

## SIMPLE, MILD, AND HIGHLY EFFICIENT SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES AND BIS-BENZIMIDAZOLES

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A new convenient method for preparation of 2-substituted benzimidazoles and bis-benzimidazoles is presented. In this method, *o*-phenylenediamines were condensed with bisulfite adducts of various aldehydes and di-aldehydes under neat conditions by microwave heating. The results were also compared with results of synthesis by conventional heating under reflux. Structures of the products were confirmed by infrared, <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy. Short reaction times, good yields, easy purification of products, and mild reaction conditions are the main advantages of this method.

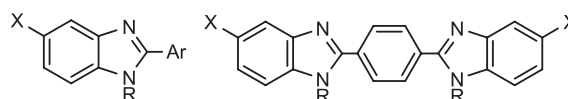
Keywords: benzimidazole; microwave heating; synthesis.

## INTRODUCTION

Natural biological substances such as purine bases and vitamin B12 include benzimidazole moiety in their structure. Several benzimidazole derivatives are reported to exhibit antimicrobial,<sup>1-3</sup> anticancer,<sup>4,5</sup> antifungal,<sup>6,7</sup> antiparasitic,<sup>8</sup> antiviral,<sup>9</sup> anti-inflammatory,<sup>10</sup> and antihistaminic<sup>11</sup> activities. Therefore, methods for their preparations are important for synthetic organic chemists and biologists. There are two fundamental methods for the preparation of 2-substituted benzimidazole derivatives. One method is condensation of *o*-phenylenediamines with corresponding carboxylic acids via a strong acid,<sup>12-15</sup> PPA,<sup>15-17</sup> or a catalyst.<sup>18,19</sup> High-temperature-pressurised systems<sup>20</sup> or microwaves (MWs)<sup>17,18</sup> are also used to promote these reactions. The other method is condensation of *o*-phenylenediamines with aldehydes under oxidative conditions.<sup>15,21</sup> Various reagents such as I<sub>2</sub>/KI,<sup>22</sup> In(OTf)<sub>3</sub>,<sup>23</sup> nitrobenzene,<sup>24</sup> benzoquinone,<sup>25</sup> Oxone,<sup>26</sup> Fe(HSO<sub>4</sub>)<sub>3</sub><sup>27</sup> and atmospheric air<sup>28</sup> are used for this purpose. Nevertheless, some of these reported methods have limitations such as low yields, high reaction temperatures, long reaction times, harsh reaction conditions, purification difficulties, and formation of by-products.

In contrast to a conventional heating source, MW energy couples directly with polar molecules or ions and leads to a rapid rise in the temperature of reaction medium.<sup>29,30</sup> Reactions that require hours or even days using conventional heating can usually be completed in minutes or seconds using MWs. Several reactions have been performed under MW-assisted conditions with significant rate enhancements, improved yield, and selectivity.<sup>30</sup>

Owing to the immense importance of the benzimidazole moiety and the aforementioned limitations in their synthesis, we believed it would be worthwhile to develop a practical method for their synthesis. Aldehyde bisulfite adducts were first used by Ridely *et al.*<sup>31</sup> for the preparation of some benzimidazoles and aza-analogs under classical reflux conditions. This article reports the first MW-assisted neat (to right doughy consistency) synthesis of some 2-substituted benzimidazoles and bis-benzimidazoles from a wide variety of aldehyde and dialdehyde bisulfite adducts (Scheme 1). The observed yields under classical heating (24–70%) is increased to higher values when the reaction is performed under MW-assisted conditions (65–95%). The increase in the reaction rates were also in a good range.



Scheme 1. Synthesized benzimidazole structures

## EXPERIMENTAL

The 2-substituted benzimidazole and bis-benzimidazole derivatives were synthesized under 180 W MW irradiation. A domestic microwave (Bosch HMT 812 C) oven that was modified to accommodate a reflux system and an internal camera was used in all syntheses. MWs at 2450 MHz frequency, which corresponds to a wavelength of 12.2 cm and an energy of 0.23 cal/mol (= 0.94 J/mol), were used. All raw materials and solvents were purchased from Merck or Sigma-Aldrich and were used without further purification. IR spectra were recorded on a Bruker Vertex 80v spectrometer. The <sup>1</sup>H- (400 MHz) and <sup>13</sup>C- (100 MHz) NMR spectra were recorded on a Bruker Avance II-400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-*d*<sub>6</sub> as solvent. Melting points were measured with a Gallenkamp electrothermal apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on plates procured from Merck.

General procedure for conversion of aldehydes to NaHSO<sub>3</sub> adducts

Equivalent moles (50 mmol) of aldehyde and sodium hydrogen sulfite were dissolved in ethanol (25 mL) and water (25 mL), respectively. For dialdehydes, mole ratio of dialdehyde/sodium hydrogen sulfite was 1:2. Sodium hydrogen sulfite solution was added in portions to a vigorously stirred solution of aldehyde in an ice bath and the stirring was continued for 1 h at room temperature. The mixture was filtered and dried in vacuo to provide the crude aldehyde-bisulfite adduct (yield = 60–95%).

## General procedure for the synthesis of 2-substituted benzimidazoles and bis-benzimidazoles

## Microwave Method

Substituted *o*-phenylenediamine (for benzimidazoles, 2 mmol; bisbenzimidazoles, 4 mmol) and the appropriate aldehyde-bisulfite

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adduct (2.1 mmol) were ground thoroughly and transferred to a 50 mL flask. After adding a few drops of DMF, the mixture was irradiated in a microwave oven at 180 W. The progress of the reaction was monitored by TLC, with a mixture of ethanol and water (9:1) as the eluent. On completion, the reaction mixture was cooled, ice-cold distilled water was added, and stirred for a while wherein a precipitate was observed. The precipitate was collected by filtration, washed with water, dried, and recrystallised from ethanol/water.

#### Classical Heating Method

Substituted *o*-phenylenediamine (for benzimidazoles, 2 mmol; bisbenzimidazoles, 4 mmol) and the appropriate aldehyde-bisulfite adduct (2.1 mmol) were ground thoroughly and transferred to a 50 mL flask. The mixture was refluxed in DMF (20 mL) over a hotplate stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was purified as described above.

#### Selected Data for Synthesized Compounds

**Data for 1.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3150-2540, 1600, 1548, 1319, 1268;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.17-7.21 (m, 2H, H-5, H-6), 7.40-7.67 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 8.15-8.18 (m, 2H, H-4, H-7) 12.89 (s, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 118.80, 121.60, 126.40, 128.80, 129.80, 130.10, 134.90, 151.20

**Data for 4.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3259, 3080-2500, 1676, 1600, 1310, 1268;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  6.99-7.03 (m, 2H, H-3', H-5'), 7.27 (bs, 2H, H-5, H-6), 7.64 (bs, 2H, H-4, H-7), 7.37 (t,  $J=7.2$  Hz, 1H, H-4'), 8.03 (d,  $J=8$  Hz, 2H, H-6'), 13.10 (s, 2H, NH, OH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 115.38, 116.05, 117.01, 121.05, 123.24, 128.80, 131.72, 140.50, 154.42, 156.03

**Data for 10.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3080-2528, 1625, 1574, 1319, 1242, 578;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.21 (dd,  $J=6.0, 4.0$  Hz, 2H, H-5, H-6), 7.24 (dd,  $J=4.0, 4.0$  Hz, 1H, H-3'), 7.54 (d,  $J=4.0$  Hz, 1H, H-7), 7.60 (d,  $J=4.0$  Hz, H-4), 7.73 (dd,  $J=6.0, 4.0$  Hz, 1H, H-4'), 7.85 (dd,  $J=4.0, 4.0$  Hz, 1H, H-2'), 13.02 (s, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 111.11, 118.48, 121.86, 122.55, 126.69, 128.28, 128.75, 133.59, 134.67, 143.50, 147.00

**Data for 13.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3145-2666, 2925, 2856, 1621, 1588, 1313, 1273;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.36 (s, 3H,  $\text{CH}_3$ ), 7.14-7.21 (m, 2H, H-5, H-6), 7.34 (d,  $J=8$  Hz, 2H, H-3', H-5'), 7.50 (d,  $J=7.2, 1\text{H}, \text{H}-7$ ), 7.63 (d,  $J=7.6, 1\text{H}, \text{H}-4$ ), 8.05 (d,  $J=8$  Hz, 2H, H-2', H-6') 12.82 (s, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 21.41, 119.13, 122.02, 122.79, 127.87, 126.83, 129.96, 135.37, 140.03, 151.82

**Data for 16.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3146-2666, 2920, 2843, 1610, 1585, 1250, 1182;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  3.79 (s, 3H,  $\text{OCH}_3$ ), 6.93 (d,  $J=8.4$  Hz, 2H, H-3', H-5'), 7.08 (dd,  $J=6, 8.3$  Hz, 2H, H-5, H-6), 7.39 (bs, 1H, H-7), 7.56 (bs, 1H, H-4), 8.05 (d,  $J=8.4$  Hz, 2H, H-2', H-6') 12.38 (bs, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 55.41, 114.24, 118.67, 122.25, 123.03, 128.32, 136.25, 151.98, 160.93

**Data for 22.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3052-2544, 1602, 1586, 1320, 1272;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.20 (dd,  $J=6, 3.2$  Hz, 2H, H-5, H-6), 7.59 (bs, 2H, H-4, H-7), 7.61 (d,  $J=8.4$  Hz, 2H, H-3', H-5'), 8.18 (d,  $J=8.8$  Hz, 2H, H-2', H-6'), 12.95 (bs, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 122.78, 128.59, 129.49, 129.51, 134.96, 150.62

**Data for 23.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3100-2500, 1624, 1586, 1304, 1224, 731;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.23 (dd,  $J=8.4, 2$  Hz, 1H, H-6), 7.59 (bs, 1H, H-7), 7.62 (s, 1H, H-4), 7.63 (d,  $J=8.8$  Hz, 2H, H-3', H-5'), 8.16 (d,  $J=8.8$  Hz, 2H, H-2', H-6');  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 123.07, 127.08, 128.74, 129.01, 129.60, 135.35, 152.62

**Data for 24.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3200-2615, 2918, 2865, 1629, 1602, 1314, 1229;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.49 (s, 3H,  $\text{CH}_3$ ), 7.02 (d,  $J=8$  Hz, 1H, H-6), 7.39 (bs, 1H, H-4), 7.47 (bs, 1H, H-7),

7.60 (d,  $J=8.8$  Hz, 2H, H-3', H-5'), 8.14 (d,  $J=8.8$  Hz, 2H, H-2', H-6'), 12.82 (bs, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 21.78, 124.50, 128.45, 129.47, 129.62, 134.73, 138.10, 150.50

**Data for 25.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3055, 2944, 1605, 1524, 1328, 1241;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  3.86 (s, 3H,  $\text{NCH}_3$ ), 7.31-7.22 (m, 2H, H-5, H-6), 7.68-7.53 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.84 (dd,  $J=7.2, 2.4$  Hz, 2H, H-4, H-7);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 32.10, 111.01, 119.44, 122.39, 122.81, 129.11, 129.75, 130.09, 130.59, 137.03, 142.92, 153.47

**Data for 27.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3032, 2970, 2812, 1610, 1570, 1320, 1277;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.98 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 3.84 (s, 3H,  $\text{NCH}_3$ ), 6.84 (d,  $J=9.2$  Hz, 2H, H-3', H-5'), 7.24-7.16 (m, 2H, H-5, H-6), 7.60 (d,  $J=7.6$  Hz, 1H, H-4), 7.50 (d,  $J=8.8$  Hz, 1H, H-7), 7.68 (d,  $J=8.8$  Hz, 2H, H-2', H-6');  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 32.20, 40.20, 110.54, 112.10, 117.41, 118.81, 122.05, 130.60, 137.12, 143.07, 151.37, 154.28

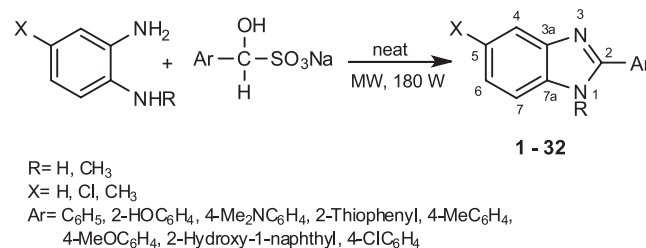
**Data for 29.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3040, 2944, 2859, 1611, 1482, 1325, 1249;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.39 (s, 3H,  $\text{CH}_3$ ), 3.84 (s, 3H,  $\text{NCH}_3$ ), 7.29-7.21 (m, 2H, H-5, H-6), 7.37 (d,  $J=8$  Hz, 2H, H-3', H-5'), 7.66 (d,  $J=7.6$  Hz, 1H, H-4), 7.58 (d,  $J=7.6$  Hz, 1H, H-7), 7.73 (d,  $J=8$  Hz, 2H, H-2', H-6');  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 21.40, 32.48, 110.91, 119.31, 122.31, 122.66, 129.74, 129.65, 129.68, 137.02, 139.78, 142.92, 153.56.

**Data for 30.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3047, 2948, 2843, 1613, 1536, 1379, 1249;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  3.83 (s, 3H,  $\text{NCH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 7.11 (d,  $J=8.8$  Hz, 2H, H-3', H-5'), 7.28-7.19 (m, 2H, H-5, H-6), 7.65 (d,  $J=7.2$  Hz, 1H, H-4), 7.56 (d,  $J=7.2$  Hz, 1H, H-7), 7.79 (d,  $J=8.8$  Hz, 2H, H-2', H-6');  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 32.09, 55.77, 110.81, 114.55, 119.17, 122.24, 122.49, 122.83, 131.22, 137.03, 142.93, 153.47, 160.75

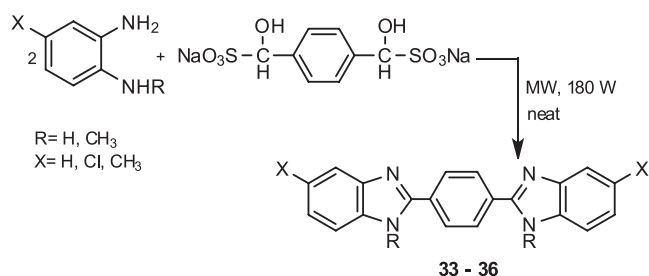
**Data for 33.** IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3163-2544, 1623, 1587, 1322, 1269;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.22 (bs, 2H, H-5, H-6), 7.56 (d,  $J=6.4$  Hz, 1H, H-7), 7.69 (d,  $J=6.8$  Hz, 1H, H-4), 8.33 (s, 1H, H-2'), 13.03 (s, 1H, NH);  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 119.43, 123.31, 127.36, 131.57, 135.52, 151.02

## RESULTS AND DISCUSSION

Aldehyde bisulfite adducts were easily prepared according to the conventional method as described in the experimental section. They are whitish solids that remain stable for a long time when stored in a refrigerator. The compounds, 2-substituted benzimidazoles (**1-32**) and bis-benzimidazoles (**33-36**) were synthesized via condensation of *o*-phenylenediamines with aldehyde bisulfite adducts under MW irradiation. MW reactions were performed under a neat protocol, using only a few drops of DMF to homogenize the reaction mixture. Eight aromatic aldehydes, a dialdehyde, and four *o*-phenylenediamines, including those bearing electron-donating or electron-withdrawing substituents, were used to investigate the efficiency of the method. The synthetic schemes for the synthesis of benzimidazoles and bisbenzimidazoles are described in Scheme 2 and Scheme 3, respectively.



Scheme 2. Synthetic procedure for the benzimidazole derivatives



**Scheme 3.** Synthetic procedure for the bis-benzimidazole derivatives

The current experimental results are summarized in Table 1 and Table 2. Benzimidazoles bearing either electron-donating (entries 4-9 and 13-18) or electron-withdrawing substituents (entries 22-24) were successfully produced in very short times with excellent yields. Considering the reaction times, a significant effect of the substituents on either aldehydes or *o*-phenylenediamines were not observed. A methyl substitution on nitrogen atom of *o*-phenylenediamine decreased the rate, possibly because of steric hindrance (entries 25-32). The reactions with *N*-methyl *o*-phenylenediamine were completed

in longer times with lower yields compared with their unsubstituted analogues (entries 1, 4, 7, 10, 13, 16, 19, and 22).

The developed protocol was specifically significant for the synthesis of bisbenzimidazoles. As indicated in the literature, their synthesis by conventional heating required prolonged reaction times<sup>32-34</sup> and harsh conditions such as high temperatures,<sup>20</sup> high pressures,<sup>20</sup> and toxic solvents.<sup>33-35</sup> In this study, the synthesis was performed in short times (e.g., 10 min for compound 33) with good yields (80–92%) under mild (MW/180 W) and solvent-free conditions.

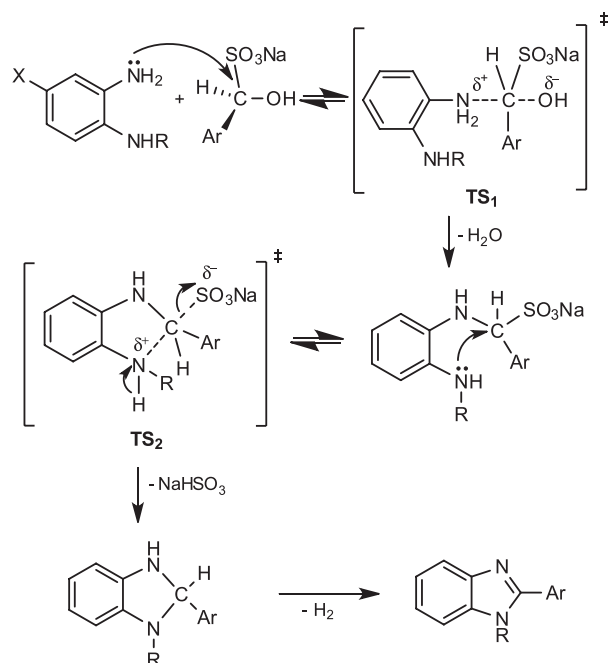
A mechanism has been proposed for the preparation of benzimidazoles based on some information in the literature<sup>27,36</sup> (Scheme 4). The reaction begins with the nucleophilic attack of the amine group on the *o*-phenylenediamine to the carbon atom of aldehyde bisulfite adduct. One mole of water is eliminated. Subsequently, the resulting alkyl sulfonate further reacts with the other amine group of *o*-phenylenediamine, resulting in the formation of dihydroimidazole intermediate. Finally, aromatization gives benzimidazole nucleus. Dipolar transition state structures (TS<sub>1</sub> and TS<sub>2</sub>) are formed in the course of the reaction. As indicated in the literature,<sup>29</sup> this type of reactions are expected to proceed at a faster rate and provide high yields under MW irradiation.

**Table 1.** Physical data and reaction times of the synthesized benzimidazoles under microwave irradiation

Entry	Compound			m.p. (°C)	Reaction Time (min)	Yield (%)
	Ar	R	X			
1	C <sub>6</sub> H <sub>5</sub>	H	H	290–292	8	85
2	C <sub>6</sub> H <sub>5</sub>	H	Cl	206–208	4	76
3	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	234–236	2	83
4	2-HOC <sub>6</sub> H <sub>4</sub>	H	H	237–238	4	90
5	2-HOC <sub>6</sub> H <sub>4</sub>	H	Cl	276–277	2	85
6	2-HOC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	252–254	2	84
7	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	H	292–294	16	77
8	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	Cl	243–246	20	79
9	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	249–251	12	81
10	2-Thiophenyl	H	H	333–334	6	75
11	2-Thiophenyl	H	Cl	223	20	64
12	2-Thiophenyl	H	CH <sub>3</sub>	248–249	6	76
13	4-MeC <sub>6</sub> H <sub>4</sub>	H	H	275–276	25	87
14	4-MeC <sub>6</sub> H <sub>4</sub>	H	Cl	233–235	10	85
15	4-MeC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	189–190	25	81
16	4-MeOC <sub>6</sub> H <sub>4</sub>	H	H	225–226	10	89
17	4-MeOC <sub>6</sub> H <sub>4</sub>	H	Cl	179–181	5	87
18	4-MeOC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	85–87	5	80
19	2-Hydroxy-1-naphthyl	H	H	239–241	6	80
20	2-Hydroxy-1-naphthyl	H	Cl	233–235	8	95
21	2-Hydroxy-1-naphthyl	H	CH <sub>3</sub>	218–220	8	81
22	4-ClC <sub>6</sub> H <sub>4</sub>	H	H	289–290	2	88
23	4-ClC <sub>6</sub> H <sub>4</sub>	H	Cl	228–230	2	81
24	4-ClC <sub>6</sub> H <sub>4</sub>	H	CH <sub>3</sub>	220–222	6	88
25	C <sub>6</sub> H <sub>5</sub>	Me	H	91–92	20	65
26	2-HOC <sub>6</sub> H <sub>4</sub>	Me	H	164–165	6	80
27	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Me	H	155–156	20	71
28	2-Thiophenyl	Me	H	71–73	8	77
29	4-MeC <sub>6</sub> H <sub>4</sub>	Me	H	122–124	25	74
30	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	H	115–117	10	80
31	2-Hydroxy-1-naphthyl	Me	H	280–283	10	72
32	4-ClC <sub>6</sub> H <sub>4</sub>	Me	H	109–110	20	70

**Table 2.** Physical data and reaction times for the synthesized bisbenzimidazoles under microwave irradiation

Entry	Compound		m.p. (°C)	Reaction Time (min)	Yield (%)
	R	X			
33	H	H	>350	10	87
34	H	Cl	>350	20	92
35	H	CH <sub>3</sub>	350 dec.	25	89
36	CH <sub>3</sub>	H	281-283	35	80

**Scheme 4.** Plausible mechanism for the synthesis of benzimidazoles

To compare the MW-assisted synthesis method with the classical heating method, the synthesis of some benzimidazoles were also performed under reflux in DMF. Related experimental results are shown in Table 3. It is clear that in all cases much shorter reaction times and higher yields were achieved under MW irradiation compared with classical heating. For example, with conventional heating, 2-(5-chlorobenzimidazolyl)phenol **5** was obtained in 45% yield in 120 min; under MW conditions, after 2 min the yield of the reaction was 85%. Similarly, classical and MW-assisted synthesis yielded 2-(5-chlorophenyl)benzimidazole **22** in 43% (180 min) and 77% (2 min), respectively. The MW method also provided good results for bisbenzimidazole derivatives. For example, 1,4-bis(2-benzimidazolyl)benzene **33**, was synthesized in 300 min with 56% yield by classical heating method; using MWs, it was obtained in 10 min with 87% yield.

The structures of the products were confirmed by IR, <sup>1</sup>H-, and <sup>13</sup>C-NMR, and the details are given in the experimental section. The IR spectra of the synthesized 1*H*-benzimidazole derivatives show strong bands in the 3200–2400 cm<sup>-1</sup> region, which is a characteristic of such compounds and indicate N-H...N type hydrogen bonds.<sup>37</sup> In addition, the absence of any band corresponding to N–H stretching vibrations, in the 3200–3600 cm<sup>-1</sup> region indicates that the *o*-phenylenediamine has reacted with the aldehyde bisulfite adducts and formed the benzimidazole ring system. Moreover,

**Table 3.** Comparison of microwave and classical heating for synthesis of some benzimidazoles

Entry	Classical heating <sup>a</sup>		Microwave conditions <sup>b</sup>	
	React. Time (min)	Yield (%)	React. Time (min)	Yield (%)
<b>1</b>	120	70	8	85
<b>4</b>	120	55	4	90
<b>5</b>	120	45	2	85
<b>7</b>	180	55	16	77
<b>10</b>	120	66	6	75
<b>13</b>	180	63	25	87
<b>14</b>	180	65	10	85
<b>15</b>	180	56	25	81
<b>16</b>	180	65	10	89
<b>17</b>	180	68	5	87
<b>18</b>	180	66	5	80
<b>19</b>	150	70	6	80
<b>22</b>	180	43	2	88
<b>23</b>	180	53	2	81
<b>24</b>	180	54	6	88
<b>25</b>	300	24	20	65
<b>26</b>	240	38	20	71
<b>33</b>	300	56	10	87
<b>36</b>	360	49	35	80

<sup>a</sup>Reflux in DMF; <sup>b</sup>Neat conditions under 180 W microwave irradiation.

the IR spectra of the compounds include strong/medium bands in the 1650–1400 cm<sup>-1</sup> region and correspond to the C=C and C=N stretching vibrations.<sup>37-40</sup> <sup>1</sup>H- and <sup>13</sup>C-NMR results also support the formation of the synthesized compounds.<sup>41,42</sup> The NH protons of compounds containing 1*H*-benzimidazole ring appear as broad singlets at 12.0–13.3 ppm. Because of the 1,3-tautomerisation<sup>41</sup> 3a/7a, 4/7, and 5/6 positions of the unsubstituted benzimidazoles are equivalent and generally appears at the same region in the <sup>1</sup>H- and <sup>13</sup>C-NMR spectra. In <sup>13</sup>C-NMR spectra of the compounds, the signal at the lowest field (145–155 ppm) is assigned to the C2 carbon of the benzimidazole ring in C=N form which indicates the formation of the benzimidazole ring system.

## CONCLUSIONS

A simple and efficient methodology for the synthesis of 2-substituted benzimidazoles and bis-benzimidazoles was developed. The reaction times were reduced from hours to minutes by our MW-assisted method. Benzimidazoles with different kinds of derivatives were easily synthesized in good yields under neat conditions with an easy purification procedure.

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