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Hypervalent iodine(III) catalyzed oxidative C-N bond formation in water: Synthesis of benzimidazole-fused heterocycles†

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Iodine (III) catalyzed C(sp^2)–H functionalization/intramolecular amination reaction of *N*-aryl-2-amino-*N*-heterocycles has been developed in water and under ambient conditions. This metal-free/open-flask chemistry is general and successfully applied in synthesizing benzimidazole-fused heterocycles pyrido[1, 2-*a*]benzimidazole, benzimidazo[1,2-*a*]quinoline and benzimidazo [2,1-*a*] isoquinoline derivatives.

Direct cross-dehydrogenative amination of inert C(sp^2)–H bond became a valuable tool in organic synthesis.[1] Over the years, numerous protocols for intramolecular direct C–N bond formations have been developed, and most of these methods involve the catalytic use of Pd complexes[2] or Cu salts.[3] Generally, the transition metal catalyzed carbon-heteroatom bond formation reactions are required elevated temperatures and high loading of the catalyst and/or metal oxidant. Furthermore, the presence of heavy metal contaminants in the final product mitigates their application in the bulk synthesis of active pharmaceutical ingredients (API) for commercial use. Hence, reaction protocols that enable the preparation of nitrogen containing compounds through C–N cross-coupling reactions in the absence of transition metals are attractive and considered greener.[4] In this context, the hypervalent iodine reagents promoted oxidative C-N bond formation received much attention due to their low toxicity, comparable reactivity with transition-metal and easy availability.[5,6] However, in this iodine (III) mediated cross-coupling chemistry, for most of the cases fluorinated solvents[6a,e,h,i] remained the preferred one which severely impedes the application particularly in large scale synthesis. Therefore a new, more efficient and environmentally benign metal-free catalytic system for oxidative C-H amination is highly desirable.

The benzimidazole-fused heterocyclic scaffold exists in a wide range of biologically active compounds (Fig. 1).[7] Consequently, substantial synthetic methods have been developed for the preparation of this class of molecules.[8,9,10]

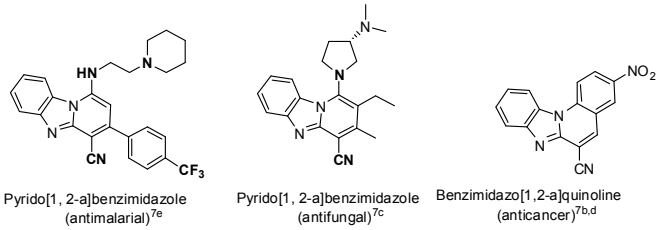
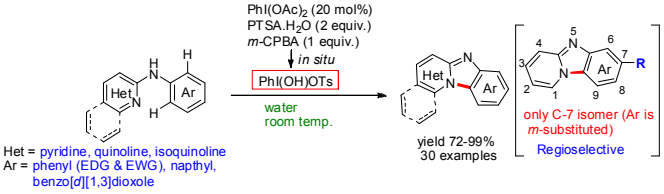


Fig. 1 Medicinal interest with benzimidazole-fused heterocycles

In this aspect synthesis of pyrido[1, 2-*a*]benzimidazoles by copper(II) catalyzed intramolecular C-H amination of *N*-aryl-2-aminopyridines in acidic medium has been reported by Zhu[8d] and Maes[8e] independently. However, both of the approaches require high reaction temperature (120 °C), and the substrate scope is limited in terms of substituents on the pyridine moiety. An alternative approach mediated by iodine (III) has also been reported by Zhu recently.[6i] But this methodology failed in terms of regioselectivity and the use of expensive fluorinated alcohol remains the drawback of this synthesis. To overcome these issues, herein, we report, an oxidative C-N bond formation with catalytic amount of *in situ* generated hypervalent iodine (III) reagent [hydroxy(tosyloxy)iodo] benzene (Koser's reagent, HTIB)[11] in water[12,13] and under ambient conditions (Scheme 1).

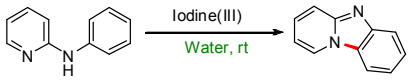


Scheme 1. Formation of benzimidazole-fused heterocycles

This protocol is general, regioselective and has been successfully utilized in synthesizing medicinally important heterocycles pyrido[1, 2-*a*]benzimidazole, benzimidazo[1,2-*a*]quinoline and benzimidazo [2,1-*a*]isoquinoline derivatives.

At the outset, *N*-phenyl-2-aminopyridine[14] **1a** was selected as the model compound to explore the optimized reaction conditions with iodine (III) in water and at room temperature (Table 1). It was found that the reaction of **1a** with phenyliodine diacetate (PIDA, 1equiv.) in water at room temperature was unsuccessful (entry 1, Table 1). Product was not formed even at the elevated temperature, 100 ^{o}C (entry 2, Table 1). To our delight when we performed the reaction with PIDA (1equiv.) in the presence of *p*-toluenesulphonic acid monohydrate (PTSA.H_2O) (2 equiv.) as an additive, the desired product was isolated in 90 % yield (entry 3, Table 1).[11*a*] When methane sulphonic acid (2 equiv.) was combined with PIDA poor yield (15%) was obtained (entry 4, Table 1). When we reduced the amount of PIDA from 1 to 0.5 equiv., the yield of the isolated product dropped to 30% (entry 5, Table 1). The yield also diminished when amount of PTSA. H_2O was reduced from 2 equiv. to 1equiv. (entry 6, Table 1). Next we turned our attention to make the reaction catalytic and performed the reaction by using PIDA with several oxidants (entries 7-9, Table 1). It was observed that combination of PIDA (0.2 equiv.) with PTSA. H_2O (2 equiv.) in *m*-CPBA (1equiv.) in water gave **2a** in best yield (90 %) (entry 7, Table 1). Oxidants like TBHP (entry 8, Table 1) and H_2O_2 (entry 9, Table 1) remained ineffective. Use of 10 mol% PIDA gave the desired product only in 60% isolated yield (entry 10, Table 1). When we tried to promote the cyclization by *in situ* generated HTIB by using PhI (0.2 equiv.) as an iodine source[11*b*] with PTSA.H_2O and *m*-CPBA as an oxidant in water, annulated product was obtained in 75% yield (entry11, Table 1).

Table 1 Optimization of the reaction conditions [a]



1a **2a**

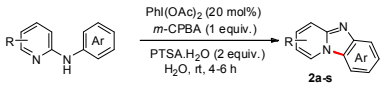
Entry	Precat.	Amount	Additive	Oxidant	*t*(h)	Yield (%)[b]
1	PIDA	1 equiv	--	--	24	n.r.
2[c]	PIDA	1 equiv	--	--	24	n.r.
3	PIDA	1 equiv	PTSA.H_2O	--	4	90
4	PIDA	1 equiv	CH_3SO_3H	--	8	15
5	PIDA	0.5 equiv	PTSA.H_2O	--	8	30
6	PIDA	1 equiv	PTSA.H_2O[d]	--	8	40
7	PIDA	0.2 equiv	PTSA.H_2O	*m*-CPBA	4	90
8	PIDA	0.2 equiv	PTSA.H_2O	TBHP[e]	8	n.r.
9	PIDA	0.2 equiv	PTSA.H_2O	H_2O_2[f]	8	n.r.
10	PIDA	0.1 equiv	PTSA.H_2O	*m*-CPBA	4	60
11	PhI	0.2 equiv	PTSA.H_2O	*m*-CPBA	4	75
12	HTIB	1 equiv	--	--	4	85

[a]Reaction conditions: **1a** (1.0 equiv.), PIDA (0.2 equiv.), PTSA.H_2O (2 equiv.), *m*-CPBA (1 equiv.), H_2O (1 mL), rt ; [b] isolated yields; [c] reaction carried out at 100 ^{o}C; [d]1.0 equiv used [e]70 vol% in water; [f]30 vol% in water; n. r. = no reaction.

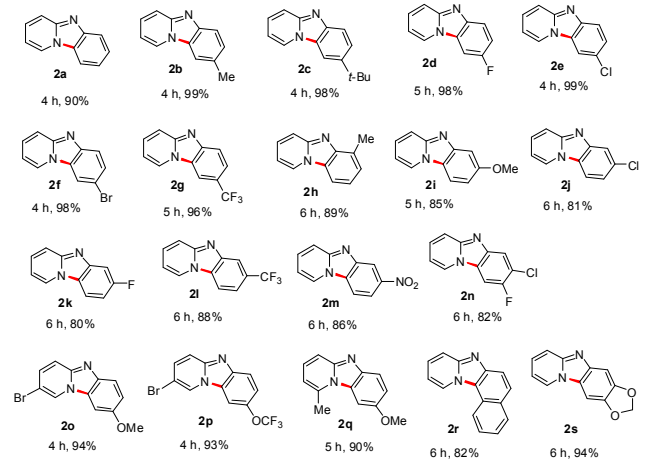
When we used Koser's reagent (HTIB) (1.0 equiv.) in absence of *m*-CPBA and PTSA **2a** isolated in 85% yield, which indicates that the Kosers's reagent is the active species (entry12, Table 1).

Reaction of a variety of *N*-arylated-2-aminopyridines[14] was investigated under the optimized reaction conditions (Table 2). As depicted in Table 2, *N*-aryl-2-aminopyridines bearing electron-donating (Me and *t*-Bu) or electron-withdrawing groups (F, Cl, Br, CF_3) at the *para* position of the aniline moiety proceeded with almost quantitative yields (**2b-g**). High yield was also obtained with *ortho* substitution as compound **2h** was isolated in 89% yield. Both electron donating (OMe) and electron withdrawing (F, Cl, CF_3, NO_2) substituents at the *meta*-position of the aniline of *N*-aryl-2-aminopyridine derivatives proceeded in a highly regioselective manner to afford exclusively C-7 substituted pyrido[1, 2-*a*]benzimidazoles (**2i-m**).[8*d*,*e*] Interestingly, no other regioisomer *i.e.* C-9 substituted pyrido[1, 2-*a*]benzimidazoles were detected. In this context, disubstituted derivative has been tested under these optimized conditions and the product **2n** was isolated in 82% yield with complete regioselectivity. To further enhance the generality of the reaction, substitution on the pyridine ring was also investigated. 5-Bromo or 2-methyl derivatives reacted efficiently to give the corresponding products **2o-p** and **2q,** respectively in excellent yields (90-94%). Cyclization of *N*-napthyl-2-aminopyridine was also performed under the optimized condition and the novel pyridine annulated naptho imidazo product (**2r)** was isolated in 82% yield. By applying this optimized condition benzo[*d*][1,3]dioxole annulated pyridoimidazo compound (**2s**) has been synthesized in 94% yield.

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



2a-s

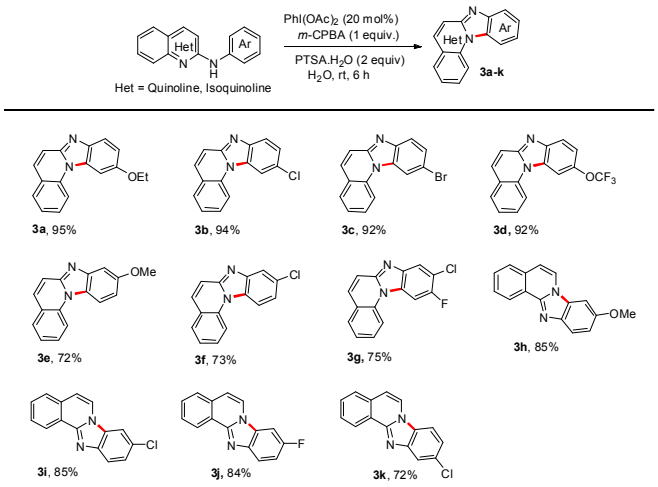


[a] Reaction conditions: *N*-arylpyridine-2-amine (0.29 mmol), $PhI(OAc)_2$ (0.058 mmol), *m*-CPBA (0.29 mmol), PTSA.H_2O (0.58 mmol), H_2O (1 mL,), rt, air

Next we turned our attention in applying the present protocol for the synthesis of another important complex heterocyclic

system benzimidazo[1,2-*a*]quinoline (Table 3). Under the optimized condition *N*-aryl-2-aminoquinolines[14] bearing electron donating (**3a**) or electron withdrawing group (**3b-d**) produced the desired heterocycles in high yields (92-95%). Here also the reaction was highly regioselective as substrates having *meta*-substitution in the aniline ring gave exclusively C-9 substituted products (**3e-g**) in good yields (72-75%). We have further applied the optimized condition in synthesizing benzimidazo [2,1-*a*] isoquinolines (Table 3).

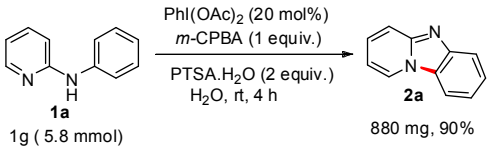
Table 3 Synthesis of benzimidazo[1,2-*a*]quinoline and benzimidazo[2,1-*a*]isoquinoline derivatives[a]



[a] Reaction conditions: *N*-arylquinolin-2-amine/*N*-arylisoquinolin-1-amine (0.29 mmol), $PhI(OAc)_2$ (0.058 mmol), *m*-CPBA (0.29 mmol), $PTSA.H_2O$ (0.58 mmol), H_2O (1 mL,), rt, air

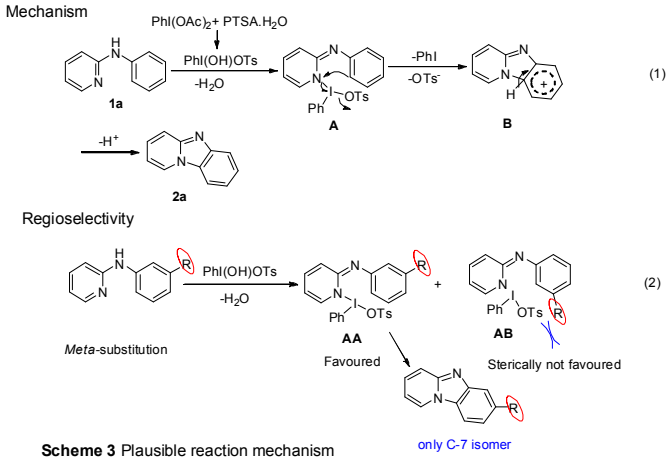
We were pleased to find that the iodine (III) promoted C-H amination of *N*-arylisoquinoline-1-amine derivatives[14] was facile and the cyclic compounds were isolated in excellent yields (84-85%) (Table 3). The electronic nature of the substituents at *para*-position (**3h-j**) had no effect on the cycloamination reaction. In this case also the reaction remained completely regioselective and only C-10 substituted product (**3k**) was isolated in 72% yield.

The scalability of this reaction was tested by performing the reaction of **1a** in gram scale (5.8 mmol) under the optimized conditions (Scheme 2).



Scheme 2 Gram scale synthesis of pyrido[1,2-*a*] benzimidazole

Based on these findings and previous literature reports[15,6c,h,i] we put forward a plausible mechanism for amination of **1a**. The operating mechanism for this reaction is suggested to start from an interaction between the *in situ* generated PhI(OH)OTs (Koser's reagent) and *N*-phenyl-2-aminopyridine (**1a**) (Scheme 3), to result the electrophilic *N*-iodo species **A**. In subsequent steps the electrophilic annulation on the pyridine nitrogen of **A** generates intermediate **B** which upon deprotonation forms **2a** (eq 1, Scheme 3). The eliminated PhI enters the catalytic cycle upon oxidation by *m*-CPBA in presence of PTSA. H_2O to generate the reactive iodine (III) PhI(OH)OTs and complete the catalytic cycle. The explanation for the high regioselectivity can be put forward, where the intermediate **AA** is favoured over **AB** due to steric effect (eq 2, Scheme 3), in order to give one regioisomer exclusively.



Scheme 3 Plausible reaction mechanism

In conclusion, we have developed a practical method for the synthesis of benzimidazole-fused heterocycles from readily available *N*-aryl-2-amino-*N*-heterocycles under metal-free conditions. The reaction is catalyzed by *in situ* generated hypervalent iodine (III) at room temperature. Use of water as solvent and open-flask chemistry makes this process greener and more attractive for large scale synthesis. To the best of our knowledge, this is one of the rare example where water has been used as solvent in the hypervalent iodine (III) catalyzed oxidative C-N bond formation. More significantly, complete control on the regioselectivity was achieved in this C-H cycloamination process. In view of the growing understanding of hypervalent iodine C-H activation/ functionalization processes, the reaction described herein showcased a reactivity profile that is notably different to those previously reported.[6h,i,8c] It is believed that the new hypervalent iodine (III) promoted protocol will add value in developing a number of efficient and practical methods for C-N bond construction from unactivated C-H bonds.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [experimental details and spectroscopic data for all comounds]. See DOI: 10.1039/c000000x/

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