

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*-phenylenediamine with a carboxylic acid¹³ 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 MnO₂,¹⁹ NaHSO₃,²⁰ Na₂S₂O₅,²¹ IBD,²² I₂²³ and air.²⁴ In addition, other methods from *o*-dibromobenzene,²⁵ N-aryl amidoxime²⁶ and N-benzyl-2-nitrobenzenamines²⁷ 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

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

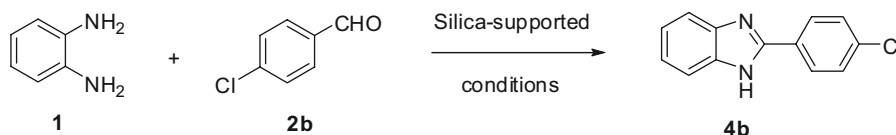
Entry	Temp/°C	Time/min	Yield/% ^a
1	25 °C	5	45
2	25 °C	15	50
3	25 °C	30	51
4	50 °C	5	65
5	50 °C	15	70
6	50 °C	30	73
7	90 °C	5	70
8	90 °C	15	86
9 ^b	90 °C	30	93
10	90 °C	60	93

^aIsolated yield based on **1**.

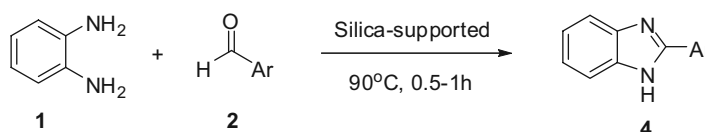
^bThe optimum condition of using grinding.

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).

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-nitrobenzaldehyde and 2-thiophenecarboxaldehyde which required 1 h or longer to obtain an acceptable yields.



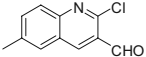
Scheme 1



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 ₆ H ₄	0.5 (93)	7 (93)	4b
3	4-FC ₆ H ₄	0.5 (92)	7 (93)	4c
4	3-BrC ₆ H ₄	0.5 (94)	7 (95)	4d
5	2-Cl-6FC ₆ H ₃	0.5 (88)	7 (89)	4e
6	3-NO ₂ C ₆ H ₄	1.0 (80)	10 (82)	4f
7	4-CNC ₆ H ₄	0.5 (89)	7 (90)	4g
8	4-OHC ₆ H ₄	0.5 (88)	7 (90)	4h
9	4-CH ₃ C ₆ H ₄	0.5 (87)	7 (89)	4i
10	3-CH ₃ OC ₆ H ₄	0.5 (85)	7 (88)	4j
11	3,4-(CH ₃) ₂ C ₆ H 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.

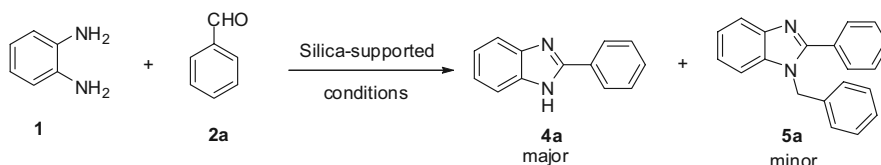
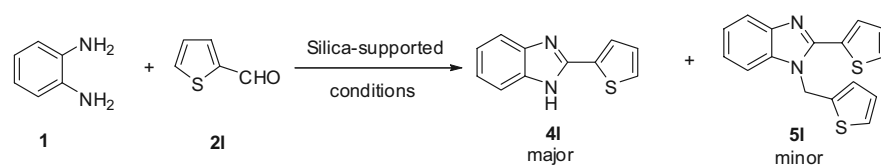
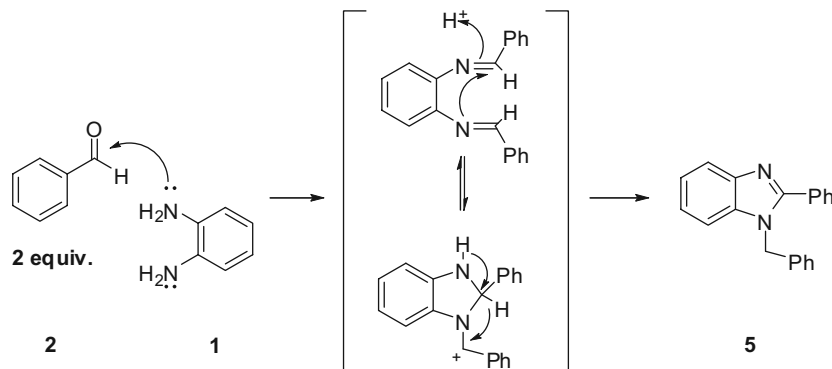
^cIn parentheses, isolated yields of product **5**.

^dThe 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.

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). ¹H 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). ¹³C 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). ¹H 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). ¹³C 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). ¹H 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). ¹³C 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. ¹H 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). ¹³C 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 (C₁₅H₁₄N₂ + H) 223.1235. Found 223.1230.

2-(2-Thienyl)benzimidazole (4l): Pale yellow solid; m.p. 332–333 °C (Lit.²² 330–332 °C). ¹H 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). ¹³C 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. ¹H 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). ¹³C 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). ¹H 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). ¹³C 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). ¹H 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). ¹³C 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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References

- P.N. Preston, *Chem. Rev.*, 1974, **74**, 279.
- T. Roth, M.L. Morningstar, P.L. Boyer, S.H. Hughes, R.W. Buckheitjr and C.J. Michejda, *J. Med. Chem.*, 1997, **40**, 4199.
- M.T. Migawa, J.L. Girardet, J.A. Walker, G.W. Koszalka, S.D. Chamberlain, J.C. Drach and L.B. Townsend, *J. Med. Chem.*, 1998, **41**, 1242.
- I. Tamm and P.B. Sehgal, *Adv. Virus Res.*, 1978, **22**, 187.
- T. Hisano, M. Ichikawa, K. Tsumoto and M. Tasaki, *Chem. Pharm. Bull.*, 1982, **30**, 2996.
- A.R. Porcari, R.V. Devivar, L.S. Kucera, J.C. Drach and L.B. Townsend, *J. Med. Chem.*, 1998, **41**, 1252.
- P.W. Erhardt, *J. Med. Chem.*, 1987, **30**, 231.
- B.E. Tomczuk, C.R. Jr. Taylor, L.M. Moses, D.B. Sutherland, Y.S. Lo, D.N. Johnson, W.B. Kinnier and B.F. Kilpatrick, *J. Med. Chem.*, 1991, **34**, 2993.
- A.A. Spasov, I.N. Yozhitsu, L.I. Bugaeva and V.A. Pharm. Anisimova, *Chem. J.*, 1999, **33**, 232.
- G.L. Gravatt, B.C. Baguley, W.R. Wilson and W.A. Denny, *J. Med. Chem.*, 1994, **37**, 4338.
- D.A. Horton, G.T. Bourne and M.L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
- J.S. Kim, B. Gatto, C. Yu, A. Liu, L.F. Liu and E.J. LaVoie, *J. Med. Chem.*, 1996, **39**, 992.
- Y. Wang, K. Sarris, D.R. Sauer and S.W. Djuric, *Tetrahedron Lett.*, 2006, **47**, 4823.
- A. Czarny, W.D. Wilson and D.W. Boykin, *J. Heterocycl. Chem.*, 1996, **33**, 1393.
- R.R. Tidwell, J.D. Geratz, O. Dann, G. Volz, D. Zeh and H. Loewe, *J. Med. Chem.*, 1978, **21**, 613.
- T.A. Fairley, R.R. Tidwell, I. Donkor, N.A. Naiman, K.A. Ohemeng, R.J. Lombardy, J.A. Bentley and M. Cory, *J. Med. Chem.*, 1993, **36**, 1746.
- R.S. Harapanhalli, L.W. McLaughlin, R.W. Howell, D.V. Rao, S.J. Adelstein and A.I. Kassir, *J. Med. Chem.*, 1996, **39**, 4804.
- K.J. Lee and K.D. Janda, *Can. J. Chem.*, 2001, **79**, 1556.
- I. Bhatnagar and M.V. George, *Tetrahedron*, 1968, **24**, 1293.
- S.C. Austen and J.M. Kane, *J. Heterocycl. Chem.*, 2001, **38**, 979.
- R.L. Lombardy, F.A. Tanious, K. Ramachandran, R.R. Tidwell and W.D. Wilson, *J. Med. Chem.*, 1996, **39**, 1452.
- L.H. Du and Y.G. Wang, *Synthesis*, 2007, **5**, 675.
- P. Gogoi and D. Konwar, *Tetrahedron Lett.*, 2006, **47**, 79.
- S. Lin and L. Yang, *Tetrahedron Lett.*, 2005, **46**, 4315.
- R.D. Viirre, G. Evindar and R.A. Batey, *J. Org. Chem.*, 2008, **73**, 3452.
- Y. Yamamoto, T. Tsuritani and M. Toishiaki, *Tetrahedron Lett.*, 2008, **49**, 876.
- J.W. Hubbard, A.M. Piegols, Soederberg and C.G. Bjoern, *Tetrahedron*, 2007, **63**, 7077.
- S. Kumar and K.K. Kapoor, *Synlett*, 2007, **18**, 2809.
- J.C. Lewis and A.M. Berman, *J. Am. Chem. Soc.*, 2008, **130**, 2493.
- S. Hashem, A. Omid and T.S.M. Hossem, *J. Heterocycl. Chem.*, 2008, **45**, 1293.
- S. Jaroslav and D. Jaroslav, *Collect. Czech. Chem. Commun.*, 1981, **46**, 2703.
- C. Manas and K. Sulakshana, *Heterocycles*, 2006, **68**, 967.