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# Facile and Efficient Method for Synthesis of Benzimidazole Derivatives Catalyzed by Zinc Triflate

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## ABSTRACT

**We report the synthesis of benzimidazole derivatives using zinc triflate as an efficient catalyst. One-pot synthesis of 2-substituted benzimidazole derivatives from *o*-phynelyenediamine and substituted aldehydes were developed under zinc triflate in ethanol solvent at reflux temperature.**

## KEYWORDS

**Benzimidazole Derivatives; *O*-Phynelyenediamine; Substituted Aldehydes; Zinc Triflate**

## 1. Introduction

Benzimidazole derivatives have received much interest in the field of medicinal chemistry [1,2]. Benzimidazole group of substances has found practical applications in a number of fields. Recently the interest in benzimidazole chemistry has been revived by the discovery that the 5,6-dimethyl benzimidazole moiety is part of the chemical structure of vitamin B12 [3]. Substituted Benzimidazoles display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as albendazole/mebendazole/thiabendazole (antihelmentic), omeprazole (anti-ulcer), etc. (**Figure 1**). Considerable interest has been focused on the benzimidazole structure. The discovery of this class of drugs provides an outstanding case history of modern drug development and also points out the unpredictability of pharmacological activity from structural modification of a prototype drug molecule. It is having a variety of medicinal applications. Benzimidazole derivatives carrying different substituent's in the benzimidazole structure were associated with a wide range of biological activities including anticancer, antiviral, antibacterial, antifungal, antihelmentic, anti-inflammatory, antihistaminic, proton pump inhibitor, antioxidant, antihypertensive and anticoagulant activities. Their derivatives were also found to exhibit cytotoxic activity. Substituted benzimidazole derivatives are evaluated by their ability to inhibit gastric $H^+/K^+$ ATPase and by blocking the gastric acid secretion [4]. Recently, benzimidazoles have also been used as ligands for asymmetric catalysis [5].

Many methods have been reported for the synthesis of these benzimidazole derivatives. The condensation of 1,2-phenylenediamines with carboxylic acids or their derivatives is a common method, but it needs harsh conditions like polyphosphoric acid [6] at 170˚C - 180˚C. Another alternative approach is the condensation of aldehyde with 1,2-phenylenediamine in presence of different catalysts like Indion 190 resin [7], $BF_3.OEt_2$ [8], Ceric ammonium nitrate [9], iodine, [10] Silica sulfuric acid [11], $In(OTf)_3$ [12], $SiO_2/ZnCl_2$ [13], silica supported sodium hydrogen sulphate [14], PEG [15], $H_2O_2/Fe(NO_3)_3$ [16]. In recent years, Solvent-free synthesis of benzimidazoles under microwave irradiation using $Yb(OTf)_3$ [17], KSF clay [18], metal halide supported alumina [19] and solid support [20,21] has been reported. However, many of these methods suffer from one or more drawbacks such as requirement of strong acidic conditions, long reaction times, low yields, tedious work-up procedures, requirement of excess amounts of reagents, and use of toxic reagents, catalysts or solvents.

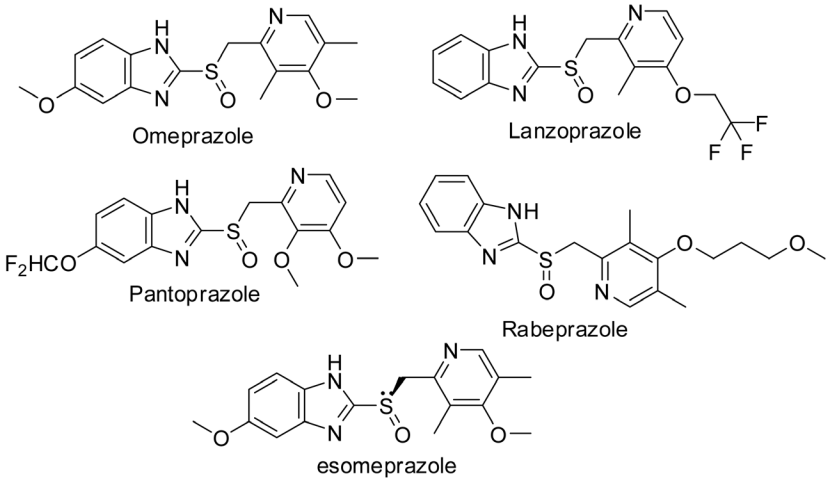



**Figure 1. Established antiulcer agents in clinical practice.**

Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of these heterocycles.

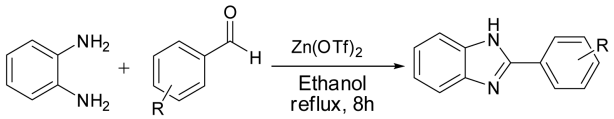
As part of our research program in developing various synthetic methodologies, we report the synthesis of benzimidazoles using zinc triflate as an efficient catalyst (**Scheme 1**). The catalyst is known as an efficient catalyst in the literature for various organic transformations [22-26].

## 2. Results and Discussions

In order to establish the optimum reaction condition for this reaction, different solvents and various mole ratios of zinc triflate were examined. In our preliminarily investigation was carried out on the model reaction of *o*-phenylenediamine and 4-methoxy benzaldehyde. As shown in **Table 1**, different solvents can result in different yields. It was found that ethanol is the best solvent for condensation reaction, with its fast conversion, high yield and low toxicity. Zinc triflate was added in various mole ratios in ethanol at reflux. As shown in **Table 2**. The best yields were obtained with 10 mol% of zinc triflate. The electronic effects of the different substituted aldehydes have been investigated in **Table 3** and it was observed that aldehydes bearing both electron donating and electron with drawing substituents gave the desired benzimidazoles in good yields. Products were confirmed by comparing with authentic sample ($^1$H NMR, MR and Mass).

## 3. Conclusions

In conclusion, Zinc triflate was found to be an efficient catalyst for the formation of benzimidazole from aldehydes and *o*-phenylenediamine. The use of this inexpensive and easily available catalyst makes this protocol practical, environment friendly and economically attractive. The simple work-up procedure, high yields of products and nontoxic nature of the catalyst are other advantages of the present method.




**Scheme 1. Synthesis of Benzimidazole derivatives catalyzed by zinc triflate.**

**Table 1. Effect of Solvent in the synthesis of 2-(4-Methoxyphenyl) benzimidazole.**

| Entry | Solvent | Temperature(˚C) | Time (hr) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 | 12 | 58 |
| 2 | $CH_3OH$ | 65 | 10 | 70 |
| 3 | $CH_3CH_2OH$ | 80 | 8 | 95 |
| 4 | THF | 68 | 12 | 62 |
| 5 | $CH_3CN$ | 85 | 10 | 72 |

[a]All are isolated yields.

**Table 2. various mole ratios of zinc triflate for the synthesis of 2-(4-Methoxyphenyl) benzimidazole.**

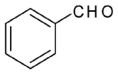
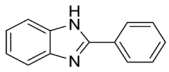
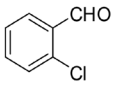
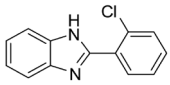
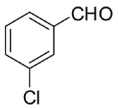
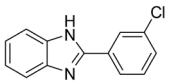
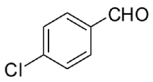
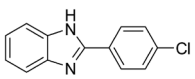
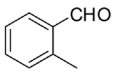
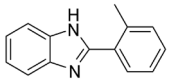
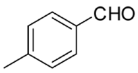
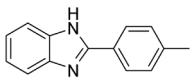
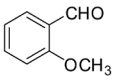
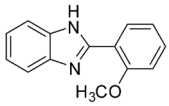
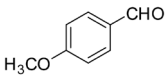
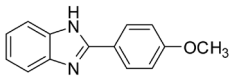
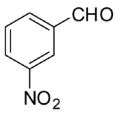
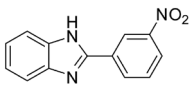
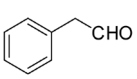
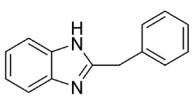
| Entry | Zinc triflate (mol%) | Time (hr) | Yield (%)[a] |
|---|---|---|---|
| 1 | 0 | 12 | 18 |
| 2 | 5 | 8 | 68 |
| 3 | 10 | 8 | 95 |
| 4 | 15 | 8 | 95 |
| 5 | 20 | 8 | 94 |

[a]All are isolated yields.

### 3.1. Experimental

All $^1$H NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ

**Table 3. synthesis of 2-substituted benzimidazoles from *O*-Phenylenediamine and aldehydes[a].**

| Entry | aldehyde | Benzimidazole | Yield[b] |
|---|---|---|---|
| 1 |  |  | 94 |
| 2 |  |  | 84 |
| 3 |  |  | 88 |
| 4 |  |  | 89 |
| 5 |  |  | 89 |
| 6 |  |  | 90 |
| 7 |  |  | 90 |
| 8 |  |  | 95 |
| 9 |  |  | 81 |
| 10 |  |  | 95 |

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), $Zn(OTf)_2$ (10 mol%) were stirred for 8h under reflux in Ethanol ,[b] isolated yields.

value with reference to Tetra methyl silane (TMS) as an internal standard. Products were purified by flash chromatography on 100 - 200 mesh silica gel. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

## 3.2. Zinc Triflate Catalyzed Synthesis of 2-Substituted Benzimidazole Derivatives from Aldehydes

A mixture of *o*-phenylenediamine (1 mmol), benzaldehyde (1.0 mmol) and $Zn(OTf)_2$ (10 mol%) in Ethanol (5 ml) was placed in a 50 ml round bottom flask and stirred at reflux for 8 h. The progress of the reaction was monitored by TLC Hexane: EtOAc (8:2) after completion of the reaction, the reaction mixture was cooled and treated by dilution with EtOAc (20 mL). Total organic layer was washed with water, brine solution and dried over $Na_2SO_4$ and evaporated under vacuum. Obtained crude residue was purified by column chromatography to give 2-substituted benzimidazoles.

**2-Phenylbenzimidazole [**27]**:** Off white solid; m.p: 289˚C - 291˚C; $^1$H NMR (DMSO-$d_6$): δ13.02 (br s, 1H), 8.20 (d, *J* = 7.6 Hz, 2H), 7.67 - 7.65 (m, 1H), 7.56 - 7.49 (m, 4H), 7.22 - 7.18 (m, 2H); (LC-MS) m*/z:* 195.08 [M + H]$^+$; IR (KBr, cm$^{-1}$): 3420, 2920, 2627, 1623, 1410, 1276, 1119, 970, 738.

**2-(2-Chlorophenyl) benzimidazole** [28]**:** Light pink red solid; m.p: 231˚C - 233˚C; $^1$H NMR (DMSO-$d_6$): δ12.80 (br s, 1H), 7.91 - 0.89 (m, 1H), 7.67 - 7.62 (m, 3H), 7.57 - 7.52 (m, 2H), 7.25 - 7.23 (m, 2H); (LC-MS) m*/z:* 229.04 [M + H]$^+$

**2-(3-Chlorophenyl) benzimidazole** [28]**:** Colourless solid; m.p: 234˚C - 236˚C; $^1$H NMR (DMSO-$d_6$): δ13.06 (br s, 1H), 8.40 (s, 1H), 8.27 (d, *J* = 6.8 Hz, 1H), 7.81 - 7.72 (m, 4H), 7.49 - 7.47 (m, 2H); (LC-MS) m*/z:* 229.04 [M + H]$^+$

**2-(4-Chlorophenyl) benzimidazole** [29]**:** Colour less solid; m.p: 289˚C - 291˚C; $^1$H NMR (DMSO-$d_6$): δ12.9 (br s, 1H), 8.15 (d, *J* = 8 Hz, 2H), 7.64 - 7.49 (m, 4H), 7.20 (d, *J* = 8 Hz, 2H); (LC-MS) m*/z:* 229.04 [M + H]$^+$

**2-*o*-tolylbenzimidazole** [27]**:** Colour less solid; m.p: 220˚C - 222˚C; $^1$H NMR (DMSO-$d_6$): δ13.03 (br s, 1H), 7.82 - 7.79 (m, 3H), 7.60 - 7.58 (m, 1H), 7.56 - 7.45 (m, 4H), 2.58 (s, 3H); (LC-MS) m*/z*: 209.10 [M + H]$^+$

**2-*p*-tolylbenzimidazole** [27]**:** Colourless solid; m.p: 265˚C - 267˚C; $^1$H NMR (DMSO-$d_6$): δ12.81 (br s, 1H), 8.06 (d, *J* = 8 Hz, 2H), 7.56 (m, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.19 (m, 2H), 2.38 (s, 3H); (LC-MS) m*/z*: 209.10 [M + H]$^+$

**2-(2-Methoxyphenyl) benzimidazole** [30]**:** Colourless solid; m.p: 173˚C - 175˚C; $^1$H NMR (DMSO-$d_6$): δ13.5 (br s, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 7.76 - 7.74 (m, 2H), 7.63 - 7.59 (m, 1H), 7.39 - 7.32 (m, 3H), 7.22 - 7.18 (m, 1H), 4.06 (s, 3H); (LC-MS) m*/z*: 225.07 [M + H]$^+$

**2-(4-Methoxyphenyl) benzimidazole** [27]**:** Colourless solid; m.p: 218˚C - 221˚C; $^1$H NMR (DMSO-$d_6$): δ12.90 (br s, 1H), 8.21 (d, *J* = 8.4 Hz, 2H), 7.70 - 7.68 (m, 2H), 7.38 - 7.36 (m, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); (LC-MS) m*/z*: 225.07 [M + H]$^+$

**2-(3-nitrophenyl) benzimidazole** [29]**:** Off-white so-

lid; m.p: 203˚C - 205˚C; $^1$H NMR (DMSO-$d_6$): δ13.2 (br s, 1H), 9.02 (s, 1H), 8.60 (d, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 7.85 (t, *J* = 7.9 Hz, 1H), 7.7 - 7.52 (m, 2H), 7.25 (t, *J* = 6.8 Hz, 2H); (LC-MS) m/*z*: 240.06 $[M + H]^+$

**2-benzylbenzimidazole** [27]**:** Off white solid; m.p: 177 - 179˚C; $^1$H NMR (DMSO-$d_6$): δ13.0 (br s, 1H), 7.52 - 7.50 (m, 2H), 7.34 - 7.16 (m, 7H), 4.21 (s, 2H); (LC-MS) m/*z*: 209.10 $[M + H]^+$

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