Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Research Article

Synthesis of various substituted benzimidazole derivatives using various solvents used for reaction

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Received 16 January 2019; received in revised form 04 February 2019; accepted 05 February 2019
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ABSTRACT
Benzimidazole is the heterocyclic compound formed from benzene and imidazole ring containing nitrogen, oxygen sulphur and its derivatives are of wide interest because of their diverse biological activity. A new method for synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k) are developed by using simple method, green approach in good yields. We have synthesized 33 molecules in gram scale. This method is extremely useful for the synthesis of benzimidazole derivatives in excellent yields.

KEYWORDS
Green approach, benzimidazole, aldehydes

1. INTRODUCTION

The imidazole and benzimidazole nucleus are important building blocks in the drug discovery. The imidazole ring system is considered to be one of the most imperative heterocyclic substructures found in a large number of natural products and pharmacologically active compounds. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-malarial, cytotoxic and anti-tubercular agents [1]. An examination of literature revealed that imidazole and their analogues usually possess diverse biological activities like antimicrobial, antioxidant, antihemolytic, cytotoxic and antimycobacterial [2-3]. Based on several literature surveys, imidazole derivatives show a range of pharmacological activities, such as antimicrobial, anti-tubercular, antiviral [4-9], antioxidant and antifungal [10], antidepressant [11], anti-inflammatory and analgesic [12], anti-tuberculosis [13] anticancer [14-15]. The imidazole scaffold is present in many natural products and is a bioactive substance in human metabolism [16].

With this in mind, we initiated a program to synthesized benzimidazole derivatives by using DMSO solvent, phase transfer catalyst under reflux as well as using green approach.

2. MATERIALS AND METHODS

Scheme 1. Synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

2.1. General procedure synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

To a mixture of substituted aromatic aldehyde 10 mmole and orthophenyldiamine 10 mmole along with 20 ml of DMSO in round bottom flask reflux for definite time. To monitored the reaction by thin layer chromatography. After completion of reaction cool the reaction mixture at room temperature, solid obtained, filter and dry the product. Solvent reused for reaction.

Spectral data of 2-phenyl-1H-benzo[d]imidazole **(3a)**

Yellow solid, Yield: 75%, mp 290–292 ºC; ES-MS m/z: 194.33 IR (νmax/ cm^{-1}): 3027 (NH), 2843 (aromatic CH), 1578 (C=N), 1461 (C=C), 1415 (C=C), ^{1}H NMR (400 MHz, $CDCl_3$): δppm = 7.70–7.80 (m, 5H, H-Aromatic), 7.80-7.82 (d, 2H, H-Aromatic), 8.13-8.15 (d, 2H, H-Aromatic), 8.70 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δppm = 115.2, 123.5, 129.3, 131.2, 131.8, 134.7, 138.8, 141.4.

Table 1. Physical data of synthesized compounds **(3a-k)**

Sr. No.	Entry	Aromatic group	Time (min)	Yield (%)	M.P. (^0C)
1.	3a	C_6H_5	90	75	290
2.	3b	2-ClC_6H_4	80	78	136

3.	3c	3- ClC_6H_4	80	76	238
4.	3d	4- $MeOC_6H_4$	95	70	218
5.	3e	2-$NO_2C_6H_4$	70	90	258
6.	3f	3- $NO_2C_6H_4$	70	90	303
7.	3g	4- $NO_2C_6H_4$	70	90	307
8.	3h	4-MeC_6H_5	90	70	264
9.	3i	4-$Me_2NC_6H_4$	90	70	236
10.	3j	2-Furanyl	90	70	287
11.	3k	4-$OCH_2OC_6H_3$	95	60	248

Using Octane

Octane is non-polar solvent. It have higher boiling point than other lower hydrocarbons. It is used as solvent in many reactions.

Simple condensation reaction is carried using orthophenyl diamines and aromatic aldehydes under reflux condition and green approach.

Scheme 2. Synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

2.2. General procedure synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

To a mixture of substituted aromatic aldehyde 10 mmole and orthophenyldiamine 10 mmole along with 30 ml of octane in round bottom flask reflux for definite time. Reaction is monitored by thin layer chromatography. After completion of reaction cool the reaction mixture at room temperature, solid obtained, filter and dry the product. Solvent reused for reaction.

Table 2. Physical data of synthesized compounds **(3a-k)**

Sr. No.	Entry	Aromatic group	Time (min)	Yield (%)	M.P. (^{0}C)
1.	3a	C_6H_5	150	50	292
2.	3b	2-ClC_6H_4	130	70	135
3.	3c	3- ClC_6H_4	130	70	238
4.	3d	4- $MeOC_6H_4$	150	50	217
5.	3e	2-$NO_2C_6H_4$	120	80	258
6.	3f	3- $NO_2C_6H_4$	120	80	301
7.	3g	4- $NO_2C_6H_4$	120	80	306
8.	3h	4-MeC_6H_5	140	70	266
9.	3i	4-$Me_2NC_6H_4$	140	60	237
10.	3j	2-Furanyl	150	60	288

11.	3k	4-$OCH_2OC_6H_3$	150	60	245

Using Phase Transfer Catalyst

Condensation reactions using suitable oxidants are very important in synthetic organic chemistry and are employed for the synthesis of various organic compounds Phase transfer catalysis (PTC) is relatively a new technique to carry out various reactions with high yield and under mild conditions. PTC are able to transfer the inorganic oxidant from aqueous phase to organic phase and the reaction takes place smoothly in the organic phase. Cost reduction and pollution prevention which are the driving force of a chemical industry today can be achieved by implementing PTC technique.

Tetrabutyl ammonium bromide (TBAB), tetrabutyl phosphonium bromide(TBPB), tetrabutylammonium hydrogen sulphate (TBAHS) and cetyltrimethylammonium bromide (CTMAB).

Simple condensation between orthophenyl diamines and aromatic aldehyde in presence of phase transfer catalyst and catalyst reaction carried using green approach and conventional approach.

Scheme 3. Synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

2.3. General procedure synthesis of 2-(substituted phenyl)-1H-benzo[d]imidazole (3a-k)

To a mixture of substituted aromatic aldehyde 10 mmole and orthophenyldiamine 10 mmole along with 2 gm of phase transfer catalyst in solvent like toluene and reflux for appropriate time reaction is monitored by thin layer chromatography. After completion of reaction, filter the reaction mixture and cool, solid obtained and recrystallization from ethyl alcohol.

Table 3. Physical data of synthesized compounds **(3a-k)**

Sr. No.	Entry	Aromatic group	Time (min)	Yield (%)	M.P. (^{0}C)
1.	3a	C_6H_5	100	75	294
2.	3b	2-ClC_6H_4	90	80	136
3.	3c	3- ClC_6H_4	90	86	236
4.	3d	4- $MeOC_6H_4$	90	74	218
5.	3e	2-$NO_2C_6H_4$	80	89	257
6.	3f	3- NO $_2C_6H_4$	80	89	300
7.	3g	4- $NO_2C_6H_4$	80	90	305
8.	3h	4-MeC_6H_5	95	70	265
9.	3i	4-$Me_2NC_6H_4$	95	70	237

10.	3j	2-Furanyl	100	80	289
11.	3k	4-$OCH_2OC_6H_3$	110	78	247

3. RESULTS AND DISCUSSION

In scheme 1, Reaction is carried at reflux condition in high boiling solvent DMSO. The DMSO solvent is recovered and reused for the next reaction. This procedure gives 70-90 % yield and no need for any catalyst used for the reaction. This is better approach for the synthesis of benzimidazole derivatives.

In scheme 2, this is better approach for synthesis of benzimidazole derivatives. It cannot use any catalyst for reaction. It is carried under reflux condition. This is low boiling solvent it requires more time and yield is also less than high boiling solvent.

In scheme 3, this is green approach for the synthesis of benzimidazole derivatives. This reaction carried using toluene as non-polar solvent. Phase transfer catalyst remains as residue on the filter paper. It gives 70-90% yield for the reaction.

4. CONCLUSION

In summary, an efficient and convenient synthesis and this is green approach for the synthesis of benzimidazole derivatives in good to excellent yields. The importance of the substituted benzimidazole derivatives would render this protocol attractive for both synthetic and medicinal chemistry.

5. ACKNOWLEDGEMENT

The authors thankful to Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004 (MS), India for providing the laboratory facility.

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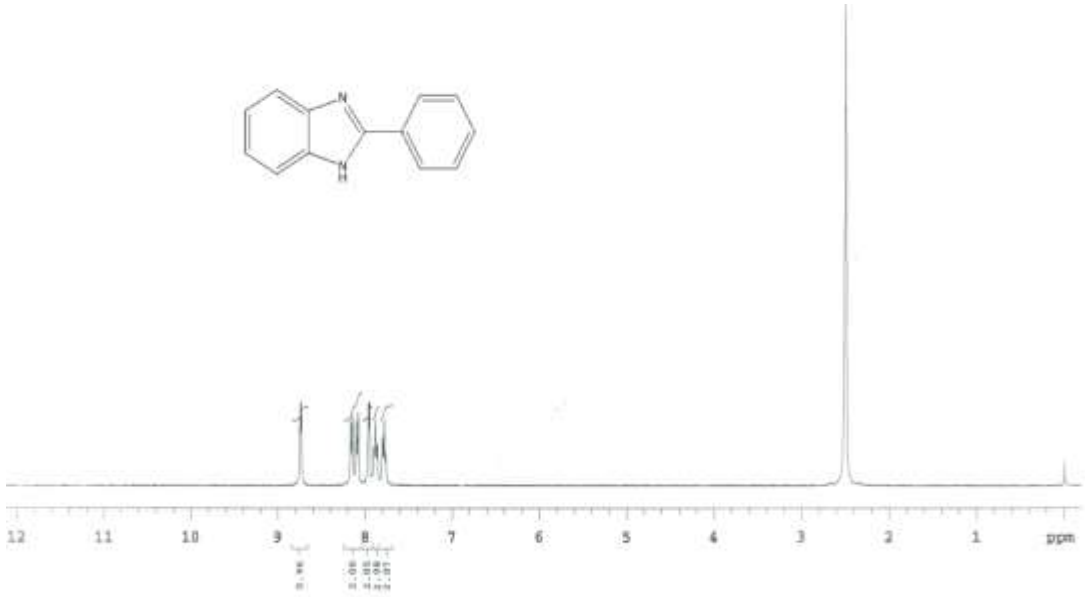

Figure 1. ^{1}H NMR spectra of 2-phenyl-1H-benzo[d]imidazole **(3a)**

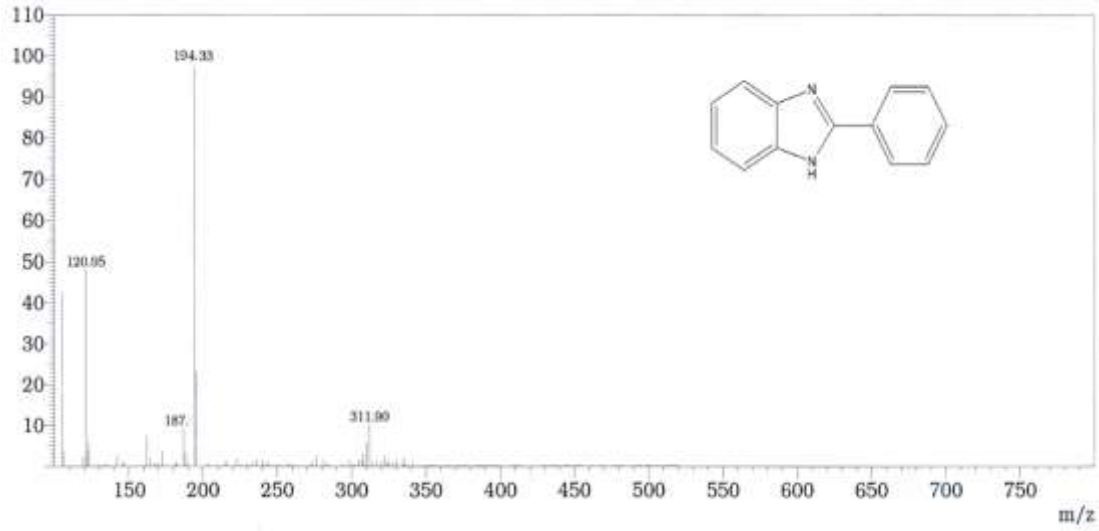

Figure 2. Mass spectra of 2-phenyl-1H-benzo[d]imidazole **(3a)**

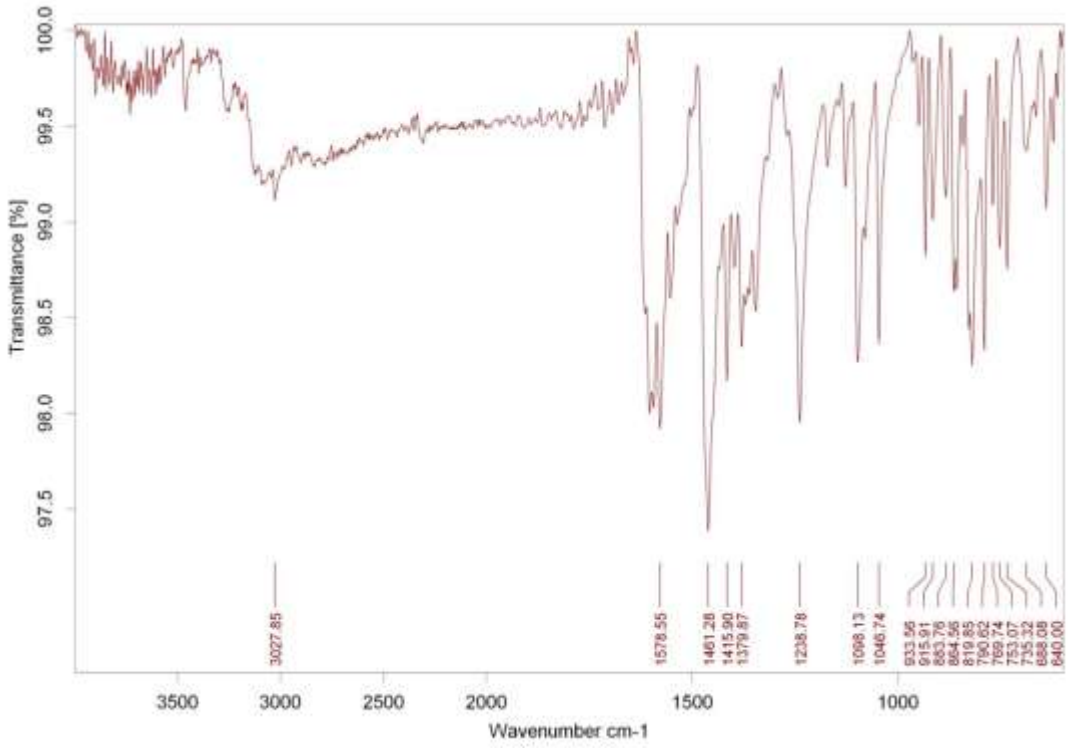

Figure 3. IR spectra of 2-phenyl-1H-benzo[d]imidazole (**3a)**