C–H Amination

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Metal-Free Annulation of Arenes with 2-Aminopyridine Derivatives: The Methyl Group as a Traceless Non-Chelating Directing Group**

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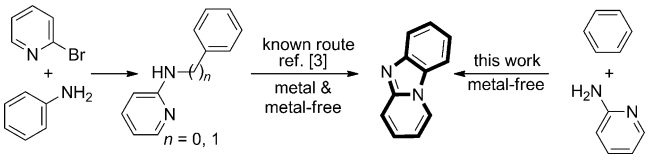
Abstract: *A novel annulation reaction between 2-aminopyridine derivatives and arenes under metal-free conditions is described. The presented intermolecular transformation provided straightforward access to the important pyrido[1,2-a]benzimidazole scaffold under mild reaction conditions. The unprecedented application of the methyl group of methylbenzenes as a traceless, non-chelating, and highly regioselective directing group is reported.*

Benzimidazoles are prevalent in many natural products and pharmaceuticals.[1] For example, rifaximin is a semisynthetic antibiotic obtained from the secondary metabolite rifamycin. The introduction of 4-methylpyridine-2-amine to the aromatic part of the natural product to form the pyrido[1,2-*a*]benzimidazole derivative led to improved pharmacological properties for clinical application.[2] Owing to their interesting biological properties, pyrido[1,2-*a*]benzimidazoles are of synthetic importance.[3,4] Reported synthesis routes to pyrido-[1,2-*a*]benzimidazoles rely on multistep protocols and often require harsh reaction conditions.[3,4] The most common route to pyrido[1,2-*a*]benzimidazoles is an intramolecular cyclization of *N*-aryl-2-aminopyridines (Scheme 1). The efficacy of



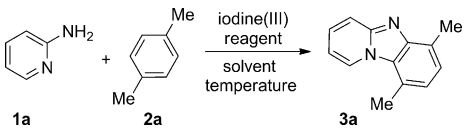
Scheme 1. Synthesis routes to pyrido[1,2-*a*]benzimidazole compounds.

intramolecular cyclization was initially investigated in the presence of transition-metal catalysts.[3d] Very recently an organocatalytic cyclization by in situ generated hypervalent iodine reagent was also elegantly demonstrated.[3a] However, the required *N*-aryl-2-aminopyridines were synthesized by Buchwald–Hartwig coupling of 2-halopyridines with anilines using an expensive transition-metal complex and ligands (Scheme 1).[3] In this context, the discovery of a direct intermolecular annulation of 2-aminopyridine and non-prefunctionalized arene would be a significant advance (Scheme 1). Moreover, a mild and efficient method under metal-free conditions with a substrate scope beyond 2-aminopyridines would be in great demand. Herein we report a metal-free, selective annulation of 2-aminoazarenes and arenes for the synthesis of the pyrido[1,2-*a*]benzimidazole scaffold. Furthermore, a novel application of the methyl group of methylbenzenes as a traceless directing group in a highly regioselective synthesis is reported.

Among the C–N bond-forming reactions, direct C–H amination is an atom-economical and highly demanding transformation in organic synthesis.[5] Recently, environmentally benign hypervalent iodine reagents[6] proved to be exceptional in driving C–H amination under mild conditions.[7] Our group was actively involved in developing metal-free direct C–H amination reactions using hypervalent iodine compounds in selective syntheses.[8] We were curious to investigate the anticipated intermolecular annulation via C–H amination under metal-free conditions as well.

For the initial studies, we chose 2-aminopyridine (**1a**) and *para*-xylene (**2a**) as substrates to explore the anticipated annulation mediated by hypervalent iodine reagents (Table 1). Initially, when **1a** and **2a** were reacted with two

Table 1: Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Solvent	I^{III} reagent (equiv)	*T* [°C]	Yield [%][b]
1	HFIP	$PhI(OAc)_2$ (2)	reflux	19
2	HFIP	$PhI(OAc)_2$ (2)	RT	63
3	HFIP	$PhI(OAc)_2$ (2)	40	74
4	DCM	$PhI(OAc)_2$ (2)	40	n.d.
5	HFIP:DCM (1:1)	$PhI(OAc)_2$ (2)	40	31
6	CF_3CH_2OH	$PhI(OAc)_2$ (2)	40	n.d.
7	HFIP	$PhI(OCOCF_3)_2$ (2)	40	n.d.
8	HFIP	$PhI(OCOtBu)_2$ (2)	40	33
9	HFIP	$PhI(OAc)_2$ (2.5)	40	68
10	HFIP	$PhI(OAc)_2$ (3)	40	44
11[c]	HFIP	$PhI(OAc)_2$ (2)	40	55
12[d]	HFIP	$PhI(OAc)_2$ (2)	40	75

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), I^{III} reagent (equiv) in solvent (1.5 mL) at the given temperature for 12 h. [b] Yield refers to isolated products after column chromatography. [c] **2a** (0.4 mmol) used. [d] **2a** (2.0 mmol) used. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

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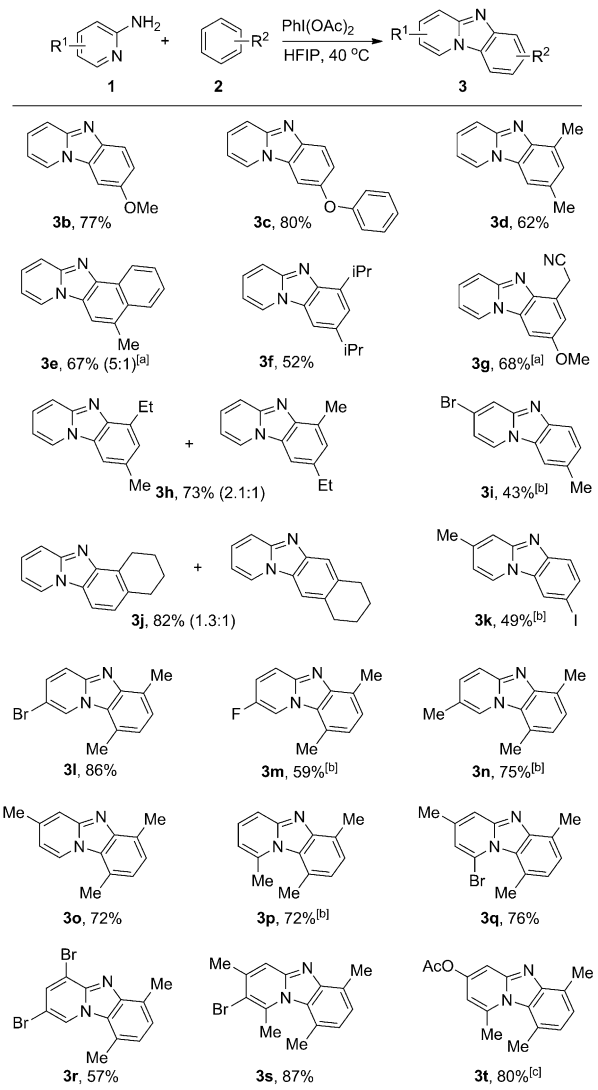
equivalents of $PhI(OAc)_2$ at reflux in HFIP, the desired pyrido[1,2-*a*]benzimidazole derivative (**3a**) was isolated in 19% yield (Table 1, entry 1). To our delight, the reaction was also very facile at room temperature giving **3a** in 63% yield (Table 1, entry 2). Changing the reaction temperature to 40°C was found to provide the product in 74% yield (Table 1, entry 3). Among the solvents screened for the reaction, only HFIP proved to be efficient (Table 1, entries 3–6). Our investigations focused afterwards on varying the iodine reagent. Highly reactive $PhI(OCOCF_3)_2$ did not provide the desired product, and less reactive $PhI(OCO{t}Bu)_2$ was inferior to $PhI(OAc)_2$ (Table 1, entries 7 and 8). Increasing the amount of $PhI(OAc)_2$ led to a decrease in yield (Table 1, entries 9 and 10). Finally, increasing the amount of arene did not prove beneficial, while decreasing provided lower yields (Table 1, entries 11 and 12).

With a set of optimized reaction conditions in hand, we moved on to investigate the scope of this metal-free annulation. A series of arenes were subjected to the annulation conditions (Scheme 2). The reaction was found to be very facile with both electron-rich and moderately electron-deficient arenes (Scheme 2). Simple electron-rich arenes, anisole and diphenyl ether, provided products in excellent yields (Scheme 2, compounds **3b** and **3c**). To our delight the reaction preceded selectively and formation of regioisomers was not detected. Various disubstituted arenes also provided the desired products with excellent to moderate yields (Scheme 2, compounds **3d, 3f–h, 3j**). Among the unsymmetrically disubstituted arenes, product **3g** was isolated as single regioisomer, whereas **3h** was obtained as mixture of two isomers. Application of 1-methylnaphthalene in the metal-free annulation provided the desired product in good yield with 5:1 ratio of regioisomers(Scheme 2, compound **3e**, major isomer is shown). Tetrahydronaphthalene gave a mixture of regioisomers (Scheme 2, compound **3j**). Furthermore, toluene and iodobenzene also provided the desired products in acceptable yields (Scheme 2, compounds **3i** and **3k**).

Next, we investigated the scope of various 2-aminopyridines in the metal-free annulation (Scheme 2). Pleasingly we found that the reaction tolerated various electronic influences on the 2-aminopyridines well. Very good yields were consistently observed with 2-aminopyridines having electron-donating or electron-withdrawing groups at various positions (Scheme 2, compounds **3i**, **3l**, and **3m**). Furthermore, disubstituted 2-aminopyridines also provided moderate to good yields (Scheme 2, products **3q** and **3r**). Trisubstituted 2-aminopyridine provided the product in excellent yield, too (Scheme 2, compound **3s**). It is noteworthy that product **3t** could be directly obtained by selective oxidation of product **3p** using an additional equivalent of $PhI(OAc)_2$ in a one-pot reaction.

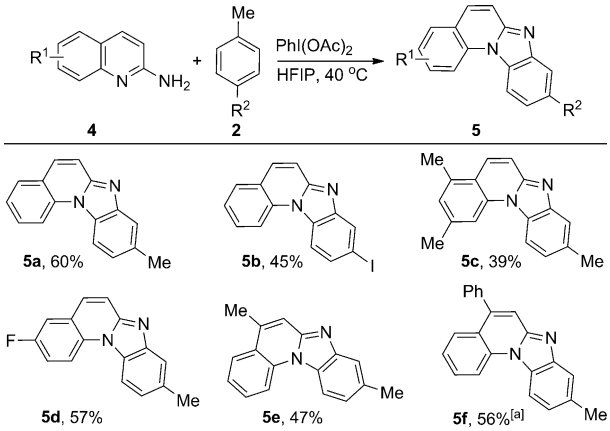
Having described the annulation between 2-aminopyridines and arenes, we were interested in expanding the scope to other derivatives. In this context, 2-aminoquinoline and *para*-xylene were subjected to our optimized reaction conditions (Scheme 3). Although anticipated cross-coupling occurred, we isolated product **5a** which lacks a methyl group (Scheme 3). Unlike the reaction of 2-aminopyridine, the analogous reaction of 2-aminoquinoline providing mono-



Scheme 2. Scope of the metal-free annulation of arenes. Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), $PhI(OAc)_2$ (0.4 mmol) in HFIP at 40°C for 12 h. [a] **2** (0.6 mmol) used. [b] After 12 h $PhI(OAc)_2$ (0.2 mmol) was added and the reaction continued for 24 h. [c] Obtained from product **3p** by adding additional $PhI(OAc)_2$ (0.2 mmol) and after a reaction time of 24 h.

demethylated product is unprecedented. Furthermore, the reaction proceeds absolutely selectively and the formation of isomers or other annulated products was not observed. Product **5a** reflect the introduction of toluene with non-innate regioselectivity. In general, one methyl group of *para*-xylene has the unprecedented function of a traceless, non-chelating, directing group.[9,10]

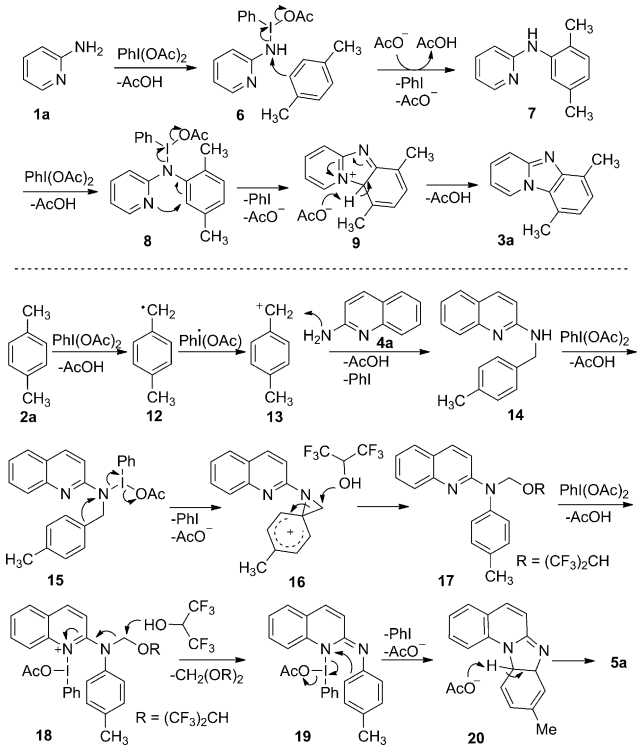
We then investigated the generality of this unprecedented annulation. 4-Iodotoluene reacted in analogy to *para*-xylene and provided compound **5b** in moderate yield (Scheme 3). Furthermore, various 2-aminoquinolines also provided the corresponding products in moderate yields and regioselectivity (Scheme 3, compounds **5c–f**). In general, electronic effects on the arene ring in 2-aminoquinoline have some influence on the product yield. Substrates with electron-poor substituents provided better yields than electron-rich 2-aminoquinolines



Scheme 3. Scope of application of the methyl-directed reaction. Reaction conditions: **5** (0.2 mmol), **2** (1.0 mmol), $PhI(OAc)_2$ (0.6 mmol total; added in 0.2 mmol portions every 6 h) in HFIP at 40 °C for 18 h. [a] $PhI(OAc)_2$ (0.8 mmol) used, reaction time 24 h.

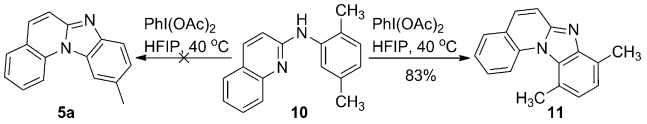
(Scheme 3, compounds **5c** and **5d**). Substituents on the heteroaromatic ring had little influence and moderate yields were consistently observed (Scheme 3, compounds **5e** and **5f**).

A proposed mechanism for the $PhI(OAc)_2$-mediated annulation of 2-aminopyridine with arenes is described in Scheme 4. Based on our previous experience,[8] we propose initially a ligand exchange between **1a** and $PhI(OAc)_2$ which provides intermediate **6**. Then nucleophilic attack of arene **2a** on **6** provides *N*-arylated 2-aminopyridine **7**. Subsequent oxidation of **7** with a second equivalent of $PhI(OAc)_2$ and



Scheme 4. Proposed mechanism for metal-free annulation.

nucleophilic attack of pyridine nitrogen on xylene produces intermediate **9**.[3a] Finally, rearomatization of **9** produces the annulated product **3a** (Scheme 4). In the control experiment under optimized reaction conditions intermediate **7** provided exclusively **3a** in 95 % yield (see the Supporting Information). In contrast, a similar experiment with compound **10** provided product **11** instead of **5a** suggesting a different mechanism for the annulation of 2-aminoquinoline (**4a**) with arenes (Scheme 5). In a plausible mechanism for the formation of **5a**, the reaction of xylene (**2a**) with $PhI(OAc)_2$ generates benzylic radical **12**, which is subsequently converted to cation



Scheme 5. Reaction of compound **10** with $PhI(OAc)_2$.

13. Nucleophilic attack of amine **4a** onto cation **13** gives benzylic amine **14** (Scheme 4).[7j] The difference in the reaction mechanisms might be explained by the fact that the reactivity of 2-aminoquinoline (**4a**) with $PhI(OAc)_2$ is less than that of 2-aminopyridine (**1a**). In a control experiment, amine **14** in thepresence of $PhI(OAc)_2$ was converted to the desired product **5a** with a yield of 80 % (see the Supporting Information). Nevertheless, when deuterated **2a** was used in the reaction with **4a**, a relative small kinetic isotope effect (KIE = 1.4) was observed. Therefore, the abstraction of deuterium is not the rate-limiting step in the annulation (see the Supporting Information for details). Intermediate **15** obtained from oxidation of amine **14** with $PhI(OAc)_2$ is engaged in an intramolecular cyclization via *ipso* substitution to give **16**.[3b] Attack of HFIP on **16** gives intermediate **17**. Subsequent reaction of **17** with $PhI(OAc)_2$ provides **18**. Cleavage of the C–N bond in intermediate **18** by HFIP initiates annulation onto the quinoline moiety to produce intermediate **20**. Finally, rearomatization provides product **5a**.[3b] It is notable that intramolecular demethylative cyclization during the cleavage of carbon–heteroatom bonds has been reported[11] but to the best of our knowledge not in the context of C–C bond cleavage. Further studies of the mechanism of demethylative annulation are in progress.

In conclusion, we have developed a novel annulation of arenes with 2-aminopyridine derivatives mediated by a hypervalent iodine reagent under mild reaction conditions. This intermolecular approach was applied to the efficient synthesis of pyrido[1,2-*a*]benzimidazoles and quinolino[1,2-*a*]benzimidazoles under metal-free conditions. For the first time, we demonstrated the application of the methyl group in methyl arenes as a directing, non-chelating, and traceless group in a highly regioselective cross-annulation.

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