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Metal-free synthesis of 2-aminobenzoxazoles using hypervalent iodine reagent

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ABSTRACT

A facile, simple, mild, and metal-free protocol for the synthesis of 2-aminobenzoxazoles has been developed via C–H bond amination of benzoxazoles with amines through a ring-opening and subsequent ring-closure approach. The reaction was performed in two steps wherein nucleophilic addition of amines across benzoxazoles takes place in the absence of any reagent or catalyst under solvent-free condition, followed by oxidative ring closure using 2-iodoxybenzoic acid as a hypervalent iodine reagent. Various cyclic, acyclic, and functionalized aliphatic amines were well tolerated under optimized reaction conditions and provided good to excellent yield of respective 2-aminobenzoxazoles.

Oxidative C–H functionalization reactions are of great interest in organic synthesis as they have high atom-efficiency compared to related cross-coupling reactions using organometallic compounds.[1] Oxidative C–H bond amination reaction of heteroaromatic compounds is particularly important because of its applications in the synthesis of biologically active molecules and advanced organic materials.[2] These heteroaromatic compounds such as 2-aminobenzoxazoles can be synthesized by oxidative C–H bond amination of benzoxazoles with a variety of amines.[3] Such types of 2-aminobenzoxazole derivatives are invariably found in a number of therapeutically important molecules and some 2-(*N*-alkylpiperazyl)benzoxazoles have already been described as potent 5-HT_3-receptor agonists.[4] These 2-aminobenzoxazoles can be synthesized by palladium-catalyzed N-arylation reaction of 2-halo derivatives of benzoxazoles with amines.[5] However, use of expensive metals, specialized ligands, harsh reaction conditions, and long reaction time are the major drawbacks of N-arylation reaction. In comparison with N-arylation, amination by C–H activation is more attractive as it can directly couple C–H of heteroaromatic compound with N–H of amines and can take place without ligands under milder reaction conditions. In this direction various metal-catalysts such as Ag(I), Co(II), Mn(II), Fe(III), and Cu(II) are reported for the oxidative C–H bond amination of azoles.[6] However, metal catalysts themselves have some drawbacks like they are expensive and not environmentally benign. They are needed to remove at trace levels for pharmaceutical applications. Hence, some metal-free protocols using various non-metal catalysts such as TBAI, I_2, TEMPO, and NIS have been designed by several reseachers.[7] Furthermore, Chang and co-workers explored DIB as a hypervalent iodine reagent for the oxidative C–H bond amination of benzoxazoles at room temperature.[8] Nowadays, hypervalent iodine reagents are extensively employed for a variety of chemical transformations and particularly as oxidative reagents. Because of ready availability, convenience of use, unique oxidizing properties, and eco-friendly features they are widely utilized in the synthesis of complex natural products of biological interest.[9] Recently, 2-iodoxybenzoic acid (IBX) has become an alternative oxidizing agent for various metal based oxidants.[10]

Although there are many reports on oxidative C–H bond amination of benzoxazoles, the reported protocols still suffer from some drawbacks such as necessity of stoichiometric amount of acid/base additive and co-oxidant. Also, they either require harsh reaction conditions or it takes more time at room temperature for completion of the reaction. Hence, there is a need to develop a protocol which works at milder reaction condition and metal-free conditions in shorter reaction time.

In this context, herein we report oxidative C–H bond amination of benzoxazoles with amines in the presence of IBX as a hypervalent iodine reagent (Scheme 1). Here, 2-aminobenzoxazoles have been successfully synthesized in two steps.

First step is direct nucleophilic addition of secondary amine at C-2 position of benzoxazole at 25 °C under solvent-free and aerobic conditions and gives ring opened amidine intermediate **3**. Further in the second step cyclization of this intermediate **3** takes place by using IBX reagent at 25 °C within 5-30 min to give 2-aminobenzoxazoles **4**.[11]

Benzoxazole (**1a**) and morpholine (**2a**) were selected as model substrates for the optimization of the ring-opening and subsequent

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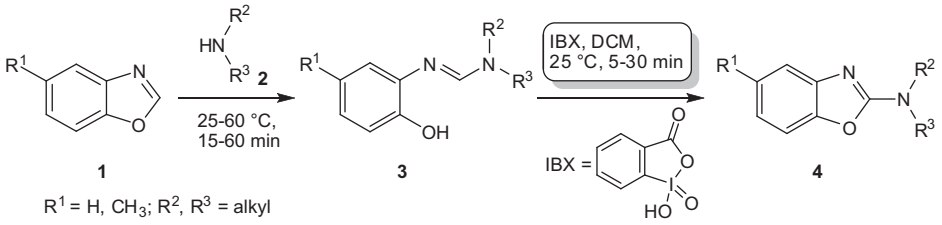
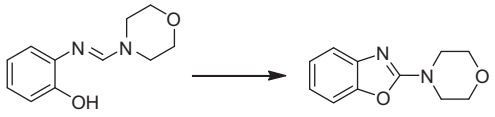


Scheme 1. Oxidative C–H amination of benzoxazoles.

Table 1
Optimization of reaction conditions[a]



Entry	Reagent	Solvent	Time (min)	Yield[b] (%)
1	KIO_3	CH_2Cl_2	10	65
2	KIO_4	CH_2Cl_2	10	60
3	HIO_4	CH_2Cl_2	10	55
4	IBX	CH_2Cl_2	10	95
5[c]	H_2O_2	CH_2Cl_2	60	—
6[d]	O_2	CH_2Cl_2	60	—
7	IBX	$CHCl_3$	10	92
8	IBX	CH_3CN	10	10
9	IBX	THF	10	8
10	IBX	Toluene	10	—
11	IBX	DMSO	10	28
12	IBX	CH_2Cl_2	5	94

[a] Reaction conditions: **3a** (0.5 mmol) and hypervalent iodine reagents (1 equiv) at 25 °C.
[b] GC yield.
[c] 30% aqueous solution of H_2O_2.
[d] 1 atm O_2 pressure.

oxidative ring-closing reaction (Table 1). Chang and co-worker demonstrated such type of ring opening of azoles under neat and mild conditions to give the amidine adducts.[8] Later, Studer and co-worker observed amidine formation for the reaction of benzoxazoles with amines in the presence of TfOH or $Sc(OTf)_3$.[7c] Hence, we treated **1a** with **2a** for ring opening reaction to give amidine and it was observed that the reaction proceeded smoothly at 25 °C and required only 15 min for completion under an air atmosphere and solvent-free conditions with 98% yield of **3a**. The reaction completion was constantly monitored using thin layer chromatography. One significant visual observation during the reaction course was the phase change from liquid to semisolid/solid indicating the maximum formation of intermediate **3a**.

Next, the oxidative ring closing reaction of **3a**–**4a** was optimized with the help of various reaction conditions such as screening of various reagents, solvents, and reaction time (Table 1). Various iodine reagents such as KIO_3, KIO_4, HIO_4, and IBX as well other normal oxidants such as dihydrogen dioxide and oxygen were screened for the ring closing reaction of **3a** to **4a** in CH_2Cl_2 solvent at 25 °C under an air atmosphere (Table 1, entries 1–6). It has been observed that IBX shows excellent activity and offered 95% overall yield of **4a**. Other iodine reagents gave lower yields of **4a** in comparison with IBX. Dihydrogen dioxide and oxygen were found to be inactive for the ring closing of **3a** in to **4a** under present reaction conditions (Table 1, entries 5 and 6). Further various solvents such as CH_2Cl_2, $CHCl_3$, CH_3CN, THF, toluene, and DMSO were screened to find the best solvent for oxidative ring closing reaction of **3a** (Table 1, entries 7–11). CH_2Cl_2 was found to be the best among all the above solvents screened and furnished 95% yield of **4a**. Also, it has been observed that the reaction provides comparative yield after decrease in reaction time up to 5 min at 25 °C (Table 1, entry 12). Hence, the optimized reaction conditions for ring closing reaction of **3a** to **4a** are: IBX (1 equiv) in CH_2Cl_2 solvent at 25 °C for 5 min.

These optimized reaction conditions were then applied for the synthesis of various 2-aminobenzoxazoles by ring opening reaction of benzoxazole with various amines and then subsequent oxidative ring closing reaction mediated by IBX reagent (Table 2). Initially various cyclic amines such as morpholine, piperidine, and pyrrolidine were treated with **1a** for ring opening reaction at 25 °C under solvent-free conditions (Table 2, entries 1–3). All these amines reacted smoothly with **1a** and provided respective amidine adducts in excellent yields. Then the respective 2-aminobenzoxazoles were synthesized in good to excellent yields by subsequent cyclization of these amidines using IBX in CH_2Cl_2 at 25 °C. Further, the other cyclic amines bearing various functional groups like *N*-methylpiperazine, 1-(piperazin-1-yl)ethanone, *N*-benzylpiperazine, and 1,2,3,4-tetrahydroisoquinoline were also treated with **1a** under optimized reaction conditions (Table 2, entries 4–7). However, the ring opening reactions of these amines need to be performed at 60 °C to get higher yields of respective amidine adduct. The further cyclization of these amidine adducts occurred smoothly under optimized reaction conditions and provided good to excellent yield of respective 2-aminobenzoxazoles. Acyclic secondary amines such as diethylamine, dibutylamine, and *N*-methyl-1-phenylmethanamine also turned out to be facile reactants (Table 2, entries 8–10). However, they require higher reaction temperatures and longer duration of time to obtain full conversion in the ring-opening step. The reaction of these amines (**2h**, **2i,** and **2j)** with **1a** was performed at 60 °C and it proceeded efficiently to give adduct **3h**, **3i,** and **3j** respectively, which subsequently cyclized to form **4h**, **4i,** and **4j** respectively with good to excellent overall yields.

To widen the applicability of the present protocol, we provided 5-methylbenzoxazole substrate for oxidative C–H bond amination with various cyclic amines such as morpholine, piperidine, and *N*-methylpiperazine (Table 2, entries 10–13). All these cyclic amines tolerated very well and afforded good to excellent yields in the ring opening as well as IBX mediated cyclization step.

In conclusion, we have developed an efficient metal-free methodology for oxidative C–H bond amination of benzoxazoles with amines by ring-opening and subsequent ring-closing in the presence of IBX as a hypervalent iodine reagent. IBX as a source of oxidizing agent gave the most significant results. Secondary amines can be concluded as the best substrates for this reaction at ambient temperature and pressure. The overall reaction is highly attractive from a synthetic point of view, since the reaction conditions are milder and free from acids,