Journal of Applied Organometallic Chemistry

2024, Volume 4, Issue 2

Original Article

# Efficient Synthesis of Benzimidazole Incorporated by PFPAT Catalyst at Room Temperature

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**Citation** S.B. Jagtap, A.S. Patki, D.B. Muley **Efficient Synthesis of Benzimidazole Incorporated by PFPAT Catalyst at Room Temperature.** *J. Appl. Organomet. Chem.*, **2024**, *4*(2), 167-177.

https://doi.org/10.48309/JAOC.2024.444613.1168



**Article info:**
**Submitted:** 18 February 2024
**Revised:** 11 March 2024
**Accepted:** 17 April 2024
**ID:** JAOC-2402-1168
**Checked for Plagiarism:** Yes
**Language Editor Checked:** Yes

**Keywords:**
Benzimidazole, PFPAT, Room temperature, *O*-Phenyl diamine, Benzaldehyde

## ABSTRACT

In the present protocol, we have developed a new and competent route for the development of benzimidazole staring with the aromatic diamine with differently substituted benzaldehyde in presence of catalyst Pentafluorophenylammonium triflate (PFPAT) at room temperature. The synthesized compound was further purified by recrystallisation with hot ethyl alcohol. The protocol works effectively for the benzimidazole synthesis and produces good yield. The incorporated method is environmental friendly, requires very less energy and catalyst can be good at activity even after 2-cycle run. The synthesized compounds were characterized by several analytical tools. The key advantages of this method are simple process, trouble-free work up procedure, and easy isolation of catalyst at the end of the reaction.

## Introduction

Among heterocyclic compounds, the benzimidazole moieties were often found. They found significance in organic synthesis due to their wide reappearance in bioactive compounds. Although there is huge interest in benzimidazoleligands and medicinal chemistry, the main interest is in their biological actions. The benzimidazole application started around in 1990 onward, a huge number of benzimidazole derivative synthesis were reported, which gives improved stability, bioavailability, and noteworthy biological activity. There are typically two approaches used to prepare benzimidazole. First, there is the simple heating reaction between phenylene diamines and carboxylic acids or their derivatives. The second approach is a two-step procedure that involves the oxidative cyclodehydrogenation of Schiff bases. Schiff bases are commonly produced using an acidic reagent to condense phenylenediamines and aromatic aldehydes [1,2]. Benzimidazole derivatives find a number of applications in pharmaceutical industry showing a wide range of biological activity. In veterinary medicine, substituted benzimidazole derivatives have found marketable use as anthelmintic agent such as antibacterial [3], fungicidal [4,5], analgesic [6],antihistaminic [7], anti-cancer [8],

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and anti-viral properties [9], antimicrobial [10-11], antiviral [12], anti-inflammatory [13-14], and antioxidant [15] activities, and anti-diabetics [16-17].

Some benzimidazole derivative finds application in heart related disease [18] while somederivatives have been prepared and screened for inhibition of HIV-1 infectivity [19].

Woolley postulated that benzimidazole had a purine structure and had biological applications, which led to the discovery of the benzimidazole core's biological activity in 1944 [20]. Thus, the structure of benzimidazoles is similar to that of naturally occurring nucleotides. Later, Brink found that 5, 6-dimethylbenzimidazole was produced as a byproduct of the breakdown of cobalaminand those certain of its derivatives had properties like those of cobalamin [21,22]. Some of the famous active drugs with benzimidazole moiety are shown in Figure 1. These are omeprazole, bendamustine, albendazole, mebendazole, etc. Plentiful methods are noted for the condensation of substituted OPD with alkyl/arylaldehydes catalyzed throughdiverse oxidizing agents or metal triflate for instance sulfamic acid [23], 1,4-benzoquinone [24], $LaCl_3$ [25], $PhI(OAc)_2$ [26],$H_5IO_6$-$SiO_2$ [27], 2,3-dichloro-5, benzofuroxan [28], $NaHSO_4$-$SiO_2$ [29], manganese dioxide [30], $I_2$/TBHP [31], mercury (II) [32], and Yb $(OTf)_3$ [33]. Some other reusable efficient catalysts used in this type of synthesis are metals like iron, cobalt, and copper doped tartrate complex [34-36]. Excellent yields of 2-substituted benzimidazoles with heterocyclic, aryl, and alkyl substituted moiety were isolated using this technique. The current endeavor involves the creation of a benzimidazole derivative by reacting substituted benzaldehyde with o-phenyl diamine while using pentafluorophenylammonium triflate catalyst as a catalyst. The reaction took place at room temperature, and mass spectra, $^1$H-NMR, $^{13}$C-NMR, and infrared spectra were used to examine the produced derivatives.

## Experimental

### *Material*

All chemicals and solvents were taken from commercial provider and were utilized without any further purification. Reactions were carried out in dried glassware. Melting points were taken on melting point calculating apparatus and which is correct. Aluminum covered silica plates taken from Merck which was utilized to perform thin layer chromatography (TLC). IR spectra were determined on a Perkin-Elmer spectrophotometer, and NMR data were recorded on a Bruker Avance-300 spectrophotometer by means of TMS as an internal reference.

### *Process for the synthesis of benzimidazole derivative*

In a round bottom flask mixture of *o*-phenyl diamine (**1**) and aromatic aldehyde (**2a**-**2j**) was taken in equimolar quantity (0.1 mmol). In addition, ethanol was added as a solvent to the reaction mixture along with a specified amount of PFPAT to function as a catalyst. The final combination was then magnetically agitated for the

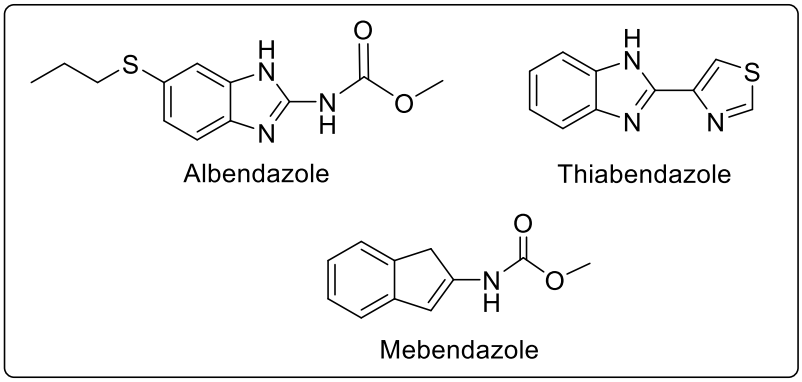
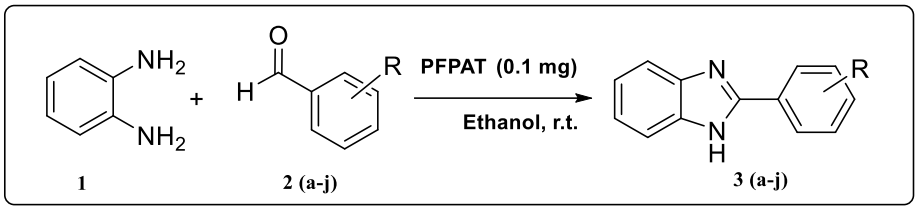



**Figure 1**. Benzimidazole based commercial drugs




Scheme 1. Development of benzimidazole catalysed by PFPAT in ethanol at r.t.

appropriate amount of time at room temperature in an open environment (Scheme 1). The reaction's completion was verified by periodically applying TLC. When the reaction was completed ethyl acetate was added in the reaction mixture and concurrently filtered with the filter paper. The catalyst was repeatedly cleaned using ethyl acetate. The resultant crude solid product was refined further using hot ethanol recrystallization to provide pure benzimidazole products (**3a**-**3j**), which were then further examined using IR, $^{1}$H-NMR, and $^{13}$C-NMR spectroscopy.

*Characterization of some synthesized benzimidazole derivative*

*2-Phenyl-1H benzimidazole (**3a**)*

White colored solid, m.p-297 °C, IR (cm$^{-1}$): 3426, 3042, 1742, and 1631; $^{1}$H-NMR (DMSO): δ 6.86 (d, 2H), 6.98 (d, 2H), 7.10 (t, 1H), 7.34 (m, 2H), 7.53 (m, 2H), and 12.13 (d, 1H). $^{13}$C-NMR ($CDCl_3$): δ 117.1, 122.3, 123.4, 124.2, 126.5, 128.8, 142.4, and 153.4; m/z 195 (M+). Elemental analysis, Found, %: C, 80.37; H, 5.20; and N,14.43. $C_{13}H_{10}N_2$. Calculated, %: C 80.41; H 5.13; N 14.42.

*2-(o-Tolyl) 1H-benzo[d]imidazole (**3b**)*

White colored solid, m.p. 213-216 °C. $^{1}$H-NMR ($CDCl_3$): δ2.94 (s, 3H), 7.20-7.27 (m, 2H), 7.35-7.39 (m, 3H), 7.67 (s, 2H), 7.72 (d, 1H), and 12.15 (s, 1H). $^{13}$C-NMR ($CDCl_3$): δ 20.91, 122.79, 126.13, 129.63, 129.82, 131.36, 137.15, and 152.15. m/z 208 (M+). Elemental analysis, Found, %: C 80.76; H 5.80; and N 13.44. $C_{14}H_{12}N_2$. Calculated, %: C 80.72; H 5.82; and N 13.46.

*2-(p-Tolyl)1H-benzo[d]imidazole (**3c**)*

IR (cm$^{-1}$): 3378, 2913, 2838, 1821, 1516, 1452, 1398, 1482, 1242, 1173, and 1147; $^{1}$H-NMR (DMSO): 2.64 (s, 3H), 6.92 (d, 2H), 7.08 (d, 2H), 7.28 (d, 2H), 7.51 (d, 2H), and 12.35 (s, 1H). $^{13}$C-NMR (DMSO): δ 21.34, 122.69, 126.89, 127.81, 129.97, 140.22, and 158.83. m/z 208 (M+). Elemental analysis, Found, %: C 80.41; H 5.18; and N 14.41. $C_{13}H_{10}N_2$. Calculated, %: C 80.40; H 5.18; N 14.42.

*2-(2-Methoxyphenyl) 1H-benzo[d]imidazole (**3d**)*

White colored solid, m.p. 217-219 °C. $^{1}$H-NMR (DMSO): δ 3.73 (s, 3H), 7.22 (d, 2H), 7.39-7.34 (m, 3H), 7.54 (s, 1H), 7.68 (s, 1H), 7.76 (d, 1H), and 12.17 (s, 1H); $^{13}$C NMR (DMSO): δ 55.35, 114.22, 122.84, 125.23, 128.68, 134.57, 150.43, and 162.09; m/z 225. Elemental analysis, Found, %: C 75.00; H 5.38; N 12.48; and O, 7.14. $C_{14}H_{12}N_2O$. Calculated, %: 74.96; H 5.40; N 12.49; and O, 7.14.

*2-(3,4,5-Trimethoxyphenyl) 1H-benzo[d]imidazole (**3e**)*

White colored solid, m.p. 265-267 °C. IR (KBr, cm$^{-1}$): 2928, 2856, 1608, 1475, 1463, 1426, 1262, and 1097; $^{1}$H-NMR (400 MHz, DMSO): δ 3.93 (s, 3H), 4.10 (s, 6H), 7.44- 7.65 (m, 2H), 7.65 (s, 2H), and 7.86-7.97 (m, 2H). m/z 285 (m+1). Elemental analysis, Found, %: C 67.58; H 5.68; N 9.86; and O, 16.87. $C_{16}H_{16}N_2O_3$. Calculated, %: 67.62; H 5.40; N 12.48; and O, 7.12.

*2-(2-Chlorophenyl)-1H-benzo[d]imidazole (**3f**)*

White solid, m.p. 213-216 °C. $^{1}$H-NMR (DMSO): δ 7.63-7.88 (m, 1H), 7.65-7.68 (m, 1H), 7.57-7.68 (m, 3H), 7.27 (m, 2H), and 12.63 (s, 1H); $^{13}$C-

NMR (DMSO): δ115.67, 125.49, 126.48, 130.33, 131.54, 134.32, and 158.11. m/z: 228 (M+). Elemental analysis, Found, %: C 68.29; H 3.96; Cl, 15.52; and N 12.23. $C_{13}H_9ClN_2$. Calculated, %: C 68.29; H 3.96; Cl, 15.51; and N 12.24.

*2-(2, 4-Cholorophenyl) benzimidazole (**3g**)*

White Powder, m.p.: 289-291 °C, IR ($cm^{-1}$): 3435, 2988, 3059, 2736, 1925, 1619, 1440, 1104, and 1052; $^1$H-NMR ($CDCl_3$): δ 5.29 (s, 1H), 7.19-7.32 (m, 4H), 7.34-7.66 (m, 4H), and 8.29-7.31 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 76.88, 77.20, 77.56, 116.22, 122.28, 127.34, 128.12, 129.22, 130.84, 139.53, and 153.918; m/z = 267 (M+). Elemental analysis, Found, %: C 59.36; H 3.04; Cl, 26.96; and N 10.64. $C_{13}H_8Cl_2N_2$. Calculated, %: C, 69.38; H, 3.05; Cl, 26.94; and N, 10.64.

*2-(4-Bromophenyl)-1H benzo[d]imidazole (**3h**)*

White colored solid, m.p. 286-288 °C. $^1$H-NMR (DMSO): 7.16 (d, 2H), 7.22-7.28 (m, 2H), 7.76 (d, 2H), and 7.58 (s, 2H), δ12.85 (s, 1H); $^{13}$C-NMR (DMSO): δ, 122.84, 123.75, 128.83, 129.76, 132.45, and 156.64; m/z 272 (M+). Elemental analysis, Found, %: C, 57.18; H, 3.31; Br, 29.27; and N, 10.25. $C_{13}H_9BrN_2$. Calculated, %: C, 57.16; H, 3.33; Br, 29.25; and N, 10.27.

*2-(2-Nitrophenyl)-1H benzo[d]imidazole (**3i**)*

Yellow colored solid, m.p. 264-266 °C; $^1$H-NMR (DMSO) δ: 12.85 (s, 1H), 8.11 (dd, 2H), 7.84 (m, 1H), 7.76 (m, 1H), 7.65 (s, 2H), and 7.22 (s, 2H). m/z 240 (m+). Elemental analysis, Found, %: C 65.27; H, 3.79; N, 17.56, O, 13.38. $C_{13}H_9N_3O_2$. Calculated, %: 65.29; H, 3.78; N, 17.56, O, 13.37.

*2-(4-Nitrophenyl)-1H benzo[d]imidazole (**3j**)*

Faint yellow solid, m.p. 315-317 °C. IR (KBr, $cm^{-1}$) 3102, 1621, 1593, 1488, 1425, 1315, 1049, and 860; $^1$H-NMR (DMSO, 400 MHz): δ 5.28 (s, 1H), 7.13-7.29 (m, 4H), 7.30-7.61 (m, 4H), and 8.29-8.31 (d, 2H); $^{13}$C-NMR (DMSO): δ 77.08, 77.35, 77.86, 116.12, 123.12, 126.64, 129.85, 135.46, 138.58, 149.10, and 154.22; m/z 240 (m+). Elemental analysis, Found, %: C, 65.26; H, 3.80; N, 17.55; and O, 13.39. $C_{13}H_9N_3O_2$. Calculated, %: 65.28; H, 3.77; N, 17.59; and O, 13.36.

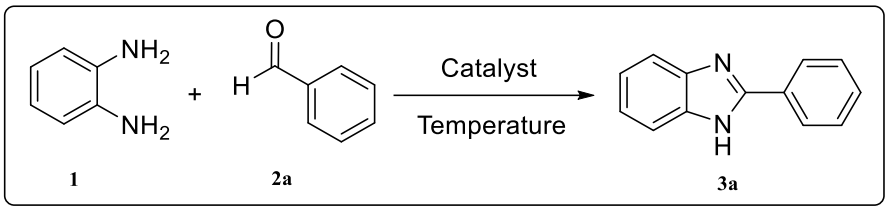
## Result and Discussion

*Catalytic activity*

Reaction conditions were optimized by the reaction of *o*-phenyl diamine and benzaldehydewere preferred as replica substrates. As a preliminary point, the initially reaction was started in absence of a catalyst and solvent free reaction which was carried at RT for 24 h, but reaction was not looking successful and deliver 0% of product yield (Table 1, Entry 1). Moving further to check effect of temperature for the synthesis of benzimidazole derivative in solvent free condition without any catalyst from o-phenyl diamine and benzaldehyde at 60 °C and 90 °C in a separate set of reaction was able to convert some starting material into product and afford 20% and 45% of yield, respectively (Table1, Entries 2-3). So far from above result it was clear that catalyst must be required to accelerate reaction. Regarding with this fact pentafluorophenylammonium triflate (0.8 mg) was used as a catalyst for bezimidazole synthesis without solvent at room temperature stirred continuously for 7 h to give 56% of product (Table1, Entry 4).

Accordingly, in next sequence of experiment taking the same reaction condition throughout as taken above but only the catalyst amount was changed to 0.5 mg, 0.3 mg, and 0.1 mg in different sets of reaction were formed 60%, 66% and 66% yield, respectively of the benzimidazole derivative within 7 h (Table 1, Entries 5-7). Solvent also play a vital role in the development of organic compound. Therefore, to justify solvent effect the process for the synthesis of benzimidazole starting from o-phenyl diamine and benzaldehyde at RT were proceeded with ethanol, benzene and dichloromethane in different set of reaction to produce 88, 74, and 68% yield of the product in 4 h, 9 h, and 7 h, respectively (Table1, entries 8-10). So far from result described above it was accomplished that development of benzimidazole begins with benzaldehyde, diamine at RT using ethanol as a solvent and

**Table 1.** Optimization of reaction condition for the synthesis of benzimidazole derivative **3a** from diamine and aromatic aldehyde **2a**




| Entry | Catalyst | Cat. Amount (mg) | Solvent | Temp. (°C) | Time (h) | Yield (%)[x] |
|---|---|---|---|---|---|---|
| **1** | - | - | - | r.t. | 24 | 00 |
| **2** | - | - | - | 60 | 24 | 20 |
| **3** | - | - | - | 90 | 24 | 45 |
| **4** | PFPAT | 0.8 | - | r.t. | 07 | 56 |
| **5** | PFPAT | 0.5 | - | r.t. | 07 | 60 |
| **6** | PFPAT | 0.3 | - | r.t. | 07 | 66 |
| **7** | PFPAT | 0.1 | - | r.t. | 07 | 66 |
| **8** | PFPAT | 0.1 | $C_2H_5OH$ | r.t. | 4 | 88 |
| **9** | PFPAT | 0.1 | $C_6H_6$ | r.t. | 09 | 74 |
| **10** | PFPAT | 0.1 | $CH_2Cl_2$ | r.t. | 07 | 68 |

*All reactant were taken in an equimolar quantity, X indicates isolated yield of the product*

**Table 2.** Benzimidazole synthesis from diamine and benzaldehyde and comparison of commercially available catalyst

| Entry | Catalyst (0.1 mg) | Time (h) | Conversion (%) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $ZnCl_2$ | 16 | 75 | 58 |
| 2 | $AlCl_3$ | 12 | 62 | 32 |
| 3 | $TiCl_4$ | 14 | 64 | 38 |
| 4 | $SnCl_2$ | 08 | 88 | 66 |
| 5 | $FeCl_3$ | 08 | 84 | 63 |
| 6 | $NiCl_2$ | 10 | 78 | 60 |
| 7 | $CuCl_2{\cdot}2H_2O$ | 09 | 63 | 40 |
| 8 | $Al(NO_3)_3$ | 14 | 50 | 28 |
| **9** | **PFPAT** | **04** | **100** | **88** |

*All reactants were taken in an equimolar quantity stirred at rt in ethanol as a solvent*
*[a] Isolated yield of the product*

PFPAT as a catalyst generate satisfactory yield with prominent reaction condition.

Comparison of various commercially available catalysts was done for the synthesis of benzimidazole from benzaldehyde and diamine at room temperature. In first attempt $ZnCl_2$ was used as a catalyst for the synthesis of corresponding benzimidazole, but reaction proceeded very slowly requires 16 h for the completion and gives only 58% of product (Table 2, Entry 1). With this unsatisfactory result, next synthesis carried out with $AlCl_3$ and $TiCl_4$ as a catalyst in separate reaction set for the synthesis of benzimidazole derivative from o-phenyl diamine and benzaldehyde stirring at room temperature using ethanol as a solvent to produce 32% and 38% yield of the product with 12 to 14 h of time required for completion (Table 2, Entries 2-3) which was still not enough. Moving forward with continuing the series of experiment using $SnCl_2$, $FeCl_3$ and $NiCl_2$for the benzimidazole preparation in ethanol as a solvent displayed 88, 84and 78% of conversion of starting material in to end product with 66%, 63%, and 60% of respective

**Table 3.** Optimization of amount of yield of benzimidazole derivative (**3a**-**3j**) synthesized from diamine and various aromatic aldehyde at room temperature

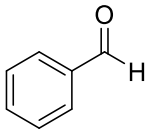
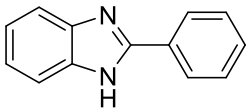
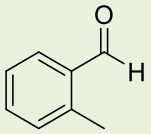
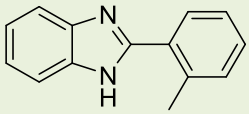
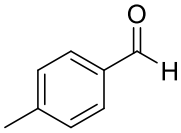
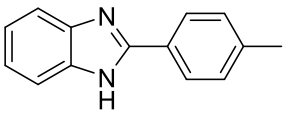
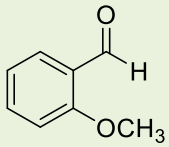
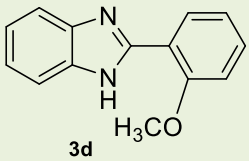
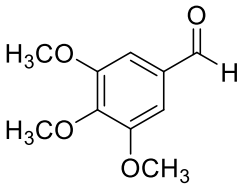
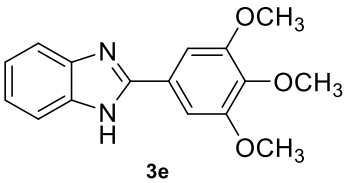
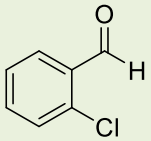
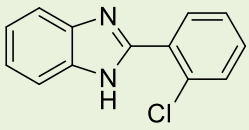
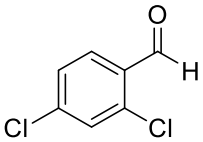
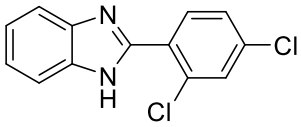
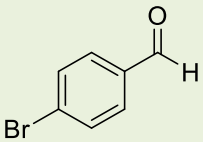
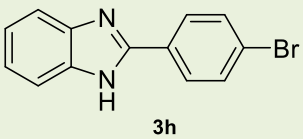
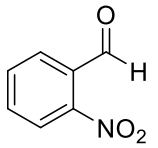
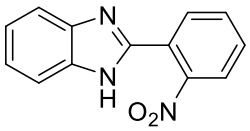
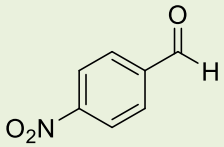
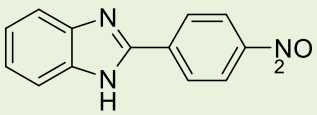
| Entry | Aromatic aldehyde | Product | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| **1** |  **2a** |  **3a** | 4 | 88 |
| **2** |  **2b** |  **3b** | 5 | 78 |
| **3** |  **2c** |  **3c** | 6 | 80 |
| **4** |  **2d** |  **3d** | 6 | 74 |
| **5** |  **2e** |  **3e** | 5.5 | 78 |
| **6** |  **2f** |  **3f** | 3 | 90 |
| **7** |  **2g** |  **3g** | 3.5 | 92 |
| **8** |  **2h** |  **3h** | 3 | 89 |

**Table 3.** Continued

| | | | | |
|---|---|---|---|---|
| 9 |  2i |  3i | 3.5 | 90 |
| 10 |  2j |  3j | 2.5 | 93 |

*All reactants were taken in an equimolar quantity stirred at rt in ethanol as a solvent in presence of PFPAT (0.1 mg) as a catalyst*

[a] *Isolated yield of the product*

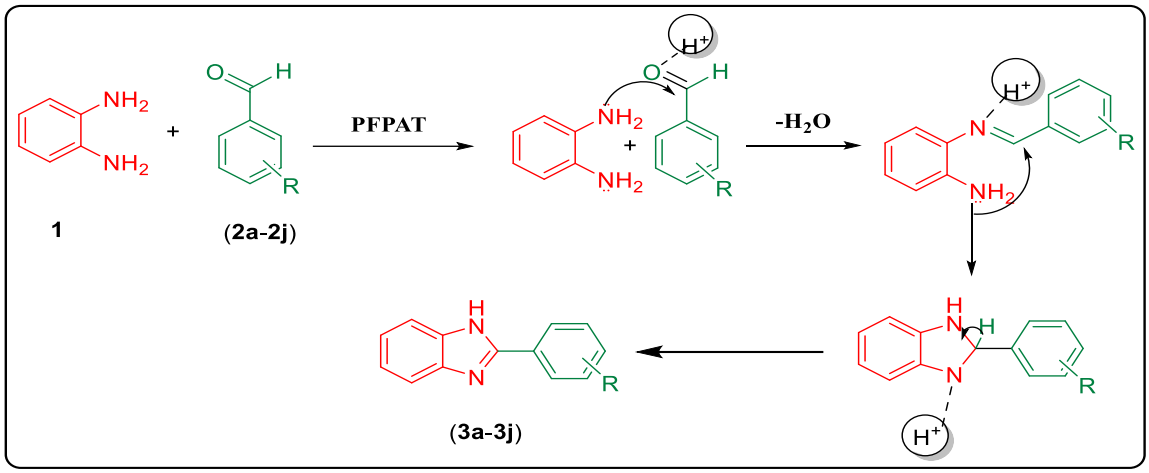
yield (Table 2, Entries 4-6). From above result, it was concluded that the synthesis using these catalyst was failed to reach optimum amount of product. Proceeding further with $CuCl_2 \cdot 2H_2O$ and $Al(NO_3)_3$ for the present protocol with the similar scenario described above generate again dissatisfactory result (Table 2, Entries 7-8). All the catalyst described above carried out reaction very sluggishly and unable to convert completely starting material into desired amount of product. Therefore, PFPAT was finally used as catalyst for the synthesis of benzimidazole from diamine and benzaldehyde at room temperature using ethanol as a solvent shows 100% conversion with 88% yield of respective product with short of time of 4 h only (Table 2, Entries 9). So from the above tabulated result, it was clear that the synthesis of benzimidazole from o-phenyl diamine and benzaldehyde at room temperature using ethanol as a solvent in presence of PFPAT as catalyst gives promising yield and it was considered as prominent condition for further synthesis of benzimidazole derivative. The obtained yield using catalyst after 2 cycle run was stable enough.

The result for optimization of amount of yield regarding the preparation of benzimidazole from *o*-phenyl diamine and aromatic aldehyde at RT using ethanol as a solvent in presence of PFPAT as a catalyst were tabulated in Table 3. In the first attempt, benzaldehyde was allowed to react with o-phenyldiamine to produce 88% product in 4 h (Table 3, Entry 1). The yield obtained was good and satisfactory. In this study, we approached to examine the effects of EDG and EWG on benzaldehyde for the synthesis of benzimidazole derivative.

The EDG such as 2-methyl benzaldehyde, 4-methyl benzaldehyde, 2-methoxy benzaldehyde, 3,4,5 methoxy benzaldehyde were allowed to react with o-phenyl diamine in separate set of reaction with stirring at RT using ethanol as a solvent in presence of PFPAT as a catalyst offers an 78%, 80%, 74%, and 78%, yield in 5, 6, 6, and 5.5 h, respectively (Table 3, Entry 2-5). Moreover, comparison of these result with EWG group substituted benzaldehyde such as 2-chloro benzaldehdye, 2,4 dichloro benzaldehyde, 2-nitro benzaldehyde, and 4-nitro benzaldehyde were allowed to react with o-phenyl diamine in separate set of reaction under presence of PFPAT as a catalyst within ethanol as a solvent at RT afford 90%, 92%, 89%, 90%, and 93% of corresponding yield of benzimidazole in 3, 3.5, 3, 3.5, and 2.5 h, respectively.

These results indicate that EWG group containing benzaldehyde is more reactive in the synthesis to generate excellent yield. Specifically elaborating, 4-nitrobenzaldehyde is highly reactive and gives dominating yield of 93% within the short time of 2.5 h.

The mechanism depicted in Scheme 2 shows catalyst activity as proton donor carries reaction forward and in the last step, catalyst releases from reaction which was isolated and purified later for next reaction.




**Scheme 2.** Possible mechanism for the development of benzimidazole from benzaldehyde and aromatic diamine catalysed by PFPAT

## Conclusion

A straight forward, proficient, and eco-friendly move toward for the development of substituted benzimidazoles by a single step reaction of o-phenylenediamine (1.0 mmol) with aromatic substituted aldehyde (1.0 mmol) in the attendance of pentafluorophenylammonium triflate (0.1 mg) catalyst. There are ten derivatives of synthesized benzimidazole. Among the previous methods, the advantages of the current method comprises simple process, easy work-up procedure, less reaction time, simple purification, mild reaction conditions, and admirable yields.

## Disclosure Statement

The authors declare that there is no conflict of interests in this study.

## Acknowledgments

The authors are thankful to the management and principals of their respective colleges for encouragement and assistance. They are also thankful to Solapur University for providing spectral and analytic data.

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