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A simple and efficient procedure for the synthesis of benzimidazoles using air as the oxidant

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Abstract—Direct one-step synthesis of various benzimidazoles from phenylenediamines and aldehydes is described using air as the oxidant. The salient features of this method include a simple procedure, mild conditions, no coupling agents or commercial oxidants/additives used, no waste produced (only by-product being water), easy purification, and high generality.

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics to name just a few.[1–3]

The widespread interest in benzimidazole-containing structures has prompted extensive studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids[4] or their derivatives (nitriles, imidates, or orthoesters),[5] which often requires strong acidic conditions, and sometimes combines with very high temperatures (i.e., PPA, 180 °C) or the use of microwave irradiation.[6] The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of aniline Schiff's bases, which are often generated in situ from the condensation of phenylenediamines and aldehydes. Various oxidative reagents such as nitrobenzene (high-boiling point oxidant/solvent),[7] 1,4-benzoquinone,[8] DDQ,[9] tetracyanoethylene,[10] benzofuroxan,[11] MnO_2,[12] $Pb(OAc)_4$,[13] Oxone®,[14] $NaHSO_3$,[15] and $Na_2S_2O_5$[16] have been employed. Partially due to the availability of a vast number of aldehydes, the later method has been extensively used. However, all these processes require stoichiometric or excess amount of oxidants to be used. Many of these procedures produce toxic or environmentally problematic by-products, often require laborious workup and purifications (i.e., to remove quinones and related products), and/or suffer from low isolation yields. Thus, during our recent research involving the synthesis of benzimidazoles, the frequent frustrations resulting from employing the literature procedures prompted us to search for a more efficient method.

In the context of developing environmentally friendly green chemistry, we decided to look at the use of air or oxygen-containing gases as the oxidant for the synthesis of benzimidazoles. It has been reported that Fe(III)/Fe(II) redox system can be used as the catalyst for the preparation of benzimidazoles in MeCN (90 °C) or in DMF (120 °C), using oxygen as the oxidant.[17] More recently, conditions using activated carbon–oxygen (air) were reported, producing 2-phenylbezimidazole in 64% yield in xylene at 120 °C for 26 h.[18] Herein, we would like to describe a simple, mild, and efficient procedure for the synthesis of benzimidazoles that employs only air (or oxygen) as the oxidant.

To minimize the formation of by-product(s) and to streamline the isolation of the desired product, we decided to investigate the possibility of avoiding any metal or organic/inorganic oxidant/additive in this reaction. Thus, equal molar amounts of benzaldehyde and 3,4-diaminotoluene were dissolved in various commonly used organic solvents, and the mixture was heated to reflux (when the boiling point of solvent is below 100 °C) or to 100 °C for 4 h in the presence of air.[19] As Table 1 shows, we were surprised and pleased to

Keywords: Benzimidazoles; Heterocycle; Aldehydes; Air oxidation; Simple procedure; Mild conditions; Green chemistry.
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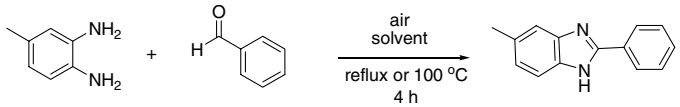
Table 1. Effect of solvent in the synthesis of 2-phenyl-5-methylbenzimidazole[a]



Entry	Solvent	Conditions	Yield (conversion)[b] (%)[c]
1	CH_2Cl_2	Reflux	24 (29)
2	Et_2O	Reflux	23 (25)
3	THF	Reflux	48 (50)
4	Hexane	Reflux	43 (50)[d]
5	MeOH	Reflux	64 (88)
6	EtOH	Reflux	68 (93)
7	$ClCH_2CH_2Cl$	Reflux	30 (30)
8	MeCN	Reflux	61 (66)
9	**Dioxane**	**100 °C**	**90 (98)**
10	Toluene	100 °C	63 (80)
11	DMF	100 °C	72 (98)
12	H_2O	100 °C	58 (80)[d]
13	(none)	100 °C	58 (76)

[a] The reaction was carried out with 0.25 mmol of 3,4-diaminotoluene and 0.25 mmol of benzaldehyde in 1 mL of solvent or neat in a 50 mL sealed tube (with a screw cap) flushed with air at refluxing or 100 °C for 4 h (see Table 1).
[b] Consumption of 3,4-diaminotoluene.
[c] Determined by HPLC.
[d] The reaction mixture was not homogeneous.

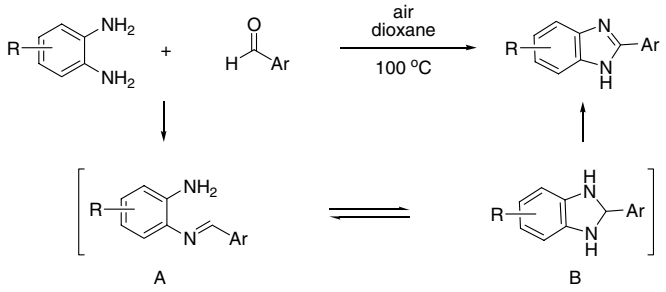
see that a significant amount of the desired 2-phenyl-5-methylbenzimidazole was produced under these mild conditions.[20] Virtually, all commonly used laboratory solvents, including low boiling point solvents such as dichloromethane and ether (entries 1 and 2), can be used in this reaction. With the increase in the solvent's boiling point, the conversion of 4-methyl-1,2-phenylenediamne also increases, except for the case of 1,2-dichloroethane (entry 7). Alcoholic solvents (methanol and ethanol, entries 5 and 6), 1,4-dioxane (entry 9), and DMF (entry 11) gave excellent conversions. In the absence of solvent, significant conversion (76%, entry 13) was also observed. Similar results were observed in the presence of water (entry 12). Clearly, 1,4-dioxane (entry 9) stands out as the solvent of choice, with its fast conversion, high yield, and easy removal.

To test the general scope and versatility of this procedure in the synthesis of a variety of substituted benzimidazoles, we examined a number of differently substituted aryl aldehydes and phenylenediamines. Thus, equal molar amount of phenylenediamines and aryl aldehydes were heated to 100 °C in 1,4-dioxane in the presence of air for the periods of time indicated in Table 2.[21] We were pleased to find that moderate to high yields were obtained for the coupling of virtually all aryl aldehydes and phenylenediamines examined. As Table 2 shows, both aldehydes bearing electron-donating (entries 2–4, 14) and electron-withdrawing (entries 5–13, 15) substituents gave desired benzimidazoles in excellent yields. Heteroaryl aldehydes, such as 2-furyl, 2-thiophene, 2-pyrrolyl, and 2-pyridinyl carboxaldehydes (entries 16–19), were well tolerated under these mild conditions. With 4-methoxycarbonylbenzaldehyde (entry 15), only mono-benzimidazole was isolated, and no bis-imidazole was formed. This procedure is also applicable to various electron-deficient (entries 21–24) or electron-rich (entries 25–27) phenylenediamines, which produced 2-phenylbenzimidazoles smoothly in excellent yields. The reactions were generally completed in ca. 24 hours, and in many cases less than 10 hours, except for the cases of 4-nitrobenzaldeyde, 4-methylbenzadehyde, and 4-methoxycarbonylbenzaldehyde, where ca. 48 hours were required to complete the reaction. All the reactions were clean as indicated by TLC and LCMS,[22] and the only work-up being the easy removal of 1,4-dioxane. The benzimidazole products were conveniently obtained by silica gel chromatography.

To extend the scope of this method, we also examined the coupling of 3,4-diaminotoluene with alkenyl and alkyl aldehydes under these conditions (Scheme 1). The coupling of cinnamaldehyde with diamines was known to be problematic when strong oxidants are used to affect the cyclodehydrogenation step, partially due to the non-selective oxidation of cinnamaldehyde double bond.[14] However, under these mild air/dioxane conditions, the desired 2-(2-phenylethylenyl)benzimidazole was obtained in excellent yield. In addition, this method can be extended to the synthesis of 2-alkylbenzimidazoles as exemplified by the successful coupling/oxidation of cyclohexanecaboxaldehyde with 3,4-diaminotoluene.

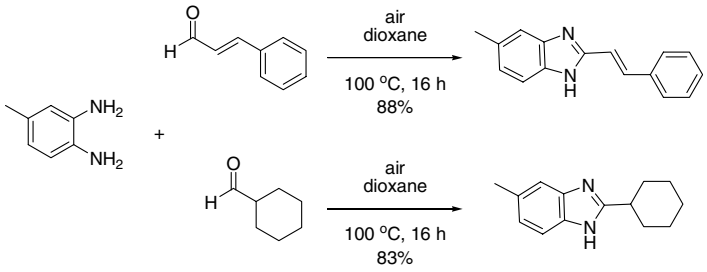
To access the feasibility of applying this method in a preparative scale, we carried out the coupling of 3,4-diaminotoluene with benzaldehyde in 100 mmol scale. Briefly, continuous bubbling of air through the reaction mixture was used in this case instead of a static atmosphere of air (see detailed experimental procedure).[23] As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (entry 1, Table 2), and the desired 2-phenyl-5-methylbenzimidazole was obtained in 84% isolated yield (Scheme 2).

Table 2. Synthesis of benzimidazoles[a]



Entry	R=	Ar=	Reaction time (h)	Yield (%)[b]
1	4-Me	Ph	17	89
2	4-Me	2-MeO-Ph	17	89
3	4-Me	3-MeO-Ph	17	84
4	4-Me	4-MeO-Ph	17	85
5	4-Me	3-CN-Ph	17	86
6	4-Me	4-CN-Ph	3	86
7	4-Me	2-Cl-Ph	20	90
8	4-Me	3-Cl-Ph	20	82
9	4-Me	4-Cl-Ph	20	84
10	4-Me	4-F-Ph	24	88
11	4-Me	4-Br-Ph	2	91
12	4-Me	4-NO_2-Ph	45	81
13	4-Me	4-CF_3-Ph	31	87
14	4-Me	4-Me-Ph	45	83
15	4-Me	4-CO_2Me-Ph	50	85
16	4-Me	2-Furyl	16	86
17	4-Me	2-Thiophene	16	84
18	4-Me	2-Pyrrolyl	28	81
19	4-Me	3-Pyridinyl	22	77
20	H	Ph	16	85
21	4-Cl	Ph	4	80
22	4-Br	Ph	6	79
23	4-NO_2	Ph	8	81
24	4-CF_3	Ph	16	87
25	4-*t*-Bu	Ph	20	83
26	4,5-DiMe	Ph	4	86
27	4-MeO	Ph	6	90

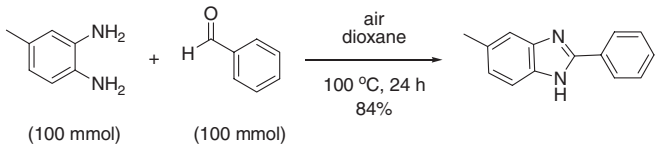
[a] The reaction was carried out with 0.25 mmol of phenylenediamine and 0.25 mmol of aldehyde in 1 mL of dioxane in a 50 mL sealed tube (with a screw cap) flushed with air at 100 °C for the time indicated (see Table 2).
[b] Isolated yield after silica gel chromatography.



Scheme 1. Synthesis of 2-alkenyl- and 2-alkylbenzimidazoles.

The advantage of this procedure is the employment of only atmospheric air as the oxidant. The elimination of metal or organic/inorganic oxidant/additive made this procedure simple to be carried out. No toxic reagent(s) or byproduct(s) were involved, and no laborious purification was necessary. These conditions are also environmentally friendly, cost-effective, and possess high generality.

Although the obvious beneficial role of 1,4-dioxane when used as the solvent needs to be further investigated, we believe that the formation of benzimidazoles



Scheme 2. Synthesis of 2-phenyl-5-methylbenzimidazole.

under these conditions follows through the known[7–17] intermediate Schiff's bases **A**, which exist in equilibrium with the cyclic hydrobenzimidazoles **B** that were oxidized to benzimidazoles by oxygen.

In summary, efficient synthesis of benzimidazoles from phenylenediamines and aldehydes using air as the oxidant was investigated, and a simple and efficient procedure using dioxane as the solvent was developed. The salient features of this method include a simple procedure, mild conditions, no coupling agents or commercial oxidants/additives used, no waste produced (only by-product being water), easy purification, and high generality.

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References and notes

1. (a) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231; (b) Tomczuk, B. E.; Taylor, C. R., Jr.; Moses, L. M.; Sutherland, D. B.; Lo, Y. S.; Johnson, D. N.; Kinnier, W. B.; Kilpatrick, B. F. *J. Med. Chem.* **1991**, *34*, 2993; (c) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232; (d) Preston, P. N. *Chem. Heterocycl. Compd.* **1980**, *40*, 531; (e) Zimmer, C.; Wahnert, U. *Prog. Biophys. Mol. Biol.* **1986**, *47*, 31; (f) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 4338; (g) Soderlind, K.-J.; Gorodetsky, B.; Singh, A. K.; Bachur, N.; Miller, G. G.; Lown, J. W. *Anti-cancer Drug Design* **1999**, *14*, 19.
2. As inhibitors of DNA topoisomerases: (a) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1996**, *39*, 992; (b) Chen, A. Y.; Yu, C.; Gatto, B.; Liu, L. F. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8131; (c) Woynarowski, J. M.; McHugh, M. M.; Sigmud, R. D.; Beerman, T. A. *Mol. Pharmacol.* **1989**, *35*, 177.
3. As HIV-reverse transcriptase inhibitors: Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W., Jr.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199.
4. (a) Grimmet, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds., 1984; Vol. 5, p 457; (b) Wright, J. B. *Chem. Rev.* **1951**, *48*, 396; (c) Middleton, R. W.; Wibberley, D. G. *J. Heterocycl. Chem.* **1980**, *17*, 1757; (d) Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. *Chem. Pharm. Bull.* **1982**, *30*, 2996; (e) Geratz, J. D.; Stevens, F. M.; Polakoski, K. L.; Parrish, R. F. *Arch. Biochem. Biophys.* **1979**, *197*, 551–559.
5. (a) Czarny, A.; Wilson, W. D.; Boykin, D. W. *J. Heterocycl. Chem.* **1996**, *33*, 1393; (b) Tidwell, R. R.; Geratz, J. D.; Dann, O.; Volz, G.; Zeh, D.; Loewe, H. *J. Med. Chem.* **1978**, *21*, 613–623; (c) Fairley, T. A.; Tidwell, R. R.; Donkor, I.; Naiman, N. A.; Ohemeng, K. A.; Lombardy, R. J.; Bentley, J. A.; Cory, M. *J. Med. Chem.* **1993**, *36*, 1746–1753.
6. (a) Bourgrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055–8064; (b) Reddy, G. V.; Rao, V. V. V. N. S. R.; Narsaiah, B.; Rao, P. S. *Synth. Commun.* **2002**, *32*, 2467; (c) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1998**, *39*, 4481.
7. (a) Dubey, P. K.; Ratnam, C. V. *Indian J. Chem. B* **1979**, *18*, 428; (b) Yadagiri, B.; Lown, J. W. *Syn. Commun.* **1990**, *20*, 955; (c) Bathini, Y.; Rao, K. E.; Shea, R. G.; Lown, J. W. *Chem. Res. Toxicol.* **1990**, *3*, 268; (d) Singh, M. P.; Joseph, T.; Kumar, S.; Bathini, Y.; Lown, J. W. *Chem. Res. Toxicol.* **1992**, *5*, 597; (e) Harapanhalli, R. S.; McLaughlin, L. W.; Howell, R. W.; Rao, D. V.; Adelstein, S. J.; Kassis, A. I. *J. Med. Chem.* **1996**, *39*, 4804.
8. (a) Verner, E.; Katz, B. A.; Spencer, J. R.; Allen, D.; Hataye, J.; Hruzewicz, W.; Hui, H. C.; Kolesnikov, A.; Li, Y.; Luong, C.; Martelli, A.; Radika, K.; Rai, R.; She, M.; Shrader, W.; Sprengeler, P. A.; Trapp, S.; Wang, J.; Young, W. B.; Mackman, R. L. *J. Med. Chem.* **2001**, *44*, 2753–2771; (b) Kumar, S.; Kansal, V.; Bhaduri, A. *Indian J. Chem. B* **1991**, *20*, 254.
9. (a) vanden Eynde, J. J.; Delfosse, F.; Lor, P.; van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 5813–5818; (b) Lee, K. J.; Janda, K. D. *Can. J. Chem.* **2001**, *79*, 1556–1561.
10. Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737.
11. Pätzold, F.; Zeuner, F.; Heyer, T. h.; Niclas, H.-J. *Synth. Commun.* **1992**, *22*, 281.
12. Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293.
13. Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971.
14. Beaulieu, P. L.; Hache, B.; von Moos, E. *Synthesis* **2003**, *11*, 1683–1692.
15. (a) Weidner-Wells, M. A.; Ohemeng, K. A.; Nguyen, V. N.; Fraga-Spano, S.; Macielag, M. J.; Werblood, H. M.; Foleno, B. D.; Webb, G. C.; Barrett, J. F.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1545–1548; (b) Austen, S. C.; Kane, J. M. *J. Heterocycl. Chem.* **2001**, *38*, 979–980.
16. Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 1452–1462.
17. Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, *10*, 1380–1390.
18. Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713–3715.
19. General procedure: A solution of 3,4-diaminotoluene (0.25 mmol) and benzaldehyde (0.25 mmol) in 1 mL of solvent or neat was placed in a 50 mL capped tube. The tube was flushed with air, capped, and heated for 4 h at refluxing or at 100 °C (see Table 1). The reaction mixture was then cooled to room temperature, and diluted to 10 mL with methanol. The crude mixture was then analyzed by a reverse-phase HPLC using a 0.025 M methanol solution of 3,4-diaminotoluene and a 0.025 M methanol solution of 2-phenyl-5-methylbenzimidazole as the standards.
20. The rate of oxidation by mere O_2 was reported earlier to be slow in acetonitrile and 'insufficient' for complete

product formation (see Ref. 17). Formation of benzimidazoles in 10–50% yields in refluxing ethanol 'without oxidant' was noted by Mackman and co-workers earlier and was explained as possible 'atmospheric oxidation' (see Ref. 8a).

21. General procedure: A solution of 1,2-phenylenediamine (0.25 mmol) and aryl aldehyde (0.25 mmol) in 1 mL of 1,4-dioxane was placed in a 50 mL capped tube. The tube was flushed with air, capped, and heated at 100 °C for the time indicated (see Table 2). The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel preparative thin layer chromatography or flush column chromatography (CH_2Cl_2/MeOH = 15:1) to afford the desired benzimidazole.
22. In some cases, small amounts (<5%) of bis-Schiff's bases resulting from the condensation of one equivalent of diamines with two equivalents of aldehydes were observed.
23. Experimental procedure: To a 500 mL two-necked round bottomed flask equipped with a water-cooled condenser and a gas inlet were added 3,4-diaminotoluene (12.2 g, 100 mmol), 1,4-dioxane (200 mL), and benzaldehyde (10.6 g, 100 mmol). The mixture was heated for 24 h at 100 °C with continuous air bubbling. CAUTION: *Heating dioxane in the presence of air is potentially explosive!* The mixture was then cooled down to room temperature, and dioxane was removed in vacuo. The residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH (20:1) as the eluant to afford 2-phenyl-5-methylbenzimidazole as pale yellow solids (17.5 g, 84%): R_f = 0.79 (CH_2Cl_2/MeOH = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 7.10 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.43 (m, 3H), 7.55 (d, J = 8.0 Hz, 1H), 8.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 114.6, 115.3, 124.8, 126.8, 129.3, 130.1, 130.3, 133.2, 151.8; LCMS (ES) m/z 209.1 (MH^+).