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One-pot sequential synthesis of 1,2-disubstituted benzimidazoles under metal-free conditions

Priyabrata Roy, Animesh Pramanik *

Department of Chemistry, University of Calcutta, 92, A.P.C. Road, Kolkata 700009, India

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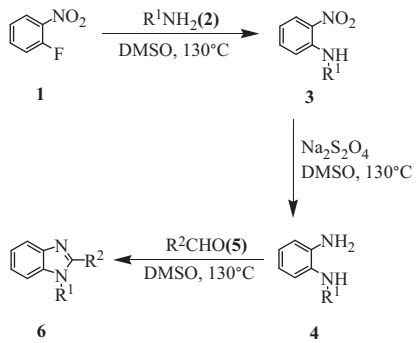
ABSTRACT

An easy and inexpensive method has been developed to access 1,2-disubstituted benzimidazoles following a one-pot sequential coupling/reduction/cyclization process under metal-free neutral conditions.

Benzimidazole and its derivatives are a very important class of compounds due to their pharmacological and biological activities.[1] 1,2-Disubstituted benzimidazoles represent an important branch of this family. These structures are valuable bioactive structures and have been reported as specific angiotensin II receptor type 1 selective antagonists,[2] or hepatitis C virus NS5B polymerase inhibitors.[3] Furthermore, they exhibit several other pharmacological activities[4] and have been used in antidiabetic, antihistamine, analgesic, antiviral, antifungal, and antiparasitic applications.

Although a number of methods for the synthesis of 1- or 2-monosubstituted benzimidazoles have been reported,[5] the assembly of 1,2-disubstituted benzimidazoles still encounters challenges in controlling regioisomeric selectivity, increasing efficiency, and improving generality.[6,7] Most of the methods toward 1,2-disubstituted benzimidazoles such as the condensation of carboxylic acids with N-substituted 1,2-diaminoarenes and N-arylation/alkylation reactions of 1*H*-benzimidazoles have often suffered from a limited scope[7g] and led to a mixture of two regioisomers because of the difficulty of differentiating the two N-atoms.[6] Alternatively, the palladium-,[8] copper-,[9] indium-,[10] ruthenium-,[11] and cobalt-[5e,12] catalyzed intramolecular N-arylation starting from *o*-haloanilines/*o*-halonitrobenzene has been used. However, most of these protocols involve multistep synthetic transformations and engage a complex isolation process leading to a high cost and/or they suffer from poor availability of starting materials. In some cases the use of strong acid-catalyzed conditions also limits the functional group tolerance. In addition, the employed metals are not environmentally friendly and are not attractive for commercial adoption due to a low catalyst activity and the generation of corrosive waste. These drawbacks prompted us to investigate a more practical access to the 1,2-disubstituted benzimidazole scaffold.

Herein, we wish to describe a simple one-pot multicomponent reaction sequence to access these ring systems under metal-free neutral conditions (Scheme 1). The synthetic approach involves (i) coupling of a primary amine **2** with 1-fluoro-2-nitrobenzene **1**, by nucleophilic aromatic substitution, (ii) reduction of the coupled nitroarene **3** by sodium dithionite, and (iii) cyclization of the corresponding diamine **4** using an aldehyde **5**.



Scheme 1. Strategy toward synthesis of 1,2-disubstituted benzimidazoles.

* Corresponding author. Tel.: +91 33 24841647; fax: +91 33 23519755.
E-mail address: animesh_in2001@yahoo.co.in (A. Pramanik).

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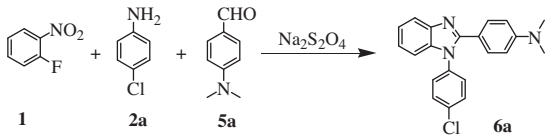
To test the viability of the proposed pentannulation reaction, we first considered the coupling of 1-fluoro-2-nitrobenzene **1** with *p*-chloroaniline **2a** and *p*-dimethylaminobenzaldehyde **5a** (Table 1). Thus, exposure of amine **2a** to 1-fluoro-2-nitrobenzene **1** in DMSO at 90 °C for 2 h followed by treatment with *p*-dimethylaminobenzaldehyde and sodium dithionite at the same temperature for another 1 h gave benzimidazole derivative **6a** in only 41% yield along with starting material **1** and **2a** (Table 1, entry 1). A higher yield of product **6a** was obtained when the reaction was performed at higher temperature using DMSO as the solvent (entry 2). Reaction temperature and solvents were found to have dramatic effects on the reaction, and DMSO was found to be the best solvent in our study as the use of other solvents, for example DMF, CH_3CN, DCM, and toluene decreased the product yield (entries 3–7). The reaction was carried out for 6 h and increase of reaction time did not improve the product yield (entry 8). The yield of the product was considerably lower in dilute solution (entry 9).

Table 1
Optimization of reaction conditions[a]



1 2a 5a 6a

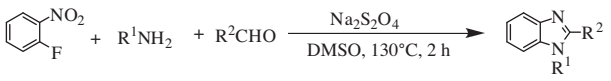
Entry	Solvent	Time[b] (h)	Concn[c] (M)	*T* (°C)	Yield[d] (%)
1	DMSO	3	0.5	90	41
2	**DMSO**	**3**	**0.5**	**130**	**91**[e]
3	DMF	3	0.5	100	13
4	DMF	6	0.5	150	19
5	CH_3CN	3	0.5	—	4[f]
6	DCM	3	0.5	—	15[f]
7	Toluene	3	0.5	—	Trace[f]
8	DMSO	6	0.5	130	90
9	DMSO	3	0.1	130	78

[a] The reaction was carried out using a 1:1:1.2:1.5 ratio of 1-fluoro-2-nitrobenzene–amine–aldehyde–sodium dithionite.
[b] Typical reaction time (see the Supplementary data).
[c] Concentration of 1-fluoro-2-nitrobenzene and amine in respective solvents.
[d] Isolated yields.
[e] For a representative procedure see, Ref. 13.
[f] Reactions were conducted at the reflux temperature.

Having prepared benzimidazole **6a** successfully, we decided to explore the scope and generality of this reaction in the synthesis of other analogues varying the substituent at N-1 and C-2. Accordingly, a variety of commercially available primary amines **2** and aldehydes **5** were reacted with 1-fluoro-2-nitrobenzene **1** (Table 2) under the optimized conditions (Table 1, entry 2). As evident from Table 2, all the primary amines and aldehydes participated well in this substitution/reduction/cyclization reaction affording the desired products in good yields. In case of entry e the corresponding diamine intermediate **4e** was isolated in 5% yield with desired benzimidazole derivative **6e** in 81% yield. All the structures of the cyclized products were determined by a detailed study of the spectroscopic data. Furthermore, the formation of products **6a** and **6k** was unambiguously confirmed through X-ray crystallographic analysis (Figs. 1 and 2).

In conclusion, a straightforward, efficient, and more sustainable metal-free one-pot sequential synthesis of 1,2-disubstituted benzimidazoles has been described. The protocol involves coupling of a primary amine with 1-fluoro-2-nitrobenzene, reduction of the

Table 2
Synthesis of 1,2-disubstituted benzimidazoles **6**[a]



1 2 5 81-92% 6

Entry	R^1	R^2	Product	Yield[b] (%)	Mp (°C)	Ref. Mp (°C)
a	Cl	N	**6a**	91	164–166	–
b	Cl		**6b**	87	144–145	–
c	O		**6c**	89	118–120	119–120[12]
d	Cl	HO	**6d**	90	>300	–
e	Cl	O	**6e**	81	169–170	–
f	Cl	F	**6f**	87	166–168	–
g		F	**6g**	85	100–101	–
h			**6h**	88	124–125	123–124[7c]
i		Br	**6i**	92	132–133	130–131[7c]
j		F	**6j**	85	119–121	–
k		NC	**6k**	85	160–162	–
l			**6l**	91	92–94	95–97[14]
m	O	F	**6m**	90	118–120	–
n	NH_2	O	**6n**	85	189–190	–
o			**6o**	87	110–112	109–110[12]

[a] The reaction was carried out using a 1:1:1.2:1.5 ratio of 1-fluoro-2-nitrobenzene–amine–ldehyde–sodium dithionite. Reaction time was typically 3 h (see the Supplementary data).
[b] Isolated yields.

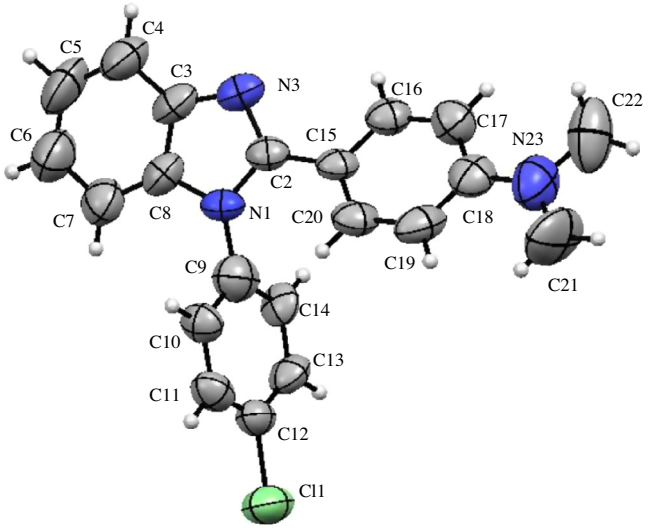


Figure 1. X-ray crystal structure of **6a** with atom-labeling scheme.

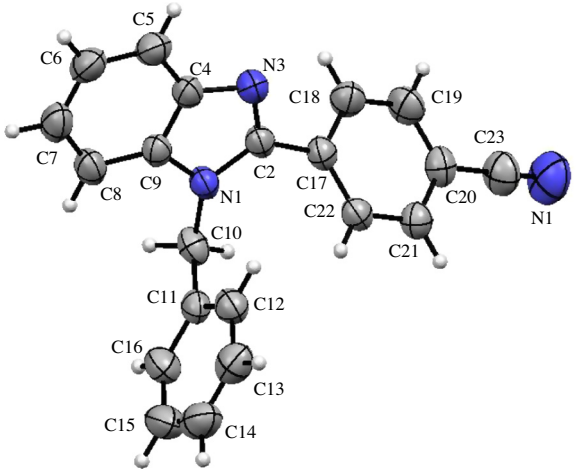


Figure 2. X-ray crystal structure of **6k** with atom-labeling scheme.

coupled nitroarene by sodium dithionite, and cyclization of the corresponding diamine using an aldehyde.

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Supplementary data

Supplementary data (detailed experimental procedures and spectral data (IR, ^{1}H, ^{13}C) for all new compounds (PDF) and X-ray structural data of **6a** and **6k** (CCDC 939808 and CCDC 939807)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.083.

References and notes

1. (a) Boiani, M.; González, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409–424; (b) Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. *Pharm. Chem. J.* **1999**, *33*, 232–243.
2. (a) Naik, P.; Murumkar, P.; Giridhar, R.; Yadav, M. *Bioorg. Med. Chem.* **2010**, *18*, 8418–8456; (b) Vyas, V. K.; Ghate, M. *Mini-Rev. Med. Chem.* **2010**, *10*, 1366–1384.
3. Ishida, T.; Suzuki, T.; Hirashima, S.; Mizutani, K.; Yoshida, A.; Ando, I.; Ikeda, S.; Adachi, T.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1859–1863.
4. (a) Dang, Q.; Kasibhatla, S.; Xiao, W.; Liu, Y.; Dare, J.; Taplin, F.; Reddy, K.; Scarlato, G.; Gibson, T.; van Poelje, P.; Potter, S.; Erion, M. *J. Med. Chem.* **2010**, *53*, 441–451; (b) Bielory, L.; Lien, K.; Bigelsen, S. *Drugs* **2005**, *65*, 215–228; (c) Gaba, M.; Singh, D.; Singh, S.; Sharma, V.; Gaba, P. *Eur. J. Med. Chem.* **2010**, *45*, 2245–2249; (d) Miller, J. F.; Turner, E. M.; Gudmundsson, K. S.; Jenkinson, S.; Spaltenstein, A.; Thomson, M.; Wheelan, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2125–2128; (e) Chen, C.; Yu, J.; Bi, C.; Zhang, Y.; Xu, J. Q.; Wang, J. X.; Zhou, M. G. *Phytopathology* **2009**, *99*, 1403–1411; (f) Pérez-Villanueva, J.; Santos, R.; Hernandez-Campos, A.; Giulianotti, M. A.; Castillo, R.; Medina-Franco, J. L. *Med. Chem. Commun.* **2011**, *2*, 44–49.
5. (a) Inamdar, S. M.; More, V. K.; Mandal, S. K. *Tetrahedron Lett.* **2013**, *54*, 579–583; (b) Bachhav, H. M.; Bhagat, S. B.; Telvekar, V. N. *Tetrahedron Lett.* **2011**, *52*, 5697–5701; (c) Surpur, M. P.; Singh, P. R.; Patil, S. B.; Samant, S. D. *Synth. Commun.* **2007**, *37*, 1375–1379; (d) René, O.; Souverneva, A.; Magnuson, S. R.; Fauber, B. P. *Tetrahedron Lett.* **2013**, *54*, 201–204; (e) Chari, M. A.; Shobha, D.; Sasaki, T. *Tetrahedron Lett.* **2011**, *52*, 5575–5580; (f) VanVliet, D. S.; Gillespie, P.; Scicinski, J. J. *Tetrahedron Lett.* **2005**, *46*, 6741–6743.
6. For the latest review on regioselective synthesis of 1,2-disubstituted benzimidazoles, see: Carvalho, L. C. R.; Fernandes, E.; Marques, M. B. *Chem. Eur. J.* **2011**, *17*, 12544–12555.
7. For the selected examples, see: (a) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814–6816; (b) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 7841–7844; (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934; (d) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem. Eur. J.* **2009**, *15*, 7292–7296; (e) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742–5745; (f) Alonso, J.; Halland, N.; Nazaíe, M.; R'kyek, O.; Urmann, M.; Lindenschmidt, A. *Eur. J. Org. Chem.* **2011**, 234–237; (g) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295–5308.
8. (a) Zhao, D.; Hu, J.; Wu, N.; Huang, X.; Qin, X.; Lan, J.; You, J. *Org. Lett.* **2011**, *13*, 6516–6519; (b) Hornberger, K. R.; Adjabeng, G. M.; Dickson, H. D.; Davis-Ward, R. G. *Tetrahedron Lett.* **2006**, *47*, 5359–5361; (c) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893–1895; (d) Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H.; Buchwald, S. *Angew. Chem., Int. Ed.* **2007**, *119*, 7653–7656; (e) Blatch, A. J.; Chetina, O. V.; Howard, J. A.; Patrick, L. G.; Smethurst, C. A.; Whiting, A. *Org. Biomol. Chem.* **2006**, *4*, 3297–3302.
9. (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934; (b) Deng, X.; Mani, N. S. *Eur. J. Org. Chem.* **2010**, 680–686; (c) Saha, P.; Ramana, T.; Purkait, N.; Ali, M.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719–8725; (d) Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. *J. Org. Chem.* **2011**, *76*, 716–719; (e) Wang, F.; Cai, S.; Liao, Q.; Xi, C. *J. Org. Chem.* **2011**, *76*, 3174–3180; (f) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598–2601.
10. (a) Santra, S.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2012**, *53*, 1974–1977; (b) Kommi, D. N.; Jadhavar, P. S.; Chakraborti, D.; Kumar, A. K. *Green Chem.* **2013**, *15*, 798–810.
11. Cho, C. S.; Kim, J. U. *Bull. Korean Chem. Soc.* **2008**, *29*, 1097–1098.
12. Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. *Org. Biomol. Chem.* **2010**, *8*, 5692–5699.
13. Representative procedure. *Synthesis of benzimidazole derivative* ***6a***: A mixture of 1-fluoro-2-nitrobenzene **1** (141 mg, 1.0 mmol) and *p*-chloroaniline **2a** (127 mg, 1.0 mmol) in DMSO (2 mL) was stirred for 2 h at 130 °C temperature. Sodium dithionite (261 mg, 1.5 mmol) and *p*-dimethyl amino benzaldehyde **5a** (179 mg, 1.2 mmol) were then added and heating was continued for 1 h. Water (10 mL) was added to the mixture and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed on rotary evaporator and the residue was purified by column chromatography (silica gel, ethylacetate/petroleum ether,1:2) to yield the benzimidazole derivative **6a** (316 mg, 91%) as a white solid. Mp: 164–166 °C; IR (KBr, cm^{-1}): 1610; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, 1H, *J* = 7.8, 0.6 Hz), 7.47 (ddd, 4H, *J* = 15.3, 8.4, 1.2 Hz), 7.35–7.13 (m, 5H), 6.62 (d, 2H, *J* = 7.8 Hz), 3.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 150.5, 142.5, 136.5, 135.6, 133.7, 130.1, 129.6, 128.4, 122.5, 122.3, 118.8, 116.0, 111.0, 109.3, 39.6; Anal. Calcd for $C_{21}H_{18}ClN_3$: C, 72.51; H, 5.22; N, 12.08. Found: C, 72.37; H, 5.14; N, 12.01.
14. López-Alvarado, P.; Avendano, C.; Menéndez, J. C. *J. Org. Chem.* **1995**, *60*, 5678–5682.