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C–H cycloamination of *N*-aryl-2-aminopyridines and *N*-arylamidines catalyzed by an *in situ* generated hypervalent iodine(III) reagent†

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A metal-free synthesis of diversified pyrido[1,2-*a*]benzimidazoles and 1*H*-benzo[*d*]imidazoles from *N*-aryl-2-aminopyridines and *N*-arylamidines has been developed. The C–H cycloamination reaction was catalyzed by hypervalent iodine(III) species generated *in situ* from iodobenzene (catalytic) and peracetic acid (stoichiometric). The reaction proceeded smoothly at ambient temperature to provide the corresponding N-heterocycles in good to excellent yields.

Over the past decade, intramolecular C–N bond formation through direct C–H functionalization catalyzed by transition-metals such as Pd, Rh, Ru, and Cu complexes has emerged as a step-efficient and atom-economic alternative to traditional methods for the synthesis of N-heterocycles.[1] However, these transition-metal-catalyzed reactions generally suffer from high reaction temperature, narrow substrate scope, and the use of stoichiometric or even excess amounts of metal salts as oxidants.[2] In large scale synthesis, these metal-based methods are not only costly, but also problematic to remove heavy metal contaminants from products. As a result, they are less applicable to drug synthesis especially at a late stage, despite their virtue of step-efficiency and atom-economy. Therefore, the development of alternative metal-free (for both catalysts and oxidants) reactions that can be performed at ambient temperature starting from unprefunctionalized precursors is highly desirable.

Recently, significant achievements have been made in hypervalent iodine(III)-mediated C–H amination, amidation, and imidation reactions under mild metal-free conditions.[3] For instance, Chang *et al.* and DeBoef *et al.* reported elegant research on PIDA-mediated intermolecular C–H imidation of both aryl sp^2 and benzylic sp^3 C–H bonds.[4] Hypervalent iodine(III)-promoted intramolecular oxidative C–N formation was also realized, and thus provided an efficient approach to the construction of N-heterocycles.[5] However, these reactions are hard to scale up unless the hypervalent iodine reagents are used in catalytic amounts.[6] In this context, studies on *in situ* generated hypervalent iodine(III)-catalyzed C–C,[7] C–O,[8] and C–N[9] bond-forming reactions grow rapidly. For example, Antonchick *et al.* reported an efficient intramolecular C(sp^2)–H amidation reaction using biaryliodide as a precatalyst in the presence of peracetic acid as a stoichiometric oxidant at room temperature.[10] Herein, we report an *in situ* generated hypervalent iodine(III)-catalyzed intramolecular C(sp^2)–H amination of *N*-aryl-2-aminopyridines and *N*-arylamidines, providing efficient approaches to construction of diversified pyrido[1,2-*a*]-benzimidazoles and 1*H*-benzo[*d*]imidazoles, respectively.

The pyrido[1,2-*a*]benzimidazole scaffold exists in a wide range of biologically active compounds.[11] Consequently, substantial synthetic methods have been developed for the preparation of this class of molecules. Conventional methods often suffer from lengthy synthetic routes, formation of regioisomers, limited substrate scope, and/or unsatisfactory yields.[12] We and the group of Maes independently reported a novel synthesis of pyrido[1,2-*a*]benzimidazoles through direct intramolecular C–H amination of *N*-aryl-2-aminopyridines catalyzed by copper(II) in the presence of iron(III) and protic acid, respectively.[13,14] However, both of the approaches require high reaction temperature (above 120 °C), and the substrate scope is limited in terms of substituents on the pyridine moiety. Inspired by recent advances in hypervalent iodine(III)-catalyzed C–N formation,[9] we envisioned that this metal-free strategy can be applied to the synthesis of pyrido[1,2-*a*]benzimidazoles starting from the same *N*-aryl-2-aminopyridines which are readily available by coupling anilines with 2-bromopyridines.[15]

The reaction conditions were optimized with *N*-phenyl-2-aminopyridine **1a** as a substrate in the presence of Bu_4NI (10 mol%) and TBHP (1.05 equiv.) in CH_3CN at room temperature (entry 1, Table 1). Unfortunately, no annulation product was detected. There was no desired product formation either when the oxidants were changed to H_2O_2 (30 vol% in water) in CH_3CN or HFIP (entries 2 and 3). Gratifyingly, a combination of PhI (10 mol%) as an iodide source and *m*-CPBA (1.05 equiv.) as an oxidant in HFIP led to the

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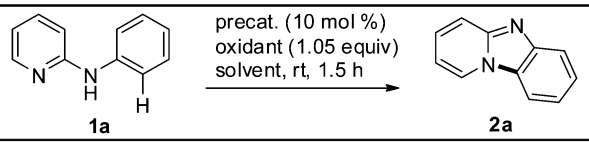
Table 1 Optimization of the reaction conditions[a]



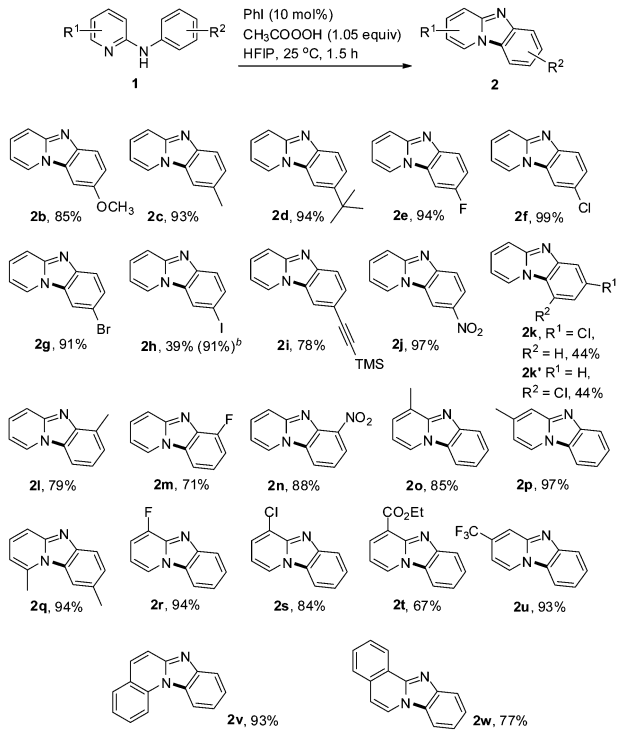
1a **2a**

Entry	Precat.	Oxidant	Solvent	Yield[b] (%)
1	Bu_4NI	TBHP[c]	CH_3CN	n.r.
2	Bu_4NI	H_2O_2[d]	CH_3CN	n.r.
3	Bu_4NI	TBHP[c]	HFIP	n.r.
4	PhI	H_2O_2[d]	HFIP	n.r.
5	PhI	TBHP[c]	HFIP	n.r.
6	PhI	*m*-CPBA	HFIP	66
7	**PhI**	CH_3CO_3H[e]	**HFIP**	**91**

[a] Reaction conditions: **1a** (0.2 mmol), precatalyst (10 mol%), oxidant (0.21 mmol, 1.05 equiv.) in solvent (2 mL) at 25 °C for 1.5 h; TBHP = *tert*-butyl hydroperoxide, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, *m*-CPBA = *m*-chloroperbenzoic acid, n.r. = no reaction. [b] Isolated yields of **2a**. [c] 70 vol% in water. [d] 30 vol% in water. [e] 43 wt% in HOAc.

formation of pyrido[1,2-*a*]benzimidazole **2a** in 66% yield (entry 6). Switching the oxidant to peracetic acid improved the yield of **2a** significantly to 91%. It was notable that the high-yield formation of **2a** was realized at ambient temperature in only 1.5 h in the absence of any metal catalysts or oxidants. Although **2a** could be obtained from **1a** in a comparable yield of 88% by following our previous method,[13] high loading of the copper catalyst (50 mol% of $Cu(OAc)_2$ together with 10 mol% of $Fe(NO_3)_3{\cdot}9H_2O$) under much harsher conditions (5 equivalents of PivOH, 130 °C, 28 h) was required.

Table 2 Synthesis of derivatives of pyrido[1,2-*a*]benzimidazoles[a]



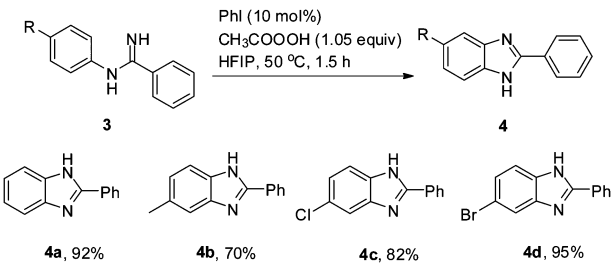
[a] Reaction conditions: **1** (0.2 mmol), PhI (3 μL, 10 mol%), CH_3CO_3H (34 μL, 1.05 equiv.) in HFIP at 25 °C, isolated yields of **2**. [b] Dropwise addition of a solution of peracetic acid (34 μL) in HFIP (1.0 mL) for 5 min to a HFIP (1.0 mL) solution of *N*-(4-iodophenyl)-2-aminopyridine at 25 °C.

With the optimal reaction conditions in hand, we next examined the substrate scope for the synthesis of pyrido[1,2-*a*]-benzimidazoles. As illustrated in Table 2, reactions of *N*-aryl-2-aminopyridines bearing electron-donating (OMe, Me, *t*-Bu) or electron-withdrawing (F, Cl, Br, NO_2) groups at the *para* position of the aniline moiety proceeded efficiently with good to excellent yields (85–99%). However, when the same functional groups (Me, F, NO_2) were in the *ortho* position, the yields were 9–23% lower than their *para*-substituted counterparts (**2l**–**2n**), presumably due to the increased steric bulkiness. The substrate with an iodo group was less compatible with the current protocol, affording **2h** in only 39% yield. To our delight, when the reaction procedure was slightly modified by slow addition of a solution of peracetic acid (34 μL) in HFIP (1.0 mL) for 5 minutes to a HFIP (1.0 mL) solution of *N*-(4-iodophenyl)-2-aminopyridine, the yield of **2h** was improved significantly to 91%. It was notable that acetylene functionality also survived the oxidative conditions (**2i**). Unfortunately, a mixture of 1 : 1 regioisomers **2k** and **2k′** was obtained for *meta*-substituted substrates. The scope of substituents on the pyridine ring was then investigated. Substrates with Me, F, Cl, CO_2Et, or CF_3 on the pyridine moiety reacted smoothly to furnish the corresponding products (**2o**–**2u**) in good yields (67–97%). In addition, quinoline and isoquinoline derived substrates were also compatible with the reaction conditions (**2v**–**2w**).

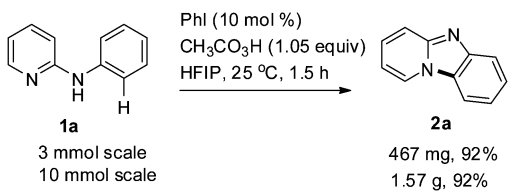
N-Phenylbenzamidine derivatives **3** were also applicable to the oxidative cycloamination process (Table 3).[9d] Both electron-rich and electron-poor *N*-phenylbenzamidines afforded the corresponding 2-phenyl-1*H*-benzo[*d*]imidazoles **4a**–**4d** in good yields at slightly elevated temperature (50 °C). This catalytic method provides a complementary approach to the synthesis of benzo[*d*]imidazoles, a class of N-heterocycles with broad bioactivities.[16]

The scalability of the method was verified by running the reaction of **1a** on both 3 and 10 mmol scales (Scheme 1).

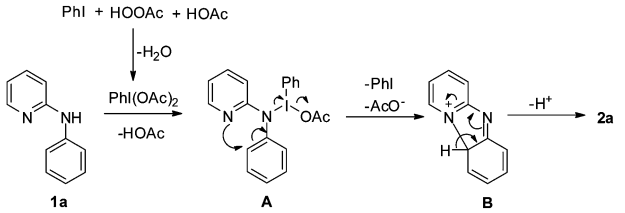
Table 3 Synthesis of 2-phenyl-1*H*-benzo[*d*]imidazoles[a]



[a] Reaction conditions: **3** (0.2 mmol), PhI (10 mol%), CH_3CO_3H (1.05 equiv.) in HFIP at 50 °C, 1.5 h, isolated yields of **4**.



Scheme 1 Large scale synthesis of **2a**.



Scheme 2 Proposed reaction mechanism.

Pyrido[1,2-*a*]benzimidazole **2a** was isolated in identical high yields in both of the cases.

Based on literature reports,[9,10] a plausible reaction pathway was proposed as in Scheme 2. Initially, iodobenzene is oxidized by peracetic acid, forming phenyliodine diacetate (PIDA) in the presence of acetic acid. Then, nucleophilic substitution of the aniline nitrogen on the iodine(III) center in PIDA forms intermediate A which contains an electrophilic *N*-iodo moiety. Subsequent nucleophilic attack of the pyridine nitrogen on the aniline ring gives the intermediate B with concurrent release of PhI and AcO–. Finally, deprotonic rearomatization furnishes the desired product **2a**, generating acetic acid and water as only by-products during the whole process. The released PhI enters the catalytic cycle again upon reoxidation by peracetic acid acting as a stoichiometric oxidant.

In summary, we have developed a metal-free synthesis of pyrido[1,2-*a*]benzimidazoles and benzo[*d*]imidazoles with high step-efficiency and atom-economy. The reaction is catalyzed by hypervalent iodine(III) species generated *in situ* from catalytic amounts of PhI and peracetic acid which is used as a stoichiometric oxidant. The cycloamination reaction proceeded smoothly at relatively low temperature within short reaction time (1.5 h). A variety of functional groups are compatible with the reaction conditions, providing the corresponding diversified N-heterocycles in good to excellent yields. The pyrido[1,2-*a*]benzimidazole derivatives with electron-withdrawing groups on the pyridine moiety are inaccessible by similar Cu-catalyzed C–H cycloamination approaches.[13,14] The features of scalability and free of metals make this approach potentially valuable in drug synthesis.

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