The synthesis of benzimidazole derivatives in the absence of solvent and catalyst

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Differently substituted benzimidazoles have been synthesised from *o*-phenylenediamine and arylaldehydes or arylmethylene-malononitriles absorbed on silica gel. The reaction was carried out by intermittent grinding or by a microwave-assisted technique under solvent- and catalyst-free conditions giving good yields of the products.

Keywords: benzimidazole, *o*-phenylenediamine, solventless, silica gel, arylmethylene-malononitriles

Benzimidazole and its derivatives are of significance in medicinal chemistry, because of their biological activity.[1] Activity has been reported against viruses such as HIV,[2] herpes (HSV-1),[3] RNA,[4] influenza,[5] and human cytomegalovirus (HCMV).[6] Substituted benzimidazole derivatives have also found application as anti-ulcer, anti-hypertensive, anti-viral, anti-fungal, anti-cancer, and anti-histamine agents.[7-12] Therefore, the discovery of mild and practical routes for the synthesis of 2-substituted benzimidazoles continues to attract attention.

The traditional synthesis of 2-substituted benzimidazoles usually started from *o*-phenylenediamine. There are two general routes. The first is the condensation of *o*-phenylene-diamine with a carboxylic acid[13] or a derivative (nitriles, amidates or orthoester)[14-16] which often requires strong acidic conditions. The second is the oxidative cyclodehydration of *o*-phenylenediamine with aldehydes using various oxidative reagents such as nitrobenzene,[17] DDQ,[18] MnO_2,[19] $NaHSO_3$,[20] $Na_2S_2O_5$,[21] IBD,[22] I_2[23] and air.[24] In addition, other methods from *o*-dibromobenzene,[25] N-aryl amidoxime[26] and N-benzyl-2-nitrobenzenamines[27] have also been reported recently. However, many of these methods have drawbacks including low yields, prolonged reaction times, harsh reaction conditions, tedious work-up procedures, use of toxic solvents, and the use of metals and expensive reagents. We report here a convenient, inexpensive and green method for the preparation of benzimidazoles in the solid state using *o*-phenylenediamine and aromatic aldehydes which were supported on silica gel under solvent- and catalyst-free conditions.

Initially, in order to optimise the reaction conditions, *o*-phenylenediamine (**1a**) and 4-chlorobenzaldehyde (**2b**) were used in a model reaction in order to examine the reaction time and temperature.

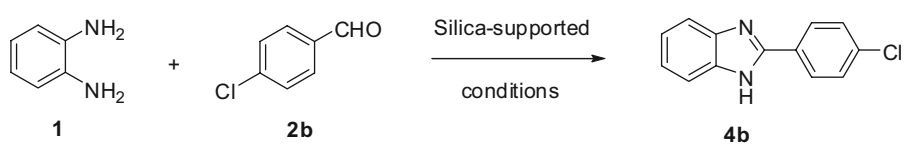
As shown in Table 1, the reaction gave low yield at room temperature for 30 min. The yield was improved by increasing the reaction temperature. Finally, we established the optimum temperature of about 90 °C. The effect of reaction time was also examined. Although air plays an important role in this reaction as an oxidant and long reaction time was of benefit to the reaction, 0.5 h was enough to produce excellent conversions (by TLC).

Table 1 Effects of temperature and time in the synthesis of benzimidazole under intermittent grinding

Entry	Temp/°C	Time/min	Yield/%[a]
1	25 °C	5	45
2	25 °C	15	50
3	25 °C	30	51
4	50 °C	5	65
5	50 °C	15	70
6	50 °C	30	73
7	90 °C	5	70
8	90 °C	15	86
9[b]	90 °C	30	93
10	90 °C	60	93

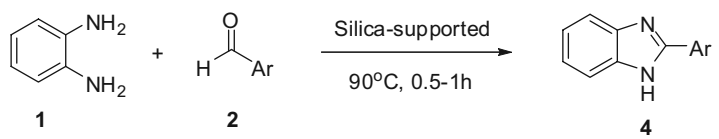
[a]Isolated yield based on **1**.
[b]The optimum condition of using grinding.

To test the generality of this procedure for the synthesis of 2-substituted benzimidazoles **4a–m**, a series of aldehydes were investigated (Table 2, entries 1–13) using the optimised reaction conditions (90 °C, 0.5–1 h). As shown in Table 2 (Method A), we found that both aldehydes bearing electron-withdrawing (entries 2–7) and electron-donating (entries 8–11) substituents gave the corresponding benzimidazoles in good yields. Surprisingly halogenated aldehydes (entries 2–4) gave high yields. When the phenyl ring was replaced with thiophene, the corresponding product was obtained in moderate yield (Table 2, entry 12, 74% yield). As expected, the reactions were generally complete within 0.5 h, except for the cases of 4-nitrobenzaldeyde and 2-thiophenecarboxaldehyde which required 1 h or longer to obtain an acceptable yields.



1 **2b** **4b**

Scheme 1



1 **2** **4**

Scheme 2

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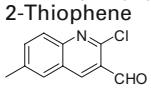
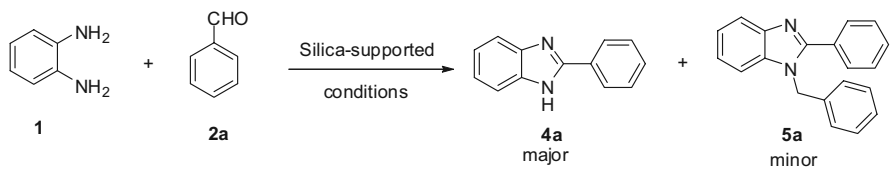
Table 2 The synthesis of benzimidazole under different methods[a.b.c]

Entry	Aldehyde (Ar =)	Method A[a] Time/h (Yield/%)[a]	Method B[b] Time/min (Yield/%)[b]	Product
1	Ph	0.5 (80),(7)[c]	7 (83),(7)[c]	**4a**
2	4-ClC_6H_4	0.5 (93)	7 (93)	**4b**
3	4-FC_6H_4	0.5 (92)	7 (93)	**4c**
4	3-BrC_6H_4	0.5 (94)	7 (95)	**4d**
5	2-Cl-6FC_6H_3	0.5 (88)	7 (89)	**4e**
6	3-$NO_2C_6H_4$	1.0 (80)	10 (82)	**4f**
7	4-CNC_6H_4	0.5 (89)	7 (90)	**4g**
8	4-OHC_6H_4	0.5 (88)	7 (90)	**4h**
9	4-$CH_3C_6H_4$	0.5 (87)	7 (89)	**4i**
10	3-$CH_3OC_6H_4$	0.5 (85)	7 (88)	**4j**
11	3,4-$(CH_3)_2C_6H_3$	0.5 (84)	7 (86)	**4k**
12	2-Thiophene	1.0 (74),(9)[c]	7 (77),(9)[c]	**4l**
13		0.5 (85)	7 (88)	**4m**

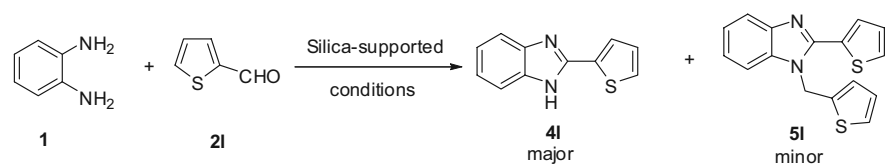
Reaction conditions:
[a]**1** (1.0 mmol), **2** (1.1 mmol), the reactions were carried out at 90 °C for 0.5–1 h.
[b]**1** (1.0 mmol), **2** (1.1 mmol), the reactions were carried out at microwave irradiation(320 W) for 7–10 min.
[c]In parentheses, isolated yields of product **5**.
[d]The reaction was monitored by TLC.

As a novel, effective and universal technique in organic synthesis, microwave irradiation (Method B) was used to promote the reaction. As shown in Table 2 (Method B), microwave irradiation of the reactions were achieved at 320 W, and in all cases, the reaction was complete in about 7–10 minutes. Compared with method A, the reaction time was significantly shortened.

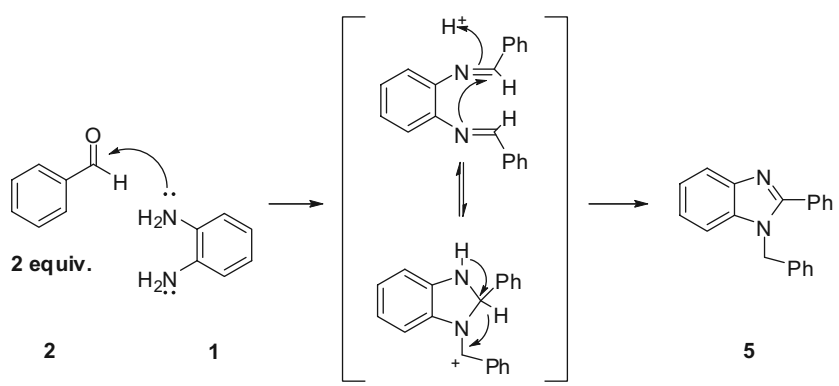
Under the optimised reaction conditions, in most cases the yields were high and product **4** was formed exclusively as shown in Table 2. Nevertheless, in two cases (entries 1 and 12), not only was product **4** detected, but also an unexpected by-product **5** was obtained (Scheme 3, 4). A possible mechanism for the formation of this 1,2-disubstituted benzimidazole is shown in Scheme 5. There are three steps: (1) condensation of benzaldehyde with *o*-phenylenediamine to form the dibenzylidene-derivative; (2) protonation of this and ring closure leading to a five-membered ring either in a sequential or concerted manner; and (3) 1,3-hydride transfer and deprotonation. Based on this mechanism, a reaction using a 1:2 of *o*-phenylenediamine and 4-chlorobenzaldehydes was examined. It was found that **4b** was the major product, whereas very little of product **5b** was detected by TLC. The result indicated that this procedure have high selectivity for the synthesis of 2-substituted benzimidazoles.



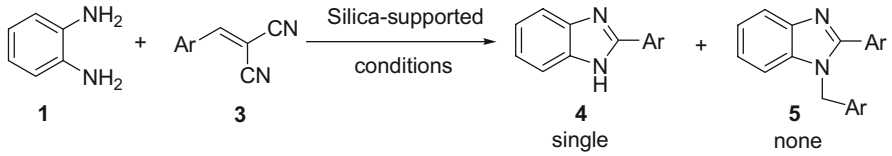
Scheme 3



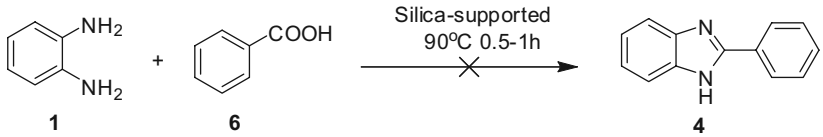
Scheme 4



Scheme 5 Proposed mechanism for the formation of 1,2-disubstituted benzimidazoles.



Scheme 6



Scheme 7

Surprisingly we found that the *o*-phenylenediamine reacted with arylmethylene-malononitriles (Scheme 6) using the grinding technique to give excellent yields of a single desired product with a 1:1 mol ratio of reactions. With two equivalents of arylmethylene-malononitriles, an extra reductive product was formed.[28] It was interesting that most of the 2-substituted benzimidazoles were obtained in slightly higher yields (*e.g.* **4a**, **4h**, **4k** and **4l** Table 3). This is presumably due to the better stability of aryl-methylenemalononitriles compared to some aldehydes. This reaction had excellent selectivity and no product **5** was detected. Benzoic acid was also used to investigate the scope of this method, but no desired product was obtained either by the grinding or microwave-assisted technique (Scheme 7).

In summary, we have reported alternative and highly efficient methods for the synthesis of benzimidazoles under solvent- and catalyst-free conditions. The desired benzimidazoles were obtained in good to excellent yields. The notable advantages of this procedure include the substrates being loaded onto silica gel without any other catalyst (using atmospheric air as the oxidant). No toxic reagent(s) were involved, and there was a simple work-up procedure. The method is environmentally friendly, and possesses high generality. The study of the potential bioactivities of these benzimidazole derivatives are in progress in our laboratory.

Experimental

The NMR spectra were measured with a Bruker Advance III 500 or Varian Mercury Plus-400 instrument using TMS as an internal standard and DMSO as the solvent. Mass spectra were measured with a Finnigan Trace DSQ spectrometer, HRMS analysis was measured on an Agilent 6210. Melting points (m.p.) were recorded on digital melting point apparatus WRS-1B and uncorrected. Flash column chromatography was carried out on 200–300 mesh silica gel. Microwave assisted reactions were carried out in an APEX reactor.

General experimental procedure for the synthesis of **4a**–**m**: *(arylaldehydes as the reagents)*
o-Phenylenediamine (1.0 mmol) and benzaldehyde **2a** (1.1 mmol) were ground in a mortar with 0.4 g silica gel (200–300 mesh) each to give a homogeneous mixture. The two mixtures were combined and ground intermittently at 90 °C or reacted under microwave-irradiation for an appropriate time given in Table 2 in the presence of air. The reaction was monitored by TLC. After completion of the reaction and cooling to room temperature, the residue was directly purified by column chromatography with EtOAc–petroleum ether (1 : 5) to afford compounds **4a** and **5a**.

General experimental procedure for the synthesis of **4a**–**m**: *(arylmethylene–malononitriles as the reagents)*
o-Phenylenediamine (1.0 mmol) and aryl-methylenemalononitriles **3a** (1.0 mmol) were ground in a mortar with 0.4 g silica gel (200–300 mesh) each to give a homogeneous mixture. The two mixtures were combined and ground intermittently for 0.5 h at 90 °C in the presence of air. The reaction was monitored by TLC. After completion of the reaction and cooling to room temperature, the residue was directly purified by column chromatography with EtOAc–petroleum ether (1:5) to afford compounds **4a**–**m**.

Table 3 The synthesis of benzimidazole using arylmethylene-malononitriles[a,b]

Entry	Ar =	Time/h	Yield/%	Product
1	Ph	0.5	92	**4a**
2	4-ClC_6H_4	0.5	95	**4b**
3	2-Cl-,6-FC_6H_3	0.5	90	**4e**
4	3-$NO_2C_6H_4$	0.5	87	**4f**
5	4-CNC_6H_4	0.5	94	**4g**
6	4-OHC_6H_4	0.5	91	**4h**
7	4-$CH_3C_6H_4$	0.5	90	**4i**
8	3-$CH_3OC_6H_4$	0.5	88	**4j**
9	3,4-$(CH_3)_2C_6H_3$	0.5	88	**4k**
10	2-Thiophene	0.5	86	**4l**

[a]Reaction conditions: **1** (1.0 mmol), **3** (1.0 mmol), the reactions were carried out under intermittent grinding at 90 °C for 0.5 h. [b]The reaction was monitored by TLC.

2-Phenylbenzimidazole **(4a):** Colourless solid; m.p. 295–296 °C (Lit.[23] 295 °C). ^{1}H NMR δ: 7.21 (d, 2H, J = 4.8 Hz), 7.48–7.58 (m, 4H), 7.66 (s, 1H), 8.18 (d, 2H, J = 8.0 Hz), 12.91 (s, 1H). ^{13}C NMR δ: 122.1, 126.4, 128.4, 128.9, 129.2, 129.8, 130.1, 151.2. MS (ESI): m/z = 195 (M^+ + 1).

2-(4-Chlorophenyl)benzimidazole **(4b)**: White solid; m.p. 292–294 °C (Lit.[22] 292–294 °C). ^{1}H NMR δ: 7.22 (d, 2H, J = 6.2 Hz), 7.63–7.70 (m, 4H), 8.19 (d, 2H, J = 9.2 Hz), 12.99 (s, 1H). ^{13}C NMR δ: 111.4, 118.9, 121.9, 122.5, 128.1, 129.0, 134.5, 150.1. MS (ESI): m/z = 231 ([M^+ + 2], 33), 229 ([M^+ + 1], 100).

2-(4-Fluorophenyl)benzimidazole **(4c)**: White solid; m.p. 250–252 °C (Lit.[22] 250–251 °C). ^{1}H NMR δ: 7.21 (dd, 2H, J_1 = 7.2, J_2 = 9.2 Hz), 7.39–7.43 (m, 2H), 7.54 (d, 1H, J = 7.2 Hz), 7.67 (d, 1H, J = 7.6 Hz), 8.21–8.25 (m, 2H), 12.92 (s, 1H). ^{13}C NMR δ: 111.3, 115.9, 116.1, 118.8, 121.7, 122.5, 126.8, 128.7, 128.8, 135.0, 143.8, 150.4, 163.1 (d, J = 246.5 Hz). MS (EI): m/z (%) = 212 (M^+, 100).

2-(3-Bromophenyl)benzimidazole **(4d)**: White solid; m.p. 250–251 °C. ^{1}H NMR δ: 7.20–7.27 (m, 2H), 7.51–7.56 (m, 2H), 7.69 (t, 1H, J = 6.4 Hz), 8.19 (d, 1H, J = 8.0 Hz), 8.38 (s, 1H), 13.05 (s, 1H). ^{13}C NMR δ: 111.4, 119.0, 121.9, 122.2, 122.9, 125.3, 128.8, 131.1, 132.4, 134.9, 143.6, 149.6. MS (EI): m/z (%) = 274 ([M^+ + 2], 90), 272 (M^+, 100).

2-(2-Chloro-6-fluorophenyl)benzimidazole **(4e)**: Pale yellow solid; m.p. 217–219 °C. ^{1}H NMR δ: 7.22–7.30 (m, 2H), 7.46 (t, 1H, J = 8.4 Hz), 7.54–7.57 (m, 2H), 7.62–7.68 (m, 1H), 7.72 (d, 1H, J = 8.0 Hz), 12.90 (s, 1H). ^{13}C NMR δ: 111.5, 114.7, 114.9, 119.2, 119.7, 119.9, 121.6, 122.8, 125.8 (d, J = 2.3 Hz), 132.5 (d, J = 9.1 Hz), 134.2 (d, J = 5.3 Hz), 143.4 (d, J = 24.2 Hz), 160.7 (d, J = 248.7 Hz). MS (EI): m/z (%) = 248 ([M^+ + 2], 33), 246 (M^+, 100). HRMS (ESI): Calcd for ($C_{13}H_8ClFN_2$ + H) 247.0438. Found 247.0433.

2-(3-Nitrophenyl)benzimidazole **(4f)**: Yellow solid; m.p. 203–205 °C (Lit.[30] 202–203 °C). ^{1}H NMR δ: 7.26 (s, 2H), 7.60 (s, 1H), 7.72 (s, 1H), 7.87 (t, 1H, J = 8.0 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.62 (d, 1H, J = 8.0 Hz), 9.02 (s, 1H), 13.30 (s, 1H). ^{13}C NMR δ: 111.7, 119.2, 120.8, 122.1, 123.2, 124.2, 130.6, 131.7, 132.5, 148.3, 149.0. MS (ESI): m/z = 240 (M^+ + 1).

2-(4-Cyanophenyl)benzimidazole **(4g)**: White solid; m.p. 262–263 °C (Lit.[30] 262 °C). ^{1}H NMR δ: 7.26 (s, 2H), 7.65 (s, 2H), 8.04 (d, 2H, J = 8.4 Hz), 8.35 (d, 2H, J = 8.8 Hz), 13.20 (s, 1H). ^{13}C NMR δ:

111.9, 118.6, 119.3, 122.2, 123.2, 126.4, 127.0, 132.9, 134.2, 149.3. MS (EI): *m/z* (%) = 219 (M^+, 100).

2-(4-Hydroxyphenyl)benzimidazole **(4h)**: Pale yellow solid; m.p. 294–296 °C (Lit.[29] 294–296 °C). ^{1}H NMR δ: 6.92 (d, 2H, *J* = 8.4 Hz), 7.15 (d, 2H, *J* = 5.6 Hz), 7.48–7.59 (m, 2H), 8.01 (d, 2H, *J* = 8.0 Hz), 9.97 (s, 1H), 12.66 (s, 1H). ^{13}C NMR δ: 115.7, 121.1, 121.6, 128.2, 151.8, 159.1. MS (ESI): *m/z* = 211 ($M^+ + 1$).

2-(4-Ethylphenyl)benzimidazole **(4i)**: White solid; M.p. 277–278 °C (Lit.[30] 276–277 °C). ^{1}H NMR δ: 2.39 (s, 3H), 7.17–7.21 (m, 2H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.58 (s, 2H), 8.06 (d, 2H, *J* = 8.0 Hz), 12.81 (s, 1H). ^{13}C NMR δ: 20.9, 121.9, 126.4, 127.4, 129.5, 139.5, 151.4. MS (EI): *m/z* (%) = 208 (M^+, 100).

2-(3-Methoxyphenyl)benzimidazole **(4j)**: White solid; m.p. 210–211 °C (Lit.[31] 210–210.4 °C). ^{1}H NMR δ: 3.87 (s, 3H), 7.05–7.08 (m, 1H), 7.18–7.25 (m, 2H), 7.47 (t, 1H, *J* = 6.8 Hz), 7.54 (d, 1H, *J* = 7.8 Hz), 7.67 (d, 1H, *J* = 7.6 Hz), 7.76–7.78 (m, 2H), 12.90 (s, 1H). ^{13}C NMR δ: 55.3, 111.3, 111.4, 115.8, 118.7, 118.9, 121.7, 122.6, 130.1, 131.5, 135.0, 143.7, 151.1, 159.6. MS (EI): *m/z* (%) = 224 (M^+, 100).

2-(3,4-Dimethylphenyl)benzimidazole **(4k)**: White solid; m.p. 235–236 °C. ^{1}H NMR δ: 2.30 (s, 3H), 2.33 (s, 3H), 7.15–7.21 (m, 2H), 7.31 (d, 1H, *J* = 7.6 Hz), 7.50 (d, 1H, *J* = 6.8 Hz), 7.63 (d, 1H, *J* = 6.8 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 7.98 (s, 1H), 12.78 (s, 1H). ^{13}C NMR δ: 19.3, 19.4, 111.1, 118.6, 121.5, 122.2, 123.9, 127.5, 127.7, 130.0, 136.7, 134.9, 138.3, 143.8, 151.5. MS (EI): *m/z* (%) = 222 (M^+, 100). HRMS (ESI): Calcd for ($C_{15}H_{14}N_2$ + H) 223.1235. Found 223.1230.

2-(2-Thienyl)benzimidazole **(4l)**: Pale yellow solid; m.p. 332–333 °C (Lit.[22] 330–332 °C). ^{1}H NMR δ: 7.17–7.24 (m, 3H), 7.55 (dd, 1H, J_1 = 3.2, J_2 = 5.2 Hz), 7.72 (dd, 1H, J_1 = 1.2, J_2 = 5.2 Hz), 7.84 (dd, 1H, J_1 = 1.2, J_2 = 3.6 Hz), 12.94 (s, 1H). ^{13}C NMR δ: 115.0, 122.1, 126.6, 128.2, 128.6, 133.7, 147.0. MS (EI): *m/z* (%) = 200 (M^+, 100).

3-(1H-benzimidazol-2-yl)-2-chloro-6-methyl-Quinoline **(4m)**: White solid; m.p. 273–275 °C. ^{1}H NMR δ: 2.55 (s, 3H), 7.28 (t, 2H, *J* = 8.4 Hz), 7.63 (d, 1H, *J* = 7.6 Hz), 7.74–7.79 (m, 2H), 7.95–7.98 (m, 2H), 8.87 (s, 1H), 12.93 (s, 1H). ^{13}C NMR δ: 21.1, 111.8, 119.1, 121.9, 123.0, 124.4, 126.3, 127.1, 127.4, 134.2, 134.8, 137.8, 140.6, 143.3, 145.5, 146.2, 147.8. MS (EI): *m/z* (%) = 295 ([M^+ + 2], 33), 293 (M^+, 100).

1-Benzyl-2-phenylbenzimidazole **(5a)**: White solid; m.p. 132–133 °C (Lit.[30] 132 °C). ^{1}H NMR δ: 5.48 (s, 2H), 7.11 (d, 2H, *J* = 6.4 Hz), 7.23–7.26 (m, 2H), 7.31–7.35 (m, 4H), 7.46–7.49 (m, 3H), 7.70 (dd, 2H, J_1 = 1.6, J_2 = 8.0 Hz), 7.90 (d, 1H, *J* = 7.6 Hz). ^{13}C NMR δ: 48.4, 110.5, 119.9, 122.7, 123.0, 125.9, 127.7, 128.7, 129.0, 129.2, 129.9, 136.0, 136.4, 143.1, 154.1. MS (ESI): *m/z* = 285 ($M^+ + 1$).

1-(2-Thienylmethyl)-2-(2-thienyl)benzimidazole **(5l)**: Pale yellow solid; m.p. 146–147 °C (Lit.[32] 146–148 °C). ^{1}H NMR δ: 5.71 (s, 2H), 6.87 (d, 1H, *J* = 2.4 Hz), 6.95 (t, 1H, *J* = 4.4 Hz), 7.15 (t, 1H, *J* = 4.4 Hz), 7.24–7.33 (m, 3H), 7.38 (dd, 1H, J_1 = 2.4, J_2 = 6.8 Hz), 7.48 (d, 1H, *J* = 2.8 Hz), 7.52 (d, 1H, *J* = 4.8 Hz), 7.84 (dd, 1H, J_1 = 2.4, J_2 = 7.2 Hz). ^{13}C NMR δ: 44.1, 109.9, 119.9, 123.0, 123.3, 125.4, 125.5, 127.2, 127.8, 128.1, 128.8, 131.8, 135.9, 138.8, 143.0, 147.6. MS (ESI): *m/z* = 297 ($M^+ + 1$).

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