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Iodine-mediated arylation of benzoxazoles with aldehydes†

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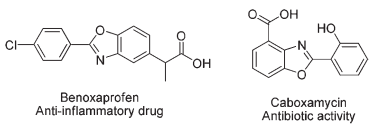
A simple and efficient methodology for the arylation of benzoxazoles with aldehydes using iodine as the mediator has been developed. The reaction proceeded smoothly with a range of substrates to give the corresponding arylated products in moderate to good yields.

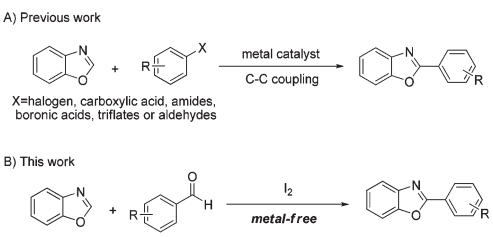
Aryl-substituted benzoxazoles are important structural motifs in many biologically active molecules, pharmaceuticals and natural products (Scheme 1).[1] The development of efficient protocols to construct such biaryl moieties is therefore of great importance to drug discovery. There are several strategies employed for the synthesis of 2-aryl substituted benzoxazoles. Conventional synthetic methods include the condensation of 2-aminophenols with aromatic carboxylic acids or aldehydes,[2] oxidative cyclization of phenolic Schiff bases promoted by oxidants[3] and metal-catalyzed intramolecular cross-coupling of 2-halo anilides or benzanilides.[4] While good yields can be obtained with a wide substrate scope, these protocols often suffer from various drawbacks such as the synthesis of starting materials as precursors and the use of harsh reaction conditions.

Alternatively, direct arylation of benzoxazoles represents a straightforward and versatile method for 2-arylbenzoxazoles synthesis. It has been reported that the transition metals could catalyze the direct C–H activation and subsequent C–C coupling of benzoxazole (Scheme 2A) with aromatic carboxylic acids,[5] aryl halides,[6] arylsilanes,[7] aryl triflates,[8] aryl boronic acids,[9] arylamides,[10] simple arenes[11] and, more recently, aldehydes.[12] These convenient direct arylation methods have received increasing attention as they avoid the use of stoichiometric amounts of expensive organometallic reagents and eliminate the need for pre-installation of activating agents, thereby generating less waste.[13] While these direct coupling strategies between benzoxazoles and an arylating agent are often efficient, there are some limitations such as the utility of relatively expensive transition metal catalysts or ligands and the risk of metal impurities in the synthesized drug intermediates or bioactive molecules. Therefore, the development of an alternative metal-free approach for the arylation of benzoxazoles remains highly desirable. Although several metal-free approaches have been demonstrated for the synthesis of 2-arylbenzothiazoles or 2-acylbenzothiazoles from benzothiazoles and aryl aldehydes or aromatic ketones, none of these methodologies are suitable for arylation of benzoxazole.[14,15] Aromatic aldehydes are ideal arylation reagents as they are readily available and cheap. We envision that a reaction between benzoxazoles and aldehydes could occur by using a suitable oxidant. Molecular iodine has often been used as a catalyst/reagent in effecting certain organic transformations owing to its oxidative properties and low cost.[16] Herein, we report a simple and efficient method for the direct arylation of benzoxazoles with aromatic aldehydes mediated by molecular I_2 (Scheme 2B).

We began our investigation by using benzoxazole (**1a**) and 4-bromobenzaldehyde (**2a**) as the model substrates. When the model reaction was carried out in DMSO at 85 °C in the presence of I_2 (2 equiv.), we were pleased to find that the desired



Scheme 1 Medicinal applications of 2-aryl substituted benzoxazoles.



Scheme 2 Strategies for arylation of benzoxazole.

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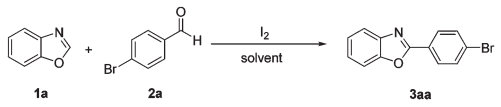
Table 1 Optimization of the reaction conditions[a]



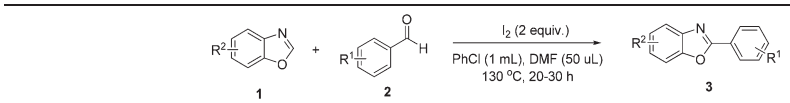
Entry	Additives	T (°C)	Solvent	Yield[b] (%)
1	—	85	DMSO	10
2	—	85	1,2-Dichloroethane	12
3	—	85	MeCN	11
4	—	85	Toluene	15
5	—	85	Toluene–DMSO (1 : 1)	11
6	—	85	DMF	<10
7	—	85	Dioxane	22
8	—	85	PhCl	21
9	—	120	Dioxane	56
10	—	120	PhCl	56
11	—	130	Dioxane	55
12	—	130	PhCl	60
13	—	140	PhCl	51
14	—	130	PhCl–dioxane (1 : 1)	57
15[c]	—	130	PhCl	46
16[d]	—	130	PhCl	48
17	H_2O (2 equiv.)	130	PhCl	43
18	Dioxane (5%)	130	PhCl	52
19	DMSO (5%)	130	PhCl	27
20[e]	**DMF (5% v/v)**	**130**	**PhCl**	**73 (71)**
21[f]	—	130	PhCl	0

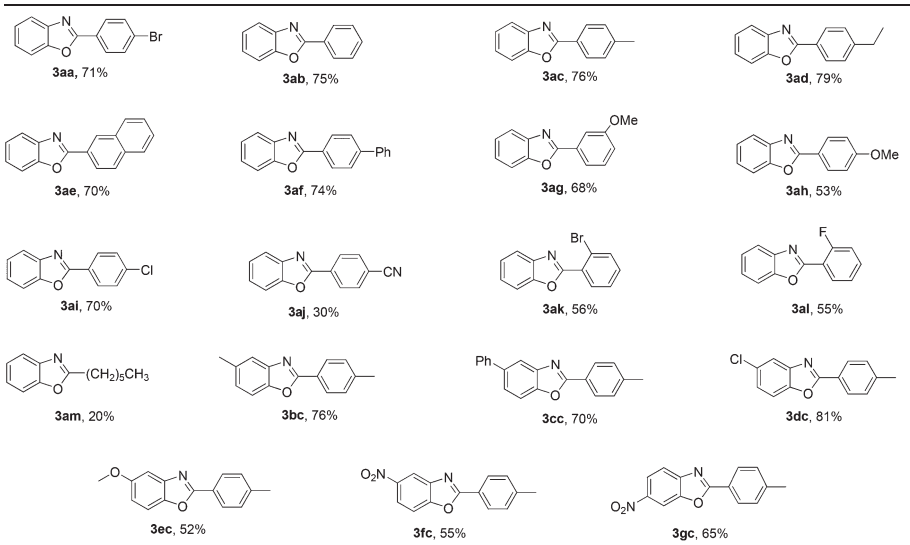
[a] Conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), I_2 (1.0 mmol), solvent (1.0 mL), 40 h. [b] ^{1}H NMR yield based on **2a**, isolated yield in parentheses. [c] Reaction conducted under argon. [d] Reaction conducted under an O_2 atmosphere. [e] Reaction time: 30 h. [f] No I_2 added.

product (**3aa**) was detected, albeit in low yield (Table 1, entry 1). We proceeded to screen several organic solvents and found that a higher yield was obtained when the reaction was conducted in dioxane or PhCl (Table 1, entries 2–8). Further optimization by screening the reaction temperature (Table 1, entries 9–14) using dioxane, PhCl and a mixed solvent of dioxane–PhCl (1 : 1) showed that a temperature of 130 °C using PhCl as the solvent was optimal for the arylation reaction (Table 1, entry 12). Lower yield was obtained when the reaction was conducted under an argon or O_2 atmosphere (Table 1, entries 15 and 16). The addition of H_2O (2 equiv.) to the reaction proved to be undesirable as it resulted in a reduction in yield to 43% (Table 1, entry 17). As prolonged heating was required for 4-bromobenzaldehyde (**2a**) to go into complete conversion, the effects of additives were studied next in an attempt to improve the reaction efficiency (Table 1, entries 18–20). However, the addition of DMSO (5% v/v) to the reaction resulted in poor yield and the formation of a black precipitate during the reaction (Table 1, entry 19). We were delighted to find that the reaction yield could be improved to 73% and the reaction time reduced to 30 h in the presence of DMF (5% v/v) (Table 1, entry 20). The reaction certainly benefited from the addition of the DMF aliquot; however, the exact role of DMF in the reaction system still remains unclear. The maximum yield was achieved with two equivalents of benzoxazole. In the absence of I_2, no desired product was observed (Table 1, entry 21).

With the established optimized conditions, the substrate scope of the iodine-mediated arylation reaction was investigated (Table 2). The reaction with benzaldehyde afforded the

Table 2 Arylation of benzoxazoles with aldehydes[a]



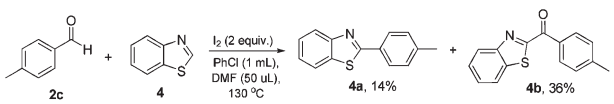


[a] Conditions: **1** (1.0 mmol), **2** (0.5 mmol), I_2 (1.0 mmol), PhCl (1 mL), DMF (50 μL), 130 °C, isolated yield.

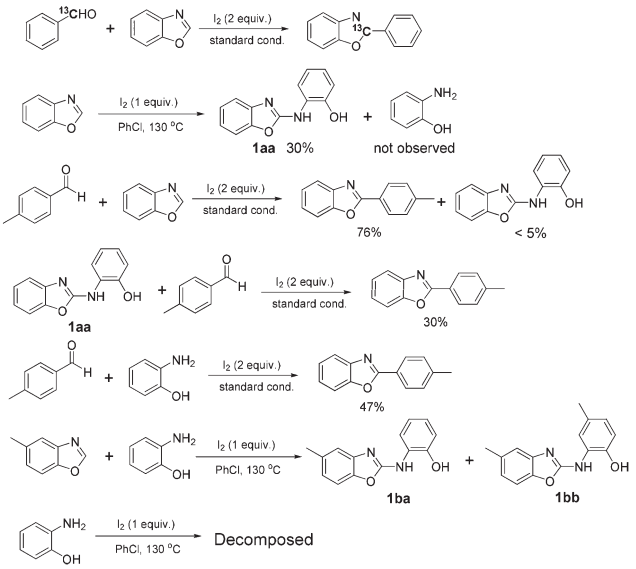
desired arylated product (**3ab**) in good yield. A range of aromatic aldehydes bearing electron-donating substituents (methyl, ethyl, methoxy) as well as electron-withdrawing substituents (halide) also underwent the desired reaction to provide the arylated products (**3ac–3ai**) in moderate to good yields. However, the presence of a strongly electron-withdrawing 4-cyano substituent on the benzaldehyde led to significant reduction in product yield (**3aj**). Benzaldehydes with *ortho*-substituents also resulted in lower product yields (**3ak–al**). While most aromatic aldehydes underwent the desired arylation reaction readily, a lower yield of 20% was obtained from the reaction between 1-heptanal and benzoxazole (**3am**). Several heteroaromatic aldehydes were also tested in this reaction system, and no promising results were obtained. For example, no desired product formation was observed with furfural and low yields (20%) of the desired product were observed for 2-pyridinecarboxaldehyde. Next, the scope of the reaction was expanded to include benzoxazoles bearing substituents on the phenyl ring. Benzoxazoles with electron-donating methyl groups and electron-neutral phenyl groups gave the corresponding arylated products (**3bc–cc**) in good yields. Various functional groups including chloro, methoxy and nitro on the benzoxazoles were also well tolerated under the optimized reaction conditions and the desired products were obtained in moderate to good yields (**3dc–gc**).

Next, we proceeded to explore the substrate scope with various azoles. Unfortunately, there was no desired product formation with benzimidazoles and oxazoles. Interestingly, the reaction between 4-methylbenzaldehye and benzothiazole gave both the arylated (**4a**) and acylated (**4b**) products (Scheme 3) in a ratio of 1 : 2.5. This result showed that iodine could also promote the arylation of benzothiazole with aldehyde and the formation of **4b** may go through an oxidative coupling reaction between benzothiazole and aldehyde.

To better understand the reaction mechanism, several control reactions were conducted. A ^{13}C-labeled benzaldehyde was reacted with benzoxazole under the optimized reaction conditions and a ^{13}C-labeled product was detected as the major product by using GC-MS (Scheme 4). This result clearly showed that the reaction goes through the benzoxazole ring opening pathway.[12,14,15,17] Another control experiment was set up whereby benzoxazole was reacted with I_2 at 130 °C (Scheme 4). A pale yellow solid **1aa** was isolated and its structure was confirmed by using ^{1}H NMR and mass spectroscopy (see ESI†). In fact, **1aa** is always observed as a by-product in the reaction system (Scheme 4). The formation of **1aa** thus corroborated our earlier proposal of a ring-opening mechanism. The desired product was also detected when benzaldehyde was reacted with **1aa**, suggesting that **1aa** could be an intermediate in the reaction system. However, it was well known



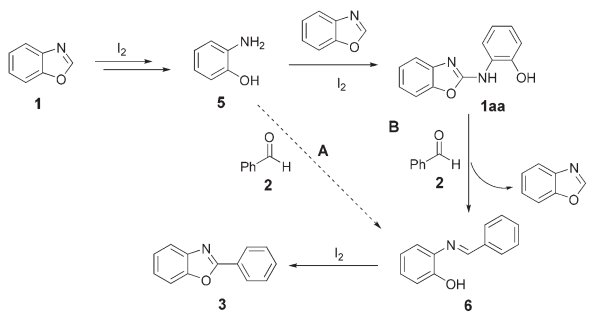
Scheme 3 Reaction of 4-methylbenzaldehyde with benzothiazole.



Scheme 4 Control experiments.

that 2-aminophenol could also be a starting material for the synthesis of 2-substituted benzoxazoles, including its reaction with aldehydes.[2] Therefore, in this reaction, 2-aminophenol is also a possible intermediate other than **1aa**. In fact, the reaction between 2-aminophenol and 4-methylbenzaldehyde also afforded the desired product **3ac**, but the yield (47%) was significantly lower as compared to the reaction using benzoxazole. However, 2-aminophenol was not observed as an intermediate or a by-product in the reaction mixture. It was also found that 2-aminophenol itself is not stable (decomposed) under the current reaction conditions. In addition, the reaction between 2-aminophenol and benzoxazole was also observed to form **1aa** analogue.

With these observations, a plausible reaction pathway is proposed as shown in Scheme 5. We postulate that I_2 could promote the oxidative ring-opening of benzoxazole[14,15] and thereafter, two possible reaction pathways can occur. The ring-opening intermediate can generate 2-aminophenol *in situ* and subsequent condensation reaction with benzaldehyde followed by oxidative ring-closure would give the final product *via* path A. Alternatively, the ring opening intermediate may be



Scheme 5 Proposed reaction mechanism for the iodine-mediated arylation of benzoxazole.

stabilized as **1aa** which would react with aldehyde to give the arylated product *via* path B. As 2-aminophenol was not detected during the course of the reaction, we believe that path B is the more probable reaction route.

In summary, we have demonstrated the first metal-free direct arylation of benzoxazoles with aromatic aldehydes mediated by molecular I_2. Mechanistic studies with the isolation of key intermediates revealed that a ring-opening mechanism is operative. This method constitutes a simple and inexpensive route to obtain 2-aryl substituted benzoxazoles which are of great importance in medicinal chemistry.

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