation

The procedure described below for the synthesis of 2-phenyl benzimidazole **3d** in [bbim][ $\text{HSO}_4$ ] and [Hbim][ $\text{HSO}_4$ ] respectively (Tables 2 and 3). A mixture of 1,2-phenyldiamine **1** (4.6 mmol) and benzoyl chloride **2d** (4.6 mmol) was dissolved in two different single neck round bottom flask to that [bbim][ $\text{HSO}_4$ ] (4.6 mmol) and [Hbim][ $\text{HSO}_4$ ] (4.6 mmol) was added respectively and both the flask with the reaction mixtures were immersed into the ultrasonic water bath, where the surface of the reactants is slightly lower than the level of the water, and irradiated at 40% of the power of the ultrasonic bath at room temperature inside for 20 min. After completion of the reaction, the reaction mixtures was diluted with water (20-30 ml) and the separated product was filtered and was washed thoroughly with water and dried. The aqueous layer consisting of the IL was subjected to distillation at  $80^\circ\text{C}$  to remove the water and leaving behind the IL here there was recovery for ([bbim][ $\text{HSO}_4$ ] 96%) and for ([Hbim][ $\text{HSO}_4$ ] 94%), thus ILs were recycled and used. The same procedure was repeated for two times. The product thus obtained was pure enough, got single spot on TLC. Then product was crystallized using (1:1) DMF-Ethanol. As the products are known compounds were characterized by comparison of their spectral data (IR, Mass,  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR) and physical properties with those reported in literature. Compound **3d**: white solid; m.p.  $294-296^\circ\text{C}$ . FTIR Model RZX (Perkin Elmer)  $\text{cm}^{-1}$ : 3049, 1542, 1278, 700.  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ , d ppm):  $\delta=7.18-7.20$  (m, 2H), 7.43-7.62 (m, 5H), 8.22-8.24 (m, 2H), 12.89 (s, 1H, -NH);  $^{13}\text{C}$ -NMR (400 MHz, DMSO- $d_6$ , d ppm):  $\delta=121.97$ , 126.44, 128.71, 129.6, 130.23, 151.30. MS (EI):  $m/z$  (%)=195 [ $\text{M}^+$ ].

**Table 2: Synthesis of 3a-3h using [bbim][ $\text{HSO}_4$ ]**

| Product | R                 | Time (min) | m.p ( $^\circ\text{C}$ ) | Yield (%) |           |           |
|---------|-------------------|------------|--------------------------|-----------|-----------|-----------|
|         |                   |            |                          | First     | Recycle 1 | Recycle 2 |
| 3a      | 4-Me              | 15         | 265 -267                 | 90        | 90        | 88        |
| 3b      | 4-Cl              | 10         | 288 -290                 | 93        | 92        | 90        |
| 3c      | 2-Cl              | 20         | 236 - 238                | 88        | 88        | 86        |
| 3d      | H                 | 15         | 296 - 297                | 90        | 88        | 87        |
| 3e      | 2-Br              | 25         | 238 - 240                | 92        | 90        | 88        |
| 3f      | 4-OMe             | 10         | 229 - 231                | 95        | 95        | 93        |
| 3g      | 2-OH              | 10         | 240 - 243                | 93        | 92        | 90        |
| 3h      | 2-NO <sub>2</sub> | 45         | 310 - 312                | 87        | 87        | 86        |

Table 3: Synthesis of 3a-3h using [Hbim][HSO<sub>4</sub>]

| Product | R                 | Time (min) | m.p. (°C) | Yield (%) |           |           |
|---------|-------------------|------------|-----------|-----------|-----------|-----------|
|         |                   |            |           | First     | Recycle 1 | Recycle 2 |
| 3a      | 4-Me              | 20         | 265-267   | 92        | 92        | 90        |
| 3b      | 4-Cl              | 20         | 288-290   | 90        | 89        | 87        |
| 3c      | 2-Cl              | 25         | 236-238   | 89        | 88        | 86        |
| 3d      | H                 | 20         | 296-297   | 90        | 89        | 86        |
| 3e      | 2-Br              | 30         | 238-240   | 93        | 93        | 90        |
| 3f      | 4-OMe             | 20         | 229-231   | 94        | 94        | 92        |
| 3g      | 2-OH              | 20         | 240-243   | 93        | 92        | 90        |
| 3h      | 2-NO <sub>2</sub> | 60         | 310-312   | 90        | 90        | 88        |

### Antibacterial activity

The novel synthesized heterocyclic compound 3d was screened for *in vitro* antimicrobial activity using agar disc-diffusion method against two Gram-positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two Gram-negative strains, *Escherichia coli* and *Pseudomonas aeruginosa* [27,28]. Ciprofloxacin was used as standard drug.

### General procedure

#### Determination of zone of inhibition by agar disc-diffusion method

Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant concentration of 125-1000 µg/ml. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. *In vitro* antibacterial activity was determined by using Mueller Hinton agar obtained from Himedia Ltd., Mumbai. Petri plates were prepared by pouring 20 ml of Mueller Hinton agar for bacteria containing microbial culture was allowed to solidify. 24 h old culture was used to get 10<sup>8</sup> suspension. This suspension of 4 pathogenic cultures was spread on Muller Hinton Agar plates by sterile cotton swabs. The impregnated discs were then kept on these plates and were incubated at 37°C for 24 h (bacteria) and after incubation zone of inhibition was measured in mm as diameter in four directions and expressed as mean. The results were compared against ciprofloxacin as a standard drug and are reported in the following Table 4.

Data obtained from antibacterial assessment are furnished in Table 4 indicates that the test compound 3d showed antibacterial activity against Gram-positive bacteria, *S. aureus* and *B. subtilis* it moderate activity against *S. aureus* no activity against *B. subtilis*. In case of gram negative bacteria, 3d showed moderate activity against *E. coli* and it is inactive against *P. aeruginosa* at all 4 concentrations. On the basis of data it is clear that 2-aryl benzimidazoles based derivatives possesses moderate antibacterial activity.

Table 4: Antibacterial activity of 3d

| S. No.                        | Concentration (µg/ml) | Zone of inhibition in mm Gram-positive, Gram-negative (3d) |             |                                    |             |                                   |             |   |             |
|-------------------------------|-----------------------|--|-------------|------------------------------------|-------------|-----------------------------------|-------------|---|-------------|
|                               |                       | Pathogen- <i>Staphylococcus aureus</i>                     |             | Pathogen- <i>Bacillus subtilis</i> |             | Pathogen- <i>Escherichia coli</i> |             | Pathogen- <i>Pseudomonas aeruginosa</i> |             |
|                               |                       | Replicate 1  | Replicate 2 | Replicate 1                        | Replicate 2 | Replicate 1                       | Replicate 2 | Replicate 1                             | Replicate 2 |
| 1                             | 125                   | -  | -           | -                                  | -           | -                                 | -           | -                                       | -           |
| 2                             | 250                   | 18   | 19          | -                                  | -           | 8                                 | -           | -                                       | -           |
| 3                             | 500                   | 22   | 23          | -                                  | -           | 10                                | 10          | -                                       | -           |
| 4                             | 1000                  | 25   | 25          | -                                  | -           | 14                                | 12          | -                                       | -           |
| <b>Standard ciprofloxacin</b> |                       |  |             |                                    |             |                                   |             |   |             |
| 1                             | 125                   | 31   | 31          | 27                                 | 27          | 26                                | 26          | 27                                      | 27          |
| 2                             | 250                   | 35   | 36          | 29                                 | 29          | 28                                | 28          | 32                                      | 32          |
| 3                             | 500                   | 40   | 41          | 30                                 | 31          | 29                                | 31          | 36                                      | 34          |
| 4                             | 1000                  | 44   | 45          | 32                                 | 33          | 30                                | 33          | 38                                      | 39          |

## RESULTS AND DISCUSSION

The present method involves a one pot cyclocondensation of 1,2-phenyldiamine 1 and benzoyl chloride 2 for this reaction the effect of different solvents such as EtOH, MeOH, THF, DMF, CH<sub>3</sub>CN, DCM and sets of ionic liquids N-butyl imidazolium [Hbim] and N,N-dibutyl imidazolium [bbim], the salts with varying basicity like [Hbim][HCOO], [Hbim][CH<sub>3</sub>COO], [Hbim][TOS], [Hbim][HSO<sub>4</sub>], [bbim][HSO<sub>4</sub>], [bbim][CH<sub>3</sub>COO], [bbim][TOS] and [bbim][HCOO] were synthesized and used on a model reaction under ultrasound irradiation (power intensity: 40%) at rt. The results were summarized in Table 1. The ionic liquids [Hbim][HSO<sub>4</sub>] and [bbim][HSO<sub>4</sub>] afforded the best yield for the reaction (Table 1, entry 10,11). Therefore [bbim][HSO<sub>4</sub>] and [Hbim][HSO<sub>4</sub>] was chosen as solvent and catalyst for the reaction.

Then to study the effect of mole ratio of chosen set ILs on yield of 3d, was performed in the presence of 0.2, 0.4, 0.8, 1.0, 2.0, 3.0 and 4.0 (mol %) with ultrasonic irradiation. As shown in Table 5 we got best result at 2.0 mol %, for the set of ILs. It is been observed that minimum of equimolar proportion of the ionic liquid is required for optimum results beyond that there is no further increase.

Table 5: Effect of mole ratio of ionic liquids on yield of 3d

| Moles ratio of IL (mmol %) | [Hbim][HSO <sub>4</sub> ] Yield (%) | [bbim][HSO <sub>4</sub> ] Yield (%) |
|----------------------------|-------------------------------------|-------------------------------------|
| 0.2                        | 08%                                 | 10%                                 |
| 0.4                        | 15%                                 | 18%                                 |
| 0.8                        | 40%                                 | 45%                                 |
| 1.0                        | 70%                                 | 76%                                 |
| 2.0                        | 93%                                 | 90%                                 |
| 3.0                        | 84%                                 | 86%                                 |
| 4.0                        | 80%                                 | 84%                                 |

Then after these two ILs were used to synthesized various 2-aryl benzimidazoles and the time for complete conversion and the yield for 2-aryl benzimidazoles (3a-3h) in the [bbim][HSO<sub>4</sub>] and [Hbim][HSO<sub>4</sub>] are respectively recorded in Table 3 and Table 4. It was observed that took more time for conversion in [Hbim][HSO<sub>4</sub>] as compared to [bbim][HSO<sub>4</sub>]. We got good conversion in less time in [bbim][HSO<sub>4</sub>]. Both the IILs were recover from the reaction and was recycled and used two times and result are reported in Table 3 and Table 4 and we got good yields each time.

The compound 3d was screened for *in vitro* antimicrobial activity using agar disc diffusion method against two Gram-positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two Gram-negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial assessment are furnished in Table 5.

### CONCLUSION

In conclusion, a simple, efficient and environmentally benign method has been developed for the synthesis of 2-aryl benzimidazoles by using ionic liquids, 1-butylimidazolium bisulphate [Hbim][HSO<sub>4</sub>] and 1,3-dibutylimidazolium bisulphate [bbim][HSO<sub>4</sub>]. There is no need of any additional catalyst. The reaction has been carried out under ultrasound irradiation, a smooth condensation occurs at shorter reaction time and the products obtained in good to moderate yields with simple work up procedure. Antibacterial screening of 3d compound was found to possess moderate activity against selected strains of bacteria also found inactive for *B. subtilis* and *P. aeruginosa* and rest of synthesized will be assessed in future study.

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