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# Mild and Highly Efficient Method for the Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzothiazoles

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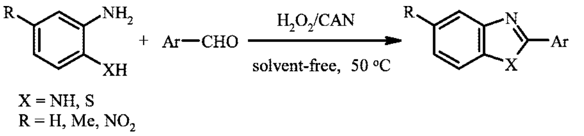

A new, convenient method for the syntheses of 2-substituted benzimidazole and benzothizole is described. Short reaction times, large-scale synthesis, easy and quick isolation of the products, excellent chemoselectivity, and excellent yields are the main advantages of this procedure.

Compounds that exhibit the functionality of benzimidazole and benzothiazole have been extensively employed in the area of pharmaceuticals.[1–4] The high profile of biological applications of compounds with benzimidazole and benzothiazole structures has prompted extensive studies for their synthesis.

Methods of benzimidazole synthesis include the condensation of 1,2-phenylendiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[5] or mineral acids[6] and the thermal or acid-promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines.[7] In another method, benzimidazoles have been prepared by classical cyclocondensation of 1,2-phenylendiamines with the corresponding aldehydes under oxidative conditions.[8–13]

While many reports are available for the preparation of 2-substituted benzothiazoles,[14] the most popular approaches generally involve condensation–dehydration of 2-aminothiophenol with carboxylic acids[15] or condensation with aldehydes under oxidative conditions.[16]

Unfortunately, many of these processes suffer limitations, such as drastic reaction conditions, low yields, tedious workup 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.

Diluted solutions of hydrogen peroxide are a universal, ecologically clean, and convenient way to handle reagents for different oxidations in the liquid phase.[17–19] Developing environmentally benign technologies that provide economical synthetic strategies is an area of research that is being vigorously pursued. Much of this impact is associated with solvent waste. The toxic and/or hazardous properties of many solvents in conjunction with crucial environmental concerns, such as atmospheric emissions and contamination of water effluents, is restricting their use.[20] Solvent-free reactions have many advantages: reduced pollution, low cost, and simplicity in process and handling.

In continuation of our work[21] on the development of useful synthetic methodologies, in this study we wish to report the use of a catalytic redox cycling for the synthesis of various benzimidazole derivatives, based on (Ce(IV)/Ce(III))-redox-mediated oxidation of the Schiff's base intermediates derived from differently substituted aromatic 1,2-phenylendiamines and a variety of aromatic aldehydes (Scheme 1).

Ceric ammonium nitrate (CAN), a very inexpensive and easily available oxidizing agent, has been widely used in organic reactions,[22] but it has not been carefully studied as a catalyst in

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(1) (a) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 4338. (b) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; La Voie, E. J. *J. Med. Chem.* **1996**, *39*, 992. (c) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W., Jr.; Michejda, C. J. *J. Med. Chem.* **1997**, *40*, 4199. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) Denny, W. A.; Rewcastle, G. W.; Baugley, B. C. *J. Med. Chem.* **1990**, *33*, 814.

(3) (a) Bradshaw, T. D.; Wrigley, S.; Shi, D. F.; Schulz, R. J.; Paull, K. D.; Stevens, M. F. G. *Br. J. Cancer* **1998**, *77*, 745. (b) Kashiyama, E.; Hutchinson, I.; Chua, M. S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172. (c) Hutchinson, I.; Chua, M. S.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446.

(4) Palmer, P. J.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 248.

(5) Preston, P. N. Benzimidazoles and Congeneric Tricyclic Compounds. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C. Eds.; Wiley: New York, 1981; Part 1, Vol. 40, pp 6–60.

(6) Grimmett, M. R. Imidazoles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W. Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 457–487.

(7) Benincori, T.; Sannicolò, F. *J. Heterocycl. Chem.* **1988**, *25*, 1029.

(8) Dubey, P. K.; Ratnam, C. V. *Indian J. Chem. B* **1979**, *18*, 428.

(9) Vanden, E. J. J.; Delfosse, Lor, F.; P.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 5813.

(10) Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293.

(11) Beaulieu, P. L.; Hache, B.; von Moos, E. *Synthesis* **2003**, 1683.

(12) 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.

(13) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 1452.

(14) (a) Couture, A.; Grandclaudon, P. *Heterocycles* **1984**, *22*, 1383. (b) Tale, R. H. *Org. Lett.* **2002**, *4*, 1641. (c) Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2005**, *46*, 1349. (d) Itoh, T.; Mase, T. *Org. Lett.* **2007**, *9*, 3687.

(15) (a) Phoon, C. W.; Ng, P. Y.; Ting, A. E.; Yeo, S. L.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1647. (b) Kashiyama, E.; Hutchinson, I.; Chua, M. S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172. (c) Boger, D. E. *J. Org. Chem.* **1978**, *43*, 2296.

(16) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395.

(17) Strukul, G. Ed. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer Academic: Dordrecht, The Netherlands, 1992.

(18) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977.

(19) Bahrami, K. *Tetrahedron Lett.* **2006**, *47*, 2009.

(20) Tanaka, F.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.

(21) Bahrami, K.; Khodaei, M. M.; Kavianinia, I. *Synthesis* **2007**, 547.

(22) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862.

10.1021/jo8010232 CCC: $40.75

**SCHEME 1**

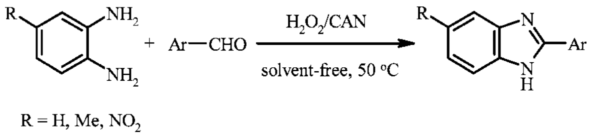
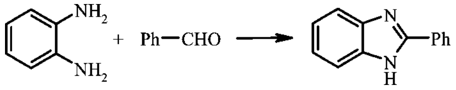


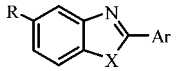
**TABLE 1. Effect of Increasing Amounts of $H_2O_2$ and CAN on the Preparation of Benzimidazole Derivatives**



| entry | 30% $H_2O_2$ (mmol) | CAN (mmol) | yield[a,b] (%) |
|---|---|---|---|
| 1 | 4 | 0.05 | 37 |
| 2 | 3 | 0.07 | 50 |
| 3 | 3 | 0.1 | 70 |
| 4 | 4 | 0.1 | 97 |
| 5 | 4 | 0.25 | 96 |

[a] Reaction conditions: The reactions were performed with benzaldehyde (1 mmol) and 1,2-phenylendiamine (1mmol) for 12 min at 50 °C. [b] Isolated yield.

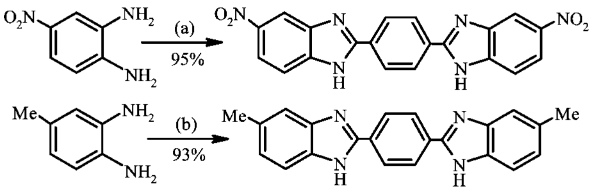
**TABLE 2. Results of $H_2O_2$/CAN System-Promoted Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzothiazoles**



| entry | Ar | R | X | time (min) | yield[a,b] (%) | ref |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | H | NH | 12 | 97 | 23a |
| 2 | 4-$MeOC_6H_4$ | H | NH | 44 | 95 | 23a |
| 3 | 4-$HOC_6H_4$ | H | NH | 10 | 94 | 24a |
| 4 | 4-$MeC_6H_4$ | H | NH | 27 | 97 | 23a |
| 5 | 4-(Me)$NC_6H_4$ | H | NH | 70 | 93 | 24b |
| 6 | 2-$HOC_6H_4$ | H | NH | 10 | 93 | 25 |
| 7 | 2-$ClC_6H_4$ | H | NH | 9 | 97 | 25 |
| 8 | 4-$ClC_6H_4$ | H | NH | 10 | 95 | 23a |
| 9 | 3-$NO_2C_6H_4$ | H | NH | 10 | 96 | 23b |
| 10 | $C_6H_5CH{=}CH$ | H | NH | 47 | 95 | 26 |
| 11 | $C_6H_5$ | Me | NH | 10 | 96 | 23c |
| 12 | 4-$MeC_6H_4$ | Me | NH | 9 | 93 | 23b |
| 13 | 4-$MeOC_6H_4$ | Me | NH | 11 | 94 | 23d |
| 14 | 4-$FC_6H_4$ | Me | NH | 9 | 94 | |
| 15 | $C_6H_5$ | $NO_2$ | NH | 26 | 97 | 23b |
| 16 | 4-$FC_6H_4$ | $NO_2$ | NH | 21 | 98 | 27 |
| 17 | $C_6H_5$ | H | S | 13 | 97 | 28 |
| 18 | 2-$HOC_6H_4$ | H | S | 16 | 95 | 24c |
| 19 | 4-$MeOC_6H_4$ | H | S | 33 | 92 | 28 |
| 20 | 4-$MeC_6H_4$ | H | S | 22 | 94 | 24d |
| 21 | 4-$ClC_6H_4$ | H | S | 10 | 94 | 28 |
| 22 | 4-$BrC_6H_4$ | H | S | 14 | 97 | 29 |
| 23 | 4-$FC_6H_4$ | H | S | 10 | 92 | 30 |
| 24 | 4-$NO_2C_6H_4$ | H | S | 10 | 94 | 28 |
| 25 | 3-$NO_2C_6H_4$ | H | S | 11 | 94 | 28 |
| 26 | 4-$PhC_6H_4$ | H | S | 9 | 95 | |
| 27 | $OHCC_6H_4$ | H | S | 28 | 96 | |

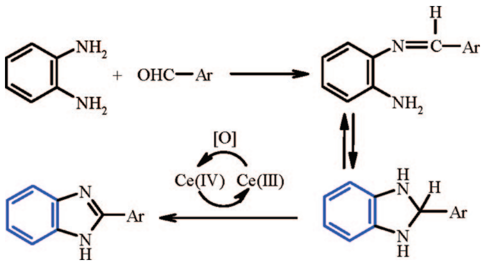
[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures. [b] Yields refer to pure isolated products.

**SCHEME 2[a]**



[a] Reagents and conditions: (a) 1,4-Ph$(CHO)_2$/30% $H_2O_2$ /CAN/solvent free, 50 °C, 20 min; (b) 1,4-Ph$(CHO)_2$/30% $H_2O_2$/CAN /solvnt free, 50 °C, 32 min.

**SCHEME 3**



the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles until now. During the research, we found that CAN could catalyze synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles in the presence of $H_2O_2$.

We also performed a set of preliminary experiments on benzaldehyde and 1,2-phenylendiamine in the presence of different amounts of $H_2O_2$ and CAN in acetonitrile at room temperature. The results are depicted in Table 1. As shown, a ratio of 1:1:4:0.1 1,2-phenylendiamine/aryl aldehyde/$H_2O_2$/Ce (IV) was found to be optimum for the coupling of aryl aldehydes and 1,2-phenylendiamines.

To evaluate the effect of reaction temperature, the reaction of benzaldehyde and 1,2-phenylendiamine in the presence of $H_2O_2$/CAN system was carried out at different temperatures. At room temperature, the reaction rate was found to be very slow, and it increased with temperature. At 50 °C, the reaction rate was found to be a maximum, and further increases in temperature did not show any enhancement.

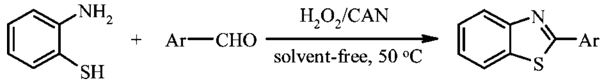
To generalize our reagent system, the applicability of the $H_2O_2$/CAN system was then examined for the reactions of a series of aromatic aldehydes with 1,2-phenylendiamines under the optimized reaction conditions (Table 2.) As shown, a variety of benzaldehydes bearing electron-donating (entries 2−6) and electron-withdrawing (entries 7−9) substituents were successfully employed to prepare the corresponding benzimidazole derivatives in excellent yields. Cinnamyl aldehyde (entry 10) also afforded the desired products in excellent yield. This procedure is also applicable to substituted 1,2-phenylendiamines, which produced the corresponding 2-arylbenzimidazoles smoothly in excellent yields (entries 11−16).

Finally, we have developed this synthetic method for the preparation of additional extended bis-benzimidazole derivatives in a 2:1:4:0.1 molar ratio of 1,2-phenylenediamine derivative to 1,4-benzenedicarboxaldehyde to $H_2O_2$ and CAN as depicted in Scheme 2.

To assess the feasibility of applying this method on a preparative scale, we carried out the coupling of 1,2-phenylenediamine with 3-nitrobenzaldehyde on a 50 mmol scale. As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (Table 2, entry 9), and the desired 2-(3-nitrophenyl)-1*H*-benzimidazole was obtained in 95% isolated yield.

The proposed mechanism for the preparation of benzimidazoles is shown in Scheme 3. That the actual oxidant is Ce(IV) and not $H_2O_2$ was confirmed in control experiments, wherein the absence of Ce(IV) resulted in an extremely sluggish reaction insufficient for complete product formation even after 10 h. In

**SCHEME 4**



this case, imine derivative was obtained as only product. In contrast, the addition of a catalytic amount of Ce(IV) typically resulted in completion of reactions within 9−70 min, rendering the procedure valuable for synthetic purposes.

Nevertheless, this protocol has its limitations. Butylaldehyde, an aliphatic aldehyde, or furfural only provided low to moderate yields of the desired products.

2-Aminothiophenol also underwent the reaction, affording the corresponding 2-arylbenzothiazoles in excellent yields (Scheme 4, Table 2, entries 17−27). The limitations on the use of the aldehydes were similar to those for 1,2-phenylenediamines. 2-Aminophenol did not give the desired products in the reaction.

In conclusion, the $H_2O_2$/CAN system has been employed as a novel, mild, and very efficient reagent for the convenient preparation of benzimidazoles and benzothiazoles in excellent yields from 1,2-phenylenediamines and 2-aminothiophenol, respectively, and a wide variety of aryl aldehydes. In addition, low-cost, solvent-free conditions, environmental friendliness, easy availability, and excellent chemoselectivity make this methodology a valid contribution to the existing processes in the field of benzimidazole and benzothiazole derivatives synthesis.

## Experimental Section

**General Procedure.** A mixture of 1,2-phenylenediamine (1 mmol), aryl adehyde (1 mmol), $H_2O_2$ (30%, 4 mmol, 0.4 mL), and $NH_4Ce(NO_3)_6$ (0.1 mmol, 0.0548 g) was heated at 50 °C for the appropriate time as mentioned in Table 2. After completion of the reaction, the reaction mixture was dissolved in EtOH (10 mL) and then poured into ice−water (30 mL). The pure solid product was filtered, washed with ice−water, and subsequently dried. An identical procedure was employed using 2-aminothiophenol (1 mmol) and aryl adehyde (1 mmol) in the presence of 30% $H_2O_2$ (4 mmol) and $NH_4Ce(NO_2)_6$ (0.1 mmol) for the synthesis of benzothiazoles (Table 2).

All of the products are known compounds and characterized easily by comparison with authentic samples ($^1$H NMR, $^{13}$C NMR, mp).[23–30]

**2-Phenyl-1*H*-benzimidazole.** $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.19−7.23 (m, 2H), 7.51−7.61 (m, 5H), 8.16−8.21 (m, 2H), 12.91 (br, 1H, NH). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 120.1, 123, 127, 127.3, 129.8, 130.8, 131, 152.1.

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**Supporting Information Available:** Complete experimental procedures and relevant spectra ($^1$H NMR and $^{13}$C NMR spectra) for some compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) (a) Al-Awadi, N. A.; George, B. J.; Dib, H. H.; Ibrahim, M. R.; Ibrahim, Y. A.; El-Dusouqui, O. M. E. *Tetrahedron* **2005**, *61*, 8257. (b) Eynde, J. J. V.; Delfosse, F.; Lor, P.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 5813. (c) Perry, R. J.; Wilson, B. D. J. *Org. Chem.* **1993**, *58*, 7016. (d) Risitano, F.; Grassi, G.; Foti, F. *Tetrahedron Lett.* **1983**, *24*, 5893.

(24) (a) Patzold, F.; Zeuner, F.; Heyer, Th.; Niclas, H.-J. *Synth. Commun.* **1992**, *22*, 281. (b) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2006**, 3715. (c) Anthony, K.; Brown, R. G.; Hepworth, J. D.; Hodgson, K. W.; May, B.; West, M. A. *J. Chem. Soc. Perkin Trans. II* **1984**, 2111. (d) Cohen, V. I. *J. Heterocycl. Chem.* **1979**, *16*, 13.

(25) Ben Alloum, A.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **2003**, *44*, 5935.

(26) Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2006**, *245*, 8.

(27) ker, H. G.; Kus, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. *Bioorg. Med. Chem.* **2002**, *10*, 2589.

(28) Bougrin, K.; Loupy, A.; Souflaoui, M. *Tetrahedron* **1998**, *54*, 8055.

(29) Paul, S.; Gupta, M.; Gupta, R. *Synth. Commun.* **2002**, *32*, 3541.

(30) Lozano, A. E.; Jimeno, M. L.; de Abajo, J.; de la Campa, J. G. *Macromolecules* **1994**, *27*, 7164.