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# A facile and "Green" synthesis of 2-substituted benzimidazoles

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**ABSTRACT**

*2-Substitutedbenzimidazoles were prepared by condensing o-phenylenediamine phosphate with carboxylic acids under solution phase conditions.*

**Keywords:** *o*-phenylenediamine phosphate, 2-Substitutedbenzimidazoles, carboxylic acids, solution-phase.

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## INTRODUCTION

Substituted benzimidazoles have found applications in diverse therapeutic areas[1-9].The wide-spread interest in benzimidazole containing structures has prompted extensive studies for their synthesis. There are two broad based and general methods for the synthesis of 2-substitutedbenzimidazoles. The first one is a two-step process involving the dehydrogenative cyclisation of aniline-schiffs bases, generated insitu from the condensation of *o*-phenylenediamines and aldehydes. Various oxidative reagents such as $PhNO_2$ [10] cupric acetate[11], DDQ[12],$Pb(OAc)_4$[13],$MnO_2$[14],oxone[15], etc. have been employed. The second method involves coupling of *o*-phenylenediamine with carboxylic acids[16] under thermal/under cyclodehydrative conditions. However, many of these procedures involve toxic reagents or environmentally non-friendly reagents or very strong conditions.

## MATERIALS AND METHODS

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. TLC analysis was performed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded on Perkin – Elmer model 446 instrument in KBr phase. $^1H$ NMR was recorded in $CDCl_3$/DMSO-$d_6$ using 400 MHz Varian Gemini spectrometer and mass spectra were recorded on LCMS spectrometer.

**a) Preparation of *o*-PDA phosphate 2**

To a solution of *o*-Phenylenediamine **1** (0.54 g, 5 mmol) in $CH_3CN$ (5 ml), conc.$H_3PO_4$ (0.8 ml) (commercial ortho phosphoric acid) was added drop by drop under ice-cold conditions over a period of 8 mts. After the completion of addition, the separated product was filtered, washed with chilled $CH_3CN$ and dried; Yield=1.0 g (98% molar).

**b) Preparation of 2-substitutedbenzimidazoles 3**

**i) Under solution phase (General procedure): a) Ethylene glycol/ Ethanol as solvent:**

A mixture of *o*-PDA Phosphate **2**& carboxylic acid (1:1.5 equiv.) in ethanol/ethylene glycol (10 ml) was refluxed for 3 h. Then, the reaction mixture was cooled to RT and poured into ice-cold water (150 ml). The reaction mixture was neutralized with aq. Ammonia. The separated solid was filtered, washed with water, dried & recrystallized from suitable solvent to obtain the pure product **3**.

**2-(2-Chloro-ethyl)-1H-benzimidazole(4g):** Light Yellowish solid, mp 122°C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$: 9.32(s, 1**H**, -N**H**), 7.25-7.39(t, 2H, Bz-**H**), 7.45-7.47(d, 1H, Bz-**H**), 7.57-7.59(d, 1H, Bz-**H**), 3.43-3.46(t, 2H, -C**H**$_2$), 2.62-2.64(t, 2H, -C**H**$_2$); - LC/MS: *m/z* = 181 ($M^+$ + 1); Elemental analysis(%) found: **C** 59.63, **H** 4.81, **N** 15.22, Calculated for $C_9H_9ClN_2$, **C** 59.84, **H** 5.02, **N** 15.51.

**1-(1H-Benzimidazol-2-yl)-ethanol (4h):** White solid,mp 111°C, $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$: 9.13(s, 1**H**, -N**H**), 7.29-7.31(t, 2H, Bz-**H**), 7.48-7.50(d, 1H, Bz-**H**), 7.62-7.63(d, 1H, Bz-**H**), 4.63-4.66(q, 1H, -C**H**), 2.46-2.47(s, 1H, -O**H**), 1.82-1.96(d, 3H, -C**H**$_3$); - LC/MS: *m/z* = 163 ($M^+$ + 1); Elemental analysis(%) found: **C** 66.48, **H** 6.03, **N** 17.11, Calculated for $C_9H_{10}N_2O$, **C** 66.65, **H** 6.21, **N** 17.27.

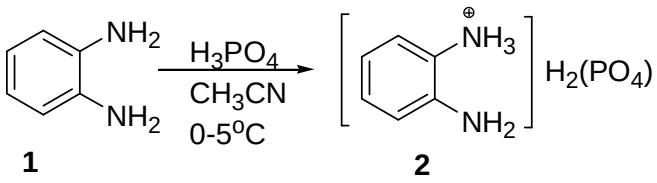
**1-(1H-Benzimidazol-2-yl)-propan-1-ol(4j):** White solid,mp 111°C, $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$: 9.21(s, 1**H**, -N**H**), 7.26-7.71(m, 4H, Bz-**H**), 4.36-4.38(t, 1H, -C**H**), 2.21-2.27(s, 1H, -O**H**), 1.63-1.84(m, 3H, -C**H**$_2$), 0.81-0.96(t, 3H, -C**H**$_3$),; - LC/MS: *m/z* = 177 ($M^+$ + 1); Elemental analysis(%) found: **C** 68.03, **H** 6.71, **N** 15.67, Calculated for $C_{10}H_{12}N_2O$, **C** 68.16, **H** 6.86, **N** 15.90.

**2-Styryl-1H-benzimidazole (4o):**Yellowish solid, mp 158°C, $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$: 9.87(s, 1**H**, -N**H**), 6.71-8.56(m, 9H, five protons of styryl-**H** and four protons of Bz-**H**), 6.42-6.47 (s, 2**H**, Vinylic); - LC/MS: *m/z* = 221 ($M^+$ + 1); Elemental analysis(%) found: **C** 81.48, **H** 5.22, **N** 12.53 Calculated for $C_{15}H_{12}N_2$, **C** 81.79, **H** 5.49, **N** 12.72.

## RESULTS AND DISCUSSION

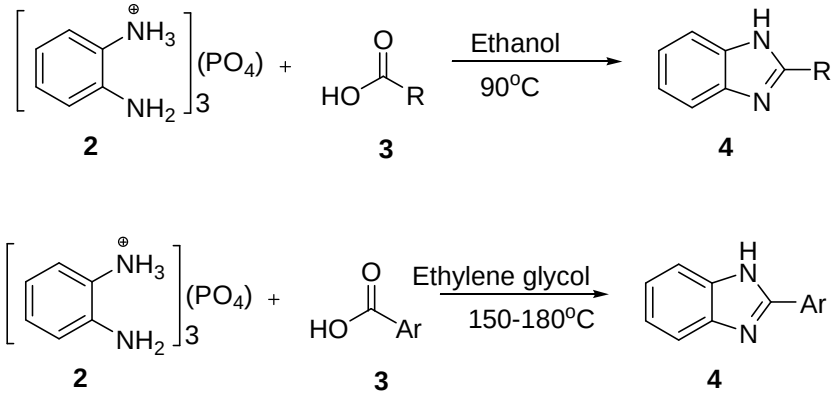
In continuation of our earlier studies [17-27] on synthesis of benzimidazole derivatives, we wanted to develop an environmentally friendly process for synthesis of 2-substituted benzimidazoles. We decided to look at the use of phosphate salt of *o*-phenylenediamine (*o*-PDA) for condensing with carboxylic acids for the synthesis of 2-substitutedbenzimidazoles.

Treatment of *o*-phenylenediamine (**1**) with orthophosphoric acid in acetonitrile under ice cold conditions resulted in the formation of *o*-phenylenediamine phosphate (**2**). The phosphoric acid content in the salt i.e. *o*-PDA-phosphate **2** was determined volumetrically by titrating solution of**2** with standard sodium hydroxide solution which was inturn standardized with primary standard oxalic acid solution. On subsequent calculation the composition was found to be *o*-PDA:$H_3PO_4$=3:1. The filtrate of acetonitrile solution was reused for the preparation of **2** in the second run (Scheme 1) showing good recyclizability.




**Scheme 1: Preparation of *o*-PDA phosphate**

Reaction of **2** with diverse carboxylic acids, viz. formic acid, acetic acid, propionic acid, butyric acid, valeric acid, hexanoic acid, benzoic acid and cinnamic acid, in an alcohol as solvent, under heating conditions, yielded the corresponding 2-substitutedbenzimidazole **3**. (Scheme 2, Table 1).




**Scheme 2: Preparation of 2-substituted Benzimidazoles**

In the above reaction, a high boiling solvent i.e. ethylene glycol was used when less reactive acids such as benzoic acid or cinnamic acid were used for condensation. When aliphatic acids such as formic acid, acetic acid, formic acid, propionic acid, butyric acid, valeric acid, hexanoic acids were used for condensation, ethanol was used as solvent (Table 1, Scheme- 2).

The products obtained were found to be identical with those of the literature products in all respects [28-33**]**.

**Plausible mechanism for the formation of benzimidazole:**

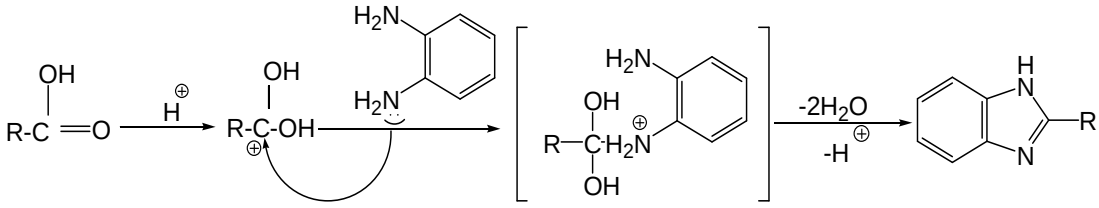



**Table 1:**

| Carboxylic acids 3(a-t) | Product 4(a-t) | M. P. (°C) | Time (Min) | Yield (%) |
|---|---|---|---|---|
| Formic acid (**3a**) | **(4a[a])** | 172 | 15 | 80 |
| Acetic Acid (**3b**) | **(4b[a])** | 178 | 12 | 88 |
| Propionic Acid (**3c**) | **(4c [a])** | 169 | 15 | 80 |
| Butyric Acid (**3d**) | **(4d[a])** | 164 | 18 | 78 |
| Pentanoic Acid (**3e**) | **(4e[a])** | 158 | 25 | 75 |
| Chloroacetic acid(**3f**) | **(4f[a])** | 147 | 20 | 70 |
| 2-chloropropionoicacid (**3g**) | **(4g)** | 128 | 25 | 60 |
| 2-hydroxyethanoic acid (**3h**) | **(4h[a])** | 173 | 25 | 55 |
| Lactic Acid (**3i**) | **(4i)** | 177 | 15 | 80 |
| Benzoic acid (**3j**) | **(4j[a])** | >250 | 25 | 85 |
| 4-chloro Benzoic acid (**3k**) | **(4k[a])** | >250 | 25 | 80 |
| 4-fluorobenzoic acid (**3l**) | **(4l[a])** | >250 | 30 | 75 |
| 4-methylbenzoic acid (**3m**) | **(4m[a])** | 195 | 30 | 75 |
| 4-methoxybenzoic acid (**3n**) | **(4n[a])** | 175 | 35 | 75 |
| Cinnamic acid (**3o**) | **(4o)** | 158 | 35 | 72 |

*[a]referes to reference 33*

In all the above set of methods, the reaction mixture was poured into ice-cold water and neutralized with aq. ammonia solution resulting in the formation of crude product and ammonium phosphate in the aq. filtrate. The crude products were used for the recrystallisation process resulting in the formation of pure products. The filtrate could be readily drained without further processing since it does not affect the environment as it contains the well-known soil friendly & fertilizer ammonium phosphate.

## CONCLUSION

In conclusion, it may be said that a new, facile method for the synthesis of 2-substituted benzimidazoles. The notable features of these procedures are high conversions, enhanced reaction rates, cleaner reaction profiles and environmentally benign effluents for the synthesis of title compounds.

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