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Metal-Free One-Pot Synthesis of *N,N′*-Diarylamidines and *N*-Arylbenzimidazoles from Arenediazonium Salts, Nitriles, and Free Anilines

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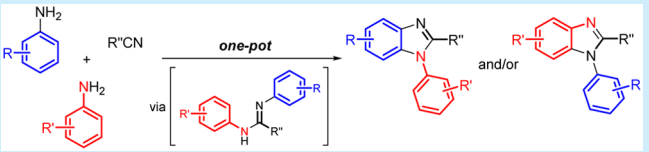
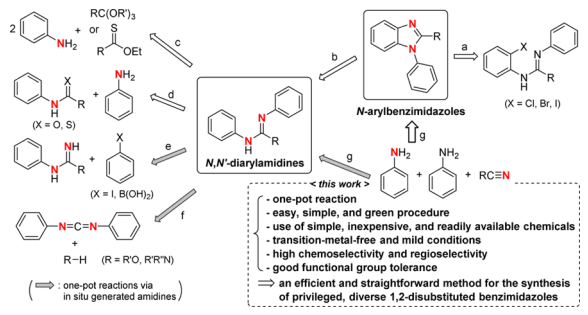
Supporting Information

ABSTRACT: A highly efficient and facile metal-free, one-pot reaction has been developed to afford diversely substituted *N*-arylbenzimidazoles through chemoselective in situ generation of *N,N′*-diarylamidines from arenediazonium salts, nitriles, and free anilines. The advantages of this protocol consist of the operationally easy and simple one-pot procedure under metal-free and mild conditions, the direct use of inexpensive and commercially available chemicals, and thus, a cost-effective and greener process.



Benzimidazoles are ubiquitous motifs found in a broad spectrum of biologically active natural products and pharmaceuticals as well as materials.[1] Among them, *N*-arylbenzimidazoles are a class of privileged heterocycles that are known to possess various biological properties,[2] and they have also been used as the backbone in dyes, polymers, and ligands.[3] Consequently, a diverse range of synthetic strategies have been reported for the construction of *N*-arylbenzimidazoles.[4] Intramolecular cyclization of *N,N′*-diarylamidines is one of the straightforward methods for the construction of an *N*-arylbenzimidazole moiety; therefore, a variety of transition-metal-catalyzed cross-coupling reactions of *N*-(*o*-haloaryl)-amidines have been developed (path a, Scheme 1).[5]

Scheme 1. Synthetic Methods for the Construction of *N*-Arylbenzimidazoles



Undoubtedly, a more efficient route toward this scaffold is a direct C–H amination of *N,N′*-diarylamidines, obviating the need for prehalogenation (path b, Scheme 1). Both transition-metal catalysis[6] and metal-free[7] reactions have been developed for this process. The requisite *N,N′*-diarylamidines for C–H amination are generally prepared by the reaction of 2 equiv of an aniline with orthoesters (path c, Scheme 1) or by the reaction of *N*-aryl(thio)amides with anilines (path d, Scheme 1). The former provides only symmetrical *N,N′*-diarylamidines, while the latter requires the use of (thio)phosgene, oxalyl chloride, PCl_5, PCl_3, or $SOCl_2$ (for amides) and $HgBr_2$ or HgO (for thioamides), which are highly toxic and corrosive.[8] Transition-metal-catalyzed domino processes for the in situ formation of *N,N′*-diarylamidines from *N*-arylamidines (path e, Scheme 1)[9] or *N,N′*-diarylcarbodiimides (path f, Scheme 1)[10] and subsequent cyclization have also been developed for the synthesis of *N*-arylbenzimidazoles.

Although progress has been made for the formation of *N*-arylbenzimidazoles, which remains more challenging than *N*-unsubstituted benzimidazoles, most of the known methods have several conspicuous drawbacks, such as requirement of not readily accessible starting materials, multistep procedures, narrow substrate scope, use of costly and/or toxic transition metals and reagents, and harsh reaction conditions, leading to cost and environmental concerns and limiting their practical utility. Hence, the development of new synthetic methods with improved efficiency and generality for the construction of the *N*-arylbenzimidazole skeleton is highly desirable.

Because of their easy preparation and wide availability from inexpensive and readily available anilines, arenediazonium salts have been used as useful and versatile precursors in a variety of organic transformations.[11] The intrinsic electrophilicity of dizonium salts offers a pathway for the introduction of various functional groups into an aromatic ring. In general, their reactions with anilines lead to the formation of triazenes and azo compounds through the addition of anilines over the diazonium moiety (Scheme 2, top).[12] In biaryl synthesis via an aryl–aryl coupling between diazonium salts and anilines, therefore, protection strategies have been developed to utilize

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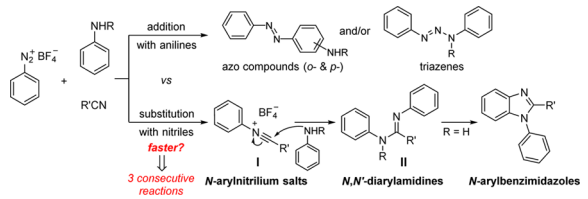
Scheme 2. Addition vs Substitution Reactions of Arenediazonium Salts



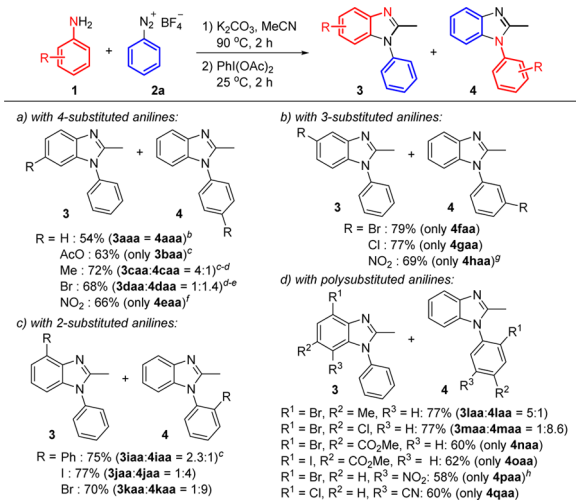
free anilines as a reactant.[13] On the other hand, substitution reaction of arenediazonium salts with nitriles is also well-known to occur along with the loss of N_2 and to afford *N*-arylnitrilium salts (**I**), which can further undergo the subsequent reaction with other nucleophiles under metal-free conditions (Scheme 2, bottom),[14] while acetonitrile (MeCN) has been used as a favorable solvent in a variety of reactions of arenediazonium salts.[11] Therefore, we were interested in the reactivity of arenediazonium salts in the presence of both nitriles and anilines, which are both good nucleophiles for arenediazonium salts. Since N_2 is readily replaced by nucleophilic solvents, such as MeCN, which exist in large quantities as reaction media, we envisaged that arenediazonium salts could be attacked preferentially by nitriles over anilines to afford *N*-arylnitrilium salts (**I**), followed by the addition of anilines as a second nucleophile, leading to *N*,*N*′-diarylamidines (**II**), which can be further transformed to *N*-arylbenzimidazoles. The realization of this proposal would make significant advances, overcoming the aforementioned deficiencies of the precedents for the synthesis of *N*-arylbenzimidazoles as well as *N*,*N*′-diarylamidines: use of simple, cheap, amenable, and easily accessible reagents, easy assembly of unsymmetrical *N*,*N*′-diarylamidines from two different aniline precursors via one-pot reaction, and a good chance of using metal-free conditions.

Herein, we report a highly effective one-pot reaction to construct a wide range of diversely substituted *N*-arylbenzimidazoles (path g, Schemes 1 and 2, bottom). This new protocol involves the chemoselective in situ formation of *N*,*N*′-diarylamidines from arenediazonium salts, nitriles, and free anilines.

We began our studies on the proposed reaction using *N*-methyl-*p*-toluidine and phenyldiazonium salt (**2a**) as the test substrates in MeCN and first examined the viability of three-component reaction to form amidines (for details, see the Supporting Information). Much to our delight, a simple mixture of these three reagents gave the desired amidine product in 58−66% yields regardless of the presence of K_2CO_3. These findings suggest that, compared to anilines, nitriles are indeed more favorable to attack arenediazonium salts, leading to *N*-arylnitrilium salts (**I**) rather than triazenes and/or azo compounds. $K_2CO_3$and MeCN were identified as the most effective base and solvent to give the desired amidine products; other bases and solvents led to no formation of amidines and/or lower efficiency. Gratifyingly, primary anilines such as *p*-toluidine and aniline also proved to be suitable substrates in this reaction. With the success of amidine formation, metal-free oxidative C−H amination of *N*,*N*′-diarylamidines (**II**, R = H) derived from primary anilines was next investigated under the previously reported conditions.[7] Reliable and reproducible outcomes could be obtained under the slightly modified conditions, using 1 equiv of $PhI(OAc)_2$ in MeCN at 25 °C. With the established optimal conditions for a stepwise process, we proceeded with the investigation of the one-pot domino reaction. Upon completion of the three-component amidine-forming reaction, $PhI(OAc)_2$ was introduced, triggering the subsequent oxidative cyclization to afford *N*-arylbenzimidazoles. In contrast to the stepwise reaction, the presence of K_2CO_3 in step 1 was beneficial to the formation of *N*-arylbenzimidazoles in step 2 of the one-pot process; thus, we speculate that the in situ generated acid (i.e., HBF_4) might have a deleterious effect on the subsequent C−H amination. Finally, the use of 2 equiv of $PhI(OAc)_2$ was required to give the optimal results. As shown in Scheme S1, a one-pot reaction was preferable to the stepwise reaction with regard to product yield and efficiency, avoiding the tedious and time-consuming step-by-step isolations and purifications of intermediates and reducing the amount of waste.

With the establishment of a viable one-pot reaction system, we set out to explore the scope of this domino process. First, we examined the reaction of various free anilines (**1**) with phenyldiazonium salt (**2a**) in MeCN (Scheme 3). A wide

Scheme 3. Substrate Scope: Anilines[a]



[a]Standard reaction conditions: (1) **1** (1 equiv), **2a** (1 equiv), and K_2CO_3 (1 equiv) in MeCN (0.1 M) at 90 °C for 2 h; (2) $PhI(OAc)_2$ (2 equiv) at 25 °C for 2 h. Combined isolated yields of two separable regioisomers (**3** and **4**) are provided. [b]For 18 h in step 2. [c]For 6 h in step 2. [d]**3** and **4** are inseparable, and ratios of **3** and **4** were determined by ^{1}H NMR. [e]For 8 h in step 2. [f]For 42 h in step 2. [g]At 40 °C for 15 h in step 2. [h]At 80 °C in step 2.

range of anilines underwent domino three-component amidine formation/oxidative cyclization smoothly to afford the corresponding *N*-arylbenzimidazoles (**3** and **4**) in good yields irrespective of their electronic properties and the position of their substituents. However, anisidine derivatives led to complicated mixtures along with significant decomposition in step 1. Consistent with the related hypervalent iodine(III)-mediated oxidative cyclization,[7] two regioisomers could be formed from the in situ generated unsymmetrical *N*,*N*′-diarylamidines: Oxidative cyclization reaction took place preferentially on the electron-rich benzene ring over electron-deficient counterparts through an electrophilic pathway. Noteworthy is the fact that this process can tolerate various functional groups such as halogen, nitro, ester, and cyano groups. This functional group tolerance could be advantageous compared to other transition-metal-catalyzed syntheses of *N*-arylbenzimidazoles[5,6,9,10] and makes this method particularly appealing, since it should permit further elaboration and enable greater structural diversity (vide infra).

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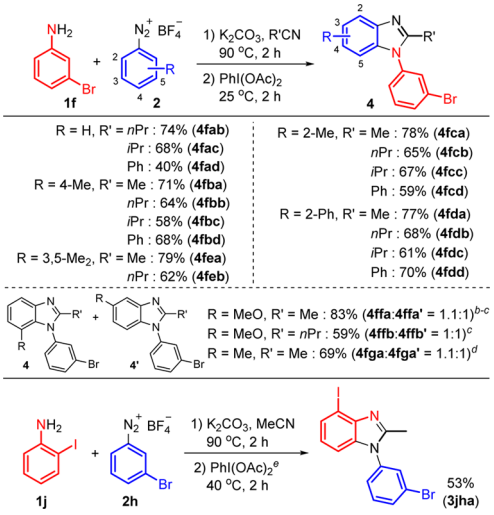
Next, we proceeded to investigate the scope of arenediazonium salts (**2**) for this reaction (Scheme 4). Electron-neutral and

Scheme 4. Substrate Scope: Arenediazonium Salts and Nitriles[a]



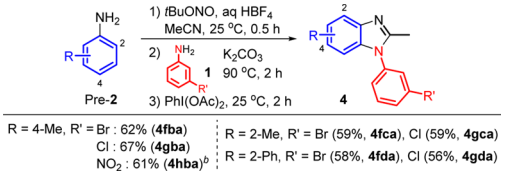
[a]Standard reaction conditions as described in Scheme 3. Isolated yields are provided. [b]For 13 h in step 2. [c]Separable isomers. [d]For 9 h in step 2. Inseparable isomers. [e]Using 3 equiv $PhI(OAc)_2$.

moderately electron-rich aryl groups were well tolerated regardless of the position of their substituents. Arenediazonium salts with a strongly electron-donating substituent, such as MeO, at the *ortho* or *para* positions led to decomposition or low conversion, respectively, while the reactions with a *meta*-substituted salt uneventfully proceeded to give the corresponding *N*-arylbenzimidazoles (**4ffa,b** and **4ffa,b′**) in good yields. In contrast, strongly electron-withdrawing substituents, such as NO_2, resulted in the formation of only azo compounds in step 1. These results suggest the S_N1 pathway seems more likely than S_NAr among ionic mechanisms involved in fragmentation of diazonium salts.[11] Oxidative cyclization of the *meta*-substituted substrates resulted in an almost 1:1 mixture of two regioisomers (**4ffa,b** and **4fga** vs **4ffa,b′** and **4fga′**). Particularly noteworthy is the fact that excellent regioselectivity was observed for the substrates bearing iodo- and bromo-substituted two-benzene rings with the cyclization taking place only on the iodo-substituted benzene ring (**3jha**) as well as with both halogens remaining intact.

Last, we explored the scope of nitriles. Primary and secondary alkyl and aryl nitriles proved to be suitable substrates for the formation of the corresponding 2-alkyl- and 2-arylbenzimidazoles. However, the reaction with bulky *tert*-alkyl nitriles such as *t*BuCN failed to afford the desired *N*-arylbenzimidazole products even at the higher reaction temperature for a longer reaction time in step 2 (at 90 °C for 24 h), leading to only the corresponding *N,N′*-diarylamidine intermediate along with significant decomposition in step 2.

Since diazonium salts are generally not commercially available, the requirement of their preparation may limit the synthetic utility of this process. Therefore, their in situ preparation from readily available anilines through diazotization followed by amidine formation with another anilines and subsequent oxidative cyclization would significantly improve the practicality and efficiency of this one-pot protocol, obviating the isolation of arenediazonium salts and leading to a direct and probably regioselective assembly of *N*-arylbenzimidazoles from two different anilines. Indeed, as shown in Scheme 5, a variety of

Scheme 5. One-Pot, Three-Step Synthesis of *N*-Arylbenzimidazoles[a]

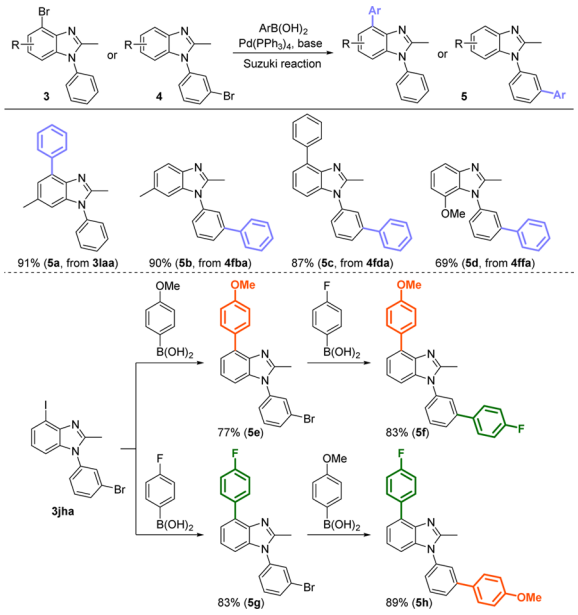


[a]Reaction conditions: (1) Pre-**2** (1 equiv), *t*BuONO (1 equiv), and aq HBF_4 (1 equiv) in MeCN (0.1 M) at 25 °C for 0.5 h; (2) **1** (1 equiv) and K_2CO_3 (1 equiv) at 90 °C for 2 h; (3) $PhI(OAc)_2$ (2 equiv) at 25 °C for 2 h. Isolated yields are provided. [b]At 40 °C for 3 h in step 3.

N-arylbenzimidazoles **4** could be synthesized regioselectively via a one-pot, three-step reaction, albeit in somewhat lower yields than those in a one-pot, two-step reaction. Again, high functional group tolerance was observed in this one-pot reaction.

To highlight the synthetic utility of this one-pot reaction, further elaboration of the halogenated *N*-arylbenzimidazoles obtained from this process has been undertaken. As illustrated in Scheme 6, Suzuki reaction of **3** and **4**, which have bromo and/or

Scheme 6. Synthetic Application[a]



[a]For details of the reaction conditions, see the Supporting Information.

iodo substituents at either the benzimidazole moiety or 1-aryl substituent, with arylboronic acids proceeded smoothly to give the highly conjugated, polysubstituted benzimidazoles in good to high yields. Particularly noteworthy is the regiocontrolled synthesis of both **5f** and **5h** from a common, dihalogenated substrate **3jha**.

In the three-component amidine formation, two reaction pathways, ionic or radical mechanisms, may be proposed.[11] To gain insight into this reaction, the amidine-forming reaction was performed in the presence of a radical scavenger, such as

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TEMPO or 1,1-diphenylethylene (for details, see the SI). Their inclusion had a deleterious effect on the amidine formation, and an arylated 1,1-diphenylethylene was obtained as a byproduct, whereas the corresponding TEMPO adduct was not observed. These results may suggest a mechanism involving a radical intermediate during the reaction. However, an alternative S_N1-type ionic pathway cannot be completely excluded.[11,14]

In summary, we developed a highly efficient and facile one-pot reaction for the synthesis of diversely substituted *N*-arylbenzimidazoles through chemoselective in situ generation of *N*,*N*′-diarylamidines from arenediazonium salts, nitriles, and free anilines. The remarkable features of this protocol are the operationally easy and simple one-pot procedure under metal-free and mild conditions and the use of inexpensive, readily available, simple chemical feedstocks: nitriles and free anilines. The three-component reaction presented herein represents an attractive and potentially powerful route for a straightforward access to a diverse range of *N*,*N*′-diarylamidines and further functionalized *N*-arylbenzimidazoles, offering a new access to *N*-heterocycles from arenediazonium salts. Further investigations to construct other privileged heterocyclic scaffolds with this strategy are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02994.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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