ORGANIC LETTERS

2011
Vol. 13, No. 24
6516–6519

Regiospecific Synthesis of 1,2-Disubstituted (Hetero)aryl Fused Imidazoles with Tunable Fluorescent Emission

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Received October 19, 2011

ABSTRACT

A palladium-catalyzed two or fourfold amination was established that allows regiospecific synthesis of a diversity-oriented library of 1,2-disubstituted (hetero)aryl fused imidazoles, and provides an exceptional tool for the discovery of fluorescent scaffolds with tunable fluorescence emission. These fluorophores have been applied as fluorescent probes for live cell imaging.

Exploiting regiospecific and high-yielding synthetic methodologies for the rapid discovery of small organic fluorophores is starting to attract increasing interest.[1] 1,2-Disubstituted (hetero)aryl fused imidazoles such as *N*-arylbenzimidazoles (Type **A**), *N*-alkylbenzimidazoles (Type **B**), N-substituted 2-aminobenzimidazoles (Type **C**), pyrido[1,2-*a*]benzimidazoles (Type **D**), and heteroaryl fused imidazoles are prevalent in advanced materials, molecules of medicinal interest, and natural products.[2] In particular, the benzimidazolyl scaffolds are frequently chosen as electron-transporting units and exhibit intense blue fluorescence emission in OLEDs.[2b,d,e] However, there has been little systematic study elucidating the relationship between the structural and photophysical properties of (hetero)aryl fused imidazoles due to the limited structural diversity of the chemical library. Therefore, developing a regiospecific and modular approach to (hetero)aryl fused imidazoles with easily tunable substitution patterns (e.g., N1/C2-substituents and π-extended conjugated systems) is highly warranted for assembling a diversity-oriented fluorescence library that spans a wide range of emission wavelengths.

Although a number of methods for the synthesis of *1- or 2-monosubstituted benzimidazoles* have been reported, the assembly of *1,2-disubstituted benzimidazoles* still encounters challenges in controlling regioisomeric selectivity, increasing efficiency, and improving generality.[3,4] Most of the methods toward 1,2-disubstituted benzimidazoles such as

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10.1021/ol202807d
Published on Web 11/15/2011

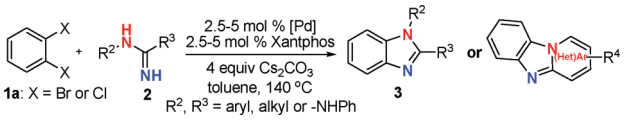
the condensation of carboxylic acids with N-substituted 1,2-diaminoarenes and N-arylation/alkylation reactions of 1*H*-benzimidazoles have often suffered from a limited scope[4g] and led to a mixture of two regioisomers because of the difficulty of differentiating the two N-atoms.[3,4b] The intramolecular C−H functionalization/C−N bond formation mainly accessed 2-substituted 1*H*-benzo[*d*]imidazoles and met regioisomeric hindrances to some extent.[4c,d] In 2007, Buchwald et al. disclosed a palladium-catalyzed synthesis of *N*-arylbenzimidazoles starting from *ortho*-haloanilides in a regioisomerically pure form.[5] However, it failed to give *N*-alkylbenzimidazoles in an acceptable yield due to a competing *β*-hydride elimination. Yet, the Cu-catalyzed systems, independently developed by Buchwald and Ma groups, were restricted to *N*-alkylbenzimidazoles.[6]

The twofold amination of N-substituted amidines with *o*-dihalo(hetero)arenes would represent an alternative strategy for the regiospecific synthesis of 1,2-disubstituted benzimidazoles. However, the reported Cu-catalytic system required more expensive and/or not easily accessible *ortho*-haloaryl iodides. More importantly, most of the examples gave low yields (10−40%),[7] which greatly diminished the industrial and academic value of this method. These drawbacks inspired us to reinvestigate this transformation. Herein, we disclose the Pd-catalyzed intermolecular tandem two- or fourfold amination starting from N-substituted amidines, guanidines, or 2-aminopyridines with generally more available *ortho*-haloaryl chlorides or bromides, which constituted a general and highly regiospecific method for the synthesis of the structurally diverse (hetero)aryl fused imidazoles. This also assembled a library of organic fluorophores with the tunable emission wavelength covering the range 366−591 nm.

Our initial investigation was aimed at the twofold amination of *N*-phenylbenzamidine with 1,2-dibromobenzene. After screening several parameters (Table S1), the tandem reaction afforded **3a** in excellent yield when a low catalyst loading of $Pd(OAc)_2$ or $Pddba_2$ (2.5 mol %) was employed in combination with Xantphos (2.5 mol %), 4 Å sieves as the additive, and Cs_2CO_3 or NaO*t*Bu as the base in toluene at 140 °C for 24 h. With optimized conditions now in hand, a variety of amidines were tested with 1,2-dihalobenzene (**1a**), and the results are summarized in Table 1. Gratifyingly, no matter whether the substituent R^2 or R^3 of amidines was aryl, alkyl (**3h** and **3p**), or heteroaryl (**3m**−**o**, and **3q**), all of them afforded 1,2-disubstituted benzimidazoles in good to excellent yields (Table 1, entries 1−19). The less reactive and inexpensive 1,2-dichlorobenzene also gave rise to **3a** in 96% yield (Table 1, entry 2). It is notable that our catalytic system could be applied to the synthesis of pyrido[1,-2-*a*]benzimidazoles by using 2-aminopyridine derivatives as the starting material (**3s**−**3u**). Moreover, the N1-substituted 2-aminobenzimidazoles could also be obtained using readily available guanidine residues (**3v**). Traditional methods for the preparation of such molecules often involve multistep approaches starting from *o*-phenyldiamine, aryl amination of 2-halobenzimidazoles, and the intramolecular aryl guanidinylation.[8]

To gain insight into the relationship of structure−photophysical properties, we tried to set up a combinatorial library of donor−acceptor (hetero)aryl fused imidazoles. Fortunately, we were pleased with the generality

Table 1. Twofold Aminations of a Variety of Amidines, 2-Aminopyridines, and Guanidines[a]



entry	compound **2**	product	yield [%]
1	R^2 = Ph; R^3 = Ph	**3a**	99
2[b]	R^2 = Ph; R^3 = Ph	**3a**	96
3	R^2 = *o*-MePh; R^3 = Ph	**3b**	95
4	R^2 = *p*-MePh; R^3 = Ph	**3c**	86
5	R^2 = 1-naphthyl; R^3 = Ph	**3d**	99
6	R^2 = 3,5-diMeOPh; R^3 = Ph	**3e**	91
7	R^2 = *p*-ClPh; R^3 = Ph	**3f**	92
8	R^2 = *m*-NO_2Ph; R^3 = Ph	**3g**	89
9	R^2 = Cy; R^3 = Ph	**3h**	99
10	R^2 = Ph; R^3 = *p*-Me_2NPh	**3i**	98
11	R^2 = Ph; R^3 = *p*-Ph_2NPh	**3j**	81
12	R^2 = Ph; R^3 = *m*-CNPh	**3k**	87
13	R^2 = Ph; R^3 = *p*-ClPh	**3l**	86
14	R^2 = Ph; R^3 = *m*-pyridyl	**3m**	96
15	R^2 = Ph; R^3 = *p*-pyridyl	**3n**	94
16	R^2 = Ph; R^3 = 2-thienyl	**3o**	82
17	R^2 = Ph; R^3 = methyl	**3p**	99
18	R^2 = *p*-Me_2NPh; R^3 = *p*-pyridyl	**3q**	93
19	R^2 = *p*-Me_2NPh; R^3 = *p*-CNPh	**3r**	91
20[c]	2-aminopyridine	**3s**	86
21[c]	2-amino-5-methylpyridine	**3t**	92
22[c]	2-aminopyrazine	**3u**	87
23[c]	R^2 = Ph; R^3 = -NHPh	**3v**	84

[a] The experimental details were described in the Supporting Information. Yield of isolated product was based on 1,2-dihalobenzene. [b] *o*-Dichlorobenzene was used. [c] K_3PO_4/NaO*t*Bu (4.0 equiv, 1/1).

(3) 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.

(4) For the selected examples, see: (a) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814. (b) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 7841. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (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. (e) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742. (f) Alonso, J.; Halland, N.; Nazaré, M.; R'kyek, O.; Urmann, M.; Lindenschmidt, A. *Eur. J. Org. Chem.* **2011**, 234. (g) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295.

(5) Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7509.

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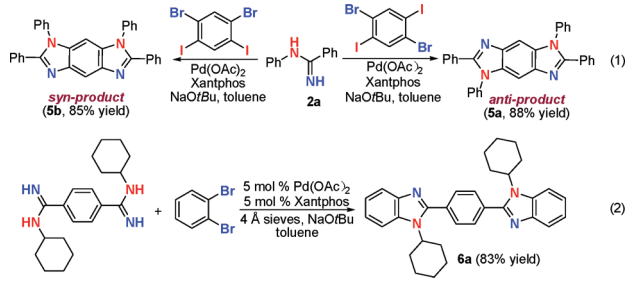
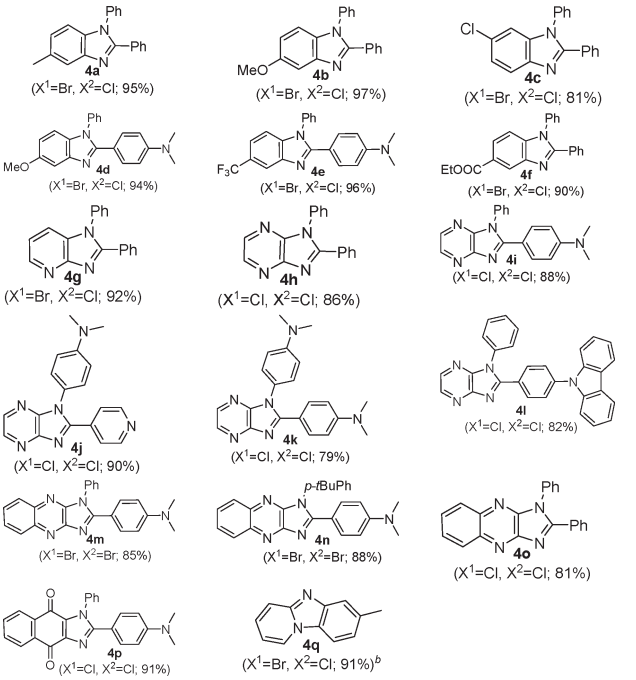
of our methodology. First, whether the asymmetrically substituted *o*-dihaloarenes bore the neutral, electron-donating, or electron-withdrawing substituents, all of them smoothly coupled with a set of amidines to generate the structurally diverse 1,2-disubstituted aryl fused imidazoles in excellent yields. In these tandem twofold aminations, the requirement of *o*-dihalo(hetero)arene derivatives containing two different halogen atoms could ensure a completely regioselective transformation (Scheme 1, **4a**–**4g**, **4q**). Second, various *o*-dihaloheteroarenes gave heteroaryl fused imidazoles in good to excellent yields (Scheme 1, **4g**–**o**). Third, 1,2-disubstituted naphtho[2,3-*d*]-imidazole-4,9-diones, which are known as key precursors for the preparation of organic electronic devices and previously prepared in three steps,[9] could be synthesized by a single tandem amination of 2,3-dichloronaphthoquinone in an excellent yield (**4p**, 91% yield). Finally, the reaction conditions were compatible with the presence of some important functional groups such as cyano, nitro, chloro, ester, and methoxy groups on the amidines or *o*-dihaloarenes, which could then be subjected to further synthetic transformations (Table 1, **3e**, **3f**, **3g**, **3k**, **3l**, **3r**; Scheme 1, **4b**, **4c**, **4f**, **4p**).

Benzobisimidazoles have proven to be the precursors of versatile electronic and fluorescent materials. The previous synthesis of these scaffolds provides a 1:1 mixture of 1,7-diphenyl-(**5b**$_{syn}$) and 1,5-diphenylbenzobis(imidazole)s (**5a**$_{anti}$).[10] The present tandem protocol could be extended to the direct and regioselective preparation of benzobisimidazoles via the fourfold C–N coupling. Both the *anti*- and *syn*-products were obtained in good yields using 1,4-dibromo-2,5- and 1,5-dibromo-2,4-diiodobenzene, respectively [eq 1]. Our primary investigation also exhibited that the fourfold C–N coupling of a diamidine afforded the 1,2-disubstituted dibenzimidazole **6a** in 83% yield [eq 2].



Having established a preparative method for a library of structurally diverse 1,2-disubstituted (hetero)aryl fused imidazoles, we next investigated in detail their fluorescent properties. Thus, we found that the structural modifications significantly affected the fluorescence characteristics. Clearly, the fluorescence emission intensity and wavelength depended on the electronic nature of C2/N1-substituents and π-extended conjugated

Scheme 1. Twofold Amination of 1,2-Dihalo(hetero)arenes[a]



[a] The experimental details were described in the Supporting Information. Yield of isolated product is given in parentheses. [b] K_3PO_4/NaO*t*Bu (4.0 equiv, 1/1).

systems. Figures 1a–e and S1 show that the emission colors could be tuned in the range blue to red (λ_{em}: 366–591 nm) by simply modifying the substituents at the C2/N1 position and π-extended framework.

The N1-alkyl **3h**, C2-alkyl **3p**, and 2-aminobenzimidazole **3v** exhibited weak fluorescent emissions. 1,2-Diphenylbenzimidazole **3a** and pyrido[1,2-*a*]benzimidazoles **3s**–**3t** showed blue fluorescent emissions in CH_2Cl_2. When the C2 position was occupied by the electron-donating *N*,*N*-dimethyl(aryl)aniline moiety, all of these exhibited stronger fluorescence in various solvents such as CH_2Cl_2, CH_3CN, and DMF (Figure 1a, c–d). The electron-withdrawing 4-pyridyl or *p*-cyanophenyl group at the C2-position in combination with the electron-donating *N*,*N*-dimethylaniline moiety at the N1-position led to a bathochromically shifted emission maximum (Table 1, **3q**, **3r**). Thus, the fluorophore **3r** showed the longest emission wavelength (λ_{em} = 591 nm, DMSO). The observations clearly reflected the existence of a "push–pull" π-electron mode, in which the nitrogen atom of the *N*,*N*-dimethyl(aryl)aniline moiety served as the electron donor and the electron-deficient groups functioned as the electron acceptor.

Notably, most of the fluorophores exhibited a large Stokes shift in the range 100–200 nm in CH_3CN (Table S2) and a strongly positive solvatofluorochromism upon irradiation in different solvents. For example, the fluorescence emission maxima of **4m** shifted to longer wavelengths from 416 to 546 nm with increasing solvent polarity (Figures 1d and S2).

(9) Bae, J.-S.; Lee, D.-H.; Lee, D.-W.; Jang, J.-G. WO2007011170A1, 2007.

(10) (a) Boydston, A. J.; Pecinovsky, C. S.; Chao, S. T.; Bielawski, C. W. *J. Am. Chem. Soc.* **2007**, *129*, 14550. (b) Boydston, A. J.; Vu, P. D.; Dykhno, O. L.; Chang, V.; Wyatt, A. R.; Stockett, A. S., II; Ritschdorff, E. T.; Shear, J. B.; Bielawski, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 3143.

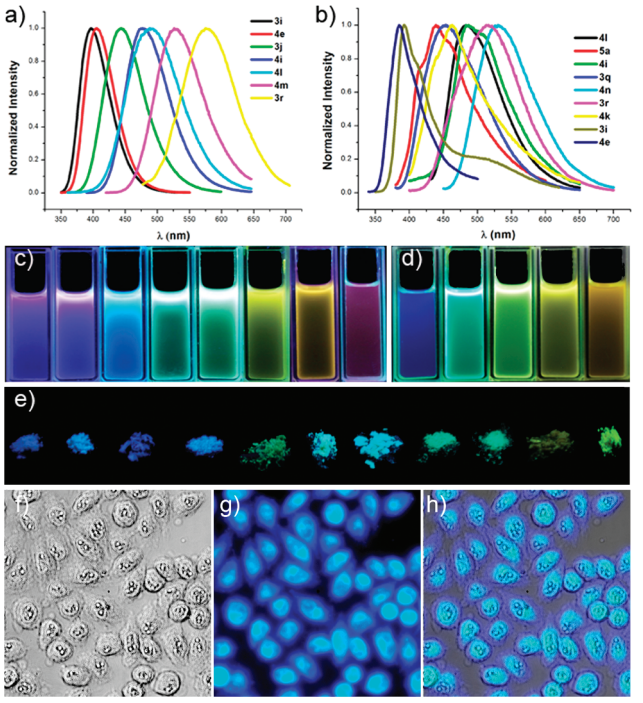


Figure 1. (a) Fluorescent spectra of benzimidazoles in CH_3CN (signal intensities have been normalized). From left to right: **3i**, **4e**, **3j**, **4i**, **4l**, **4m**, and **3r**. (b) Solid-state fluorescent spectra of benzimidazoles in powder (signal intensities have been normalized). From left to right: **4e**, **3i**, **5a**, **3q**, **4k**, **4l**, **4i**, **3r**, and **4n**. (c) Fluorescence images of benzimidazoles in CH_3CN, irradiated at 365 nm. From left to right: **3i**, **4e**, **3j**, **4i**, **4l**, **4m**, **3q**, and **3r**. (d) Fluorescence images of solvatofluorochromism upon irradiation of **4m** in different solvents. From left to right: hexane, CH_2Cl_2, acetone, CH_3CN, and DMSO. (e) Fluorescence images of benzimidazoles (powder, λ_{ex} = 365 nm). From left to right: **3i**, **4e**, **5a**, **4k**, **4j**, **4l**, **4i**, **3q**, **3r**, **4m**, and **4n**. (f–h) Bright-field transmission image, fluorescence image, and overlay of the fluorescence and bright-field transmission image of SMMC-7721 cells incubated with **4i** (20 μM), respectively.

It is a challenging project for the design and synthesis of small organic molecules exhibiting highly efficient solid-state luminescence for the development of optoelectronic devices such as OLEDs and solid-state organic lasers.[11]

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It is remarkable that most of the (hetero)aryl fused imidazoles exhibited strong solid-state fluorescence with various emission colors upon excitation with UV light (λ_{ex} = 365 nm). The solid-state emission wavelengths were observed from 386 to 532 nm (Figure 1b, e). These characteristics make them potential candidates for organic emitters and solid-state lighting devices.

Molecular fluorescent imaging techniques help us understand biological processes at a molecular level and identify diseases in their early stage. Although many luminescent probes have been used in cell imaging, the exploitation of small fluorescent labeling molecules for intracellular targets still remains an attractive and promising goal. To demonstrate the potential of structurally diverse 1,2-disubstituted (hetero)aryl fused imidazoles as bioimaging probes, human hepatocellular carcinoma cells (SMMC-7721) and human lung adenocarcinoma epithelial cells (A549) were incubated with these fluorophores (**3r**, **4i**, **4m**, and **4n**) in DMEM Dulbecco's mimimum essential medium for 40 min at 37 °C (Figures 1f–h and S3). Gratifyingly, **4i** successfully marked SMMC-7721, thus suggesting that the donor–acceptor (hetero)aryl fused imidazoles would be potentially useful reagents for fluorescence imaging in clinical diagnostics and biomedical research.

In summary, we have developed a palladium-catalyzed cascade amination that allows, for the first time, regiospecific and modular synthesis of a library of structurally diverse 1,2-disubstituted (hetero)aryl fused imidazoles comprising all the above-mentioned four structures (Tpye **A**, **B**, **C**, and **D**) and heteroaryl fused imidazoles, which exhibits various interesting fluorescent properties and elucidates the correlation between chemical structures and fluorescent characteristics. These "push–pull" fluorophores can accommodate tunable emission wavelengths from 366 to 591 nm by switching the N1/C2-substituents and π-extended conjugated systems. The fluorophores have proven to be potentially useful bioimaging fluorescence probes.

Acknowledgment. This work was supported by grants from the National NSF of China (Nos. 21025205, 20972102, 21021001, and 20872101), PCSIRT (No IRT0846), and the National Basic Research Program of China (973 Program, 2011CB808600). We thank the Centre of Testing & Analysis, Sichuan University for NMR and ESI-MS measurements.

Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.