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Microwave Assisted Aqueous Phase Synthesis of Benzothiazoles and Benzimidazoles in the Presence of Ag_2O[1]

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Abstract—A simple and high yielding method for synthesized benzothiazoles and benzimidazole in water under micro wave irradiation by the reaction of 2-amino thiophenol and *o*-phenylenediamine with various aromatic aldehydes in the presence of Ag_2O. Ag_2O can be recovered and reused without significant loss of activity.

Keywords: benzothiazoles, benzimidazole, 2-amino thiophenol, *o*-phenylenediamine, aromatic aldehydes, Ag_2O, microwave irradiation

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Benzothiazoles and benzimidazoles belong to one of the most important classes of heterocycles for the synthesis of natural products, pharmaceuticals, dyes and various other biologically active molecules, such as Riluzole a drug used to treat amyotrophic lateral sclerosis [1] and Mebendazole a drug used to treat parasitic worm infestations [2].

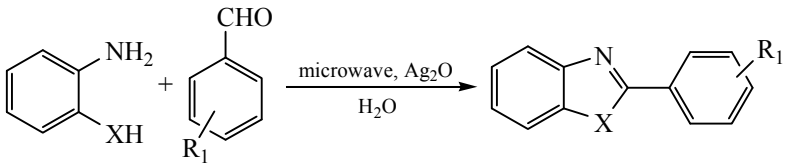
Benzothiazole derivatives have been used for diabetes [3], antitumor drugs [4], and amyloid inhibitors for treatment of Alzheimer's disease [5]. Especially benzimidazoles are useful in controlling the diseases such as hypertension [6], ischemiareperfusion injury [7], as well as obesity [8].

A number of methodologies have been developed for the synthesis of benzothiazoles and benzimidazoles. Hornberger et al. [9] have developed one-pot synthesis of disubstituted benzimidazoles from 2-nitro anilines with palladium charcoal as a catalyst in the presence of trimethyl orthoformate and catalytic pyridinium *p*-toluenesulfonate (PPTS) at room temperature. Beaulieu et al. [10] demonstrated the oxone mediated benzimidazoles, benzoxazoles and benzothiazoles by using phenylene diamines, 2-amino thiophenol, 2-aminothiol, and acid one-pot synthesis of benzimidazoles using 1,2-phenylenediamines and aldehydes in wet DMF at room temperature. Saha et al. [11] described the synthesis of 2-substituted benzimidazoles by using *o*-phenylenediamine with aromatic aldehydes in the presence of an ionic liquid, 1-methyl-3-methylimidazolium tetrauoroborate, [pmim]BF_4 at room temperature. Mirkhani et al. [12] has reported the synthesis of 2-imidazolines and bis-imidazolines by the reaction of ethylenediamine, and nitriles in the presence of sulfur under ultrasonic irradiation. Katla et al. [13] has reported the aqueous phase synthesis of benzothiazoles and benzimidazoles by using 2-amino thiophenol and *o*-phenylenediamine with aromatic aldehyde in the presence of β-cd. Banerjee et al. [14] developed synthesis of biologically active 2-aryl-1,3-benzothiazole and 1,3-benzoxazole derivatives in presence of a green efficient catalyst (ZnO nanoparticles) at room temperature.

However, the above mentioned methods have different draw backs, including the use of toxic and expensive reagents or catalysts, strongly acidic conditions, long reaction time, harsh reaction conditions, side reactions and low yields. In continuation of our attempts to develop environmentally benign methodologies, herein we report an Microwave assisted aqueous phase Ag_2O catalyzed method for the synthesis of benzothiazoles and benzimidazoles by a two component reaction, involving 2-amino thiophenol and 1,2-diamino benzene with various benzaldehydes (Scheme 1).

[1] The text was submitted by the authors in English.

Scheme 1.



X = S, NH; R_1 = F, Br, Cl, NO_2, Me, OMe, OEt, OH, H.

RESULTS AND DISCUSSION

Optimization of the reaction conditions. In order to optimize the reaction conditions, primary efforts were focused on the use of Ag_2O, water as solvent and 2-aminobenzenethiols/*o*-phenylenediamine (**1**) and benzaldehyde (**2**) were chosen as the model reactants to detect the microwave reaction conditions. The screening of different solvents was summarized in Table 1. It turned out that in the absence of theAg_2O, the product was obtained in only 20% yield (Table 1, entry 5). Among the four selected solvents. Water has the most effective (Table 1, entry 1).

a. Conventional method. A mixture of 2-amino-benzenethiols and *o*-phenylenediamine (1.1 mmol) various benzaldehyde (1 mmol), and water (5 mL) was refluxed for 1 h in the presence of Ag_2O (5 mmol). The progress of the reaction was monitored by TLC upon completion of the reaction. The reaction mixture was cooled down to room temperature and poured over crushed ice. The residue was filtered off, washed with water and purified by column chromatography (PE–EtOAc = 20 : 1) to yield title compounds **3a–3i, 4a–4h**.

b. Microwave method. Ag_2O (5 mmol) were dissolved in 10 mL water and stirred until the solid dissolved completely, then was added to a mixture of 2-aminobenzenethiols and *o*-phenylenediamine (1.1 mmol) and various benzaldehyde **2** (1.0 mmol) and mixed thoroughly. The reaction mixture was irradiated in a microwave oven at 700 W for specific period of time. The progress of the reaction was monitored by TLC upon completion of the reaction. The reaction mixture was cooled to room temperature, and then evaporated in vacuum. The product purified by column chromatography (PE–EtOAc = 20 : 1) to give solid **3a–3i, 4a–4h**.

Above two methods, microwave method is convenient method for synthesis of 2-aryl-1,3-benzothiazoles (or) 2-aryl-1,3-benzimidazoles due to less reaction time and high percentage of yield.

Encouraged by the above experiments, we further explored the synthetic protocol and the scope by employing different kinds of aldehydes functionalized with electron-rich groups (F, -Cl, -Br, -OH, -OMe). The results were summarized in Table 2. Clearly, all reactions worked well irrespective of the substituents on the aldehydes substrates (Table 2, compounds **3a–3i**). It is noteworthy that the reaction with 1*H*-indole-3-carbaldehyde (Table 2, compound **3i**) also afforded the desired product in satisfactory yield.

Viability of the methodology was examined for a series of aryl/hetero aryl aldehydes bearing electron donating as well as electron withdrawing groups under the optimized reaction conditions and corresponding products were obtained in good to excellent yields. Presence of electron withdrawing group (eg-NO_2) in aldehyde system fixed firmly the reaction while opposite effect was observed for electron donating substituent's like Cl, Me, OMe, OEt (**4b** to **4h**). Using these reaction conditions exclusively formation of 2-substituted benzimidazoles was observed. The products were characterized by their physical and spectral data. Thus, Table 3 illustrates generality and efficiency of this method for the synthesis of benzimidazoles.

Table 1. Optimization of the reaction conditions[a]

Enry no.	Solvent	Conventional method		Microwave irradiation method	
		time, h	yield,[b] %	time, h	yield,[b] %
1	H_2O	1	62	5	98
2	EtOH	3	45	10	95
3	CH_2Cl_2	2	58	8	92
4	THF	5	54	12	80
5	–	8	15	14	20

[a] Reaction conditions: Ag_2O (5 mmol) phenylenediamine **1** (1.1 mmol), and benzaldehyde **2** (1.0 mmol) 10 mL water.
[b] Isolated yields.

Table 2. Synthesis of 2-aryl-1,3-benzothiazoles in the presence of Ag_2O under micro wave irradiation

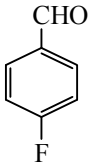
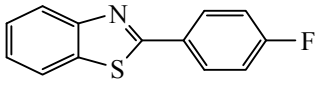
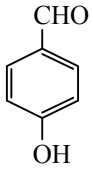
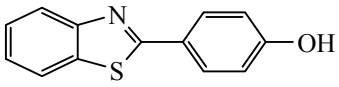
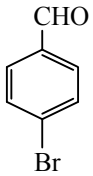
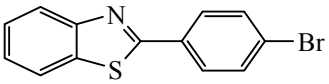
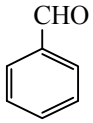
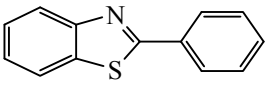
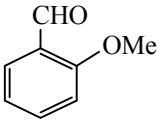
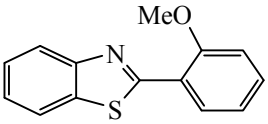
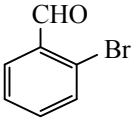
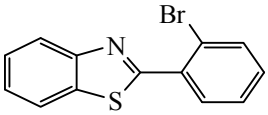
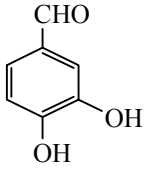
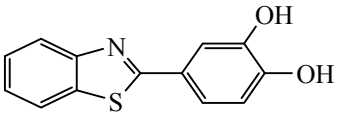
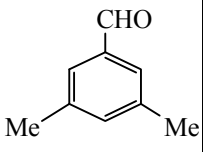
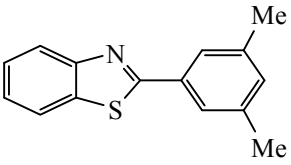
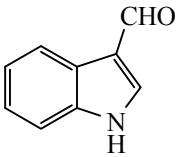
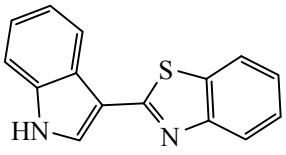
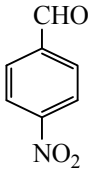
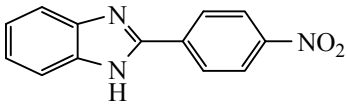
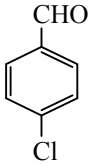
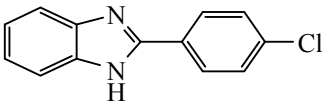
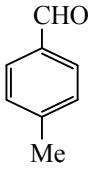
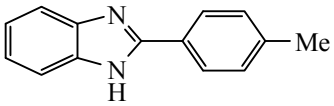
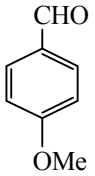
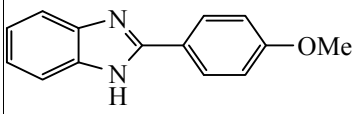
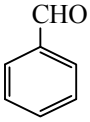
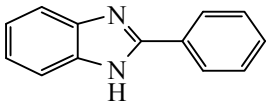
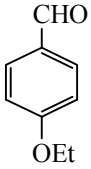
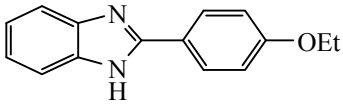
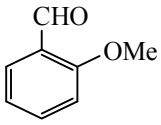
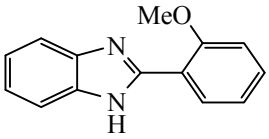
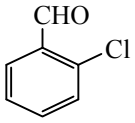
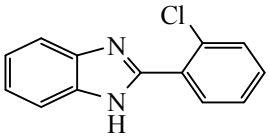
Comp. no.	Aldehyde	Product	Time, min	mp, °C		Yeild, %
				found	calculated	
3a			5	96–97	98–99 [15]	98
3b			6	231–232	230–234 [16]	96
3c			4	131–132	130–131 [17]	97
3d			5	111–113	112–114 [18]	98
3e			7	122–123	122–123 [18]	93
3f			5	68–69	66–68 [19]	95
3g			4	152–154	154–156 [20]	96
3h			8	120–122	122–124 [21]	92
3i			6	180–182	–	95

Table 3. Synthesis of 2-aryl-1,3-benzimidazoles in the presence of Ag_2O under micro wave irradiation

Comp. no.	Aldehyde	Product	Time, min	mp, °C		Yeild, %
				found	calculated	
4a			5	296–298	299–301 [22]	98
4b			6	287–289	287–289 [23]	96
4c			4	274–275	276–278 [24]	97
4d			5	220–222	221–223 [24]	98
4e			7	293–294	293–295 [24]	93
4f			5	192–195	–	95
4g			4	180–182	181–182 [24]	96
4h			8	232–234	231–233 [25]	92

EXPERIMENTAL

All reagents and solvents were procured from Aldrich/Merck and used without further purification. Melting points were recorded using a Cintex melting point apparatus and are uncorrected. Reaction progress as well as compound purity were monitored with F254 silica-gel precoated thin-layer chromatography (TLC) plates using hexane:ethyl acetate (8 : 3) as eluent, and the developed chromatogram was visualized under ultraviolet (UV) light and iodine vapors. Infrared (IR) spectra were recorded on a Bruker Tensor 27 series Fourier-transform (FT)-IR spectrophotometer using KBr pellets. Proton nuclear magnetic resonance (1H

NMR) spectra were recorded on a Bruker 400-MHz spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Jeol JMSD-400 spectrometer. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit, and the values are within ±0.4% of theoretical values. The reactions were carried out in a BPL 800 G domestic microwave oven.

General procedure for the synthesis of 2-substituted benzothiazoles (3a–3i). Ag_2O (5mmol) were dissolved in 10 mL water and stirred until the solid dissolved completely, then was added to a mixture of 2-amino thiophenol **1** (1.1 mmol) and benzaldehyde **2** (1.0 mmol) and mixed thoroughly. The reaction mixture was irradiated in a microwave oven at 700 W for specific period of time as indicated in Table 2, the reaction was complete monitored by TLC analysis The reaction mixture was cooled to room temperature, and then evaporated in vacuum. The product purified by column chroma-tography (PE–EtOAc = 20 : 1) to give white solid **3** (0.2092 g, 99%). Other products were synthesized through the same procedure. All ^{1}H NMR and ^{13}C NMR results were summarized in Supporting information. The configuration of compounds was assigned by comparing ^{1}H and ^{13}C NMR data with known compounds.

2-(4-Fluorophenyl)benzo[*d*]thiazole (3a). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.08–8.04 m (1H, ArH), 7.88 d (1H, ArH), J = 7.5 Hz), 7.48 t (1H, ArH, J = 7.1 Hz), 7.17 t (2H, ArH, J = 7.0 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 166.62, 153.93, 134.92, 129.43, 129.38, 126.32, 125.14, 123.07, 121.49, 116.13, 115.95. MS (ESI): *m/z* 230 $[M + H]^+$.

4-(Benzo[*d*]thiazol-2-yl)phenol (3b). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.35 s (1H, ArH), 8.04–7.96 m (2H, ArH), 7.88–7.76 m (2H, ArH), 7.46 t (1H, ArH, J = 7.1 Hz), 7.34 t (1H, ArH, J = 6.9 Hz), 6.93–6.91 m (2H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 167.14, 159.73, 153.26, 133.78, 128.33, 125.32, 123.98, 123.85, 121.64, 120.74, 115.31. MS (ESI): *m/z* 228 $[M + H]^+$.

2-(4-Bromophenyl)benzo[*d*]thiazole (3c). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.07 d (1H, ArH, J = 8.1 Hz), 7.98–7.95 m (2H, ArH), 7.92 d (1H, ArH, J = 7.9 Hz), 7.66–7.62 m (2H, ArH), 7.52–7.47 m (1H, ArH), 7.42–7.37 m (1H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 166.63, 154.03, 135.01, 132.17, 128.85, 126.45, 125.39, 123.27, 121.64, 132.16, 128.84, 126.44, 125.39, 123.26, 121.64. MS (ESI): *m/z* 290 $[M + 2]^+$.

2-Phenylbenzo[*d*]thiazole (3d). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.12–8.05 m (3H, ArH), 7.89 d (1H, ArH, J = 7.8 Hz), 7.53–7.45 m (3H, ArH), 7.41–7.35 m (2H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 130.94, 128.99, 127.51, 126.27, 125.13, 123.19, 121.58. MS (ESI): *m/z* 212 $[M + H]^+$.

2-(2-Methoxyphenyl)benzo[*d*]thiazole (3e). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.52 d (1H, ArH, J = 1.8 Hz), 8.51 d(1H, ArH, J = 1.6 Hz), 8.08 d (1H, ArH, J = 8.2 Hz), 7.49 d (1H, ArH, J = 1.2 Hz), 7.48–7.43 m (2H, ArH), 7.36–7.33 m (2H, ArH), 4.04 s (3H, OCH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 157.13, 152.06, 131.73, 129.43, 125.84, 124.53, 122.73, 121.14, 111.58. MS (ESI): *m/z* 242 $[M + H]^+$.

2-(2-Bromophenyl)benzo[*d*]thiazole (3f). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.14 d (1H, ArH, J = 7.9 Hz), 8.02–7.93 m (2H, ArH), 7.72 d (1H, ArH, J = 7.9 Hz), 7.54–7.29 m (4H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 165.62, 152.49, 133.95, 132.04, 131.18, 127.46, 126.25, 125.39, 123.41, 121.35. MS (ESI): *m/z* 290 $[M + 2]^+$.

4-(Benzo[*d*]thiazol-2-yl)benzene-1,2-diol (3g). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.21–7.16 m (2H, ArH), 7.12–7.06 m (2H, ArH), 7.01–6.96 m (2H, ArH), 6.83–6.76 m (1H, ArH), 5.27 s (2H, OH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 143.63, 128.21, 128.09, 127.82, 127.68, 127.61, 127.23, 126.92, 125.63, 36.91, 36.68, 31.93, 31.80, 30.16, 30.04, 29.71, 29.34, 29.24, 27.72, 27.64, 22.82, 22.68, 22.58, 14.11.MS (ESI): *m/z* 244 $[M + H]^+$.

2-(3,4,5-Trimethoxyphenyl)benzo[*d*]thiazole (3h). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.05 d (1H, ArH, J = 8.2 Hz), 7.88 d (1H, ArH, J = 7.6 Hz), 7.50–7.47m (2H, ArH), 7.31 s (1H, ArH), 7.11 s (1H, ArH), 3.98 s (9H, CH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 153.88, 153.46, 134.82, 126.33, 125.08, 122.98, 121.46, 104.62, 60.92, 56.28. MS (ESI): *m/z* 302 $[M + H]^+$.

2-(1*H*-Indol-3-yl)benzo[*d*]thiazole (3i). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.92 s (1H, ArH), 8.43 d (1H, ArH, J = 7.1 Hz), 8.03 d (1H, ArH, J = 8.1 Hz), 7.92 d (1H, ArH, J = 2.8 Hz), 7.86 d (1H, ArH, J = 7.9 Hz), 7.46–7.26 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 163.23, 153.63,

136.43, 133.79, 126.41, 126.04, 124.83, 124.17, 123.33, 121.96, 121.73, 121.28, 120.92, 112.22, 111.73. MS (ESI): *m/z* 251 $[M + H]^+$.

General procedure for the synthesis of 2-substituted benzimidazoles (4a–4h). Ag_2O (5 mmol) were dissolved in 10 mL water and stirred until the solid dissolved completely, then was added to a mixture of *o*-phenylenediamine **1** (1.1 mmol) and benzaldehyde **2** (1.0 mmol) and mixed thoroughly. The reaction mixture was irradiated in a microwave oven at 700 W for specific period of time as indicated in Table 3, the reaction was complete monitored by TLC analysis The reaction mixture was cooled to room temperature, and then evaporated in vacuum. The product purified by column chromatography (PE–EtOAc = 20 : 1) to give white solid **3a** (0.2092 g, 99%). Other products were synthesized through the same procedure. All ^1H and ^{13}C NMR results were summarized in Supporting information. The configuration of compounds was assigned by comparing ^1H and ^{13}C NMR data with known compounds.

2-(4-Nitrophenyl)-1*H*-benzo[*d*]imidazole (4a). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.64–7.62 m (2H, ArH), 7.43–7.41 m (3H, ArH), 7.31–7.26 m (3H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 160.25, 158.53, 153.97, 143.09, 136.02, 130.62, 128.13, 127.11, 122.63, 119.71, 114.62, 110.35.MS (ESI): *m/z* 240 $[M + H]^+$.

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (4b). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.58 d (1H, ArH, *J* = 7.6 Hz), 7.40 d (2H, ArH, *J* = 7.6 Hz), 7.30–7.22 m (3H, ArH), 7.14 d (1H, ArH, *J* = 7.6 Hz), 7.03 d (1H, ArH, *J* = 7.6 Hz).^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 130.91, 128.96, 127.51, 126.26, 125.13, 123.16, 121.58. MS (ESI): *m/z* 229 $[M + H]^+$.

2-(*p*-Tolyl)-1*H*-benzo[*d*]imidazole (4c). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.14 d (4H, ArH, *J* = 8.3 Hz), 7.34 d (4H, ArH, *J* = 8.1 Hz), 3.12 s (1H, NH), 2.42 s (3H, CH_3).^{13}C NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: 140.33, 137.78, 132.72, 129.75, 129.43, 128.83, 125.71, 123.22, 120.54, 110.44, 21.0. MS (ESI): *m/z* 209 $[M + H]^+$.

2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (4d). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.12 d (1H, ArH, *J* = 8.6 Hz), 7.64–7.44 m (3H, ArH), 6.96–6.91 m (3H, ArH), 6.78 d (1H, ArH, *J* = 8.6 Hz), 3.71 s (3H, OCH_3) ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 166.61, 164.12, 154.84, 132.96, 58.41. MS (ESI):*m/z* 225 $[M + H]^+$.

2-Phenyl-1*H*-benzo[*d*]imidazole (4e). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.06 d (1H, ArH, *J* = 6.2 Hz), 7.67–7.63 m (3H, ArH), 7.48–7.43 m (2H, ArH), 7.28–7.26 m (2H, ArH), 7.12 d (1H, ArH, *J* = 6.8 Hz), 5.46 s (1H).^{13}C NMR spectrum (100MHz, $CDCl_3$), δ, ppm: 151.53, 129.92, 129.23, 128.28, 126.36, 121.76. MS (ESI): *m/z* 195 $[M + H]^+$.

2-(4-Ethoxyphenyl)-1*H*-benzo[*d*]imidazole (4f). ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 7.58–7.54 m (2H, ArH), 7.24–7.12 m (3H, ArH), 6.78 d (1H, ArH, *J* = 8.3 Hz), 6.91–6.87 m (2H, ArH), 4.09–3.95 q (2H, OCH_2), 1.42 t (3H, CH_3, *J* = 7.5 Hz). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 160.27, 158.49, 153.98, 143.08, 136.02, 130.65, 128.13, 127.12 122.64, 119.69, 114.61, 110.31, 63.32, 14.82. MS (ESI): *m/z* 239 $[M + H]^+$.

2-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (4g). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.03–7.97 m (5H, ArH), 6.92–6.88 m (4H, ArH), 3.84 s (3H, OCH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 157.45, 156.36, 152.31, 143.02, 135.36, 132.24, 131.36, 128.31, 127.62, 122.42, 121.92, 120.68, 120.28, 119.58, 110.71, 109.82, 55.13, 55.04, 43.46. MS (ESI): *m/z* 225 $[M + H]^+$.

2-(2-Chlorophenyl)-1*H*-benzo[*d*]imidazole (4h). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 8.61 s (1H, ArH), 7.94 d (3H, ArH, *J* = 5.8 Hz), 7.46 s (2H, ArH), 7.24 s (1H, ArH), 6.71 d (1H, ArH, *J* = 8.3 Hz), 4.91 s (1H, NH).^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 158.21, 130.94, 128.98, 127.54, 126.24, 125.12, 123.18, 121.55. MS (ESI): *m/z* 229 $[M + H]^+$.

In summary, we have developed an efficient synthetic protocol for the synthesis of benzothiazoles and benzimidazoles derivatives in the presence of Ag_2O under micro wave irradiation. Using of Ag_2O as a highly efficient, easy handling, and nontoxic reducing reagent makes the present procedure ecofriendly and economically acceptable. The yields obtained are excellent and the products were recovered in pure form from the reaction mixture.

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