

[BMIM][Cl]-Mediated Eco-Friendly One-Pot Synthesis of Benzimidazole Derivatives Under Microwave and Ultrasound Irradiation.

Suvarna D. Shinde^a, Rajesh. K. Manjul^b, Vilas. B. Gade^a, Namdev T. Dhokale^{C*},
Mohan D. Sangale^{a*}

a. P. G. and Research Center, Department of Chemistry, S. S. G. M. College, Kopergaon, Dist: Ahmednagar, MH 423601, India.

b. P. G. and Research Center, Department of Chemistry, Sahakar Maharshi Bhausaheb Santuji Thorat College of Arts, Science & Commerce, Sangamner, Ahmednagar (MH) 422605, India.

c. P. G. and Research Center, Department of Chemistry, K. J. Somaiya College, Kopergaon
Corresponding Author: Suvarna D. Shinde

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ABSTRACT:

We present an eco-friendly and straightforward method for synthesizing benzimidazole derivatives through the multicomponent condensation of In the present work various substitute aromatic aldehydes were condensed with benzene-1,2-diamine to give 2-phenyl-1H-benzo[d]imidazole derivatives in the presence of 1-Butyl-3-Methylimidazolium Chloride as a catalyst in ethanol under conventional reflux condition, ultrasound irradiation in ethanol and microwave irradiation under solvent free condition for appropriate time. The one-pot synthesis, excellent isolated yield, underscores the efficiency of this environmentally conscious approach. Structural characterization was conducted using analytical techniques, including Fourier Transform Infrared Spectroscopy (FT-IR) and ¹H and ¹³C Nuclear Magnetic Resonance (NMR) Spectroscopy. The electronic synthesis of benzimidazole derivatives, facilitated by the catalytic action of 1-Butyl-3-Methylimidazolium Chloride, has proven highly effective in achieving maximum yields.

Keywords: solvent free conditions, one-pot synthesis, US, microwave reactions.

I. INTRODUCTION

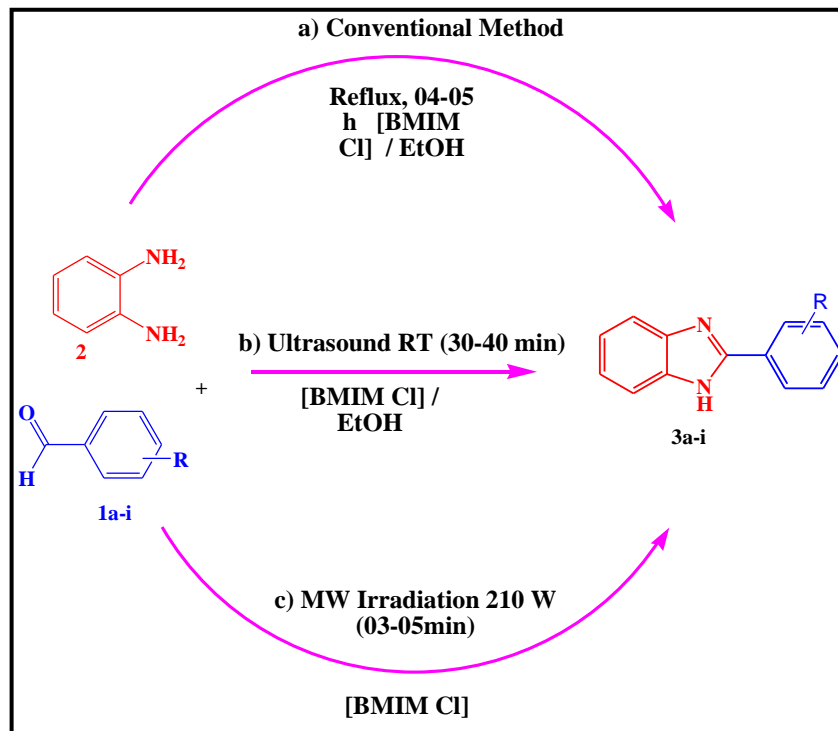
In pharmaceutical, industrial, agricultural, and synthetic organic chemistry, the benzothiazole and its derivatives represent a significant class of heterocyclic molecules. They are frequently used in bioorganic and medicinal chemistry for anticancer, anticonvulsant, and antiviral applications in drug discovery[1-3]. They also have industrial uses as vulcanization promoters, antioxidants, and dopants in light-emitting organic electroluminescent

devices. Additionally, several rigid-rod polymers with high tensile strength, thermal stability, and modulus have an essential nucleus made of benzothiazole. Microbial disorders are more common today than they were in the first half of the 20th century, although clinical diagnosis is still challenging. Clinical practice has employed a variety of synthetic and semi-synthetic antibacterial medicines to treat them[4-7]. Even though there are many antimicrobial agents available, only a few numbers of effective antimicrobial medications are employed in the treatment of microbial diseases[8]. Many of the medications that are now on the market are poisonous, encourage recurrence because they are bacteriostatic/fungistatic rather than bactericidal/fungicidal, or they create resistance development because of prolonged administration times. Due to the lack of access to desired medications, the impact is particularly severe in underdeveloped nations[9,10]. There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanisms of actions that are distinct from those of well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. One of the most adaptable classes of chemicals against microorganisms, benzimidazoles continue to be, according to the results of various attempts to generate new structural prototypes in the hunt for efficient antimicrobials [11-15]. A wide spectrum of microbiological activities are covered by the benzimidazole, which has been a significant pharmacophore and favoured structure in medicinal chemistry (Goker et al., 2005). By adding various substituents at various locations, a

total of six substituted benzimidazole derivatives were created. One of the earliest nitrogen heterocycles known as benzimidazole was created by Hoebrecker in 1872 and later by Ladenberg and Wundt between 1874 and 1878 [16-18]. In nature, the cobalt ions in vitamin B12 are axially liganded by N-ribosyl dimethylbenzimidazole. Due to its inclusion in a variety of bioactive substances, including antiparasitics, analgesics, antihypertensives, antivirals, and anticancers, benzimidazole has developed over many years of active research into an important heterocyclic system. For instance, omeprazole is used as a proton pump inhibitor, telmisartan and candesartan are used as antihypertensives, and astemizole, clemizole, and bilastine are used as anti-histaminic medications. Therefore, the creation of a process for making benzimidazoles has received a lot of interest [19-25]. The traditional method of production involves oxidative coupling with aldehydes to condense *o*-phenylenediamines with carboxylic acids or their derivatives under severe

dehydrating conditions [26]. In the meantime, reports on the synthesis of benzazoles using aerobic catalytic oxidative cross-coupling processes with either alcohols or amines as substrates have also been made. Considering these literature precedents, and drawbacks, such as the competitive formation of 2-substituted and 1,2-disubstituted benzimidazoles [8] and the need for expensive catalysts/reagents/starting materials, the development of facile and practical methods for the formation of 1,2-diphenyl-1H-benzo[d]imidazoles is the formation of 1,2-diphenyl-1H-benzo[d]imidazoles using oxygen as a hydrogen acceptor [27-3].

In the present work various substitute aromatic aldehydes (1a-j) were condensed with benzene-1,2-diamine (2) to give 2-phenyl-1H-benzo[d]imidazole derivatives (3a-i) in the presence of Ascorbic acid as a catalyst in ethanol under conventional reflux condition, ultrasound irradiation in ethanol and microwave irradiation in ethanol and microwave irradiation under solvent free condition for appropriate time.



Scheme: Synthesis of benzo[d]imidazole derivatives (3a-i)

II. EXPERIMENTAL

General procedure for the synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives

a) Under reflux condition

A mixture of Substituted aromatic aldehydes 1 (1 mmol), benzene-1,2-diamine 2 (1 mmol) and a catalytic amount of Ascorbic acid (10 mmol %) was taken in a round bottom flask containing 10 mL of ethanol. The reaction mixture was refluxed for completion of the reaction. The course of the reaction was monitored by thin layer chromatography. After completion of the reaction the mixture was poured into crushed ice. Solid product thus obtained was separated by filtration, dried well, and recrystallized by ethanol. The physical data of synthesized compounds are given in **Table 1B**.

b) Under US irradiation

A mixture of Substitute aromatic aldehydes 1 (1 mmol), benzene-1,2-diamine 2 (1 mmol) and catalytic amount of Ascorbic acid (10 mmol %) was taken in a round bottom flask containing 10 mL of ethanol. The round bottom flask was placed in an US bath for 7-9 min at room temperature. The course of the reaction was monitored by thin layer chromatography. After completion of the reaction the mixture was poured into crushed ice. Solid product derivative thus obtained was separated by filtration, dried well, and recrystallized by ethanol. The same procedure was applied for the remaining substituents for confirming the consistency of the method. The physical data of synthesized compounds are given in **Table 1**.

c) Under MW irradiation

A 10 mL round bottom flask was charged substituted aromatic aldehydes 1 (1 mmol),

benzene-1,2-diamine 2 (1 mmol), catalytic amount of Ascorbic acid (10 mmol %), and placed under MW irradiation at 210 W for 3-5min. The course of the reaction was monitored by thin layer chromatography. After completion of the reaction the mixture was poured into crushed ice, the solid product thus obtained was separated by filtration, dried well, and recrystallized by ethanol. The same procedure was applied for the remaining substituents for confirming the consistency of the method. The physical data of synthesized compounds are given in **Table 1**.

III. RESULTS AND DISCUSSION

In order to produce the best results, benzene-1,2-diamine 2 (1 mmol) and 2-phenyl-1H-benzo[d]imidazole 1a (1 mmol) were treated in ethanol with ascorbic acid as the catalyst. The synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives require the catalyst, since it was noted that the reaction could not continue in the absence of ascorbic acid and that good results could only be produced with 10 mmol% ascorbic acid under reflux conditions (**Table 5.2B**., Entry 6).

When the same reaction was conducted at room temperature while being exposed to ultrasound, the desired product was produced quickly and with a high yield (**Table 5.2B**.Entry 7). The model reaction did not function at 140 W under microwave irradiation either, but it performs best at 210 W (**Table 1**. Entry 9). Our efforts concentrated on the synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives utilising variously substituted heterocyclic aldehydes and benzene-1,2-diamine in order to assess the breadth and limitations of our study (**Table 5.3B**.) Both standard and non-conventional procedures produced compounds in good yields from aldehydes containing electron-donating and electron-withdrawing groups.

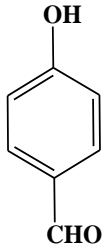
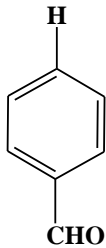
Table 1. Optimization of reaction condition to synthesize 2-phenyl-1H-benzo[d]imidazole derivatives (3a)

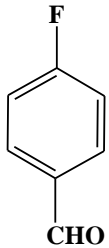
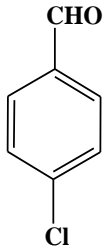
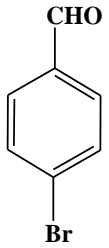
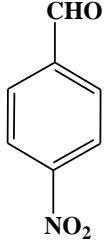
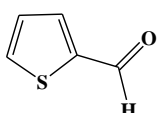
Entry	Catalyst / Solvent	Reaction Condition	Time	Yield in%
1	No Catalyst/EtOH	Stirring	5 h	NR
2	No Catalyst/EtOH	US irradiation	2 h	NR
3	No Catalyst/SF	MW irradiation	30 min	NR

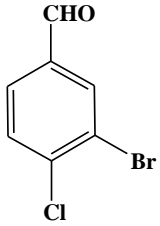
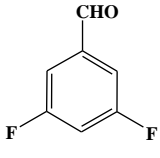
4	10 mmol % Ascorbic acid /EtOH	Stirring at RT	2 h	NR
5	5 mmol % Ascorbic acid /EtOH	Reflux	6 h	35
6	10 mmol % Ascorbic acid /EtOH	Reflux	4 h	80
7	10 mmol % Ascorbic acid /EtOH	US irradiation at RT	9 min	86
8	10 mmol % Ascorbic acid /SF	MW irradiation at 140 W	20 min	Trace
9	10 mmol % Ascorbic acid /SF	MW irradiation at 210 W	4 min	90

Reaction Condition: Substituted aromatic aldehydes 1a (1eq), benzene-1,2-diamine 2 (1eq) and 5-10 mmol% Ascorbic acid.

Table 2. Synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives(3a-i) using Ascorbic acid as a catalyst.

Entry	Ar-Group	Reaction Time in Min.			Yield in %			M.P. in (°C)
		Reflux	US	MW	Reflux	US	MW	
3a		240	9	3	80	86	90	222-225
3b		240	7	3	82	92	92	291-293

3c		240	9	4	85	86	84	275-280
3d		270	9	4	84	92	94	287-290
3e		270	9	4	80	84	86	270-272
3f		300	9	5	75	80	82	298-302
3g		240	9	3	84	90	92	287-291

3h		270	9	5	80	86	90	260-262
3i		270	9	4	82	90	92	265-270

3.1 Spectral Data:

Compound (3a)

2-(4-hydroxyphenyl)-1H-benzimidazole

FT-IR (KBr): 3476, 1718, 1600, 948, 740 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H); 7.02-8.20 (m, 4H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 4.91 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 158.08, 152.43, 138.62, 137.98, 128.33, 127.45, 126.90, 123.90, 123.06, 116.97, 115.16$; EI-MS (m/z) : 211.07 (M+1).

Compound (3b)

2-Phenyl-1H-benzimidazole

FT-IR (KBr): ν 3200, 1718, 1600, 948, 740 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1H), 7.35-7.45 (m, 5H), 7.20-8.32 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.03, 139.17, 135.89, 129.97, 129.06, 128.88, 127.90, 127.36, 126.50, 122.16, 115.16; EI-MS (m/z): 195.02 (M+1).

Compound (3c)

2-(4-fluorophenyl)-1H-benzimidazole

FT-IR (KBr): 3548, 1600, 1430, 1560, 748 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 12.23 (s, 1H), 7.45 (dd, $J = 8.4/12.3$, 2H), 7.39 (d, $J = 8.4/3$ Hz, 2H), 7.18-7.98 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): [154.15, 151.23 (d, $J=245$ Hz)], 143.98, 138.49, 135.05, 130.21, 127.45, 127.05, 123.35, 122.45, 119.40, 118.70; EI-MS (m/z): 212.09(M⁺).

Compound (3d)

2-(4-chlorophenyl)-1H-benzimidazole

FT-IR (KBr): 3442, 1615, 1600, 1455, 1550, 821 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ

12.94 (s, 1H), 7.57-7.60 (m, 4H), 78.19-8.25 (dd, $J = 2.2$ Hz, 2H), 7.19-7.24 (d, $J = 7.8$, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 150, 140.50, 134.53, 128.96, 128.84, 128.01, 122.13, 118.20; EI-MS (m/z): 230.09 (M+1).

Compound (3e)

2-(4-bromophenyl)-1H-benzimidazole

FT-IR (KBr): 3442, 1615, 1600, 1455, 1550, 821 cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6): δ 12.94 (s, 1H), 7.57-7.60 (m, 4H), 78.19-8.25 (dd, $J = 2.2$ Hz, 2H), 7.19-7.24 (d, $J = 7.8$, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 150, 140.50, 134.53, 128.96, 128.84, 128.01, 122.13, 118.20; EI-MS (m/z): 273.1 (M+1).

IV. CONCLUSION

The synthesis of 2-phenyl-1H-benzo[d]imidazole from substituted aromatic aldehyde and benzene-1,2-diamine in the presence of 1-Butyl-3-Methylimidazolium Chloride under traditional reflux conditions, US and MW irradiation has been described in this article in summary in a simple, quick, and environmentally friendly manner. Long reaction periods, harsh catalysts, and less toxic solvents are all avoided by the current approach.

LIST OF ABBREVIATIONS

ILs: Ionic liquids.

[BMIM Cl]: 1-Butyl-3-Methylimidazolium Chloride.

HDMBAB: Hexadecyldimethylbenzyl ammonium bromide.

TMAH : Tetra-methyl ammonium hydroxide.

RT: Room Temperature.

US: Ultra Sonication.

MW: Microwave.

FT-IR: Fourier Transform Infrared Spectroscopy.

TLC: Thin Layer Chromatography.

RBF: Round Bottom Flask.

SF: Solvent Free

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supporting information is available: Spectral analysis data (MS-Word).

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