Green Chemistry

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE View Online

Catalyst Free Approach to Benzimidazoles Using Air as the Oxidant at Room Temperature

Chun Zhang,[a] Liangren Zhang,[a] Ning Jiao*[a,b]

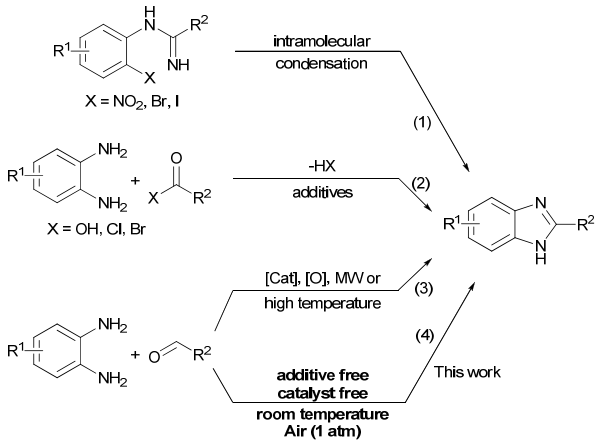
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A green and practical method to construct benzimidazoles, which are ubiquitous structural units in a number of biological active compounds, has been developed. The catalyst and additive free conditions, using air as oxidant and the mild conditions make this transformation very green, practical, and attractive.

Introduction

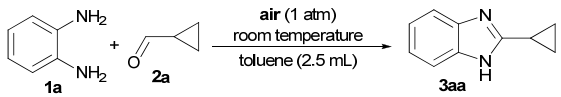
Benzimidazole nucleus has a ubiquitous presence in several bioactive molecules and is considered to be the privileged sub-structure for drug design.[1] Various benzimidazole derivatives have been found to possess anticancer, antiviral, antihypertension and some other properties.[1,2] Benzimidazoles are also important building blocks in organic synthesis.[1-3] In the past decades, a lot of significant methods to construct benzimidazoles have been subsequently developed. Among these methods, the intramolecular condensation,[4] the coupling of *o*-phenylenediamine with carboxylic acids or carboxylic halide[5] and some other methods[6] have been widely used (1 and 2, Scheme1). However, the uneasily available precursors, undesired by-products and required activating involving in these methods still stimulate chemists to develop more green and sustainable approaches.[4-7]

Aldehydes are desirable starting materials in benzimidazoles synthesis due to their ready availability and non-toxic nature.[8] Using *o*-phenylenediamine and aldehyde as the starting material to construct benzimidazoles have caught considerable attentions (3, Scheme 1).[9] Despite the advances of these methodologies, in some cases, the special reaction conditions such as using undesirable stoichiometric oxidants, at high reaction temperature or employing noble transition metal catalyst may limit their application.[9] Recently, an elegant work for the construction of benzimidazoles was reported by Han and coworkers.[10] Using molecular oxygen as oxidant, 4-OMe-TEMPO as catalyst, at 120 °C, *o*-phenylenediamine and aryl-aldehyde could be smoothly converted into the desired 2-aryl-benzimidazoles with excellent yield.[10] However, there is still room for innovation. Herein, our developed a catalyst and additive free procedure to construct 2-alkyl-benzimidazoles using air as the oxidant at room temperature (4, Scheme 1).



Scheme 1. Strategies for the synthesis of benzimidazoles.

Table 1. Aerobic oxidative cyclization of **1a** with **2a**.[a]



entry	[cat.]	additive (1.0 eq)	solvent	yield of **3aa** (%)[b]
1	CuBr	none	toluene	80
2	$FeCl_2$	none	toluene	91
3	$Pd(OAc)_2$	none	toluene	85
4	$AgNO_3$	none	toluene	80
5	$CoCl_2$	none	toluene	94
6	$RuCl_3$	none	toluene	94
7	PPh_3AuCl	none	toluene	91
8	**none**	**none**	**toluene**	**96**
9	none	AcOH	toluene	45
10	none	PivOH	toluene	90
11	none	K_2CO_3	toluene	trace
12	none	$KHCO_3$	toluene	trace
13	none	none	DMF	71
14	none	none	DCE	94
15	none	none	THF	41

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), Cat. (0.025 mmol), additive (0.25 mmol) solvent (2.5 mL), air (1 atm), 12 h. [b] Isolated yields.

Results and discussion

Our study commenced with the reactions of 2-benzene-1, 2-diamine (**1a**) and cyclopropanecarbaldehyde (**2a**) catalyzed by CuBr. Interestingly, the desired product **3aa**, which was further confirmed by single-crystal X-ray analysis (Fig. 1),[11] was obtained in 80% yield in the absence of any additives in toluene at room temperature (entry 1, Table 1). Considering the results catalyzed by other metal salts such as Fe, Pd, Ag, Co, Ru or Au were similar (entries 1-7, Table 1), we envisioned that the metals might not affect the efficiency of this transformation. The reaction in the absence of metal salts was subsequently investigated. Dramatically, **3aa** was produced in 96% yield (entry 8, Table 1). The presence of acid or base decreased the efficiency of this transformation (entries 9-12, Table 1). The effect of different solvents were then investigated. The reactions gave low yields respectively in DMF, DCE, THF or other solvents (entries 13-15, Table 1).

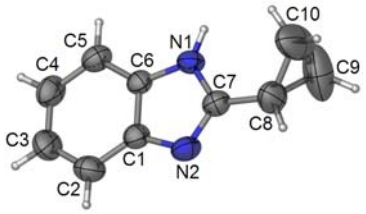
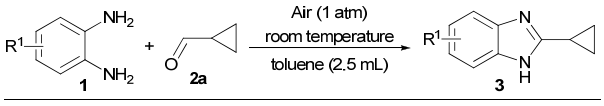
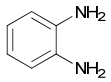
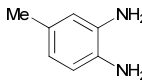
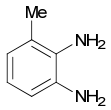
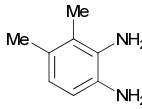
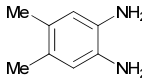
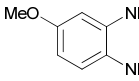
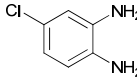
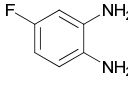
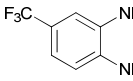


Figure 1. The crystal structure of **3aa**.

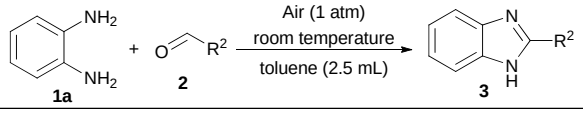
Table 2. Aerobic oxidative cyclization of different diamines **1** with **2a**.[a]

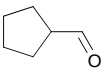
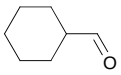
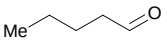
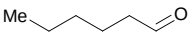
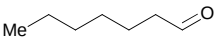
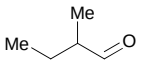
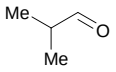
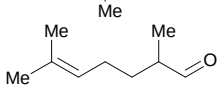
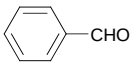


entry	1		yield of **3** (%)[b]
1		**1a**	**3aa** (96)
2		**1b**	**3ba** (86)
3		**1c**	**3ca** (91)
4		**1d**	**3da** (88)
5		**1e**	**3ea** (77)
6		**1f**	**3fa** (90)
7		**1g**	**3ja** (73)
8		**1h**	**3ha** (93)
9		**1i**	**3ia** (53)

[a] Standard reaction conditions: **1** (0.25 mmol), **2a** (0.375 mmol), toluene (2.5 mL), 25 °C, air (1 atm), 12 h. [b] Isolated yields.

Table 3. Aerobic oxidative cyclization of **1a** with different aldehyde **2**.[a]



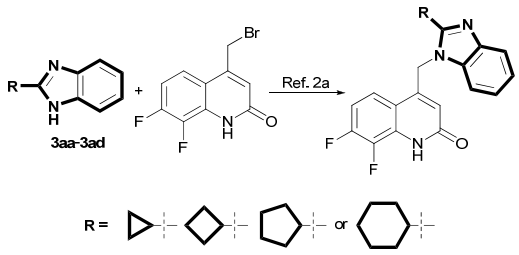
entry	2		yield of **3** (%)[b]
1		**2a**	**3aa**: 96
2		**2b**	**3ab**: 53 (77)[c]
3		**2c**	**3ac**: 54 (75)[c]
4		**2d**	**3ad**: 76
5		**2e**	**3ae**: 46 (53)[c]
6		**2f**	**3af**: 43 (50)[c]
7		**2g**	**3ag**: 41 (53)[c]
8		**2h**	**3ah**: 62
9		**2i**	**3ai**: 70
10		**2j**	**3aj**: 56
11		**2k**	**3ak**: 0

[a] Standard reaction conditions: **1a** (0.25 mmol), **2** (0.375 mmol), toluene (2.5 mL), 25 °C, air (1 atm), 12 h. [b] Isolated yields. [c] The number in the parenthesis is the yield when the reaction was carried out under O_2 (1 atm).

The optimized reaction conditions were applicable to a broad range of electron-poor and -rich aromatic substrates (Table 2). Furthermore, substituents at different positions of the arene group (*para*-, *meta*-, and *ortho*-position) do not affect the efficiency of this transformation (77-91%, **3ba-3ea**, Table 2). Many valuable functional groups such as methoxy (**3fa**), chloro- (**3ja**), fluoro- (**3fa**), and trifluoromethyl groups (**3ia**) were well tolerated.

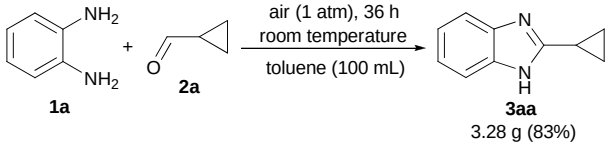
The substrate scope was further extended to a variety of substituted aldehydes **2** (Table 3). Under the optimal reaction conditions, the aldehydes with cyclopropyl (**2a**), cyclobutyl (**2b**), cyclopentyl (**2c**) and cyclohexyl (**2d**) could smoothly transform into the desired benzimidazole products in good to excellent yields (75-96%, entries 1-4, Table 3), which are reported as the important precursors for the synthesis of dual inducible/neuronal nitric oxide synthase (iNOS/nNOS) inhibitors (Scheme 2).[2a]

The aldehyde with alkyl chain also work well in this transformation. Furthermore, the steric hindrance in alkyl chain does not affect the efficiency (**2h-2i**, Table 3). In addition, using molecular oxygen as oxidant, the efficiency of this chemistry could be improved (entries 2, 3, 5-7, Table 3). Unfortunately, the desired 2-aryl-benzimidazole **3ak** was not obtained when aromatic aldehyde was used as the substrate under the optimal reaction conditions (entry 11, Table 3).



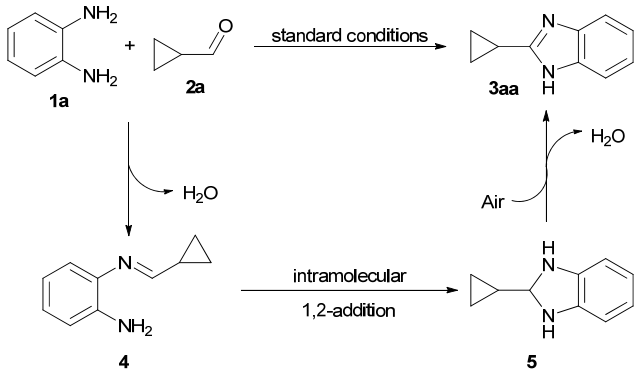
Scheme 2. The preparation of dual inducible/neuronal nitric oxide synthase (iNOS/nNOS) inhibitor.

To test the feasibility of a large-scale reaction, the reaction by taking 25 mmol of benzene-1, 2-diamine (**1a**) and cyclopropanecarbaldehyde (**2a**) (37.5 mmol) was investigated. The reaction could afford 3.28 g of **3aa** in 83% yield by recrystallization (Scheme 3). Therefore, this protocol could be used as a practical method to synthesize the precursors of some important bioactive molecule.



Scheme 3. The large-scale reaction: **1a** (25 mmol), **2a** (37.5 mmol) , toluene (100 mL), 25 °C, 36 h. Isolated yield by recrystallization.

A plausible mechanism for the green and practical method to construct benzimidazoles is illustrated in Scheme 4. benzene-1, 2-diamine (**1a**) and cyclopropanecarbaldehyde (**2a**) initially dehydrate to form imines (**4**).[12] The intermediate **5** is generated though the intramolecular 1,2-addition of intermediate **4**.[13] Finally, the intermediate **5** is easily oxidized by air to produce the desired product **3aa** with H_2O as the byproduct.[9]



Scheme 4. A proposed mechanism for the direct transformation.

In summary, we have demonstrated a green and practical method to construct benzimidazoles, which are ubiquitous structural units in a number of biological active compounds. The catalyst and additive free condition, using air as oxidant and at room temperature make this transformation very green, practical and attractive. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

View Online

Financial support from National Basic Research Program of China (973 Program 2009CB825300), National Science Foundation of China (No. 21172006) and the State Key Laboratory of Drug Research are greatly appreciated. We thank Yizhi Yuan in this group for reproducing the results of **3ja** and **3ae**.

Notes and references

[a] *State Key Laboratory of Natural and Biomimetic Drugs, Peking University, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, China. Fax: (+86)-010-8280-5297; Tel: (+86) 01082805297; E-mail: jiaoning@bjmu.edu.cn*

[b] *State key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*

† Electronic Supplementary Information (ESI) available: See DOI: XXXXXXXX

1 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.* 2003, **108**, 893.

2 (a) J. E. Payne, C. Bonnefous, K. T. Symons, P. M. Nguyen, M. Sablad, N. Rozenkrants, Y. Zhang, L. Wang, N. Yazdani, A. K. Shiau, S. A. Noble, P. Rix, T. S. Rao, C. A. Hassig and N. D. Smith, *J. Med. Chem.* 2010, **53**, 7739; (b) M. J. Tebbe, W. A. Spitzer, F. Victor, S. C. Miller, C. C. Lee, T. R. Sattelberg, E. Mckinney and C. J. Tang, *J. Med. Chem.* 1997, **40**, 3937; (c) T. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Jr. Buckheit and C. J. Michejda, *J. Med. Chem.* 1997, **40**, 4199; (d) A. M. Palmer, V. Chiesa, A. Schmid, G. Munch, B. Grobbel, P. J. Zimmermann, C. Brehm, W. Buhr, W.-A. Simon, W. Kromer, S. Postius, J. Volz and D. Hess, *J. Med. Chem.* 2010, **53**, 3645.

3 For review see: (a) P. N. Preston, *Chem. Rev*, 1974, **74**, 279; For some selected examples in recent years, see: (b) Y. V. Tomilov, D. N. Platonov, A. E. Frumkin, D. L. Lipilin and R. F. Salikov, Tetrohedron Lett. 2010, **51**, 5120; (c) J. M. Travins, R. C. Bernotas, D. H. Kaufman, E. Quinet, P. Nambi, I. Feingold, C. Huselton, A. Wilhelmsson, A. Goos-Nilsson and J. Wrobel, *Bioorg. Med. Chem. Lett.* 2010, **20**, 526; (d) M. Sime, A. C. Allan, P. Chapman, C. Fieldhouse, G. M. P. Giblin, M. P. Healy, M. H. Lambert, L. M. Leesnitzer, A. Lewis, R. V. Merrihew, R. A. Rutter, R. Sasse, B. G. Shearer, T. M. Wilson, R. X. Xu and D. J. Virley, *Bioorg. Med. Chem. Lett.* 2011, **21**, 5568; (e) S.-C. Lee, D. Shin, J. M. Cho, S. Ro and Y.-G. Suh *Bioorg. Med. Chem. Lett.* 2012, **22**, 1891.

4 For some selected examples in recent years, see: (a) J. Peng, M. Ye, C. Zong, F. Hu, L. Feng, X. Wang, Y. Wang and C. Chen, *J. Org. Chem.* 2011, **76**, 716; (b) S. Gupta, P. K. Agarwal and B. Kundu, *Tetrahedron Lett.* 2010, **51**, 1887; (c) R.-G. Xing, Y.-N. Li, Q. Liu, Q.-Y. Meng, J. Li, X.-X. Shen, Z. Liu, B. Zhou, X. Yao and Z.-L. liu, *Eur. J. Org. Chem.* 2010, 6627. (d) X. Diao, Y. Wang, Y. Jiang and D. Ma, *J. Org. Chem.* 2009, **74**, 7974; (e) M. Shen and T. G. Driver, *Org. Lett.* 2008, **10**, 3367.

5 For some selected examples in recent years, see: (a) M. M. Heravi, S. Sadjadi, H. Oskooie, R. H. Shoar and F. F. Bamoharram, *Cata. Commun.* 2007, **9**, 504; (b) V. K. Tandon and M. Kumar, *Tetrahedron Lett.* 2004, **45**, 4185; (c) K. Takeda, S. Yano, M. Sato and E. Yoshii *J. Org. Chem.* 1987, **52**, 4137; (d) S.-Y. Lin, Y. Isome, E. Stewart, J.-F. Liu, D. Yohannes and L. Yu, *Tetrohedron Lett.* 2006, **47**, 2883; (e) L. M. Dudd, E. Venardou, E. Garcia-Verdugo, P. Licence, A. J. Blake, C. Wilson, M. Poliakoff, *Green Chem.*, 2003, **5**, 187.

6 For some selected examples in recent years, see: (a) Q. Xiao, W.-H. Wang, G. Liu, F.-K. Meng, J.-H. Chen, Z. Yang and Z.-J. Shi, *Chem. Eur. J.* 2009, **15**, 7292; (b) Y. Kim, M. R. Kumar, N. Park, Y. Heo and S. Lee, *J. Org. Chem.* 2011, **76**, 9577; (c) J. Kim, J. Kim, H. Lee, B. M. Lee and B. H. Kim, *Tetrahedron*, 2011, **67**, 8027; (d) R. Cano, D. J. Ramon and M. Yus, *J. Org. Chem.* 2011, **76**, 654; (e) K. Osowska and O. S. Miljanic, *J. Am. Chem. Soc.* 2011, **133**, 724; (f) C. Siddappa, V. Kambappa, A. K. C. Siddegowda and K. S. Rangappa, *Tetrahedron Lett.* 2010, **51**, 6493; (g) H. Z. Boeini, and K. H. Najafabadi, *Eur. J. Org. Chem.* 2009, 4926; (h) A. Zarguil, S. Boukhris, M. L. E. Efrit, A. Souizi and E. M. Essassi, *Tetrahedron Lett.* 2008, **49**, 5883.

7 For reviews on green chemistry, see: (a) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; (b) C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. U.S.A.* 2008, **105**, 13197.

8 For review see: (a) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.* 2011, **40**, 3405; (b) J. Ruan and J. Xiao, *Acc. Chem. Res.* 2011, **44**, 614; (c) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.* 2011, **44**, 1182; (d) M. C. Willis, *Chem. Rev.* 2010, **110**, 725.

9 For some selected examples in recent years, see: (a) K. Bahrami, M. M. Khodaei and F. Naali, *Synlett*, 2009, 569; (b) M. A. Chari, D. Shobha and T. Sasaki, *Tetrahedron Lett.* 2011, **52**, 5575; (c) Y. Riadi, R. Mamouni, R. Azzalou, M. E. Haddad, S. Routier, G. Guillaumet and S. Lazar *Tetrahedron Lett.*2011, **52**, 3492; (d) M. A. Chari, D. Shobha, E.-R. Kenawy, S. S. Al-Deyab, B. V. S. Reddy and A. Vinu, *Tetrahedron Lett.* 2010, **51**, 5195; (e) K. Bahrami, M. M. Khodaei and A. Nejatia, *Green Chem.* 2010, **12**, 1237; (f) J.-P. Wan, S.-F. Gan, J.-M. Wu and Y. Pan, *Green Chem.* 2009, **11**, 1633; (g) D. Saha, A. Saha and B. C. Ranu, *Green Chem.* 2009, **11**, 733; (h) H. Sharghi, M. Aberi and M. M. Doroodmand, *Adv. Synth. Catal.* 2008, **350**, 2380; (i) C. Mukhopadhyay and P. K. Tapaswi, *Tetrahedron Lett.* 2008, **49**, 6237; (j) K. Bahrami, M. M. Khodaei and F. Naali, *J. Org. Chem.* 2008, **73**, 6835; (k) S. Lin and L. Yang, *Tetrahedron Lett.* 2005, **46**, 4315; (l) P. Gogoi and D. Konwar, *Tetrahedron Lett*. 2006, **47**, 79; (m) D. B. Ramachary and G. B. Reddy, *Org. Biomol. Chem.* 2006, **4**, 4463.

10 Y. X. Chen, L.-F. Qian, W. Zhang and B. Han, *Angew. Chem. Int. Ed.* 2008, **47**, 9330.

11 CCDC- 899934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

12 K. Saito and K. Harada, *Tetrahedron Lett.* 1989, **30**, 4535.

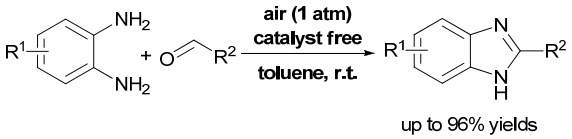
13 (a) B. D. Wagner, G. Ruel and J. Lusztyk, *J. Am. Chem. Soc.* 1996, **118**, 13; (b) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Tetrahedron*, 2012, **68**, 5258; (c) P. Chávez, J. Kirsch, C. H. Hövelman, J. Streuff, M. Martínez-Belmonte, E. C. Escudero-Adán, E. Martin and K. Muñiz, *Chem. Sci.* 2012, **3**, 2375; (d) C. Röben, J. A. Souto, Y. González, A. Lishchynskyi and K. Muñiz, *Angew. Chem. Int. Ed.* 2011, **50**, 9478. (e) F. C. Sequeira, B. W. Turnpenny and S. R. Chemler, *Angew. Chem. Int. Ed.* 2010, **49**, 6365; (f) C. Zhang and N. Jiao, *J. Am. Chem. Soc.* 2010, **132**, 28.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE View Online

C. Zhang, L. Zhang and N. Jiao*



Catalyst Free Approach to Benzimidazoles Using Air as the Oxidant at Room Temperature

A catalyst and additive free procedure to construct 2-alkyl-benzimidazoles using air as the oxidant at room temperature has been developed.