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# A Metal-Free Tandem Demethylenation/ C(sp$^2$)−H Cycloamination Process of *N*-Benzyl-2-aminopyridines via C−C and C−N Bond Cleavage

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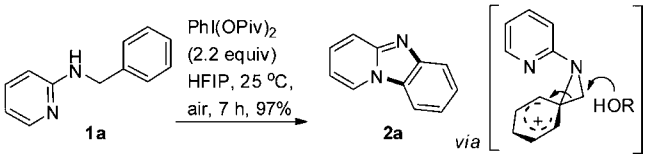
## ABSTRACT




**A mild, metal-free synthesis of pyrido[1,2-*a*]benzimidazoles starting with *N*-benzyl-2-aminopyridines, which employs PhI(OPiv)$_2$ as a stoichiometric oxidant, has been developed. The process is initiated by an unusual PhI(OPiv)$_2$-mediated *ipso* $S_EAr$ reaction, followed by solvent-assisted C−C and C−N bond cleavage.**

Tandem reactions, in which multiple chemical bonds are formed in one-pot processes, are highly useful for creating molecular complexity.[1] Transition-metal-triggered tandem processes are typically initiated by oxidative addition of a carbon−(pseudo)halogen bond to a transition metal species in its lower oxidation state followed by diverse transformations of the resulting reactive intermediates.[2] Alternatively, similar types of reactive intermediates can be generated by employing transition-metal-catalyzed C−C and/or C−O bond cleavage reactions of carbonyl containing starting materials, which frequently are more readily available than the corresponding organohalides. Representatives of this approach are decarboxylative and decarbonylative tandem reactions, in which $CO_2$ and CO are respectively excised from substrates in initial steps via C−C and C−X (X = O, H, C) bond cleavage (eqs 1 and 2).[3,4] However, a tandem reaction of a non-carbonyl substrate, driven by an analogous demethylenation process involving consecutive C−C and C−N bond cleavage, is unprecedented (eq 3).[5] In a recent study, described below, we developed a new hypervalent iodine(III)-promoted tandem reaction of *N*-benzyl-2-aminopyridines, which is initiated by oxidative demethylenation followed by intramolecular aromatic C−H amination. This process occurs under mild and transition-metal-free conditions to form pyrido[1,2-*a*]benzimidazoles in high yields.

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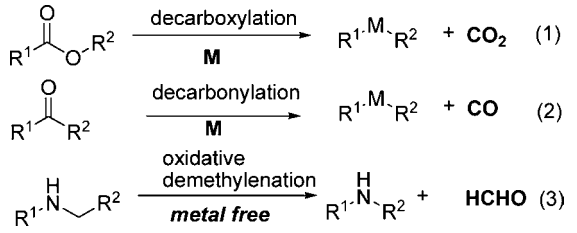
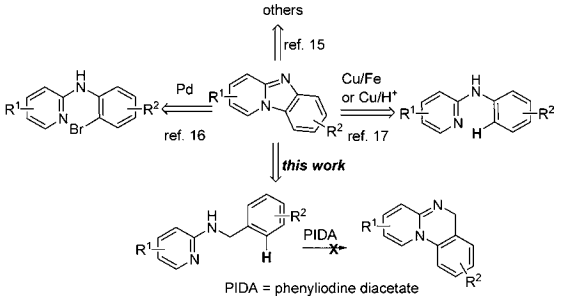



Compared with those containing transition metals, hypervalent iodine(III) reagents in many cases serve as complementary and even superior promoters of C−C[6] and C−heteroatom[7] bond forming reactions. For instance, Antonchick[8a] and Chang[8b] et al. independently developed rt hypervalent iodine(III)-mediated intramolecular C−H amidation reactions for the efficient synthesis of carbazoles. In addition, it has been shown that hypervalent iodine reagents are powerful oxidants in C−C bond cleavage of O-containing substances, such as glycols,[9] epoxides,[10] and olefins.[11] Despite these successes, hypervalent iodine(III) reagent promoted demethylenation reactions, involving C−C and C−N bond cleavage followed by intramolecular C−N bond formation, remain undocumented.

**Scheme 1.** Formation of Pyrido[1,2-*a*]benzimidazoles




Owing to their remarkable biological activities, including antibacterial,[12] antitumor,[13] and antiviral,[14] many methods[15−17] have been developed for the preparation of multisubstituted pyrido[1,2-*a*]benzimidazoles. Among the approaches devised, Pd-catalyzed intramolecular C−N coupling reactions of *N*-*ortho*-bromophenyl-2-aminopyridines in refluxing DMF are the premier methods used to construct this scaffold (Scheme 1).[16] Independently, we[17a] and Maes et al.[17b] also developed improved methods through intramolecular C−H amination. However, both of these processes need to be performed at temperatures over 120 °C and their substrate scope is limited in that substrates bearing electron-withdrawing substituents on the pyridine ring are far less reactive.

In continuing studies, we envisaged that hypervalent iodine(III)-promoted intramolecular C−H amination reactions[18] could be employed to prepare 6*H*-pyrido[1,2-*a*]-quinazolines starting with readily accessible *N*-benzyl-2-aminopyridines.[19] In fact, utilizing *N*-benzyl-2-aminopyridine **1a** as the substrate in the presence of 2.2 equiv of phenyliodine diacetate (PIDA) in HFIP at rt, this reaction leads to the formation of pyrido[1,2-*a*]benzimidazole **2a** in 85% yield. To further improve the yield of **2a**, the reaction conditions were optimized by screening additives, solvents, and other hypervalent iodines (see Supporting Information (SI) for details). The optimized conditions involving the use of 2.2 equiv of $PhI(OPiv)_2$ in HFIP at rt in air were identified (Scheme 2).

Substrates containing a variety of *para*-substituents, regardless of their electron-donating (Me and OMe) or electron-withdrawing (F, Cl, Br, and I) properties, undergo efficient (84%−96%) reactions that generate the

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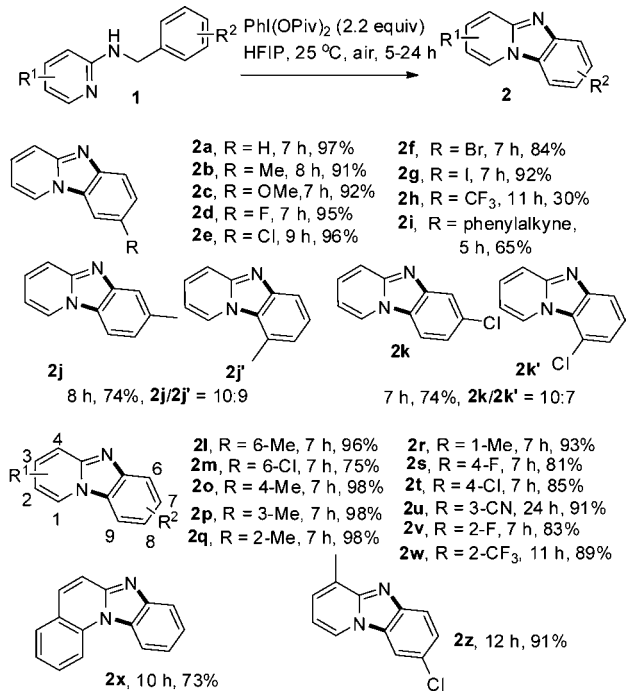
**Scheme 2.** Substrate Scope[a]

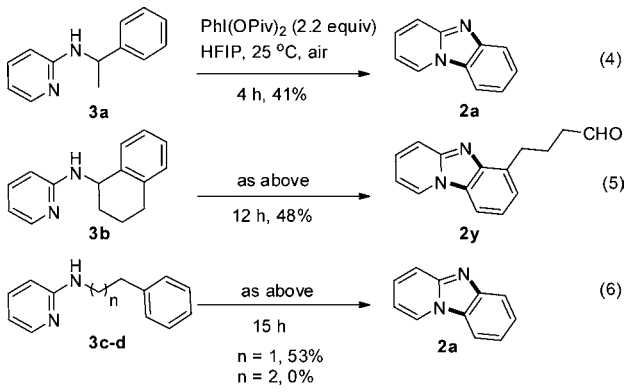



[a] Reaction conditions: **1** (0.2 mmol), HFIP (1.5 mL) at rt (25 °C) in air for 5−24 h; isolated yields.

corresponding products (**2b**−**2g**). However, the presence of the strong electron-withdrawing $CF_3$ group causes a significant reduction in the reaction yield (**2h**, 30%). Additional observations show that an alkynyl group survives the reaction conditions (**2i,** 65%). Then we observed that reactions of substrates containing *meta*-Me and -Cl substituents take place with no regioselectivity (**2j** and **2j′**, and **2k** and **2k′** are produced in near 1:1 ratios). Substituents located at *ortho*-benzyl positions do not hamper the demethylenation/annulation process (e.g., 96% for **2l** and 75% for **2m**). Substrates with methyl groups at each of the pyridine ring centers react to give the corresponding methyl-substituted pyrido[1,2-*a*]benzimidazoles (**2o**−**2r**) in excellent yields. It is noteworthy that, in Cu-mediated C−H cycloamination reactions of *N*-*p*-toluyl-6-methyl-2-aminopyridine, harsh reaction conditions (1.0 equiv of $Cu(OAc)_2$, 5.0 equiv of PivOH, 130 °C, 46 h) were required and the reaction yield was quite low (24%).[17a] In addition, substrates with electron-withdrawing groups (e.g., F, Cl, CN, and $CF_3$) on the pyridine ring undergo smooth (81−91%) demethylenative annulation to generate the corresponding products **2s**−**2w**. This is an advantageous feature of the new methodology because these types of electron-deficient pyrido[1,2-*a*]benzimidazoles cannot be prepared in acceptable yields by using Cu-mediated C−H cycloamination.[17] It is worth mentioning again that these reactions are performed at ambient temperature in good to excellent yields under metal- and additive-free conditions.

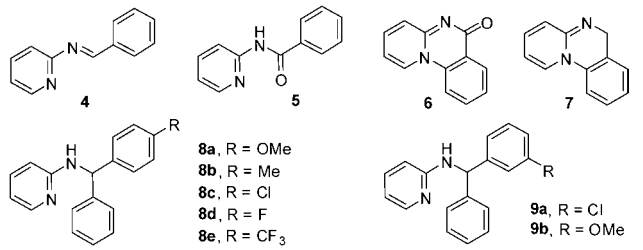
To gain information on how the methylene group is lost, the crude mixture arising from the reaction of **1a** was analyzed by using MS. An intense peak at 349 (*m*/*z*) was seen in the mass spectrum, corresponding to the protonated form of the bis((1,1,1,3,3,3-hexafluoropropan-2-yl)-oxy)methane acetal of formaldehyde. Moreover, mass spectrometric analysis of the crude product mixture arising from the reaction of substrate **3a** (41%, eq 4, Scheme 3) demonstrates that HFIP acetal of acetaldehyde is also produced (see SI). For the purpose of demonstrating the excision of the methylene group in this reaction in the form of an aldehyde, the bicyclic substrate **3b** was subjected to the reaction conditions. This process leads to the formation of **2y**, which contains a linked formyl group (eq 5). Additional information about the nature of the oxidative demethylenation reaction comes from the finding that substrate **3c**, possessing an extra $CH_2$ group between the amine nitrogen and benzylic carbon, also reacts to produce **2a**, while **3d** containing a longer linker does not undergo this reaction (eq 6).

**Scheme 3.** Substrate Extension




In further studies aimed at exploring the mechanism of the tandem process, a crossover reaction was tested using the mixture of **1a** and **1z** (see SI). The absence of crossover products shows that demethylenation and the following C−N bond formation step take place intramolecularly. We also prepared imine **4** and amide **5**, two possible oxidized intermediates in the reaction pathway. However, imine **4** decomposed and amide **5** remained unreacted when the respective substances were exposed to the reaction conditions. Two potential intermediates, diazaphenanthridone **6** and diazaphenthridine **7**, in which the C−N bond between the pyridine nitrogen and the *ortho* phenyl carbon in substrate **1a** were formed before demethylenation, were also synthesized. Surprisingly, neither **6** nor **7** reacts under the optimized conditions to produce **2a**, suggesting that the C−N bond between the amino nitrogen and the *ipso* aromatic carbon is likely formed first.

To gain more insight into the mechanism, intramolecular competition reactions were explored using benzhydryl substrates **8**, bearing both a phenyl and an electronically biased aryl ring at the benzylic carbon (see SI). Reactions at the electron-donating *p*-anisyl (in **8a**) and *p*-tolyl (in **8b**) groups were observed to occur 5−20 times faster than




those at the unsubstituted phenyl ring. In sharp contrast, the *para*-$CF_3$-phenyl in **8e** was 20 times less reactive that the electron-neutral phenyl. Finally, the results of competition reactions showed that the *p*-chloro- (in **8c**) and *p*-fluoro-phenyl (in **8d**) moieties are only ~10−20% less reactive than their neutral counterpart, a result that is in accord with the competing electron-donating conjugative and electron-withdrawing inductive effects of the halogens. Finally, a $\rho$-value of −3.39 was obtained from a Hammett plot, indicating that a positive charge develops on the arene ring in a rate-limiting mechanistic step (see SI). Further support for this proposal comes from intramolecular competition reactions of the *meta*-Cl and -OMe benzhydryl substrates **9a** and **9b**, respectively (see SI). Compared to that of **8c**, reaction at the nonsubstituted phenyl moiety in **9a** takes place ~9 times faster than at the *meta*-Cl-phenyl ring. It is interesting that when the OMe is moved from the *para*-position in **8a** to the *meta*-position in **9b**, the reactivity of the OMe-containing phenyl ring changes from being 20 times more favorable to 2 times less favorable compared to the nonsubstituted phenyl ring. Both the *meta*-OMe and -Cl groups are inductively electron-withdrawing and, as a result, destabilize the cationic intermediate in the mechanistic pathway (see SI).

Based on the results of these studies, the plausible mechanistic pathway, shown in Scheme 4 using **1a** as an example, is proposed for the oxidative, tandem demethylation C−H cycloamination reaction. In the route, initial coordination of $PhI(OPiv)_2$ with **1a** gives the electrophilic *N*-iodo species **A**, which following *ipso* $S_EAr$ on the phenyl ring generates the delocalized carbocation **B** (Wheland intermediate).[20] HFIP then participates in nucleophilic addition to the benzylic carbon in **B** causing C−C bond cleavage to give intermediate **C**, which reacts with another

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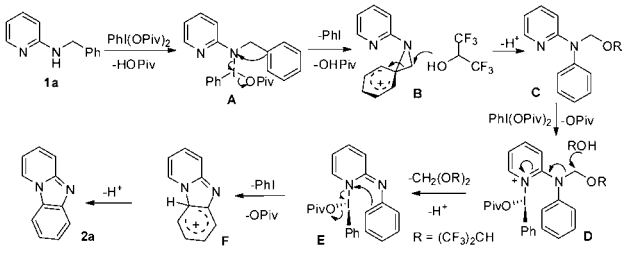
**Scheme 4.** Proposed Reaction Mechanism




equivalent of $PhI(OPiv)_2$ to form the active complex **D**. Unfortunately, the attempt to synthesize intermediate **C** failed. C−N bond cleavage in **D** occurs upon another nucleophilic substitution by HFIP, releasing the methylene group in the form of an acetal. Subsequent electrophilic annulation on the pyridine nitrogen, activated by the electrophilic iodo species, generates intermediate **F** which upon deprotonation forms **2a**.

In conclusion, the results described above led to an unexpected, yet highly efficient method for the synthesis of pyrido[1,2-*a*]benzimidazoles starting from readily available *N*-benzyl-2-aminopyridines at ambient temperature in the absence of metal catalysts and additives. Mechanistic studies reveal that the reaction is initiated by an unusual $PhI(OPiv)_2$-mediated *ipso* $S_EAr$ process followed by solvent-assisted C−C bond cleavage. Sequential annulation is promoted by a second equivalent of $PhI(OPiv)_2$. Finally, the methylene group is oxidatively cleaved and leaves in the form of an acetal. The new method serves not only as an efficient approach to pyrido[1,2-*a*]benzimidazoles but also as a rare example of a hypervalent iodine(III) reagent-mediated tandem C−C bond activation and C−N bond formation process.

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**Supporting Information Available.** Experimental procedure, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.