A Simple and Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles

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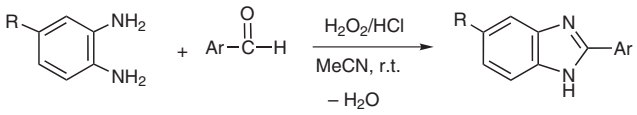
Abstract: A simple and efficient procedure for the synthesis of substituted benzimidazoles through a one-pot condensation of *o*-phenylenediamines with aryl aldehydes in the presence of H_2O_2/HCl system in acetonitrile at room temperature is described. Short reaction time, large-scale synthesis, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure.

Key words: *o*-phenylenediamines, benzimidazoles, aryl aldehydes, hydrogen peroxide

The development of simple, efficient and environmentally benign chemical processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. The benzimidazole ring is an important pharmacophore in modern drug discovery.[1] Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[2] herpes (HSV-1),[3] RNA,[4] influenza,[5] and human cytomegalovirus (HCMV).[2a] Bis-benzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity[6] and can act as ligands to transition metals for modeling biological systems.[7] In addition, benzimidazoles are very important intermediates in organic reactions.[8] Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.[9–12] Despite their importance from pharmacological, industrial, and synthetic points of view, comparatively few methods for the preparation of benzimidazoles have been reported. These include the condensation of *o*-aryldiamines and aldehyde using air as the oxidant,[13] the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[14] or mineral acids,[15] PS-PPh_3/CCl_3CN[16] and thermal or acid promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines.[17] However, a number of these methods have some drawbacks such as low yields, long reaction times, drastic reaction conditions, tedious work-up procedures, and co-occurrence of several side reactions. As a consequence, the introduction of new methods and/or further work on technical improvements to overcome the limitations is still an important experimental challenge.

A recent report by Neumann et al.[18] on the use of a combination of hydrogen peroxide and the respective hydrohalic acid as a green halogenating agent for arenes inspired us to explore the potential of this system for the synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with aryl aldehydes. In this paper, we wish to report a new and efficient method for the synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with aldehydes using aqueous HCl and H_2O_2 as efficient oxidant system in acetonitrile at room temperature. The route for the synthesis of 2-substituted benzimidazoles is shown in Scheme 1.



Scheme 1

Several solvents including acetonitrile, dichloromethane, 1,4-dioxane, and ethanol were investigated during the course of this study. The best results were achieved using acetonitrile. The applicability of the H_2O_2/HCl system was then examined for the synthesis of 2-substituted benzimidazoles in acetonitrile at room temperature. A ratio of 1:1:7:3.5 of 1,2-phenylendiamine/aryl aldehyde/H_2O_2/HCl was found to be optimum for the coupling of aryl aldehydes and phenylenediamines and the results are presented in Table 1. As shown, both aldehydes bearing electron-donating (entries 2–5) and electron-withdrawing (entries 6–10) substituents gave desired benzimidazoles in excellent yields. This procedure is also applicable to substituted *o*-phenylenediamines, which produced the corresponding 2-arylbenzimidazoles smoothly in excellent yields (entries 11–20). Finally, we have extended this synthetic method for the preparation of additional extended bis-benzimidazoles in a 2:1:7:3.5 molar ratio of 1,2-phenylenediamine/aryl dialdehyde/H_2O_2/HCl (Table 1, entries 21–23).

To access the feasibility of applying this method on a preparative scale, we carried out the coupling of 3,4-diaminotoluene with benzaldehyde on a 50 mmol scale. As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (entry 11, Table 1), and the desired 5-methyl-2-phenyl-1*H*-benzimidazole was obtained in 98% isolated yield.

Regarding the mechanism of the oxidation step, the reaction probably involves the formation of hypochlorous acid by the reaction of aqueous hydrogen peroxide with hydrochloric acid,[18] which then reacts with the cyclic hydroben-

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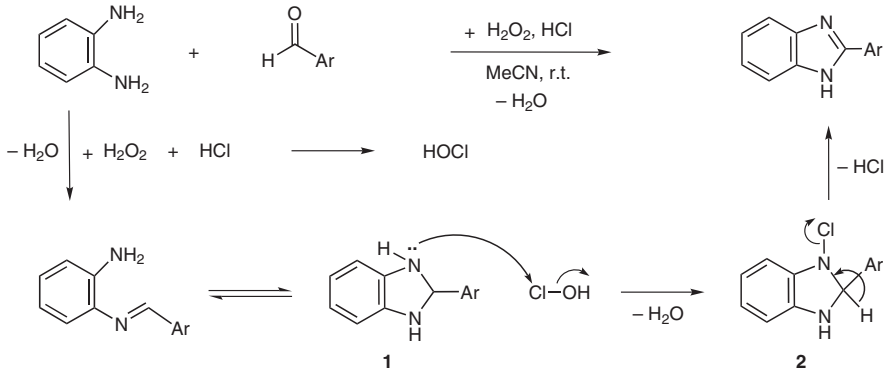


Scheme 2 Possible mechanism and tentative intermediates in the synthesis of benzimidazoles

zimidazoles **1** to afford intermediate **2** followed by the abstraction of hydrogen to yield the corresponding benzimidazoles (Scheme 2).

In conclusion, a simple and efficient procedure for the synthesis of 2-substituted benzimidazoles and bis-benzimidazoles has been explored. Short reaction time, large-scale synthesis, easy and quick isolation of the products, and excellent yields are main advantages of this procedure which make this method an attractive and useful contribution to the present methodologies.

Table 1 Reaction of Aryl Aldehydes with *o*-Phenylenediamines

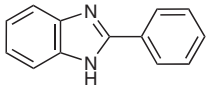
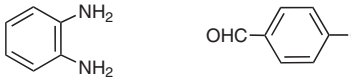
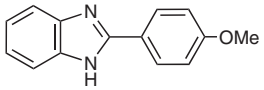
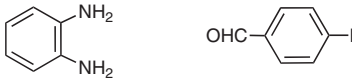
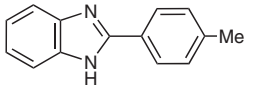
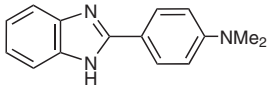
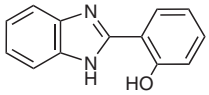
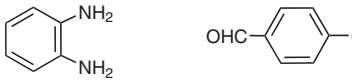
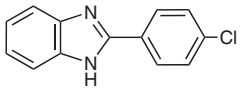
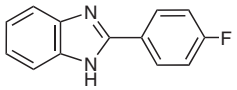
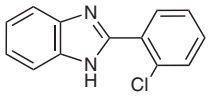
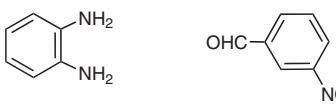
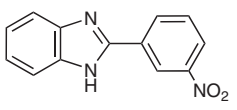
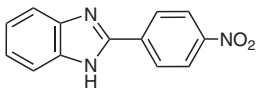
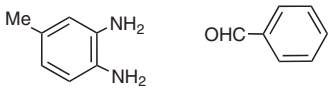
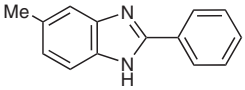
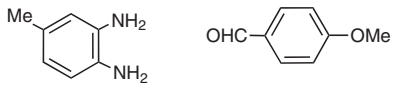
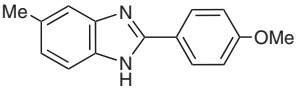
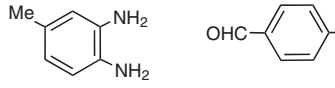
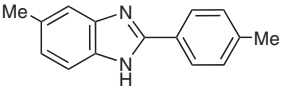
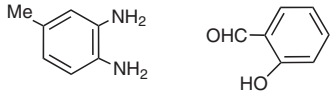
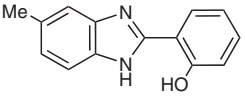
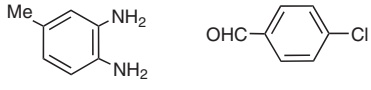
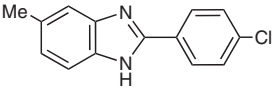
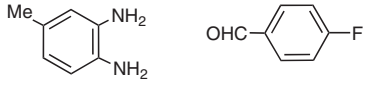
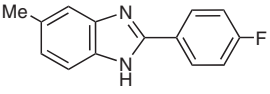
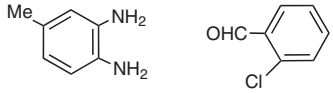
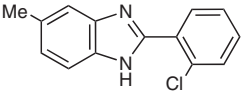
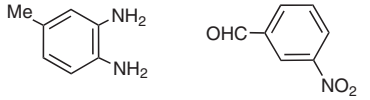
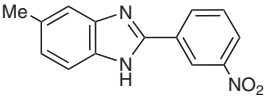
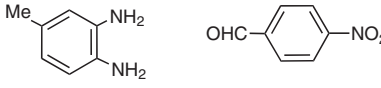
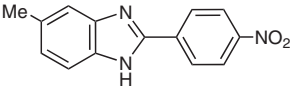
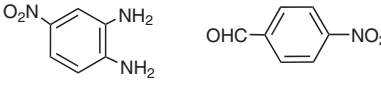
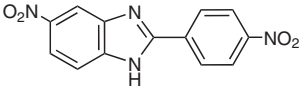
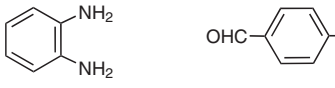
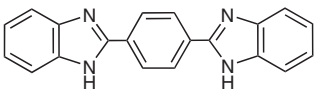
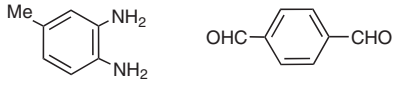
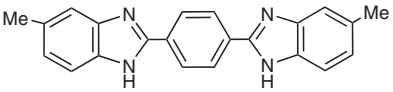
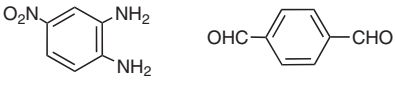
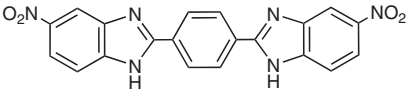
Entry	Substrates	Product[a]	Time (min)	Yield (%)[b]
1			35	97
2			30	98
3			35	98
4			40	99
5			40	99
6			40	98
7			35	96
8			40	97
9			43	99
10			47	98

Table 1 Reaction of Aryl Aldehydes with *o*-Phenylenediamines

Entry	Substrates	Product[a]	Time (min)	Yield (%)[b]
11			40	98
12			35	96
13			40	96
14			35	96
15			40	98
16			40	98
17			40	99
18			50	97
19			50	99
20			47	97
21			75	93
22			80	92
23			90	93

[a] The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures.
[b] Yields refer to pure isolated products.

Benzimidazoles; General Procedure

In a round-bottomed flask (50 mL) equipped with a magnetic stirrer, a solution of *o*-phenylenediamine (1.0 mmol), and aryl aldehyde (1.0 mmol) in MeCN (15 mL) was prepared. Aq 30% H_2O_2 (7.0 mmol) and aq 37% HCl (3.5 mmol) were added and the mixture was stirred at r.t. for the time indicated in Table 1. The progress of the reaction was monitored by TLC (eluent: *n*-hexane–EtOAc, 7:3). When the starting materials had completely disappeared, the mixture was quenched by adding H_2O (10 mL), extracted with EtOAc (4×10 mL), and the combined extracts were dried ($MgSO_4$). The filtrate was evaporated and the corresponding benzimidazole was obtained as the only product (Table 1). An identical procedure was employed using *o*-phenylenediamine (2.0 mmol) and terephthalaldehyde (134.1 mg, 1.0 mmol) in the presence of aq 30% H_2O_2 (7.0 mmol) and aq 37% HCl (3.5 mmol) for the synthesis of bis-benzimidazoles (Table 1).

Selected characterization data for some benzimidazoles prepared are given below.

2-Phenyl-1*H*-benzimidazole (Table 1, Entry 1)
Amorphous beige solid.

IR (KBr): 3248, 1683, 1648, 1580, 1523, 1302 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 7.54 (m, 2 H), 7.75 (m, 3 H), 7.85 (m, 2 H), 8.3 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 114.2, 123.9, 125.7, 128.0, 129.8, 132.5, 133.0, 149.5.

4-(1*H*-Benzimidazol-2-yl)-*N*,*N*-dimethylaniline (Table 1, Entry 4)
Amorphous pale-yellow solid.

IR (KBr): 3380, 1618, 1590, 1484, 1456, 1420 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 3.1 (s, 3 H), 6.9 (d, *J* = 9.2 Hz, 2 H), 7.5 (m, 2 H), 7.2 (m, 2 H), 8.06 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 39.5, 107.8, 111.8, 113.2, 125.1, 129.1, 131.5, 149.8, 153.2.

5-Methyl-2-phenyl-1*H*-benzimidazole (Table 1, Entry 11)
Amorphous pale-yellow solid.

IR (KBr): 3376, 1619, 1596, 1488, 1456, 1356, 1340 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.5 (s, 3 H), 7.4 (m, 1 H), 7.6 (s, 1 H), 7.75 (m, 4 H), 8.25 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 21.2, 113.4, 113.7, 123.5, 127.4, 127.8, 129.6, 130.3, 132.4, 133.0, 134.0, 148.7.

5-Nitro-2-[4-(5-nitro-1*H*-benzimidazol-2-yl)phenyl]-1*H*-benzimidazole (Table 1, Entry 23)
Amorphous brown solid.

IR (KBr): 3250, 1630, 1513, 1342 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6, TFA): δ = 8.45 (s, 2 H), 8.2 (d, *J* = 8.4 Hz, 2 H), 8.1 (m, 2 H), 7.9 (m, 2 H), 7.7 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6, TFA): δ = 150.8, 111.4, 135.7, 122.1, 115.5, 146.5, 131.8, 122.6, 133.4, 134.6.

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References

(1) Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; Mckinney, E.; Tang, C. J. *J. Med. Chem.* **1997**, *40*, 3937.
(2) (a) Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1251. (b) Roth, M.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Bukheit, R. W.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199.
(3) Migawa, M. T.; Giradet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242.
(4) Tamm, I.; Seghal, P. B. *Adv. Virus Res.* **1978**, *22*, 187.
(5) Tamm, I. *Science* **1957**, *126*, 1235.
(6) Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2001**, *44*, 138.
(7) (a) Bouwman, E.; Driessen, W. L.; Reedijk, J. *Coord. Chem. Rev.* **1990**, *104*, 143. (b) Pujar, M. A.; Bharamgoudar, T. D. *Transition Met. Chem.* **1988**, *13*, 423.
(8) (a) Bai, Y.; Lu, J.; Shi, Z.; Yang, B. *Synlett* **2001**, 544. (b) Hasegawa, E.; Yoneoka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yangi, K. *Tetrahedron* **1999**, *55*, 12957.
(9) Sazen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607.
(10) Matsushita, H.; Lee, S. H.; Joung, M.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2004**, *45*, 313.
(11) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35.
(12) Pranjal, G.; Dilip, K. *Tetrahedron Lett.* **2006**, *47*, 79.
(13) Songnian, L.; Lihu, Y. *Tetrahedron Lett.* **2005**, *46*, 4315.
(14) Preston, P. N. *Benzimidazoles, Congeneric Tricyclic Compounds,* In *Chemistry of Heterocyclic Compounds*, Part 1, Vol. 40; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, **1981**, 6.
(15) Grimmet, M. R. *Imidazoles and their Benzo Derivatives,* In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Ress, C. W., Eds.; Pergamon: Oxford, **1984**, 457.
(16) Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 4823.
(17) Benincori, T.; Sannicolo, F. *J. Heterocycl. Chem.* **1998**, *25*, 1029.
(18) Daniel, R. B.; de Visser, S. P.; Shaik, S.; Neumann, R. *J. Am. Chem. Soc.* **2003**, *125*, 12116.