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# Synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles Catalyzed by Brønsted Acidic Ionic Liquid under Ultrasonic Irradiation

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A series of 2-aryl-1-arylmethyl-1*H*-benzimidazoles were synthesized through the condensation reactions of aromatic aldehydes and *o*-phenylenediamine using Brønsted acidic ionic liquid, 3-methyl-1-(3-sulfopropyl)-imidazolium trifluoro acetate, as catalyst under ultrasonic irradiation condition. The yields of the products were in the range from 85 % to 97 %. The Brønsted acidic ionic liquid can be recovered and reused at least five consecutive cycles without significant loss of its catalytic activity. The results indicated that the proposed method is easy, efficient and environmental friendly for the preparation of 2-aryl-1-arylmethyl-1*H*-benzimidazoles.

**Keywords: Brønsted acidic ionic liquid, 2-Aryl-1-arylmethyl-1*H*-benzimidazoles, Synthesis.**

## INTRODUCTION

Benzimidazole and their derivatives have diverse applications in medicinal chemistry because of their unique biological and pharmacological activities. Many members of this family have commercial applications in various realms of therapy, including antiulcerative, antihypertensive, antiviral, antifungal, antitumor and antihistaminic agents and antihelminthic agents in veterinary medicine[1-7]. Due to their affinity towards enzymes and protein receptors, they have been appropriately classified as 'privileged sub-structures' for drug design. Moreover, benzimidazoles are very important intermediates in various organic reactions[8]. Therefore, the preparation of benzimidazoles has received considerable attention in recent years.

Until now, many synthetic strategies for the preparation of benzimidazoles have been reported in the literature. Generally, they are synthesized through the condensation reaction of *o*-phenylenediamines and carboxylic acids or their derivatives (nitriles, amidates, orthoesters)[9] in the presence of strong acids such as polyphosphoric acid[10] or mineral acids[11]. Benzimidazoles have also been prepared by the condensation reaction of aldehyde and arylenediamine under oxidative conditions[12-15]. However, each of these methodologies suffer from one or more shortcomings, such as low yields, long reaction times, using toxic catalyst and solvents, tedious work-up procedures and co-occurrence of several side reactions.

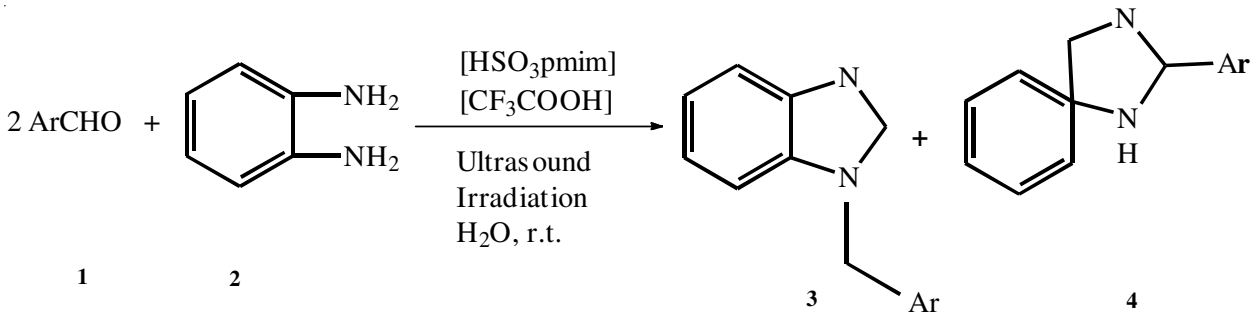
Organic reactions in aqueous media have attracted great interest due to its safety, low cost and environmental friendly[16]. Synthesis of benzimidazoles in aqueous media using Zn-proline[17], silica sulfuric acid[18] and glyoxylic acid[19] as catalyst and high temperature in water[20] have been reported in the documents.

Recently ionic liquids have been successful employed as Brønsted acidic catalysts for a variety of reactions[21-23] due to their unique properties, such as extremely low vapor pressure, excellent thermal stability, reusability, ability to dissolves many organic and inorganic substrates and their potential to enhance reaction rates and selectivity[24].

In continuation of our research in developing environmental benign synthetic methodlogies[25], we report here a simple and efficient method for the preparation of 2-aryl-1-arylmethyl-1*H*-benzimidazoles using Brønsted acidic ionic liquid 3-methyl-1-(3-sulfopropyl)-imidazolium trifluoro acetate ([$HSO_3$-pmim][$CF_3COOH$]) as catalyst under ultrasonic irradiation condition (Fig. 1).

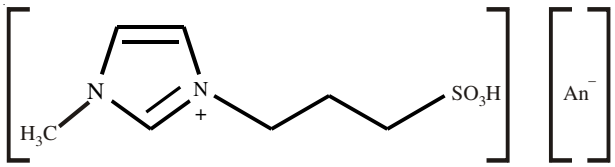
## EXPERIMENTAL

Melting points were recorded on an electrothermal apparatus and are uncorrected. $^1$H NMR (400 MHz) spectra were determined with Brucker AVANCE 400 spectrometer ($CDCl_3$-$d_6$) using TMS as internal standard. IR spectra ($cm^{-1}$) were measured with a WQF-510 spectrometer. All of the Brønsted acidic ionic liquids, [$HSO_3$-pmim][$CF_3COOH$], [$HSO_3$-pmim][*p*-toluenesulfonic acid] and [$HSO_3$-pmim] [$CHH_3SO_3H$] (**Scheme-I**), were synthesized according to the procedures described in the literature[26].




Ar = $C_6H_5$, 2-$O_2NC_6H_4$, 4-$O_2NCH_4$, 2-Cl $C_6H_4$, 4-Cl $C_6H_4$, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-$(CH_3)_2NC_6H_4$

Fig. 1. Condensation reaction of aromatic aldehydes with *o*-phenylenediamine




An = $CH_3COOH$, $CH_3SO_3H$, *p*-toluenesulfonic acid

**Scheme-I:** Structure of acidic ionic liquid

**General procedure:** A mixture of 10 mmol aldehyde **1**, 5 mmol *o*-phenylenediamine **2**, 0.25 mmol (5 mmol %) [$HSO_3$-pmim][$CF_3COOH$] and 10 mL water were placed in a 50 mL round-bottomed flask. Then, the reaction mixture was submitted to ultrasound irradiation at room temperature for a desired period of time (monitored by thin-layer chromatography, TLC). Upon completion of the reaction, the mixture was filtered and the obtained solid was washed with water. The crude product was recrystallized from 95 % ethanol and then dried to afford 2-aryl-1-arylmethyl-1*H*-benzimidazole **3** (Table-1). The products were identified by IR and $^1$H NMR. The filtrate was extracted with ether (10 mL × 2) and evaporated under reduced pressure to recover the catalyst.

**3a:** $^1$H NMR: δ 7.80 (d, *J* = 8 Hz, 1H): 7.60 (dd, *J* = 8 and 2 Hz, 2H): 7.41-7.30 (m, 3H): 7.24-7.11 (m, 6H): 7.08 (dd, *J* = 8 and 2 Hz, 2H): 5.30 (s, 2H); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3038, 2958, 1508,1473, 1235, 1196.

**3b:** $^1$H NMR: δ 8.18-8.12 (m, 2H): 7.80 (dd, *J* = 8 and 1 Hz, 1H); 7.70-7.60 (m, 2H): 7.52-7.43 (m, 3H): 7.40 (td, *J* = 8 and 1 Hz,1H): 7.32 (td, *J* = 8 and 1 Hz, 1H): 7.12 (dd, *J* = 8 and 1 Hz, 1H): 6.90 (dd, *J* = 7 and 1 Hz, 1H): 5.72 (s, 2H); IR (KBr, $\nu_{max}$, $cm^{-1}$) : 3063, 1608, 1526, 1446, 1278, 1078.

**3c:** $^1$H NMR: δ 8.30 (d, *J* = 9 Hz, 2H): 8.20 (d, *J* = 8 Hz, 2H): 7.90 (dd, *J* = 8 and 1 Hz, 1H): 7.80 (d, *J* = 9 Hz, 2H): 7.40 (td, *J* = 7 and 1 Hz, 1H): 7.30 (td, *J* = 9 and 1 Hz, 1H); 7.25 (d, *J* = 9 Hz, 2H): 7.22 (dd, *J* = 8 and 1 Hz, 1H): 5.55 (s, 2H): IR (KBr, $\delta_{max}$, $cm^{-1}$) : 3060, 1608, 1562, 1417, 1226, 1078.

**3d:** $^1$H NMR: δ 7.86 (d, *J* = 8 Hz,1H): 7.50-7.38 (m, 3H): 7.38-7.12 (m, 6H); 7.06 (td, *J* = 8 and 1 Hz, 1H): 6.60 (dd, *J* = 8 and 1 Hz, 1H): 5.34 (s, 2H): IR (KBr, $\nu_{max}$, cm-1): 3029, 2980, 2926, 1632, 1447, 1390, 1358, 1270, 1171, 1040.

**3e:** $^1$H NMR: δ 7.84 (d, *J* = 8 Hz, 1H): 7.54 (m, 2H): 7.40 (m, 2H): 7.38-7.24 (m, 4H): 7.18 (d, *J* = 8 Hz, 1H): 7.04 (d, *J* = 9 Hz, 2H): 5.42 (s, 2H): IR (KBr, $\nu_{max}$, $cm^{-1}$): 3038, 2928, 2863, 1470, 1449, 1071.

**3f:** $^1$H NMR: δ 7.82 (d, *J* = 8 Hz, 1H): 7.54 (dd, *J* = 8 and 2 Hz, 1H): 7.40 (td, *J* = 8 and 2 Hz, 1H): 7.26 - 7.12 (m, 4H): 7.05 (t, *J* = 8 Hz, 1H): 6.90 (d, *J* = 8 Hz, 1H): 6.85 (d, *J* = 8 Hz, 1H): 6.77 (t, *J* = 7 Hz, 1H): 6.66 (dd, *J* = 7 and 1 Hz, 1H): 5.25 (s, 2H): 3.78 (s, 3H); 3.58 (s, 3H); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3176, 2954, 2930, 1564, 1476, 1243.

**3g:** $^1$H NMR: δ 7.85 (d, *J* = 8 Hz, 1H): 7.64 (d, *J* = 9 Hz, 2H): 7.32-7.23 (m, 1H): 7.22 (m, 2H): 7.02 (d, *J* = 9 Hz, 2H): 6.94 (d, *J* = 9 Hz, 2H): 6.80 (d, *J* = 8 Hz, 2H): 5.38 (s, 2H): 3.83 (s, 3H): 3.79 (s, 3H): IR (KBr, $\nu_{max}$, $cm^{-1}$): 3163, 2956, 2932, 1554, 1476, 1240.

**3h:** $^1$H NMR: δ 7.87 (m, 1H): 7.59 (d, *J* = 8 Hz, 2H): 7.26 (m, 1H): 7.26 (d, *J* = 8 Hz, 2H): 7.22 (m, 2H): 7.13 (d, *J* = 8 Hz, 2H): 6.99 (d, *J* = 8 Hz, 2H): 5.41 (s, 2H): 2.40 (s, 3H): 2.33 (s, 3H): IR (KBr, $\nu_{max}$, $cm^{-1}$): 3034, 2937, 2865, 1431, 1269.

**3i**: $^1$H NMR: δ 7.72 (d, *J* = 8 Hz, 1H): 7.56 (d, *J* = 9 and 2 Hz, 2H): 7.72-7.15 (m, 3H): 6.98 (d, *J* = 9 Hz, 2H), 6.72-6.50 (m, 4H): 2.90 (s, 3H): 2.82 (s, 3H); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3043, 2969, 2919, 2780, 1592, 1440 $cm^{-1}$.

## RESULTS AND DISCUSSION

In our initial study, the condensation reaction of *o*-phenylenediamine and benzaldehyde was chosen as the model reactant in order to examine the efficiency of different catalysts. As shown in Table-2, no product was obtained in the absence of the catalyst, indicating that the catalyst was necessary for the reaction. Among the catalysts tested, [$HSO_3$-pmim][$CF_3COOH$] was found to be the most effective catalyst since it gave the highest yield of product. Meanwhile, the effect of ultrasound irradiation on the condensation reaction of *o*-phenylenediamine and benzaldehyde was also investigated. To complete the reaction, the reaction time was 120 min under the ultrasound irradiation condition and 180 min under stirring condition without ultrasound irradiation.

To generalize the proposed method, a series of aromatic aldehydes were subjected to react with *o*-phenylenediamine for the preparation of 1,2-disubstituted benzimidazoles. The results were shown in Table-1, which indicated that a wide range of structural varied aromatic aldehydes reacted smoothly to give the 1,2-disubstituted benzimidazoles in good yields. The reusability of the recycled catalyst was also investigated. The recycled catalyst could be resued for at least five cycles without loss catalytic activity.

TABLE-1
SYNTHESIS OF 1,2-DISUBSTITUTED BENZIMIDAZOLES CATALYZED BY [$HSO_3$-pmim][$CH_3COOH$][a]

| Entry | Ar | Time (min) | Yield (%) | m.p. (°C) | m.p. lit. (°C) |
|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | 120 | 85 | 129.1-132.5 | 133-134 [Ref. 27] |
| **3b** | 2-$O_2NC_6H_4$ | 60 | 95 | 118-120 | 118 [Ref. 27] |
| **3c** | 4-$O_2NC_6H_4$ | 60 | 97 | 189.6-192.6 | 189-191 [Ref. 27] |
| **3d** | 2-$ClC_6H_4$ | 100 | 88 | 157-159.7 | 158-159 [Ref. 27] |
| **3e** | 4-$ClC_6H_4$ | 100 | 92 | 136-139.3 | 137-139 [Ref. 27] |
| **3f** | 2-$CH_3OC_6H_4$ | 150 | 89 | 150-152 | 151 [Ref. 27] |
| **3g** | 4-$CH_3OC_6H_4$ | 150 | 88 | 125.5-127.9 | 127.129 [Ref. 27] |
| **3h** | 4-$CH_3C_6H_4$ | 120 | 89 | 125-127 | 126 [Ref. 27] |
| **3i** | 4-$(CH_3)_2NC_6H_4$ | 110 | 90 | 251-252 | 252 [Ref. 27] |

[a]Reaction condition: molar ratio of aldehyde to *o*-phenylenediamine is 2:1, amount of catalyst is 5 mmol %

TABLE-2
CONDENSATION REACTION OF BENZALDEHYDE AND *o*-PHENYLENEDIAMINE

| Catalyst | Yield (%) |
|---|---|
| No catalyst | – |
| [$HSO_3$-pmim][$CF_3$ COOH] | 85 |
| [$HSO_3$-pmim][*p*-Toluenesulfonic acid] | 60 |
| [$HSO_3$-pmim][$CH_3SO_3H$] | 10 |

[a]Reaction condition $C_6H_5CHO$: 10 mmol, *o*-phenylenediamine: 5 mmol, $H_2O$: 10 mL, catalyst: 0.25 mmol reaction time: 120 min

## Conclusion

In conclusion, we have developed a mild, reliable and environmentally benign procedure for the synthesis of 1,2-disubstituted benzimidazole derivatives using [$HSO_3$-pmim][$CF_3COOH$] as catalyst in water media. The advantages of this protocol are good yields, low catalyst loading and mild reaction conditions. We believe that this method can be a useful contribution to the present methodologies for the synthesis of 1,2-disubstituted benzimidazoles.

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