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Synergetic catalytic effect of ionic liquids and ZnO nanoparticles on the selective synthesis of 1,2-disubstituted benzimidazoles using a ball-milling technique

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Abstract: A solvent-free selective green synthesis of 1,2-disubstituted benzimidazoles was developed using a ball-milling technique. Recyclable ionic liquid-coated ZnO-nanoparticles (ZnO-NPs, catalyst **5**) was employed as a catalyst, which produced high yields, turnover number and turnover frequency because of synergetic catalytic properties of ionic liquid and ZnO-NPs. The present method successfully employed the synthesis of various 1,2-disubstituted benzimidazole derivatives in excellent yields with high selectivity. The reaction could also be performed at a multi-gram scale with the same efficiency. A high eco-scale score and low E-factor emphasize the ecofriendly nature of the present method.

Keywords: benzimidazole, ball-milling, ZnO-nanoparticle, ionic liquid, catalyst

Introduction

Benzimidazole derivatives are extensively employed in the pharmacological industry due to their broad biological functions.[1-4] Recently, benzimidazole derivatives have been involved in the treatment of ischemia reperfusion injury,[5] hypertension[6] and obesity.[7] Benzimidazole derivatives also show potential activities toward HIV,[4] human cytomegalovirus (HCMV),[4] herpes (HSV-1) [8] and influenza.[9]

For the synthesis of benzimidazole derivatives, condensation of *o*-phenylenediamines with carboxylic acids is the most widely employed strategy, but it requires harsh dehydrating conditions.[10,11] Other approaches, such as the rhodium-catalyzed hydroformylation of *N*-alkenyl phenylenediamines,[12] reductive cyclization reaction of *o*-nitroaniline with aldehydes,[13] palladium-catalyzed tandem carbonylation–cyclization reaction of *o*-phenylenediamines,[14] and palladium-catalyzed tandem dehydration-coupling reaction of 2-bromoaniline,[15] have been reported. A major limitation of these methodologies is forming a mixture of 2-substituted and 1,2-disubstituted benzimidazoles because of the low selectivity in terms of the *N*-1 substitution. Although a few

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methods have been reported that selectively synthesized 1,2-disubstituted benzimidazoles as a major product, they suffer from long reaction times, use of toxic catalysts and a long work-up process.[16-19]

Ball milling is an attractive mechanical technique for solvent-free synthesis, which avoids the use of harmful solvents and toxic wastes.[20] This technique has found many applications in the field of synthetic organic chemistry such as asymmetric aldol reactions,[21,22] Baylis–Hillman reactions,[23] protection of diamines,[24] oxidations,[25,26] reductions,[27] condensations,[28,29] Wittig reactions,[30] asymmetric Michael addition reactions,[31] transition metal-catalyzed coupling reactions,[32a-c] click reaction,[32d,e] and synthesis of pyrimidines,[32f] indoles,[32g] and pyrans.[32h]

Ionic liquids (ILs) gain considerable attention as they are possible environmentally benign catalysts. They offer significant properties like a wide liquid range, negligible vapor pressure, high catalytic activity, good thermal stability and adjustable physical and chemical properties that make them novel and green catalysts.[33,34] Various types of reactions using ILs as a catalyst have been reported, including alkylation, nitration, Diels−Alder reactions, Michael addition and esterification of carboxylic acids with increasing overall yields and reduction in reaction times.[35-39] Immobilization of ILs on the surface of solid materials provides more efficient protocols in terms of product separation and catalyst recovery.[40,41] Organic polymers, inorganic materials and magnetic nanoparticles have been employed as the supports.[42,43] In this context, we report recyclable IL-coated ZnO-nanoparticles (ZnO-NPs) for the selective synthesis of 1,2-disubstituted benzimidazoles using a ball milling technique.

Results and discussion

1-Ethyl-3-methylimidazolium bromide (**1**) and 1-methyl-3-carboxymethylimidazole bromide (**2**) were immobilized on the surface of ZnO-NPs by *in situ* capping ILs on the surface of ZnO-NPs **3** using a sol-gel method to produce compounds **4** and **5**, respectively. The modified ZnO-NPs **4** and **5** have different sizes and morphologies that were confirmed by dynamic light scattering (DLS) and scanning electron microscopy (SEM) analyses (Figures S1 and S2). ILs act as an organic template or a structure-directing agent that governs the growth of ZnO-NPs in a particular direction.[44] The wurtzite-type structure of ZnO-NPs was confirmed by powder X-ray diffraction (PXRD) studies (Figure S3). The structure of catalyst **4** represents the coating of ligand **1** on the surface of ZnO-NPs. In the case of catalyst **5**, the presence of carboxylic acid group on the surface of ZnO-NPs was confirmed by IR spectra of catalyst **5**, showing the peak at 3448 cm^{-1} corresponding to –OH of carboxylic acid group (Figure S4).

For a model study, *o*-phenylenediamine and 4-hydroxy-3-nitrobenzaldehyde were chosen as model compounds. Reactions of *o*-phenylenediamine with 4-hydroxy-3-nitrobenzaldehyde were performed in the presence of different catalysts **1**-**5** at room temperature. A mixture of *o*-phenylenediamine with 4-hydroxy-3-nitrobenzaldehyde in the presence of a 0.2 mol% catalyst was milled in a tungsten carbide milling jar without

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solvent for 22 min at 600 rpm under argon. The progress of the reaction was monitored by ^{1}H NMR and TLC. The results are summarized in Table 1. ILs **1** and **2** gave moderate overall chemical yields of products **6** and **7** (Table 1, Entries 1 and 2). Catalyst **2** showed a higher selectivity for 1,2-disubstituted benzimidazole *i.e.* compound **6**, compared with compound **7**. Very similar results were observed with catalysts **3** and **4** with moderate overall yields with low selectivities (Entries 3 and 4). Catalyst **5** afforded only compound **6** without detecting compound **7** with an excellent yield (Entry 5). A control experiment was performed without catalyst, resulting in a low overall yield of products with an inversion of selectivity (Entry 6). These results confirm the catalytic effect on the efficiency and selectivity of the reaction. The high selectivity of catalyst **5** was attributed to the synergetic catalytic effect of IL **2** and ZnO-NPs **3**. ZnO-NPs have a high affinity for COOH, OH and C=N groups,[45-48a] and ILs act as a structure-directing agent. Thus, a 3D network is formed between ZnO-NPs **3** and IL **2**.[44] IL **1** does not form a 3D network with ZnO-NPs **3** because of the absence of a linker group such as COOH.

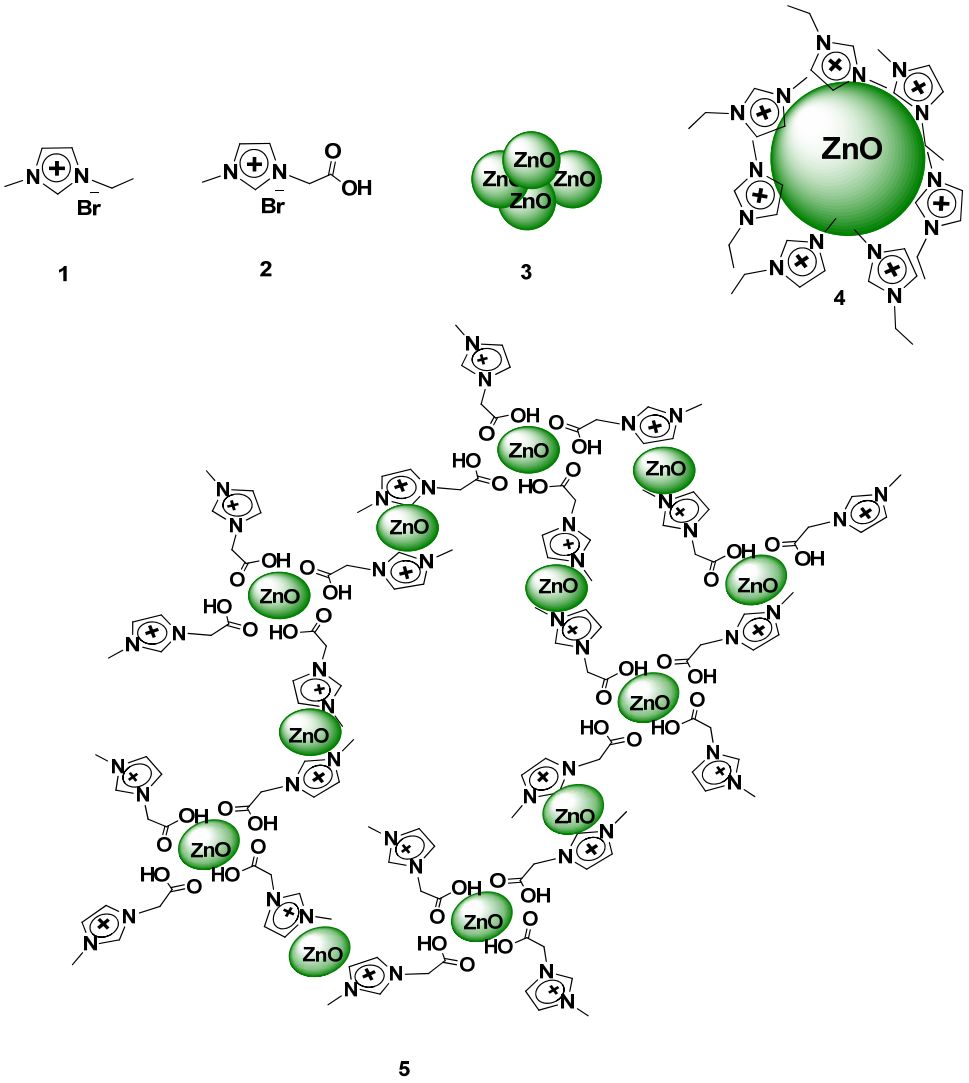

Figure 1. Structure of catalysts **1-5**.

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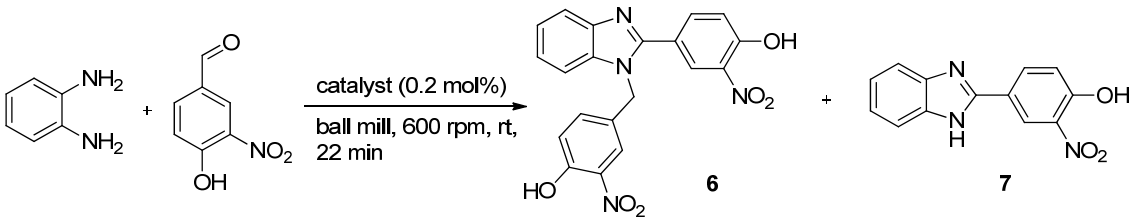
Table 1. Screening catalysts for the reaction of *o*-phenylenediamine with 4-hydroxy-3-nitrobenzaldehyde.[a]



entry	catalyst	product **6** (%)[b]	product **7** (%)[b]	overall yield (**6**+**7**) (%)	selectivity (**6**/(**6**+**7**))
1	**1**	35	22	57	0.61
2	**2**	52	14	66	0.78
3	**3**	47	19	66	0.71
4	**4**	38	33	71	0.53
5	**5**	97	0	97	1
6	-	14	39	53	0.26

[a]Reaction conditions: *o*-phenylenediamine (9.2 mmol), 4-hydroxy-3-nitrobenzaldehyde (18.5 mmol), catalyst (0.2 mol%), 600 rpm, 20 milling balls (5 mm) in a milling jar (80 mL) at room temperature under argon. [b]Isolated yield with column chromatography on silica gel.

The effect of the catalyst loading on the product yield and the catalytic activity like the turnover number (TON) and turnover frequency (TOF) was investigated by varying catalyst **5** from 0.01 to 1.0 mol%. The results are presented in Figure 2. The results show that the product yield, TON and TOF increase with increasing amount of catalyst up to 0.2 mol%. A linear relation of the product yields, TON and TOF was observed with up to 0.2 mol% catalyst. A further increase in the amount of catalyst led to a small decrease in terms of the product yield and catalytic efficiency.

The reaction parameters, including milling times, ball to powder ratio, milling speeds and molar ratios of aldehyde and amine were screened. The results are summarized in Table 2. The progress of the reaction was monitored by recording the ^{1}H NMR spectra of the reaction mixture at regular intervals. It is essential to stop the reaction at an appropriate time to obtain product **6** in high yield (Entries 1-7). The highest yield of product **6** was obtained in 22 min at a milling speed of 600 rpm (Entry 4). The longer milling time decreased the yield of product **6** (Entries 5-7). The milling speed also influenced the reaction efficiency. It took 120 min for completion of the reaction at lower speed (100 rpm) than at 600 rpm (Entries 8-10). Milling at a speed (800 rpm)

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faster than 600 rpm generated side products and made the overall yield of product **6** decrease (Entry 11). The molar ratio of aldehyde and amine was also important in attaining a high yield of product **6**. The high yields of product **6** with complete selectivities were obtained when the ratios of aldehyde and amine were 2:1. The use of the equimolar ratio of aldehyde and amine afforded product **6** as a major product along with product **7** (Entry 12).

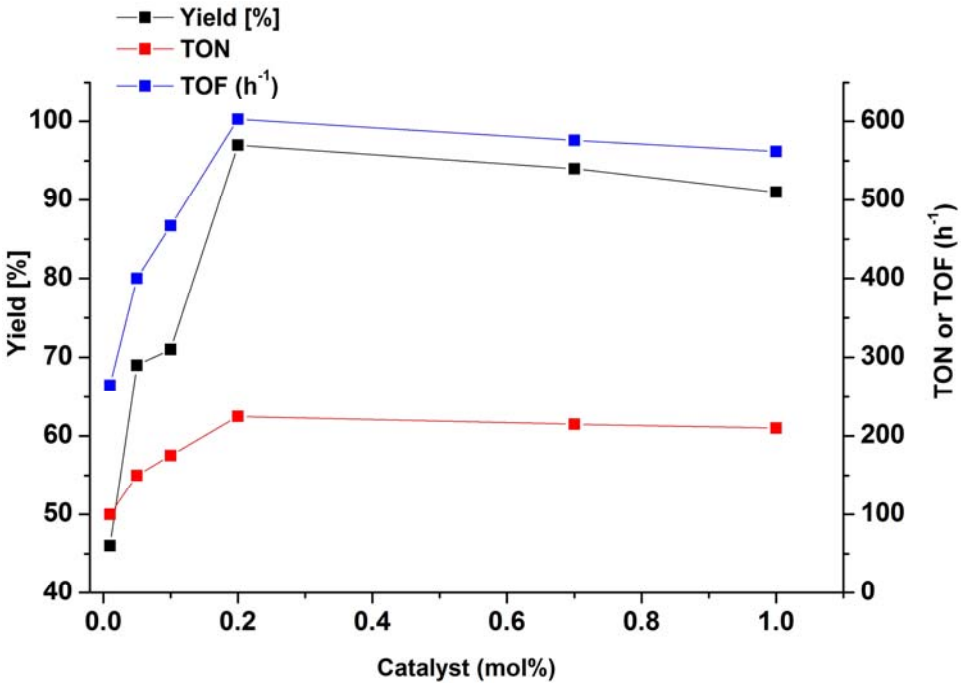

Figure 2. Relationship of the catalyst loading with the product yields calculated from the integration of ^{1}H NMR peaks, TON and TOF.

Table 2. Optimization of ball-milling conditions for the reaction of *o*-phenylenediamine with 4-hydroxy-3-nitrobenzaldehyde.[a]

entry	time (min)	speed (rpm)	yield of **6** (%)[b]
1	5	600	35
2	12	600	69
3	17	600	88
4	**22**	**600**	**97**
5	30	600	91
6	45	600	86
7	120	600	83
8	22	100	52
9	45	100	73
10	120	100	87
11	22	800	83
12	22	600	39[c]

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[a]Reaction conditions: *o*-phenylenediamine (9.2 mmol), 4-hydroxy-3-nitrobenzaldehyde (18.5 mmol), catalyst **5** (0.2 mol%), 20 milling balls (5 mm) in a milling jar (80 mL) at room temperature under argon. [b]The yield of **6** was calculated from the comparison of integration of the ^{1}H NMR peaks. [c]A 1:1 molar ratio of *o*-phenylenediamine and 4-hydroxy-3-nitrobenzaldehyde was used.

To monitor the temperature during ball milling, a reaction was performed in a particular milling jar. The milling jar had a special lid and transmitter. Temperature was monitored using EASY GTM software, observing that the temperature increased as the milling time increased as shown in Table S1. Maximum temperature at 22 min (the time required to complete the reaction) was 30.0 ºC. It shows that the milling temperature is not much far from room temperature. Ball to powder ratio is also an important parameter, significantly influencing the yields of reaction. The productivity of milling process is proportional to weight ratio because of increase in number of collision per unit time.[48b] The increase in collision frequency results in an increase in milling temperature.[48b] To avoid the excessive heating, a range of ratio of ball to powder (from 20:3 to 20:4) was employed in the present methodology with maximum temperature of 30 ºC. Further increase in ball to powder ratio increased the yield of reaction with a small extent, but the temperature of milling process increased much. Optimization of the ratio of ball to powder for each product is presented in Table S2.

With optimal reaction conditions, we investigated the scope and limitations of this methodology by varying aldehydes. The results are presented in Table 3. The interesting feature of this methodology is that the yields of the 1,2-disubstituted benzimidazole derivatives are independent of the structure of the aldehydes. Aldehydes with an electron-withdrawing group and with an electron-donating group afforded excellent yields of 1,2-disubstiuted benzimidazole derivatives. Another promising feature of the present methodology is that the products were obtained after washing with water followed by a small amount of methanol for quick drying. These advantages distinguished the present methodology from previously reported methods, which required a large amount of organic solvents and time-consuming tedious purification processes.

Table 3. Synthesis of various 1,2-disubstiuted benzimidazole derivatives under solvent-free, ball milling reaction conditions.[a,b]

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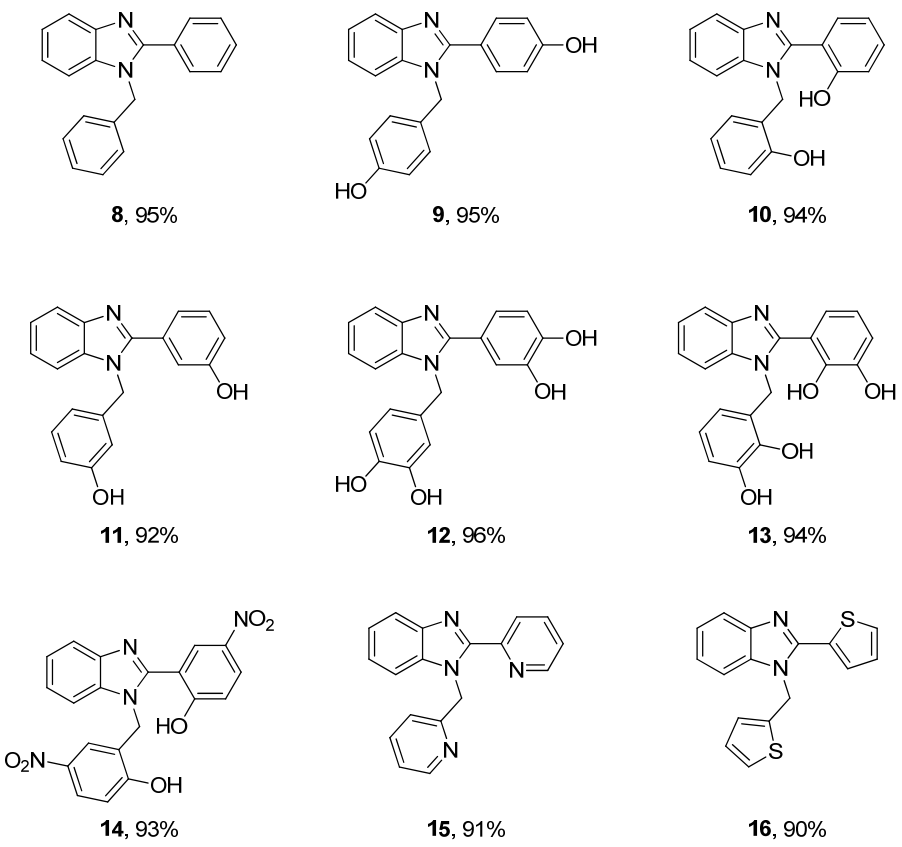

[a]Reaction conditions: *o*-phenylenediamine (9.2 mmol), aldehyde (18.5 mmol), catalyst **5** (0.2 mol%), 600 rpm, 20 milling balls (5 mm) in a milling jar (80 mL) for 22 min at room temperature under argon. [b]Isolated yield.

A plausible mechanism for the reaction was proposed to probe the role of catalyst **5** on selectivity control. Two different pathways were previously suggested as shown in Scheme 1: (i) a sequence of bisimine formation, cyclization and rearrangement (Path a)[19, 20a, 49-52] and (ii) a sequence of monoaldimine formation and cyclization, followed by immonium rearrangement (Path b).[53] Control experiments were performed to differentiate Paths a and b. A reaction was performed in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), affording no 1,2-substituted benzimidazole product. This implies that the reaction proceeds via radical intermediates. With further studies, bisimine intermediate **II** was successfully isolated and confirmed by spectroscopic data. A reaction of *o*-phenylenediamine with salicyaldehyde-d_1 was performed, resulting in the formation of a fully deuterium-labeled product at the *N*-benzyl position. This is consistent with the process occurring via a 1,3-hydrogen shift. Based on these observations, a plausible mechanism is suggested as shown as Path a in Scheme 1.

As stated earlier, ZnO-NPs have a high affinity for an imine-linkage. Ball-milling led to an increase in surface energy and the number of surface defects.[20a] The mechanical energy generated by a milling process promotes the transition of an electron from the valence band to the conduction band.[20a,54,55] The imine

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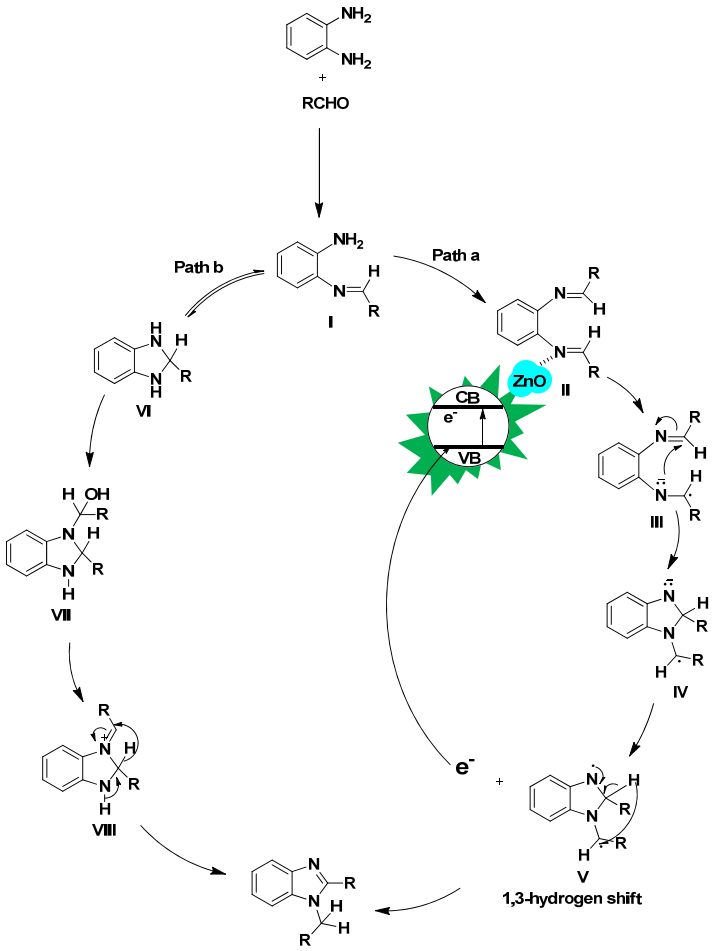
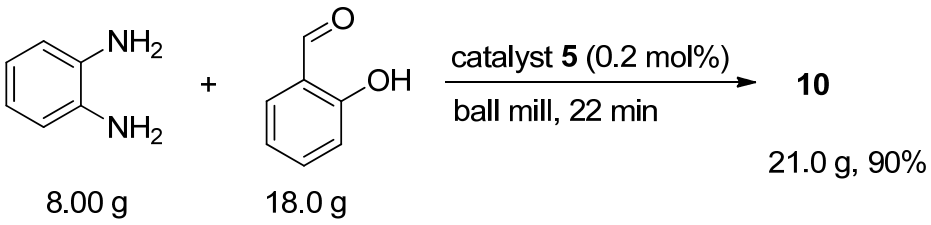
intermediate accepts an electron from the conduction band, resulting in an anionic radical **III**, which is immediately converted into another radical species **IV**.[56] This intermediate undergoes a 1,3-hydrogen shift producing the final product.



Scheme 1. A plausible mechanism for the catalytic synthesis of 1,2-substituted benzimidazole derivatives.

Scalability is an important aspect for pharmacological industries. To examine the scalability of the present methodology, a reaction of *o*-phenylenediamine with salicylaldehyde was performed at the 80 mmol-scale with catalyst **5** (0.2 mol%) when the rest of the reaction conditions remained the same. The corresponding 1,2-disubstituted derivative **10** was obtained at a 90% isolated yield as shown in Scheme 2. The catalytic cycle was one of the main factors in estimating the overall cost of the products. To examine the recyclability of catalyst **5**, a reaction of *o*-phenylenediamine and salicylaldehyde was performed. At the end of the reaction, the crude product was washed with a mixture of methanol-acetone (1:1, v/v) and the catalyst precipitated. The catalyst was washed with methanol three times. Catalyst **5** could be recycled six times without loss of the

catalytic reactivity. In the seventh run, the catalytic activity decreased, producing a 64% yield of product **10** due to changes in the morphology and size of catalyst **5** confirmed by SEM images and DLS studies (Figure S5).



Scheme 2. Scalability of the reaction to the multi-gram scale.

To fulfill the pharmacological need of benzimidazole derivatives, a direct one-pot green synthesis with a high purity is highly in demand. The eco-scale and E-factor are the most widely accepted measures of the environmental impact of the chemical processes.[57-59] The eco-scale is a parameter to compare the safety, economic and ecological features of the chemical process performed at a laboratory scale. It includes yield, cost, safety, conditions and ease of purification. The advantage of this tool is to compare the safety, economic and ecological features of the chemical reaction. The E-factor is defined as the mass ratio of waste to the desired product, including chemical yield, all reagents, solvent losses, all process aids and even the energy required as this generates waste in the form of carbon dioxide.[60] The reaction with a high E-factor produces a more negative environmental impact. The greenness of the present methodology was monitored by calculating the eco-scale score and the E-factor. For comparison with literature, a reaction of *o*-phenylenediamine and salicylaldehyde was chosen as a model reaction. The calculated environmental parameters (eco-scale score and E-factor in Tables S3 and S4) were compared with literature methods. The values are summarized in Table 4. The present methodology scored a high eco-scale value with a low E-factor. The method reported by Chebolu *et. al.* comes in second place in the eco-scale score but it has a high E-factor. Only the present method provides a good combination of the eco-scale score and E-factor, which advocates a clean and green synthetic route for the synthesis of 1,2-disubstituted benzimidazole derivatives. Moreover, a high yield, short reaction time, recyclability of the catalyst and ease of the purification make the present methodology more desirable than others.

Table 4. Comparison of the syntheses reported in literature with the present methodology[a]

group	solvent	catalyst	temp (°C)	time (h)	yield (%)	purification	ecoscale score[b]	E-factor	ref
Chebolu *et. al.*[c]	CF_3CH_2OH	-	rt	0.5	94	column chromatography	60	1.37	16
Shelkar *et. al.*	H_2O	CeO_2	rt	0.5	82	liquid-liquid extraction/column	14	0.46	17

						chromatography			
Wan *et. al.*	H_2O	TMSCl	85	8	85	filtration or EtOH recrystallization	59	1.12	18
Bahrami *et. al.* [c]	H_2O	SDS	rt	0.3	98	liquid-liquid extraction/filtration or EtOH recrystallization	55	0.55	19
Varala *et. al.* [c]	$CHCl_3$	*L*-proline	rt	5	95	liquid-liquid extraction/column chromatography	49	28.3	49
Oskooie *et. al.* [c]	no solvent	$Fe(ClO_4)_3$	rt	0.16	90	liquid-liquid extraction/column chromatography	52	0.30	50
Jacob *et. al.* [c]	no solvent	$SiO_2/ZnCl_2$	rt	0.3	72	filtration/column chromatography	41	1.19	52
Paul *et. al.*	no solvent	$Fe_2(SO_4)_3$-silicate	90	15	78	column chromatography	43	4.5	61
Present Work	*no solvent*	*ZnO-NPs*	*rt*	*0.3*	*94*	*washing with H_2O and MeOH*	*65*	*0.17*	*7*

[a]The reaction of *o*-phenylenediamine with salicylaldehyde was selected for the comparison. [b]The eco-scale score was calculated using a literature method.[57] For safety, chemicals having hazard code (B, C, Xn, Xi and O) were assigned 5 penalty points for each. [c]The reaction of *o*-phenylenediamine with benzaldehyde was chosen for comparison.

Conclusions

A novel green synthetic route was developed for the facile synthesis of 1,2-disubstitiuted benzimidazole derivatives using IL-coated ZnO-NPs as a catalyst under solvent-free conditions via a ball-mill technique. The reaction was proven to be a radical reaction with a 1,3-hydrogen shift. The present methodology has a high eco-scale and a low E-factor, which indicates greenness of the reaction. The ease of purification, solvent-free conditions, recyclability of the catalyst and scalability to a multi-gram scale make the reaction an economical and environmentally benign route for the selective synthesis of 1,2-disubsitiuted benzimidazoles on the industrial scale.

Experimental Section

General

All chemicals and solvents were purchased from Sigma Aldrich and used as received without purification. A planetary ball mill made of Fritsch "Pulverisette 7 premium line" (Fritsch GmbH, Idar-oberstein, Germany) was employed. The reaction was performed in tungsten carbide grinding cups (80 mL) and milled with tungsten carbide balls (20×5 mm). To ensure the purity of the reaction, all vessel and balls were cleaned several times with acetone followed by aqua regia. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JNM-ECS400 JEOL spectrophotometer in DMSO-d_6 solvent. The splitting patterns were indicated as s (singlet), bs

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(broad singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet). The PANalytical X'PERT PRO diffractometer was employed for analysis of the crystal structure of ZnO powder, operated at 45 KV, 40 mA using Ni-filtered Cu K_α radiation with a scan speed of 10º/min for 2θ in a range from 10 to 100. The sample was air-dried and divided into fine powder for XRD analysis. A uniform layer was spread on a zero background sample holder. The morphology of the nanoparticles was studied using scanning electron microscopy (SEM, JEOL JSM-6610LV) at a voltage of 15 KV. A dilute solution of ZnO (100 μM) in ethanol was placed on carbon tape and dried at room temperature under a vacuum. The Metrohm Microtrac Ultra Nanotrac Particle Size Analyzer (Dynamic Light Scattering) was used to measure the hydrodynamic diameter of ZnO particles using a DMSO/water (5:5, v/v) system as the dispersion medium.

Synthesis of ionic liquid and catalysts. 1-Ethyl-3-methylimidazolium bromide (**1**) was purchased from Sigma Aldrich and 1-methyl-3-carboxymethylimidazole bromide (**2**) was prepared using a literature method.[62] A sol-gel method was employed for the synthesis of ZnO nanoparticles. The ILs **1** or **2** was coated through *in-situ* addition during the synthesis of ZnO nanoparticles and produced catalysts **4** or **5**, respectively. $Zn(ClO_4)_2$ (595 mg, 2 mmol) and NaOH (120 mg, 3 mmol) was dissolved in 30 mL methanol along with the respective IL (7 mmol). The resultant solution was heated to reflux for 2 h. Filtration produced a white product. The presence of a wurtzite-type structure for ZnO-NPs was confirmed by PXRD. SEM and DLS studies were performed to examine the morphology and size of the ZnO-NPs.

General procedure for the synthesis of 1,2-disubstituted benzimidazoles. A tungsten carbide grinding beaker (80 mL) and milling balls (20 × 5 mm) were set as a reaction chamber. For each reaction, particular aldehyde (18.5 mmol) and *o*-phenylenediamine (9.2 mmol) along with 0.2 mol% (4.0 mg) of the catalyst **5** were milled for 22 min at 600 rpm at room temperature under argon. The product was purified by washing with water followed by two washes with methanol for quick drying at room temperature.

4-(1-(4-Hydroxy-3-nitrobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)-2-nitrophenol (6):[63a] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 2H, -OH), 8.13 (s, 1H, Ar), 7.85 (d, J = 8.6 Hz, 1H, Ar), 7.68 (dd, J = 5.4, 3.2 Hz, 1H, Ar), 7.51- 7.57 (m, 2H, Ar), 7.20 – 7.24 (m, 3H, Ar), 7.09 (d, J = 8.6 Hz, 1H, Ar), 7.00 (d, J = 8.5 Hz, 1H, Ar), 5.53 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.0, 153.1, 151.1, 139.3, 136.7, 136.4, 135.4, 134.3, 129.1, 126.2, 125.9, 125.5, 124.5, 123.0, 120.1, 119.2, 116.0, 112.3, 49.6. Anal. Calcd for $C_{20}H_{14}N_4O_6$: C, 59.11; H, 3.47; N, 13.79. Found: C, 59.71; H, 3.28; N, 14.03.

1-Benzyl-2-phenyl-1*H*-benzo[*d*]imidazole (8):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, J = 7.3, 1.5 Hz, 4H, Ar), 7.36–7.24 (m, 4H, Ar), 7.21 (d, J = 4.5 Hz, 5H, Ar), 7.16–7.12 (m, 1H, Ar), 5.18 (s, 2H, -CH_2), ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.7, 142.2, 137.0, 136.7, 132.9, 129.4, 129.0, 128.8, 128.5, 128.0, 126.6, 124.5, 123.0, 120.1, 112.31, 48.4. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.79; H, 5.43; N, 9.77.

4-(1-(4-Hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol (9):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H, -OH), 9.38 (s, 1H, -OH), 7.62 (dd, J = 6.4, 2.3 Hz, 1H, Ar), 7.53 (d, J = 8.6 Hz, 2H, Ar), 7.40 (dd, J = 6.4, 2.3 Hz, 1H, Ar), 7.20–7.15 (m, 2H, Ar), 6.88 (d, J = 8.6 Hz, 2H, Ar), 6.80 (d, J = 8.5 Hz, 2H, Ar), 6.62 (d, J = 8.5 Hz, 2H, Ar), 5.38 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.6, 155.4, 153.1, 139.2, 138.5, 136.7, 131.5, 124.5, 123.0, 121.7, 118.5, 115.8, 114.5, 114.0, 112.3, 49.6. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.11; H, 5.32; N, 8.73.

2-(1-(2-Hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol (10):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H, -OH), 11.06 (s, 1H, -OH), 7.67 (d, J = 8.0 Hz, 1H, Ar), 7.19–7.25 (m, 2H, Ar), 6.99 (t, J = 8.0 Hz, 3H, Ar), 6.85 (t, J = 8.0 Hz, 1H, Ar), 6.77 (d, J = 8.0 Hz, 1H, Ar), 6.66 (d, J = 8.0 Hz, 1H, Ar), 6.57 (t, J = 8.0 Hz, 1H, Ar), 6.48 (t, J = 8.0 Hz, 1H, Ar), 6.30 (d, J = 8.0 Hz, 1H, Ar), 5.35 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3, 157.1, 151.8, 139.2, 136.7, 130.6, 130.4, 129.1, 128.5, 125.3, 124.5, 123.0, 121.4, 120.2, 119.7, 118.6, 117.4, 112.8, 112.3, 44.3. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.84; H, 5.01; N, 8.97.

3-(1-(3-Hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol (11):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H, -OH), 9.35 (s, 1H, -OH), 7.67 (dd, J = 6.5, 2.2 Hz, 1H, Ar), 7.34 (dd, J = 6.3, 2.0 Hz, 1H, Ar), 7.21 (t, J = 7.9 Hz, 1H, Ar), 7.21–7.17 (m, 2H, Ar), 7.12–7.09 (m, 1H, Ar), 7.05 (t, J = 7.9 Hz, 2H, Ar), 6.88 (dd, J = 8.0, 2.1 Hz, 1H, Ar), 6.58 (dd, J = 8.0, 1.9 Hz, 1H, Ar), 6.43 (d, J = 7.6 Hz, 1H, Ar), 6.33 (s, 1H, Ar), 5.43 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 158.1, 153.8, 143.1, 138.9, 136.4, 131.7, 130.4, 123.13, 122.7, 120.0, 119.7, 117.4, 117.1, 116.5, 115.0, 113.2, 111.6, 47.9. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.07; H, 5.21; N, 8.94.

4-(1-(3,4-Dihydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)benzene-1,2-diol (12): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H, -OH), 9.19 (s, 1H, -OH), 8.82 (s, 1H, -OH), 8.78 (s, 1H, -OH), 7.59 (d, J = 7.2 Hz, 1H, Ar), 7.29 (d, J = 7.4 Hz, 1H, Ar), 7.19–7.07 (m, 3H, Ar), 6.94 (d, J = 9.7 Hz, 1H, Ar), 6.79 (d, J = 8.2 Hz, 1H, Ar), 6.60 (d, J = 8.0 Hz, 1H, Ar), 6.35 (s, 1H, Ar), 6.30 (d, J = 7.8 Hz, 1H, Ar), 5.30 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.1, 146.1, 144.4, 144.2, 139.2, 136.7, 127.6, 124.5, 124.2, 123.0, 121.7, 120.4, 120.1, 116.59, 116.2, 116.0, 114.5, 112.3, 49.6. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.12; H, 4.69; N, 7.98.

3-(1-(2,3-Dihydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl)benzene-1,2-diol (13): ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.58 (s, 2H, -OH), 9.56 (s, 2H, -OH), 8.45 (d, J = 8.4 Hz, 1H, Ar), 7.90 (d, J = 9.1 Hz, 1H, Ar), 7.78 (d, J = 8.0 Hz, 1H, Ar), 7.50 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, Ar), 7.42 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.35–7.29 (m, 1H, Ar), 7.07–6.96 (m, 2H, Ar), 6.80 (dd, J = 8.0, 1.3 Hz, 1H, Ar), 6.67 (td, J = 7.9, 1.3 Hz, 1H, Ar), 5.03 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.7, 148.7, 146.9, 145.6, 144.0, 139.2, 136.7, 126.1, 124.50, 123.0, 122.5, 121.6, 120.7, 120.1, 118.4, 114.6, 113.7, 112.3, 44.0. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.84; H, 4.73; N, 8.11.

2-(1-(2-Hydroxy-5-nitrobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)-4-nitrophenol (14): ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.17 (s, 2H, -OH), 9.17 (s, 2H, Ar), 8.75 (d, J = 2.9 Hz, 2H, Ar), 8.23 (dd, J = 9.3, 2.9 Hz, 2H Ar), 7.58 (dd, J = 6.0, 3.3 Hz, 2H, Ar), 7.47 (dd, J = 5.9, 3.4 Hz, 2H, Ar), 5.37 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 162.4, 150.0, 140.2, 139.7, 139.2, 136.7, 126.3, 125.5, 124.5, 124.1, 123.1, 120.7, 120.1, 118.7, 115.7, 112.3, 45.2. Anal. Calcd for $C_{20}H_{14}N_4O_6$: C, 59.12; H, 3.47; N, 13.79. Found: C, 59.21; H, 3.41; N, 13.77.

2-(Pyridin-2-yl)-1-(pyridin-2-ylmethyl)-1*H*-benzo[*d*]imidazole (15):[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.55 (2H, Ar), 8.47–8.41 (m, 2H, Ar), 7.86–7.80 (m, 2H, Ar), 7.47 (td, J = 7.7, 1.7 Hz, 1H, Ar), 7.37–7.32 (m, 2H, Ar), 7.31–7.26 (m, 3H, Ar), 7.14–7.10 (m, 1H, Ar), 6.88 (d, J = 8.0 Hz, 1H, Ar), 6.28 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.4, 147.0, 149.3, 148.8, 142.8, 137.4, 137.0, 124.7, 124.0, 123.8, 123.1, 122.4, 121.7, 121.0, 120.2, 110.9, 51.2. Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.62; H, 5.02; N, 19.72.

2-(Thiophen-2-yl)-1-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]imidazole (16):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80–7.76 (m, 2H, Ar), 7.69 (dd, J = 5.9, 2.1 Hz, 3H, Ar), 7.56 (d, J = 7.7 Hz, 1H, Ar), 7.45 (d, J = 7.2 Hz, 1H, Ar), 7.36 (dd, J = 5.1, 1.1 Hz, 1H, Ar), 6.99 (d, J = 4.0 Hz, 1H, Ar), 6.93–6.89 (m, 1H, Ar), 5.90 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.5, 142.9, 139.9, 130. 2, 129.3, 129.0, 128.8, 128.4, 127.6, 127.2, 126.5, 123.5, 123.1, 119.5, 111.4, 43.6. Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45. Found: C, 64.79; H, 4.12; N, 9.51.

2,2'-((1*E*,1'*E*)-(1,2-Phenylenebis(azanylylidene))bis(methanylylidene))diphenol (II):[63b] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 2H, OH), 8.90 (s, 2H, CH=N)), 7.62 (d, 2H, J = 8.0 Hz, Ar), 7.44–7.35 (m, 6H, Ar), 6.95–6.91 (m, 4H, Ar).

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Graphical Abstract

Synergetic catalytic effect of ionic liquids and ZnO nanoparticles on the selective synthesis of 1,2-disubstituted benzimidazoles using a ball-milling technique

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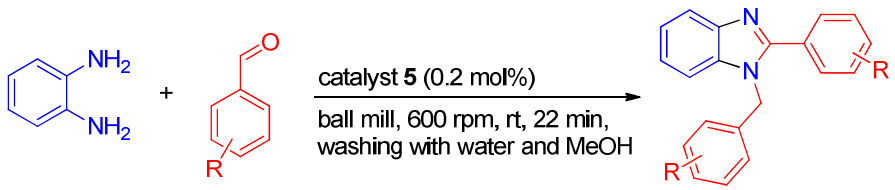

Isolated yields: 90-97%

A solvent-free selective synthesis of 1,2-disubstituted benzimidazoles was developed in the present of recyclable ionic liquid-coated ZnO-nanoparticles using a ball-milling technique.