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Introduction

The development of metal-free methods for the efficient synthesis of valuable organic compounds is an exciting area of research, due to their capability to produce non-toxic metal-free drugs and medicinally important compounds.¹⁻⁴ In this regard, molecular iodine was used as an efficient catalyst in the synthesis of many heterocyclic compounds *via* multi-component reactions.⁵⁻⁸ Benzoxazoles are one of the important classes of nitrogen-containing heterocycles with extensive utilization especially in medicinal chemistry.^{9,10} Moreover, the benzoxazole heterocycle is one of the widely found structures in nature, and a range of related natural products are known as potent pharmacophores (Fig. 1).^{9,11-15}

Considering their utmost importance, various synthetic strategies have been developed to synthesize benzoxazoles.¹⁶⁻²⁵ However, extensive efforts have been devoted toward the progress of clean and efficient preparation of benzoxazole derivatives.²⁶⁻²⁸ Metal-free syntheses of benzoxazoles have recently received attention due to the increasing demands for their metal-contamination-free synthesis. However, the synthesis of benzoxazole derivatives *via* oxidation of catechols has gained intense interest. For all of the reported methods for the synthesis of benzoxazoles using catechols, a transition metal-catalyzed process was applied. Coupling reaction of catechols with amines using copper^{29,30}/iron³¹/Co,³² with amino acids using silver³³/iron,³¹ with aldehydes and ammonium acetate using iron³⁴/NaIO₄,³⁵ and with

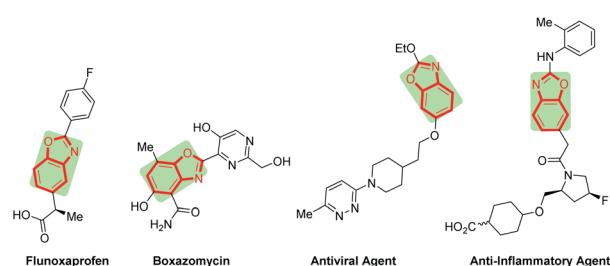
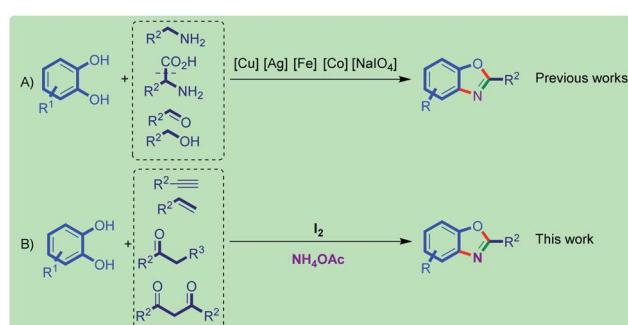


Fig. 1 Chemical structure of some naturally occurring and biologically important benzoxazole-based compounds.



Scheme 1 Synthesis of benzoxazoles using catechols.

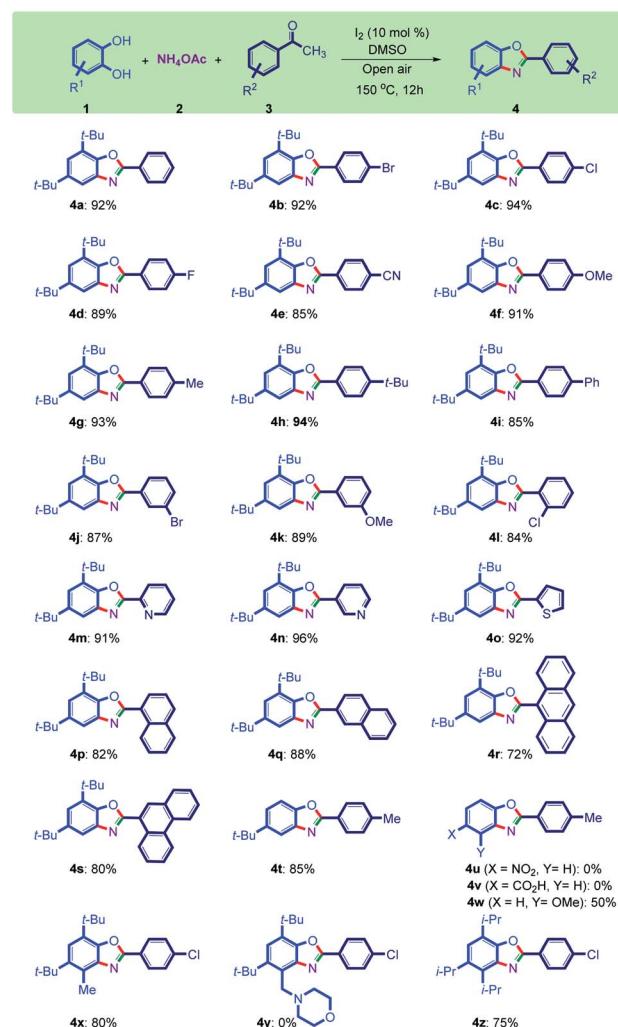
Results and discussion

The study was started by the reaction of catechol (**1a**), ammonium acetate (**2**), and acetophenone (**3a**) in the absence of catalyst in a dimethyl sulfoxide (DMSO) solvent at 140 °C; however, no benzoxazole product (**4a**) was observed (Table 1, entry 1). In another experiment, under solvent-free conditions, iodine (I_2 , 10 mol%) was used as the catalyst, and no product was observed again (Table 1, entry 2). To our delight, 75% of desired product **4a** was produced when DMSO was used as the solvent besides the use of 10 mol% of I_2 as the catalyst (Table 1, entry 3). Considering the important role of solvent here, other solvents were also tested (Table S1†). Except in DMF (about 30%), no product was observed in other solvents. The high yield in DMSO confirmed the I_2 –DMSO hybrid catalysis role, which is known.^{7,8}

By selecting DMSO as the solvent, different sources of iodine were checked, and among them, I_2 showed high activity (Table S2†). It was found that an elevated temperature of 150 °C furnished the product in a high yield of 92% (Table 1, entry 4).

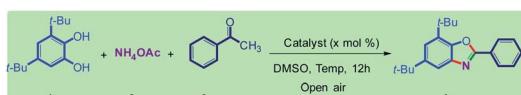
At lower temperatures, the yield decreased dramatically. For example, at 100 °C, a trace amount of product was detected (Table 1, entry 5). The catalytic loading evaluation revealed that 10 mol% of I_2 is suitable to obtain high yields of product (Table 1, entries 6 and 7). Moreover, the reaction was investigated under N_2 conditions and 81% of product was obtained (Table 1, entry 8). Among different nitrogen sources tested, ammonium acetate was recognized as the best one (Table S3†).

With the optimized reaction conditions in hand (Table 1, entry 4, bolded), the benzoxazole synthesis was then conducted using different ketones (Scheme 2). To illustrate the substrate scope and show the generality of the new method, differently substituted ketones were transformed to their benzoxazoles fruitfully (Scheme 2). Halogen-substituted acetophenone afforded the corresponding benzoxazoles (**4b**, **c**, **d**, **j**, **l**) in high yields. The synthesis of halogen-substituted benzoxazoles is important



Scheme 2 Synthesis of benzoxazoles from acetophenones under optimized conditions. Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), **3** (1.0 mmol), I_2 (10 mol%), DMSO (5.0 mL), open air. All yields are isolated.

Table 1 Optimization of the reaction conditions with acetophenone^a



Entry	Catalyst (x mol%)	Temp. (°C)	Yield 4a ^b (%)
1	None	140	0
2	I_2 (10)	140	0 ^c
3	I_2 (10)	140	75
4	I_2 (10)	150	92
5	I_2 (10)	100	Trace
6	I_2 (5)	150	61
7	I_2 (15)	150	87
8	I_2 (10)	150	81 ^d

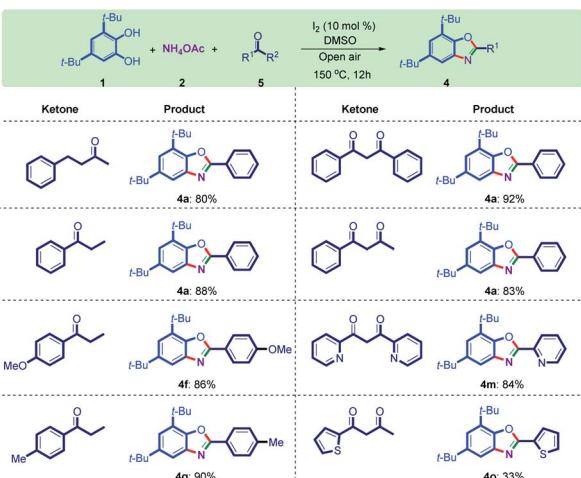
^a Reaction condition: **1a** (1.0 mmol), **2** (1.2 mmol), **3a** (1.0 mmol), DMSO (5.0 mL), open air. ^b Isolated yield. ^c No solvent was used. ^d N_2 .

because they are attachable to organic backbones using coupling reactions such as Heck, Suzuki, and Sonogashira.^{37,38}

Other acetophenones bearing functional groups such as cyano (**4e**), alkoxy (**4f**, **k**), aryl (**4i**), and alkyl (**4g**, **h**, **t**) moieties are working well under optimized conditions. The substituents in *ortho* and *meta* positions also tolerated the reaction conditions (**4j**–**l**).

As sterically hindered substrates, 2-chloroacetophenone and 1-acetonaphthone gave **4l** and **4p** in 84% and 82% yields, respectively. It seems that both electron-poor and electron-rich acetophenones worked well with this method. Heterocyclic substrates including pyridine and thiophene can be used in this protocol to synthesize bis(heterocycles) **4m**–**o** as useful ligands and/or biologically important molecules^{39–41} in more than 90% yields. Polyaromatic substrates also worked well with this methodology, and benzoxazoles containing naphthalene (**4p**, **q**), anthracene (**4r**), and phenanthrene (**4s**) were synthesized successfully in high yields.



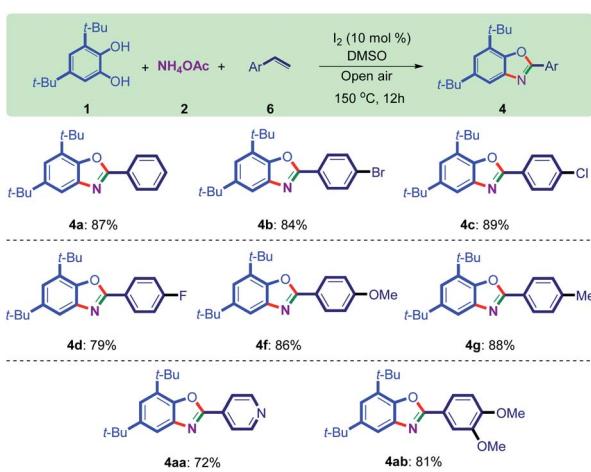


Scheme 3 Use of different ketone sources in the benzoxazole synthesis with catechols. Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), 5 (1.0 mmol), I₂ (10 mol%), DMSO (5.0 mL), open air. All yields are isolated.

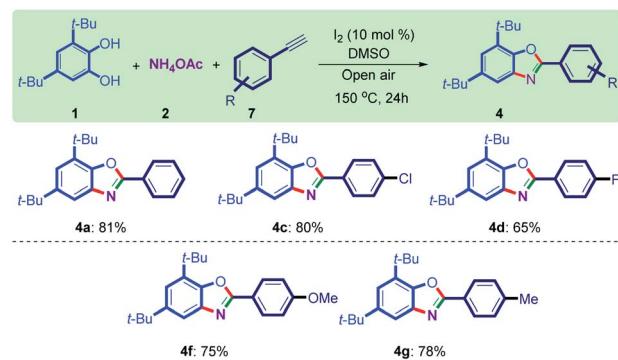
Other commercially available catechols including *tert*-butyl (4t), nitro (4u), carboxyl (4v), and methoxy (4w) groups were used in this reaction. However, only the electron-rich catechol was productively converted into benzoxazole derivatives by this procedure. The formation of compounds 4x and 4z represent the high efficiency of this method in the synthesis of poly-substituted benzoxazoles. Synthesis of compound 4y was not successful using its corresponding catechol containing a morpholine group.⁴²

This method was also checked with other ketones, and the results indicated that the method is also working with other 1,3-dicarbonyl compounds and aryl-alkyl ketones (Scheme 3).

Due to the course of our research on the development of this method for benzoxazole synthesis, it was found that styrenes can be used instead of ketones (Scheme 4).



Scheme 4 Synthesis of benzoxazoles from styrenes. Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), 6 (1.0 mmol), I₂ (10 mol%), DMSO (5.0 mL), open air. All yields are isolated.



Scheme 5 Synthesis of benzoxazoles from phenylacetylenes. Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), 7 (1.0 mmol), I₂ (10 mol%), DMSO (5.0 mL), open air. All yields are isolated.

The reaction of styrenes, catechols, and ammonium acetate was carried out in the presence of I₂ as the catalyst in DMSO at 150 °C to furnish benzoxazoles in good to excellent yields (Scheme 4). The results indicated that styrenes with electron-donating and electron-withdrawing groups are working with this procedure. Next, the applicability of this method was evaluated in the synthesis of benzoxazoles using phenylacetylenes instead of acetophenone, to further show the utility of this protocol in organic synthesis. Interestingly, the reaction of catechols, ammonium acetate, and phenylacetylenes also resulted in the production of benzoxazole 4a in 81% yield under our optimized conditions. The reaction was also checked with other phenylacetylene derivatives, and a satisfactory yield of products was obtained (Scheme 5).

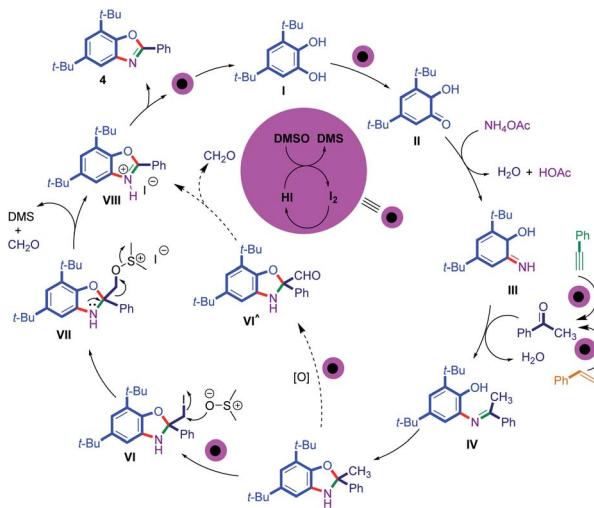
In order to highlight the utility of this methodology, a large-scale synthesis (50 mmol) of compound 4a was accomplished, and 70% of the product was isolated (Scheme 6).

In agreement with the previously reported catalytic cycle for benzoxazole synthesis and also I₂-DMSO catalysis, a possible reaction mechanism for this protocol is proposed (Scheme 7).^{7,18,20,29} According to the previous reports, phenylacetylenes and styrenes could be converted into acetophenone, thus the catalytic cycle was presented only for acetophenone.⁴³⁻⁴⁷ Moreover, we checked the reaction of styrenes and phenylacetylenes in the presence of iodine/DMSO, and the GC-mass analysis of the reaction mixture showed the presence of acetophenone. It seems that catechol (I) is converted into mono-quinone (II) in the presence of the I₂-DMSO catalyst system.^{32,35} The condensation reaction of II with ammonium acetate generates *o*-imino cyclohexadiene alcohol (III).³⁵ The generation of intermediate



Scheme 6 Large-scale synthesis of benzoxazole 4a by a new method. The TLC of the reaction is shown beside.





Scheme 7 Proposed reaction mechanism.

(IV) is possible by another condensation reaction of the imine group and carbonyl group of acetophenone.³⁵ The intermediate (V) is generated by an intramolecular cyclization reaction of intermediate (IV).^{29,31} The iodination of methyl group in intermediate (V) can produce the intermediate of VI.^{8,48} The generation of intermediate VII is assumed by the attack of DMSO to SP^3 carbon *via* a $\text{S}_{\text{N}}2$ reaction.^{8,48} The elimination of formaldehyde and dimethyl sulfide (DMS) in intermediate VII resulted in the generation of intermediate VIII.^{8,48} Eventually, oxidation of intermediate VIII using I_2 -DMSO and aerobic oxidative as an oxidant system leads to the final benzoxazole product and the catalyst system is regenerated to start the next cycle.⁸

Another plausible pathway is suggested based on the converted methyl group V to oxo derivative VI⁺ based on the reported evidence. Recently, Bathula and co-workers have monitored the oxidation of a methyl group to an oxo derivative under I_2 -DMSO by NMR spectroscopy.⁷ Finally, 2-aryl benzoxazole 4 was generated *via* loss of formaldehyde from intermediate VI⁺ and then deprotonation of VIII.⁷

Conclusions

We reported a new and practical method for the efficient synthesis of benzoxazole derivatives *via* the reaction of catechols, ammonium acetate, and alkenes/alkynes/ketones in the presence of an I_2 -DMSO catalyst system. This reaction occurs *via* some C–C and C–O bond cleavage processes to afford the final product under metal-free conditions in high yields.

Conflicts of interest

There are no conflicts to declare.

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