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Practical, Ecofriendly, and Chemoselective Method for the Synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles Using Amberlite IR-120 as a Reusable Heterogeneous Catalyst in Aqueous Media

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Abstract: A simple, efficient, and environmentally benign method has been developed for the exclusive formation of biologically significant 2-aryl-1-arylmethyl-1*H*-benzimidazoles under the heterogeneous catalysis of Amberlite IR-120 in aqueous media in excellent yields. The catalyst is recyclable without loss of activity.

Keywords: Amberlite IR-120, aqueous media, chemoselective, 1,2-disubstituted benzimidazole, heterogeneous catalysis

1,2-Disubstituted benzimidazoles are endowed with an extensive range of biological activities. They have emerged as potent nonnucleoside inhibitors of HIV-1 reverse transcriptase[1a,1b] and specific inhibitors of the NS5B polymerase of the hepatitis C virus (HCV).[1c] Appropriately functionalized 1,2-disubstituted benzimidazoles are used as agonists against γ-butyric acid A receptor ($GABA_A$).[1d] Moreover, they display potent thrombin inhibitory activity[2a] and antibacterial activity against gram-positive bacteria.[2b]

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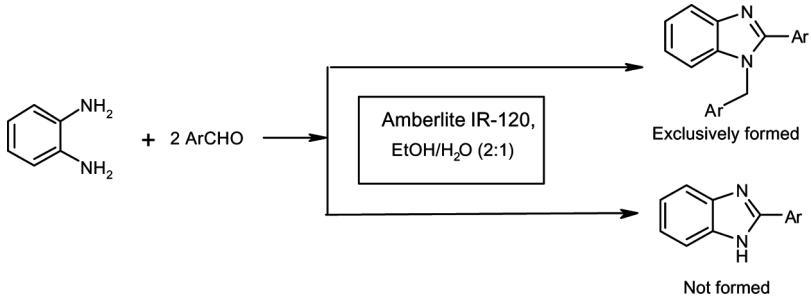
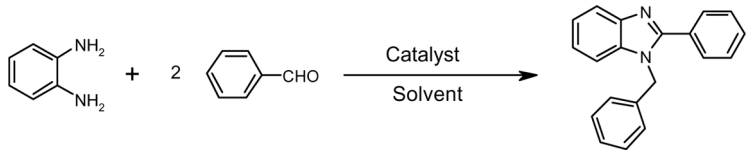
A number of improved methods have been developed for the synthesis of 1,2-disubstituted benzimidazoles, which include N-alkylation of 2-substituted benzimidazole in the presence of a strong base,[3a,3b] N-alkylation of *o*-nitroanilides followed by reductive cyclization,[1a,1b] cyclocondensation of N-substituted *o*-aminoanilides,[2a] reductive cyclization of *o*-nitroanilides followed by N-alkylation in the presence of a strong base,[1b] and condensation of N-substituted phenylenediamine with sodium salt of α-hydroxybenzylsulphonic acid.[2b] In addition, 1,2-disubstituted benzimidazoles can also be accessed by direct one-step condensation of *o*-phenylenediamines with aldehydes under the influence of different acid catalysts.[4] But one of the major limitations of these methodologies is that they show poor selectivity in terms of N-1 substitution, which results in the formation of two compounds (i.e., the formation of 2-substituted benzimidazole along with 1,2-disubstituted benzimidazole as a mixture[4a–c,4e]). We report the synthesis of 1,2-disubstituted benzimidazoles by the reaction of *o*-phenylenediamines and aldehydes in the presence of Amberlite IR-120 resin (Scheme 1).

At the beginning of this work, to evaluate the catalytic efficiency of Amberlite IR-120, the reaction of *o*-phenylenediamine and benzaldehyde was studied by employing 0.100 g of the catalyst in water at room temperature. The resulting yield was not very good (entry 1, Table 1). Optimization of the reaction condition was carried out next to increase the yield of the product, employing different catalyst loadings in a wide variety of solvents. The results are listed in Table 1. The conversion was dramatically increased to 95% within a much shorter time by adding 0.100 g of the catalyst in an ethanol/water (2:1) mixture (entry 3). It was found that a higher amount of the catalyst did not improve the yield at all (entries 6 and 7), whereas the yield was substantially reduced by decreasing the amount of Amberlite IR-120 in an ethanol/water (2:1) mixture (entries 4 and 5). Methanol/water (2:1) mixture was also found to be



Scheme 1. Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles.

Table 1. Optimization of the reaction conditions[b]



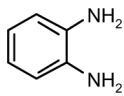
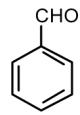
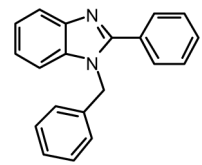
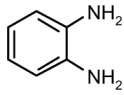
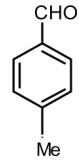
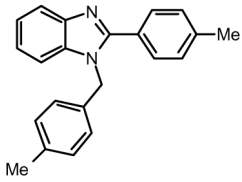
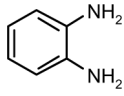
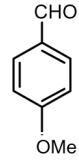
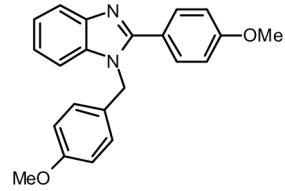
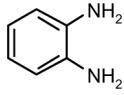
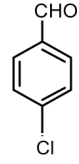
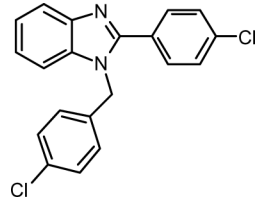
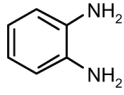
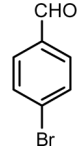
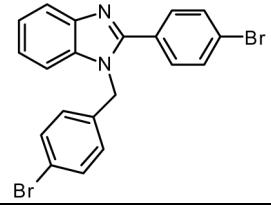
Entry	Catalyst	Catalyst load (g)	Solvents	Time (h)	Yield (%)[a]
1	Amberlite IR-120	0.100	H_2O	3.00	66
2	Amberlite IR-120	0.100	EtOH	1.45	90
3	Amberlite IR-120	0.100	EtOH + H_2O (2:1)	1.45	95
4	Amberlite IR-120	0.050	EtOH + H_2O (2:1)	7.00	80
5	Amberlite IR-120	0.075	EtOH + H_2O (2:1)	3.00	86
6	Amberlite IR-120	0.125	EtOH + H_2O (2:1)	2.00	95
7	Amberlite IR-120	0.150	EtOH + H_2O (2:1)	2.00	95
8	Amberlite IR-120	0.100	EtOH + H_2O (1:2)	2.50	83
9	Amberlite IR-120	0.100	EtOH + H_2O (1:1)	2.10	90
10	Amberlite IR-120	0.100	EtOH + H_2O (3:1)	1.45	92
11	Amberlite IR-120	0.100	MeOH	6.30	84
12	Amberlite IR-120	0.100	MeOH + H_2O (2:1)	7.00	85
13	Amberlite IR-120	0.100	MeCN	22.00	59
14	Amberlite IR-120	0.100	$CHCl_3$	10.00	47
15	Amberlite IR-120	0.100	CH_2Cl_2	10.00	37
16	Amberlite IR-120	0.100	Toluene	10.00	51
17	Amberlite IR-120	0.100	THF	9.00	62
18	Amberlite IR-120	0.100	Dioxane	9.00	53
19	Silica gel	0.100	EtOH + H_2O (2:1)	3.00	80
20	Alumina	0.100	EtOH + H_2O (2:1)	3.00	81

[a]Isolated yield.
[b]Stirring at 25–30 °C.

an effective reaction medium for this transformation (entry 12). Other solvents, such as CH_3CN, $CHCl_3$, CH_2Cl_2, toluene, tetrohydrofuran (THF), and dioxane (entries 13–18), rendered unfavorable results for this reaction. Otherwise, silica gel and alumina (entries 19 and 20) as heterogeneous catalysts also furnished high yield of products. Evidently, the reaction conditions in entry 3 of Table 1 were found to be the most optimal.

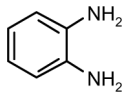
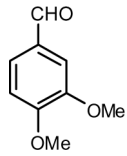
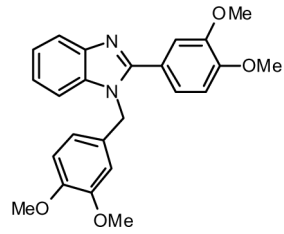
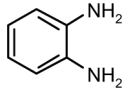
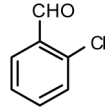
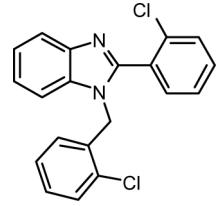
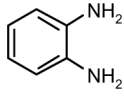
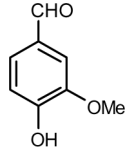
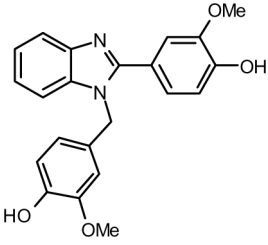
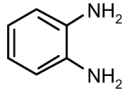
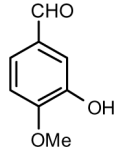
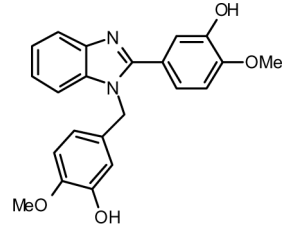
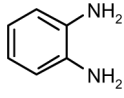
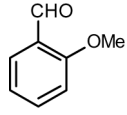
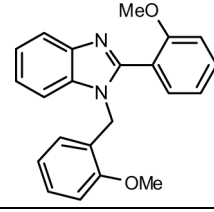
To test the generality of this reaction, a series of aromatic aldehydes and *o*-phenylenediamines was subjected to the optimal reaction conditions.

Table 2. Synthesis of 2-aryl-1-arylmethyl-*1H*-benzimidazole[b]

Entry	Diamines	Aldehydes	Products	Time (h)	Yield (%)[a]
1				1.45	95
2				2.30	89
3				2.55	86
4				4.0	83
5				4.3	84

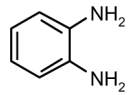
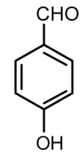
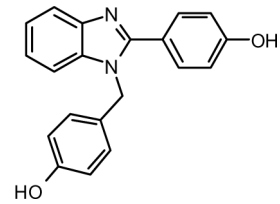
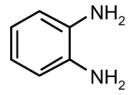
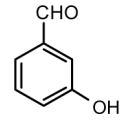
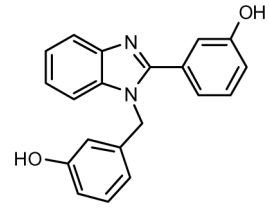
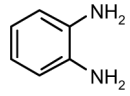
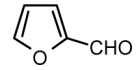
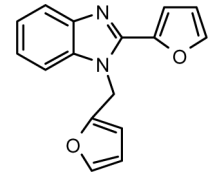
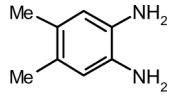
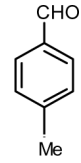
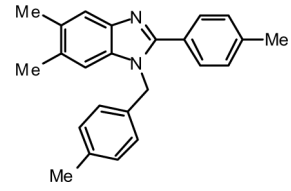
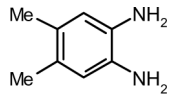
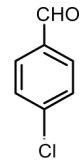
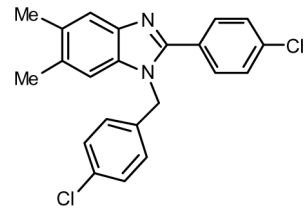
(*Continued*)

Table 2. Continued

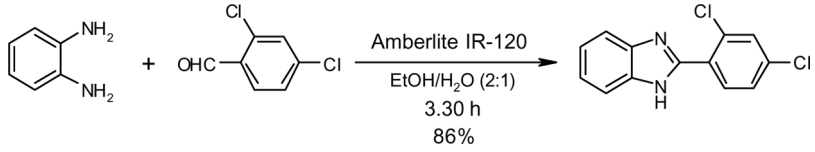
Entry	Diamines	Aldehydes	Products	Time (h)	Yield (%)[a]
6				5.4	92
7				4.4	79
8				6.5	87
9				6.4	88
10				4.0	80

(*Continued*)

Table 2. Continued

Entry	Diamines	Aldehydes	Products	Time (h)	Yield (%)[a]
11				6.3	86
12				6.4	81
13				6.5	70
14				6.0	75
15				5.4	76

[a]Isolated yield.
[b]Stirring at 25–30 °C.



Scheme 2. Synthesis of 2-(2,4-dichlorophenyl)-1*H*-benzimidazole.

Almost all substrates could give their corresponding 1,2-disubstituted benzimidazoles exclusively as a single product (i.e., without the formation of 2-substituted benzimidazoles). The results are documented in Table 2.

It is noteworthy that 2,4-dichlorobenzaldehyde represents as a single exceptional example by furnishing 2-substituted benzimidazole exclusively instead of 1,2-disubstituted benzimidazole (Scheme 2).

In conclusion, the synthetic protocol described herein allows the formation of biologically significant 2-aryl-1-arylmethyl-1*H*-benzimidazoles exclusively under the heterogeneous catalysis of Amberlite IR-120 in aqueous media in excellent yields.

EXPERIMENTAL

General Experimental Procedure for the Synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles

In a 50-ml, round-bottom flask, o-phenylenediamine (1 mmol) and aldehyde (2 mmol) were stirred in the presence of Amberlite IR-120 (0.100 g) in an EtOH/H_2 O (2:1) mixture (10 ml) at room temperature for the stipulated time. The progress of the reaction was monitored by thin-layer-chromatography (TLC). After completion of the reaction, the solution was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to furnish the crude product, which was recrystallized from methanol to afford the pure product. The catalyst could be reused for fresh reactions without any loss of activity.

Characterization Data of the 2-Aryl-1-arylmethyl-1*H*-benzimidazoles

1-Benzyl-2-phenyl-1*H*-1,3-benzimidazole (**1**)

Mp 132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34 (s, 2H), 7.01–7.28 (m, 8H), 7.34–7.40 (m, 3H), 7.62–7.64 (m, 2H), 7.83 (d, $J = 8$ Hz, 1H); FT-IR

(KBr, cm^{-1}): 1613.9; ESI-MS (m/z): 285.2 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.41; H, 5.63; N, 9.89.

1-(4-Methylbenzyl)-2-(4-methylphenyl)-1*H*-1,3-benzimidazole (**2**)

Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47 (s, 3H), 2.53 (s, 3H), 5.54 (s, 2H), 7.11 (d, $J = 7.9$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 2H), 7.33–7.37 (m, 2H), 7.35 (d, $J = 8$ Hz, 2H), 7.39 (m, 1H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.97 (d, $J = 8.1$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1621.7; ESI-MS (m/z): 313.2 ($M^+ + 1$). Anal. calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.50; H, 6.41; N, 8.90.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1*H*-1,3-benzimidazole (**3**)

Mp 130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 3H), 3.78 (s, 3H), 5.38 (s, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 8.5$ Hz, 2H), 7.01 (d, $J = 8.01$ Hz, 2H), 7.20–7.30 (m, 3H), 7.61 (d, $J = 8.6$ Hz, 2H), 7.84 (d, $J = 7.7$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1619.3; ESI-MS (m/z): 345.3 ($M^+ + 1$). Anal. calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 9.29. Found: C, 76.77; H, 5.80; N, 9.22.

1-(4-Chlorobenzyl)-2-(4-chlorophenyl)-1*H*-1,3-benzimidazole (**4**)

Mp 135–136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.35 (s, 2H), 7.14 (d, $J = 7.1$ Hz, 2H), 7.23 (d, $J = 8.7$ Hz, 1H), 7.27–7.56 (m, 8H), 7.81 (d, $J = 7.2$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1619.8; ESI-MS (m/z): 354.2 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{14}N_2Cl_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.07; H, 3.91; N, 7.98.

1-(4-Bromobenzyl)-2-(4-bromophenyl)-1*H*-1,3-benzimidazole (**5**)

Mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.38 (s, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.20–7.59 (m, 9H), 7.86 (d, $J = 7.2$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1622.0; ESI-MS (m/z): 443.1 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{14}N_2Br_2$: C, 54.33; H, 3.19; N, 6.34. Found: C, 54.29; H, 3.12; N, 6.40.

1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1*H*-1,3-benzimidazole (**6**)

Mp 171–173 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.76 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 5.44 (s, 2H), 6.61–6.68 (m, 2H), 6.80

(d, $J = 8.2$ Hz, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 7.22–7.32 (m, 4H), 7.55 (m, 1H), 7.79–7.91 (m, 1H); FT-IR (KBr, cm^{-1}): 1613.1; ESI-MS (m/z): 405.1 ($M^+ + 1$). Anal. calcd. for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.20; H, 5.93; N, 6.99.

1-(2-Chlorobenzyl)-2-(2-chlorophenyl)-1*H*-1,3-benzimidazole (**7**)

Mp 157–159 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.35 (s, 2H), 6.59 (dd, $J = 8.6$ and 1.3 Hz, 1H), 7.27–7.01 (m, 1H), 7.10–7.53 (m, 9H), 6.86 (d, $J = 8.8$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1615.9; ESI-MS (m/z): 354.2 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{14}N_2Cl_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.09; H, 4.03; N, 7.98.

1-(4-Hydroxy-3-methoxybenzyl)-2-(4-hydroxy-3-methoxyphenyl)-1*H*-1,3-benzimidazole (**8**)

Mp 184–186 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H), 3.76 (s, 3H), 5.41 (s, 2H), 6.48 (d, $J = 8.1$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 1H), 7.13–7.45 (m, 5H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.77–7.89 (m, 1H), 9.25 (s, 1H), 9.32 (s, 1H); FT-IR (KBr, cm^{-1}): 1623.3, 3447.2; ESI-MS (m/z): 377.2 ($M^+ + 1$). Anal. calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.16; H, 5.31; N, 7.49.

1-(3-Hydroxy-4-Methoxybenzyl)-2-(3-Hydroxy-4-Methoxyphenyl)-1*H*-1,3-benzimidazole (**9**)

Mp 229–231 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.82 (s, 3H), 3.90 (s, 3H), 5.35 (s, 2H), 6.77 (d, $J = 8.1$ Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 7.11–7.27 (m, 5H), 7.62–7.73 (m, 3H), 8.60 (s, 1H), 8.82 (s, 1H); FT-IR (KBr, cm^{-1}): 1621.8, 3436.9; ESI-MS (m/z): 377.2 ($M^+ + 1$). Anal. calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.24; H, 5.39; N, 7.47.

1-(2-Methoxybenzyl)-2-(2-methoxyphenyl)-1*H*-1,3-benzimidazole (**10**)

Mp 151–153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72 (s, 3H), 3.76 (s, 3H), 5.31 (s, 2H), 6.71 (dd, $J = 7.2$ and 1.3 Hz, 1H), 6.76 (m, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 1H), 7.05–7.48 (m, 6H), 7.53 (dd, $J = 8.6$ and 2.4 Hz, 1H), 7.91 (d, $J = 8.6$ Hz, 1H); FT-IR (KBr, cm^{-1}): 1618.6; ESI-MS (m/z): 345.3 ($M^+ + 1$). Anal.

calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 9.29. Found: C, 76.79; H, 5.82; N, 9.28.

1-(4-Hydroxybenzyl)-2-(4-hydroxyphenyl)-1*H*-1,3-benzimidazole (**11**)

Mp 222 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.50 (s, 2H), 6.82–7.82 (m, 12H), 9.44 (s, 1H), 9.95 (s, 1H); FT-IR (KBr, cm^{-1}): 1618.7, 3445.0; ESI-MS (m/z): 317.1 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.99; H, 5.08; N, 8.82.

1-(3-Hydroxybenzyl)-2-(3-hydroxyphenyl)-1*H*-1,3-benzimidazole (**12**)

Mp 253 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.22 (s, 2H), 6.69–7.34 (m, 12H), 8.35 (s, 1H), 8.70 (s, 1H); FT-IR (KBr, cm^{-1}): 1618.3, 3438.7; ESI-MS (m/z): 317.1 ($M^+ + 1$). Anal. calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.97; H, 5.15; N, 8.90.

1-(2-Furylmethyl)-2-(2-furyl)-1*H*-1,3-benzimidazole (**13**)

Mp 94–96 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.58 (s, 2H), 6.19 (m, 1H), 6.25 (m, 1H), 6.62 (m, 1H), 7.17 (m, 1H), 7.24–7.29 (m, 3H), 7.46–7.53 (m, 1H), 7.62–7.82 (m, 2H); FT-IR (KBr, cm^{-1}): 1622.0; ESI-MS (m/z): 265.1 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.78; H, 4.52; N, 10.55.

5,6-Dimethyl-1-(4-methylbenzyl)-2-(4-methylphenyl)-1*H*-benzimidazole (**14**)

Mp 177–178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H), 2.36 (s, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 5.39 (s, 2H), 7.01–7.70 (m, 10H); FT-IR (KBr, cm^{-1}): 1621.3; ESI-MS (m/z): 341.4 ($M^+ + 1$). Anal. calcd. for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23. Found: C, 84.62; H, 7.18; N, 8.19.

1-(4-chlorobenzyl)-2-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzimidazole (**15**)

Mp 190–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 3H), 2.37 (s, 3H), 5.42 (s, 2H), 7.04–7.81 (m, 10H); FT-IR (KBr, cm^{-1}): 1618.8; ESI-MS

(m/z): 382.4 ($M^+ + 1$). Anal. calcd. for $C_{22}H_{18}N_2Cl_2$: C, 69.30; H, 4.76; N, 7.35. Found: C, 69.26; H, 4.71; N, 7.38.

2-(2,4-Dichlorophenyl)-1*H*-benzimidazole (Scheme 2)

Mp 227 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.27–7.78 (m, 6H), 8.00 (d, $J = 8.4$ Hz, 1H), 12.67 (s, 1H); FT-IR (KBr, cm^{-1}): 1655.3, 3378.0; ESI-MS (m/z): 263.9 ($M^+ + 1$). Anal. calcd. for $C_{13}H_8N_2Cl_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.39; H, 3.10; N, 10.60.

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