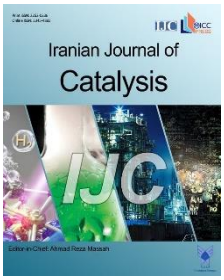

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Water Mediated Green and Efficient Synthesis of 2-Substituted Benzimidazole Derivatives Using Mandelic Acid as an Organo-Catalyst

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Abstract

An efficient and green protocol has been developed for the synthesis of 2-substituted benzimidazole derivatives using various aromatic aldehydes and o-phenylenediamine (OPD) in aqueous medium. In this procedure, mandelic acid is used as an inexpensive and efficient organo-catalyst for the synthesis of various derivatives of 2-substituted benzimidazole (3a-3m) in excellent yields (88-93%). The present method affords noteworthy advantages of an organo-catalyst, such as being highly stable, environmentally benign, and commercially readily available, and water as a green reaction medium, with high conversions of the products. All products have been confirmed by their spectroscopic technique, such as 1H NMR, 13C NMR, IR spectroscopy, and mass spectrometry.

Keywords: Benzimidazole; Mandelic acid; Organo-catalyst; Water; O-Phenylenediamine; Aldehydes

1. Introduction

Benzimidazole and its derivatives are very important nitrogen-containing bicyclic hetero-aromatic compounds, which are considered a significant class in synthetic as well as medicinal chemistry [1-5]. They exhibit numerous clinical applications including anti-inflammatory [6], analgesics [7], anti-microbial [8], anthelmintics [9], anti-ulcer [10], anti-proliferative [11], anti-oxidant [12], as well as anti-convulsant and anti-diabetic [13]. They also display significant antiviral activities against several viruses, including HIV [14], influenza [15], HCMV (human cytomegalovirus) [16], and herpes (HSV-1) [17]. Additionally, some benzimidazole derivatives have shown optical applications such as photoluminescent [18], fluorescence [19], and dye laser [20]. Due to the variety of applications of these substituted benzimidazoles, worldwide chemists have paid significant attention to their syntheses.

In viewpoint of biological importance of 2-substituted benzimidazoles, there are several approaches have been reported for their syntheses including condensation of various o-phenylenediamines with aldehyde using different catalysts such as nanomaterials [21-29], acids [30-34], metals [35-43], organo-catalyst [44-50] as well as various natural sources [51,52] and many oxidizing agents [53-57]. Furthermore, o-phenylenediamines reacted with other substrates such as primary alcohol [58-60], primary amines [61,62], β-keto ester [63,64], carboxylic acid [65], and its derivatives [66-68] as well as other functional groups [69-71]. Most of these reported approaches suffer from one or two disadvantages, such as use of strong acidic conditions, expensive catalysts, stoichiometric quantity of oxidants, high reaction temperature, extended reaction time, tedious workup procedures, or low product yields.
Thus, for the development of innovative and environmentally friendly green chemical processes, organic syntheses are major challenges.

Recently, the use of organo-catalysts has been increased in the development of various methodologies, due to their inexpensive, readily available, and environmentally benign nature as catalysts for the

synthesis of various organic molecules [72,73]. Among many other organo-catalysts, mandelic acid, which is mild, highly stable, environmentally friendly, and commercially cheaply available, is used for the synthesis of various organic compounds [74-81].

In continuation of our research interest in the development of novel and environmentally benign green methodologies [82-86], we decided to explore the use of mandelic acid as an organo-catalyst for the synthesis of 2-substituted benzimidazole derivatives in aqueous medium.

2. Experimental

2.1. General information

All chemicals and solvents were purchased from a commercial provider and utilized without any purification. Aluminum-covered silica plates purchased from Merck and used to perform thin layer chromatography (TLC). Melting points were taken on the Buchi R-535 apparatus, which is correct. ^{1}H and ^{13}C NMR spectra were recorded on a Gemini-300 spectrophotometer in DMSO-d6 using TMS as an internal reference. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer using neat or KBr disks, and mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

2.2. General procedure for synthesis of 2-substituted benzimidazole derivatives

A mixture of o-phenylenediamine (1 mmol), aromatic aldehydes (1 mmol) (3a-3m), and mandelic acid (20 % mol) was stirred in water (5 mL) for 2.0 hrs. at reflux conditions. After completion of reaction, checked by TLC, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2 × 5 mL). Combined organic solvent was dried over Na2SO4 and evaporated to obtain crude solid product, which was recrystallized using ethanol. All the pure compounds were confirmed by comparing their melting points and spectral data

2.3. Spectral data for Synthesized compounds

2-phenyl-1H-benzo[d]imidazole (3a):
White solid, (92%)m.p. 288-290 [286-288][Ref[55]] IR (KBr): ν_{max} = 3438, 3022, 1622, 1568, 1477, 1425 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (d, 2H, J = 7.2 Hz, Ar-H), 7.44 -7.66 (m, 5H, Ar-H), 8.23 (d, 2H, J = 7.2 Hz, Ar-H), 12.42 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.7, 123.1, 128.3, 129.7, 130.8, 134.2, 143.1, 151.3 ppm; ESIMS: m/z 94 $[M]^+$, 212 $[M+18]^+$.

2-(p-tolyl)-1H-benzo[d]imidazole (3b):
White solid, (89%). m.p. 264-266 [258-260] [Ref[55]] IR (KBr): ν_{max} = 3450, 3027, 2965, 2989,1633, 1450 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.64 (s, 3H, -CH_3), 7.16-7.22 (m, 2H, Ar-H), 7.43 (d, 2H, J = 7.9 Hz, Ar-H), 7.63 (s, 2H, Ar-H), 8.07 (d, 2H, J = 7.8 Hz, Ar-H), 12.57 (s, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.6, 123.1, 125.9, 127.5, 129.4, 140.3, 151.8 ppm.

4-(1H-benzo[d]imidazol-2-yl)phenol (3c):
White Solid (88%). m.p. 252-254 [253-255] [Ref[55]] IR (KBr): ν_{max} = 3362, 3263, 3023, 1651, 1457 cm-1; ^{1}H NMR (300 MHz, DMSO-d_6): δ: 6.92 (d, 2H, J = 7.9 Hz, Ar-H), 7.12 (d, 2H, J = 7.9 Hz, Ar-H), 7.45 (s, 2H, Ar-H), 8.06 (d, J = 8.0 Hz, Ar-H), 9.96 (brs, 1H, -OH), 12.44 (s, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 117.8, 120.7, 121.7, 129.3, 144.7, 152.4, 159.2 ppm.

2-(3-methoxyphenyl)-1H-benzo[d]imidazole (3d):
White Solid (90%). m.p. 204-206 [203-205] [Ref[55]] IR (KBr) ν_{max} = 3432, 3043, 2965, 2909, 1620, 1451 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.91 (s, 3H, -OCH_3), 7.04 (d, 1H, J = 7.8 Hz, Ar-H), 7.28 (d, 2H, J = 7.8 Hz, Ar-H), 7.43 (s, 1H, Ar-H), 7.58-7.68 (m, 2H, Ar-H), 7.78 (d, 2H, J = 7.2 Hz, Ar-H), 12.24 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.0, 114.0, 115.2, 116.3, 118.1, 124.6, 130.9, 132.8, 140.2, 152.4, 159.8 ppm.

2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3e):
White solid (87 %). m.p. 225-227 [226-228] [Ref[55]] IR (KBr): ν_{max} = 3445, 3063, 2932, 2860, 1618, 1457 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.94 (s, 3H, -OCH_3), 7.08-7.18 (m, 4H, Ar-H), 7.50-7.60 (m, 2H, Ar-H), 8.08 (d, 2H, J = 7.2 Hz, Ar-H), 12.22 (s, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.3, 114.5, 122.2, 123.1, 128.1, 151.8, 160.4 ppm. ESIMS: m/z 224 $[M]^+$, 242 $[M+18]^+$.

2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole (3f):
Yellow solid (89%). m.p. 230-232 [232-234] [Ref[55]] IR (KBr): ν_{max} = 3431, 3026, 2926, 1625, 1442 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, -OCH_3), 3.93 (3H, s, -OCH_3), 6.92 (d, 1H, J =8.1Hz, Ar-H), 7.18-7.28 (m, 3H, Ar-H), 7.45 (d, 1H, J =8.1Hz, Ar-H), 7.62 (s, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 11.42 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.7, 56.0, 109.7, 111.3, 119.2, 120.2, 122.1, 122.8, 135.8, 149.6, 150.9, 152.0 ppm.

4-(1H-benzo[d]imidazol-2-yl)benzonitrile (3g):
Pale yellow solid (93%). m.p. 260-262 [261-263][Ref[57]] IR (KBr): ν_{max} = 3442, 3043, 2228, 1621, 1457 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26-7.36 (m, 2H, Ar-H), 7.48 -7. 54 (m, 1H, Ar-H), 7.74-7.76 (m, 1H, Ar-H), 8.06 (d, 2H, J = 8.2 Hz, Ar-H), 8.42 (d, 2H, J = 8.2 Hz, Ar-H), 12.24 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz,

DMSO-d_6): δ 112.5, 119.3, 122.2, 123.1, 128.2, 134.1, 135.7, 136.1, 143.4, 150.1 ppm.

2-(2-nitrophenyl)-1H-benzo[d]imidazole (3h):
Yellow solid (92%). m.p. 258-260 [260-262] Ref[55] IR (KBr): ν_{max} = 3429, 3064, 1624, 1454 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.46-7.56 (m, 2H, Ar-H), 7.68-7.76 (m, 2H, Ar-H), 7.94-7.98 (m, 2H, Ar-H), 8.08 (d, 1H, J = 8.2 Hz, Ar-H), 8.36 (d, 1H, J = 8.2 Hz, Ar-H), 11.36 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 111.6, 119.7, 122.6, 124.9, 125.4, 130.3, 132.0, 132.6, 139.1, 142.4, 148.6, 148.8 ppm.

2-(4-nitrophenyl)-1H-benzo[d]imidazole (3i):
Pale yellow solid (94%). m.p. 306-308 [302-304] Ref[55] IR (KBr): ν_{max} = 3419, 3029, 2926, 1608, 1523, 1452 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (d, 2H, J = 8.2 Hz, Ar-H), 7.56 (d, 2H, J = 8.4 Hz, Ar-H), 8.32-8.42 (m, 4H, Ar-H), 11.62 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.7, 119.0, 121.9, 124.0, 124.6, 127.6, 130.0, 134.7, 140.2, 142.8, 147.7, 150.6 ppm; ESIMS: m/z 239 $[M]^+$.

2-(4-chlorophenyl)-1H-benzo[d]imidazole (3j):
White solid (92%). m.p. 290-292 [290-292] Ref[55] IR (KBr): ν_{max} = 3448, 3069, 3029, 2973, 2935, 2882, 1621, 1449 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18-7.28 (m, 2H, Ar-H), 7.66-7.76 (m, 4H, Ar-H), 8.22 (d, 2H, J = 7.1 Hz, Ar-H), 12.40 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.3, 118.3, 121.5, 122.1, 126.8, 127.5, 128.5, 129.8, 135.8, 142.4, 151.2 ppm; ESIMS: m/z 228 $[M]^+$, 230 $[M+2]^+$.

2-(4-bromophenyl)-1H-benzo[d]imidazole (3k):
Pale brown solid (90%). m.p. 260-262 [255-257] Ref[57] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.10-7.18 (m, 2H, Ar-H), 7.38-7. 50 (m, 2H, Ar-H), 7.68 (d, 2H, J = 8.5 Hz, Ar-H), 8.16 (d, 2H, J = 8.4 Hz, Ar-H), 12.60 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 121.9, 123.3, 128.3, 128.4, 129.8, 130.7, 131.7, 150.3 ppm.

2-(furan-2-yl)-1H-benzo[d]imidazole (3l):
Pale orange solid (90%). m.p. 282-284 [286-288] Ref[57] IR (KBr): ν_{max} = 3419, 3063, 2862, 1623, 1623, 1458 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.72-6.76 (m, 2H, Ar-H), 7.18-7. 26 (m, 3H, Ar-H), 7.50 (d, 1H, J = 7.2 Hz, Ar-H), 7.64 (d, 1H, J = 7.4 Hz, Ar-H), 7.96 (S, 1H, Ar-H), 12.24 (brs, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.6, 112.2, 118.6, 120.6, 122.4, 134.3, 143.3, 144.2, 146.5 ppm.

2-(1H-pyrrol-2-yl)-1H-benzo[d]imidazole (3m):
Pale yellow solid (90%). m.p. 265-267 [268-270] Ref[57] ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.18 (d, 1H, J = 1.5 Hz, Ar-H), 6.88 (d, 1H, J = 3.5 Hz, Ar-H), 6.94 (d, 1H, J = 1.5 Hz, Ar-H), 7.18-7. 26 (m, 2H, Ar-H), 7.48 (d, 1H, J = 4.5 Hz, Ar-H), 7.64 (d, 1H, J = 4.7 Hz, Ar-H), 11.78 (s, 1H, -NH), 12.47 (s, 1H, -NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 109.8, 110.7, 118.2, 121.0, 121.7, 123.3, 135.3, 137.3, 144.3, 147.2 ppm; ESIMS: m/z 183 $[M]^+$.

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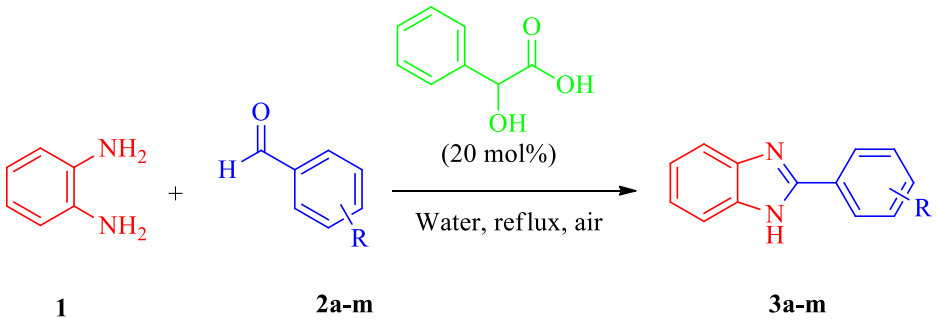


Scheme 1. Mandelic acid catalyzed synthesis of 2-substituted benzimidazole derivatives

3. Results and discussion

In a model reaction, the condensation reaction occurs between equimolar amounts of o-phenylenediamine (1) and benzaldehyde (2a) using mandelic acid (20% mol) as an organo-catalyst in water (5 mL) at reflux conditions. The reaction was completed within 2.0 hrs. to obtain corresponding product 2-substituted benzimidazoles (3a) in 92% yields (Scheme 1)To optimize reaction conditions, our studies began with an investigation of various parameters such as catalyst, temperature, and solvents for the model reaction.

Initially, the reaction was started with catalyst-free conditions in water at room temperature for an extended reaction time, but the desired product was not obtained (Table 1, entry 1). After that, we moved to increase reaction temperature by 70°C for 3 hrs. then only 20% yield of the product was obtained (Table 1, entry 2). Later, we used reflux condition for reaction, but improvement of the product yield was not observed (Table 1, entry 3). So, we realized that the role of catalyst is crucial for the progression of reaction. By considering the importance of a catalyst, we decided to use inexpensive, highly stable, environmentally benign, and

readily available mandelic acid as a catalyst. Initially, 5 mol% catalyst was screened at room temperature as well as at 70°C, yields of corresponding product (3a) were obtained with 45 and 53% respectively. (Table 1, entry 4-5). Next, we used reflux conditions with the same mole ratio of catalyst to obtain improved product yield in 72% with decreased reaction time (2.5 hrs.) (Table 1, entry 6). After getting this result, we changed mole ratios of catalyst from 10 mol% to 20 mol% at reflux conditions, it was noticed that there was a maximum increase in the yield of the product (92 %), when the amount of catalyst raised from 10 mol% to 20 mol% with again decreasing reaction time from 2.5 to 2.0 hrs. (Table 1, entry 7-9). However, further increasing the amount of catalyst by 25 mol% did not increase the yield of product (Table 1, entry 10).

After screening the catalyst and temperature, we moved towards optimizing the solvent effects. Initially, the reaction was carried out in solvent-free conditions with 20% mol of catalyst, and the corresponding product (3a) was obtained in only 40 % yield with prolonged reaction time (Table 2, entry 1).

After that, we have used various solvents such as DCM, THF, CH_3CN, acetone, as well as ethanol at reflux conditions, and yields of corresponding product (3a) were obtained with 54, 59, 67, 72, 82 % respectively, in 2.5 hrs. (Table 3, entries 2-6). Finally, we used water as solvent with 20% mol of catalyst at reflux conditions to obtain 92 % corresponding product (3a) in stipulated reaction time (Table 3, entry 7). Among all these solvents, water was found to be the best solvent in terms of reaction time as well as yield the product in comparison with others. All the results are summarized in Table 3.

Table 1. Optimization of catalyst at different temperatures in water

Entry	Mandelic acid (% mol)	Temperature (°C)	Time (hr)	Isolated Yields (%)
1	-	RT[a]	4.0	--
2	-	70	3.0	20
3	-	Reflux	3.0	38
4	5	RT[a]	3.0	45
5	5	70	3.0	53
6	5	Reflux	2.5	72
7	10	Reflux	2.5	79
8	15	Reflux	2.5	85
9	20	Reflux	2.0	92
10	25	Reflux	2.0	92

RT[a] = Room Temperature.

Based on these optimal reaction conditions, various aromatic aldehydes were reacted with *o*-phenylenediamine for the synthesis of 2-substituted benzimidazole (3a-3m) derivatives to demonstrate the scope of this catalyst. Initially, o-phenylenediamine (1) reacted smoothly with simple benzaldehyde (2a) to convert into desired product (3a) with excellent yield and achieved 5.75 TON and 2.87 TOF (Table 3, entry 1). Next, we examined the various substituted aromatic aldehydes with o-phenylenediamine under optimized reaction conditions. The electrons donating functional groups such as *p*-CH_3, *p*-OH, *m*-OCH_3, *p*-OCH_3 and 3,4-disubstituted -OCH_3 reacted with *o*-phenylenediamine to offered good yield of products 3b-3f, which provides TON ranges between 5.96 to 7.29 and TOF ranges between 2.98 to 3.64 (Table 3, entry 2-6). Further, we applied electrons withdrawing functional groups such as *p*-CN, *o*-NO_2 and *p*- NO_2, on *o*-phenylenediamine to obtained excellent yield of products 3g-3i, which provides corresponding TON ranges from 6.56 to 7.24 and TOF ranges from 3.28 to 3.62 (Table 3, entry 7-9). Next, we synthesized the halogenated 2-substituted benzimidazole of products 3j and 3k with excellent yield, while generating TONs ranging from 6.76 to 7.89 and TOFs ranging from 3.38 to 3.94. (Table 3, entry 10-11). Finally, heterocyclic aromatic aldehydes such as pyrrole-2-carboxaldehyde and furan-2-carboxaldehyde were screened, and they are converted into their products 3l and 3m with good yield, which gave TON ranges from 5.31 to 5.34 and TOF ranges from 2.65 to 2.67 (Table 3, entries 12-13). This method was found to be equally effective for aromatic aldehydes having electron-donating as well as electron-withdrawing functional groups. All the reactions were carried out using water as a green solvent and mandelic acid as an organo-catalyst. The comparison of mandelic acid with the other reported organo-catalyst employed for the synthesis of 2-substituted benzimidazole is shown in Table 4. The result shows that mandelic acid is more effective than other organo-catalysts in terms of reaction conditions and product yields.

In general, all the reactions were clean in terms of conversion and separation of their products. All the products were characterized by their spectroscopic method, such as 1H, 13C NMR, IR spectroscopy, and mass spectrometry.

Table 2. Optimization of solvents

Entry	Mandelic acid (% mol)	Solvent	Temperature	Time (min.)	Isolated Yields (%)
1	20	Solvent-free	120 °C	3.0	40
2	20	DCM	Reflux	2.5	54
3	20	THF	Reflux	2.5	59
4	20	CH_3CN	Reflux	2.5	67
5	20	Acetone	Reflux	2.5	72
6	20	Ethanol	Reflux	2.5	82
7	20	Water	Reflux	2.0	92

Table 3. Synthesis of the 2-substituted benzimidazole derivatives

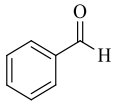
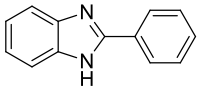
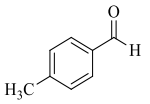
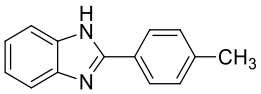
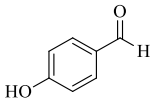
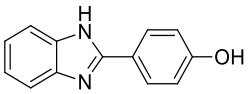
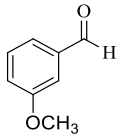
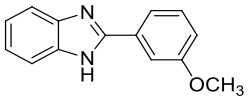
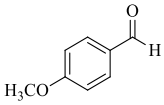
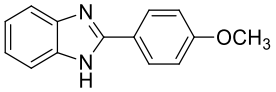
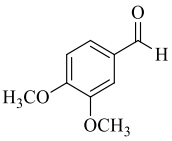
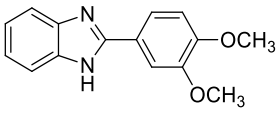
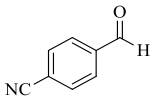
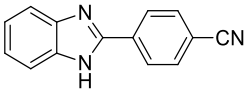
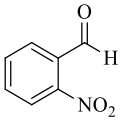
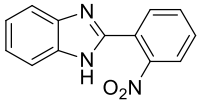
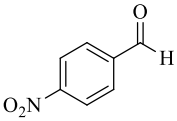
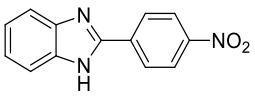
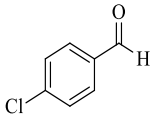
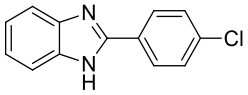
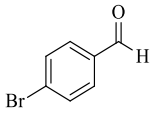
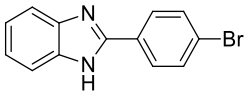
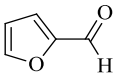
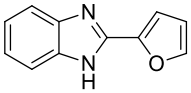
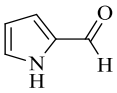
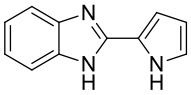
Sr No	Aldehyde	Product	Reaction Time (hrs.)	Isolated Yield (%)	TON	TOF (h^{-1})	M.P. °C [Lit. M.P.][Ref]
a			2.0	92	5.75	2.87	288-290 [286-288][55]
b			2.0	89	5.97	2.98	264-266 [258-260] [55]
c			2.0	88	5.96	2.98	252-254 [253-255] [55]
d			2.0	90	6.50	3.25	204-206 [203-205] [55]
e			2.0	87	6.28	3.14	225-227 [226-228] [55]
f			2.0	89	7.29	3.64	230-232 [232-234] [55]
g			2.0	93	6.56	3.28	260-262 [261-263] [57]
h			2.0	92	7.09	3.54	258-260 [260-262] [55]
i			2.0	94	7.24	3.62	306-308 [302-304] [55]

Table 3. Synthesis of the 2-substituted benzimidazole derivatives (continued)

Sr No	Aldehyde	Product	Reaction Time (hrs.)	Isolated Yield (%)	TON	TOF (h^{-1})	M.P. ºC [Lit. M.P.][Ref]
j			2.0	92	6.76	3.38	290-292 [290-292] [55]
k			2.0	90	7.89	3.94	260-262 [255-257] [57]
l			2.0	90	5.34	2.67	282-284 [286-288] [57]
m			2.0	90	5.31	2.65	265-267 [268-270] [57]

3.1. Plausible Reaction Mechanism

The formation of product can be explained as shown in a plausible reaction mechanism (Scheme 2). The Bronsted acidic proton from mandelic acid has activated the carbonyl carbon group of aromatic aldehydes by coordination with oxygen, which leads to formation of imine product reacting with one amino group from o-phenylenediamine, followed by removal of a water molecule. Then intra-molecular cyclisation occurred by addition of another amino group to imine, followed by air oxidation to form the desired product.

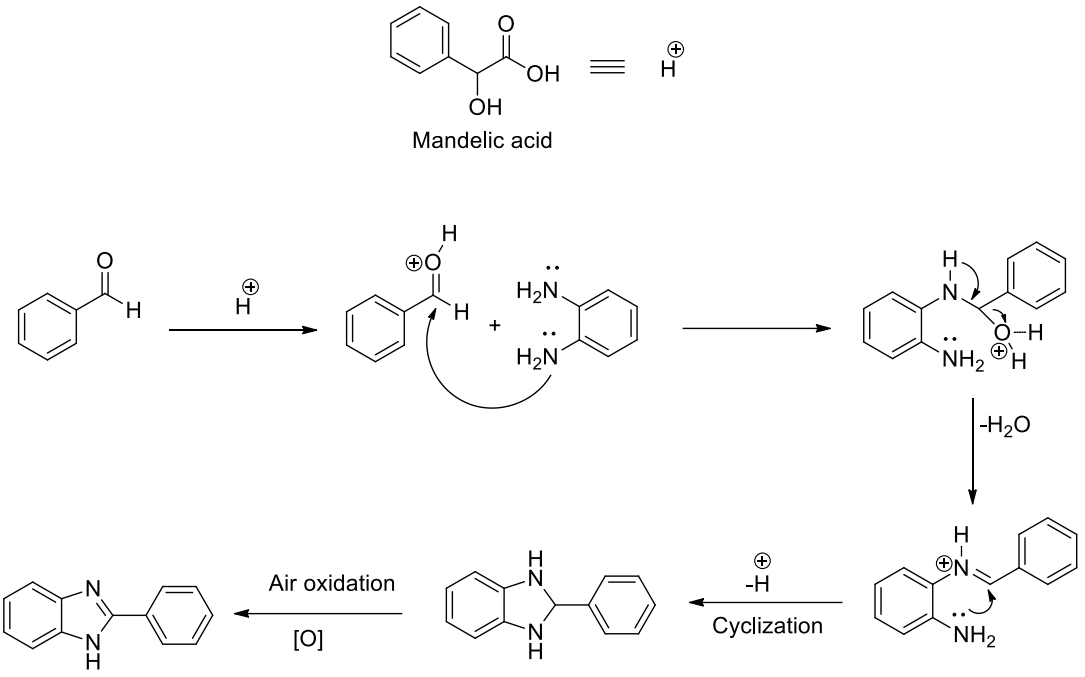
4. Conclusion

In summary, we have represented a novel and efficient green method for the synthesis of 2-substituted benzimidazole derivatives from simple, inexpensive, and readily available starting materials. Mandelic acid catalyzed reaction of o-phenylenediamine and various aromatic aldehyde proceeds smoothly under metal-free conditions in aqueous medium. This novel method has many significant features, such as being greener, environmentally benign, and highly efficient, with high conversions of the products in excellent yield.

Table 4. Comparison between the catalytic capacity of some organo-catalysts presented in this work

Entry	Catalyst	Conditions	Time	Yields (%)[Ref]
1	Sulphamic acid	EtOH, RT	5 min.-6h	75-99[44]
2	p-TsOH	DMF, 80°C	10-60 min.	Trace-85[45]
3	Glacial acetic acid	Neat, MW	25-50 min.	52-92[46]
4	5-SSA	EtOH, Reflux	55 min.-2h	70-94[47]
5	Oxalic acid	THF, MW	2-3 min.	80-95[48]
6	L-Proline, pH 4.2	H_2O, Reflux	1-7h	80-98[49]
7	CSA	EtOH:H_2O, 28-32°C	1-1.5h	79-91[50]
8	Mandelic acid	H_2O, Reflux	2h	87-94[this work]

RT = Room Temperature, MW= Microwave



Scheme 2. Plausible Reaction Mechanism

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Authors Contribution
All authors have contributed equally to prepare the paper.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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