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Metal-Free Oxidative Condensation of Catechols, Aldehydes and NH_4OAc towards Benzoxazoles

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Abstract: Benzoxazoles extensively exist in biologically active compounds, natural products, pharmaceuticals and functional materials. Thus, facile and green synthesis of such valuable compounds from easily available substrates will make a contribution to drug, material, and fine chemistry. A method for the synthesis of benzoxazoles from catechols, aldehydes and ammonium acetate is developed using $NaIO_4$ as oxidant under metal- and additive-free conditions. A broad range of benzoxazoles including some fluorescent whitening agents, JTP-426467 and tafamidis analogues are synthesized in 56–95% yields with outstanding functional group tolerance. Mechanistic investigations suggest that an interesting *o*-iminocyclohexa-diene alcohol intermediate is involved in the reaction. These salient features of the protocol make it an alternative for the synthesis of benzoxazoles.

Keywords: metal-free; oxidative condensation; benzoxazole; catechol; aldehyde

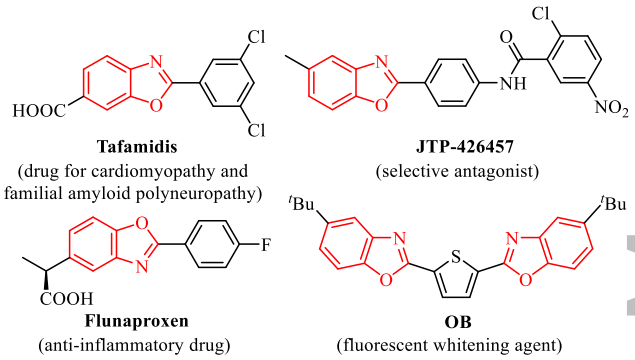

Figure 1. Representative Benzoxazole Derivatives.

Benzoxazoles are a class of ubiquitous structural motifs in biologically active compounds, natural products, pharmaceuticals and functional materials (Figure 1).[1] For example, tafamidis was approved as the first agent for the treatment of cardiomyopathy by the U.S. Food and Drug Administration (FDA) in 2019. Before this, it had been registered as a drug for familial amyloid polyneuropathy.[2] Medicinal chemistry applications of benzoxazoles also include anti-inflammatory drug flunoxaprofen and selective antagonist JTP-426467, etc.[3-5] In addition, fluorescent whitening agents such as OB, EBF, and KCB which contain benzoxazoles have been extensively applied in various fields.[6]

Traditional methods for the synthesis of benzoxazoles mainly rely on the following two strategies: (1) condensation of 2-aminophenols with carboxylic acid derivatives;[7] and (2) intermolecular coupling of halogenated aromatics with nitrogen-containing compounds (Scheme 1A).[8] Although these methods are well developed and are frequently applied,[9] the preparations of amino or halogenated substrates involve the explosive nitrification, the toxic halogenation, harsh reaction conditions (high reaction temperatures, stoichiometric amounts of strong acids or bases) and/or transition-metal catalysts. These run counter to the requirements of modern green chemistry.[10] Therefore, the synthesis of such valuable compounds from green and easily available substrates under mild reaction conditions is highly desirable,[11] which will make a great contribution to drug, material, and fine chemistry.

Catechols are structurally diverse (more than 300000 compounds containing a catechol component) and widely exist in various natural products, bioactive molecules, and drugs.[12] This type of compounds can be synthesized from phenol by oxidation or from glucose via microbial catalysis.[13] Thus, the synthesis of complex functional molecules by using these green and easily available chemicals as substrates is of great significance. In 2015, we

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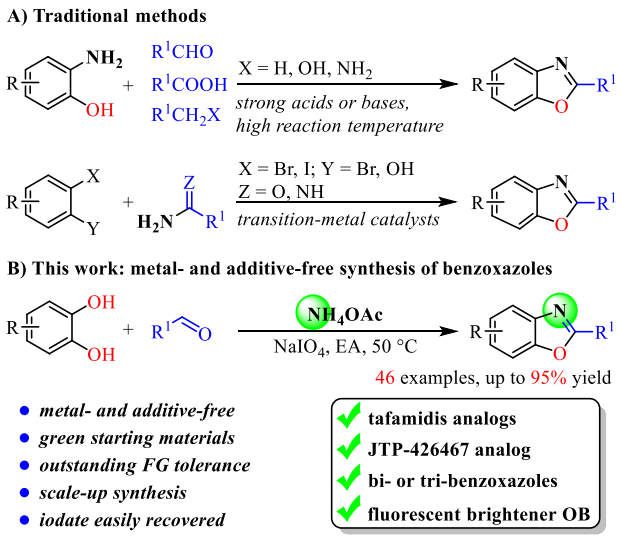


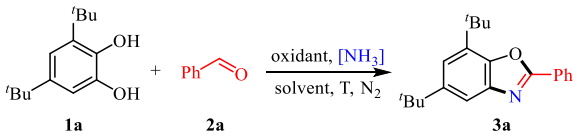
Scheme 1. Strategies toward Benzoxazoles

reported a CuBr catalyzed condensation of catechols with amines to construct benzoxazoles.[14] Afterwards, other methods for constructing benzoxazoles from catechols by Cu or Fe catalysis were also successfully developed.[15,16] However, the use of transition metals is sometimes toxic and may leave toxic traces of metals in the products, especially for the *N*-heterocycles, which makes the procedure hard to handle.

With our continuous interest in the synthesis of benzoxazoles,[14,17] herein, we describe an efficient synthesis of benzoxazoles via oxidative condensation of catechols with aldehydes and ammonium acetate (NH_4OAc, Scheme 1B). The reaction proceeds under mild conditions without the assistance of any metal and additive, which produces various benzoxazoles in totally high to excellent yields with compatibility of many sensitive functional groups, such as OH, NHR, COOH, and alkynyl groups, as well as drug analogues and fluorescent brighteners. Other than the known methods,[14-18] this reaction probably proceeds via an interesting *o*-iminocyclohexa-diene alcohol intermediate. Therefore, this protocol is highly appealing and practical.

We initially used NH_4Cl as the nitrogen source, 3,5-di-*tert*-butyl catechol (**1a**) and benzaldehyde (**2a**) as the test substrates for the optimization of reaction conditions. When the reaction was carried out in the presence of DDQ and NaOH in ethyl acetate (EA) at 50 °C for 3 h under nitrogen atmosphere, the desired oxidative condensation product (**3a**) was obtained in 50% yield (Table 1, entry 1). Other oxidants such as $NaIO_4$, $K_2S_2O_8$, $PhI(OAc)_2$, H_2O_2, $KBrO_3$, $NaIO_3$, Oxone, NaOCl, and Chloramine-T were examined (Table 1, entries 2–10), and a respectable yield (80%) of the desired product was gained using $NaIO_4$ as oxidant (Table 1, entry 2). Scanning on nitrogen sources (NH_4OAc, $HCOONH_4$, and $NH_3{\cdot}H_2O$) revealed that NH_4OAc (Table 1, entry 11) is superior to the others. Notably, due to easy decomposition of

Table 1. Optimization of the Reaction Conditions[a)]



1a 2a 3a

Entry	Oxidation	[NH_3]	Solvent	Yield (%)[b)]
1	DDQ	NH_4Cl	EA	50
2	$NaIO_4$	NH_4Cl	EA	80 (0[c)])
3	$K_2S_2O_8$	NH_4Cl	EA	53
4	$PhI(OAc)_2$	NH_4Cl	EA	trace
5	H_2O_2	NH_4Cl	EA	trace
6	$KBrO_3$	NH_4Cl	EA	20
7	$NaIO_3$	NH_4Cl	EA	9
8	Oxone	NH_4Cl	EA	21
9	NaOCl	NH_4Cl	EA	trace
10	Chloramine-T	NH_4Cl	EA	52
11	$NaIO_4$	NH_4OAc	EA	84 (92[c)])
12	$NaIO_4$	NH_4HCO_2	EA	37 (56[c)])
13	$NaIO_4$	$NH_3{\cdot}H_2O$	EA	47 (48[c)])
14[c)]	$NaIO_4$	NH_4OAc	CH_3CN	83
15[c)]	$NaIO_4$	NH_4OAc	$CHCl_3$	86
16[c)]	$NaIO_4$	NH_4OAc	DMF	91
17[c)]	$NaIO_4$	NH_4OAc	DCE	82
18[c)]	$NaIO_4$	NH_4OAc	THF	90
19[c)]	$NaIO_4$	NH_4OAc	dioxane	91
20[c)]	$NaIO_4$	NH_4OAc	ether	84
21[c)]	$NaIO_4$	NH_4OAc	toluene	69
22[c)]	$NaIO_4$	NH_4OAc	hexane	33
23[c)]	$NaIO_4$	NH_4OAc	EtOH	52
24[d)]	$NaIO_4$	NH_4OAc	EA	70
25[e)]	$NaIO_4$	NH_4OAc	EA	87
26[f)]	$NaIO_4$	NH_4OAc	EA	63
27[g)]	$NaIO_4$	NH_4OAc	EA	40
28[h)]	$NaIO_4$	NH_4OAc	EA	58
29[i)]	$NaIO_4$	NH_4OAc	EA	88
30[j)]	$NaIO_4$	NH_4OAc	EA	82

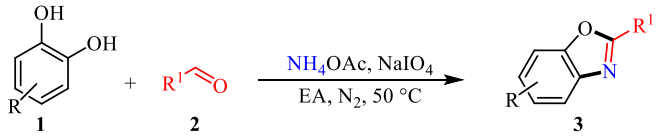
[a)] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.4 mmol), [NH_3] (0.4 mmol) and NaOH (0.4mmol) in the solvent (2 mL) at 50 °C under N_2 for 3 h. [b)] GC yield using tridecane as an internal standard. [c)] Without NaOH. [d)] 30 °C. [e)] 70 °C. [f)] $NaIO_4$ (0.2 mmol). [g)] NH_4OAc (0.2 mmol). [h)] **2a** (0.2 mmol). [i)] Air. [j)] O_2.

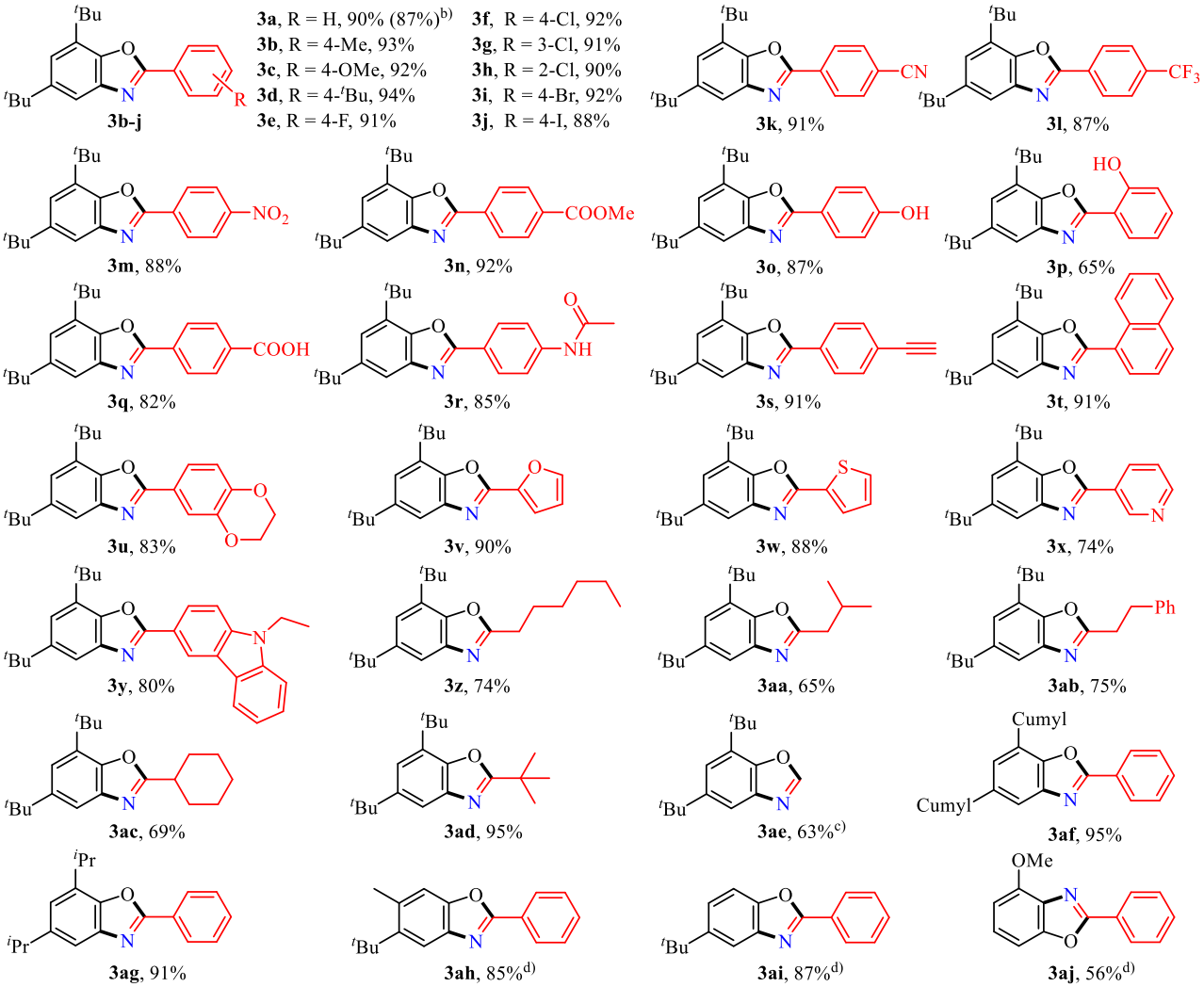
NH_4OAc, $HCOONH_4$, and $NH_3{\cdot}H_2O$ to release NH_3, higher yields without NaOH were observed (48%–92% vs 37%–84%, entries 11–13). We then sought to study the effect of solvents on the transformation. Interestingly, polar solvents such as acetonitrile (CH_3CN, 83% yield), chloroform ($CHCl_3$, 86% yield), *N*,*N*-dimethylformamide (DMF, 91% yield), 1,2-dichloroethane (DCE, 82% yield), tetrahydrofuran (THF, 90% yield), 1,4-dioxane (91% yield), and ether (84% yield) were proved to be favorable for this transformation (Table 1, entries 14–20), which allows the reaction to proceed smoothly in a variety of solvent environments. Less polar solvents (such as toluene and *n*-hexane) and protic solvents (such as

ethanol) were found to have a detrimental effect on the transformation (Table 1, entries 21–23). The reaction was also influenced by the reaction temperature, and no better results were obtained at the temperature lower or higher than 50 °C (Table 1, entries 24 and 25). Then, we attempted to reduce the loading of **2a**, $NaIO_4$ and NH_4OAc, but lower yields of **3a** were observed (Table 1, entries 26–28). Notably, the reaction provided slightly lower yields in air (88%) and O_2 (82%) to that in an inert atmosphere (Table 1, entries 29 and 30). This good compatibility of air and O_2 demonstrated the easy operation of this condensation reaction.

With the optimized conditions in hand, we investigated the scope and generality of the reaction. As shown in Table 2, this metal- and additive-free three-component condensation reaction exhibited a wide scope of substrates and an outstanding tolerance for functional groups, producing various benzoxazoles in high to excellent yields, regardless of electronic effects and positions of substituents on aldehyde skeletons. For aryl aldehydes, electron-donating benzaldehydes reacted with catechol **1a** efficiently and delivered the target products (**3b-d**) in excellent yields (92–94%). A variety of important electron-withdrawing groups such as F (**3e**, 91% yield), Cl (**3f**, 92% yield; **3g**, 91% yield; **3h**, 90% yield), Br (**3i**, 92% yield), I (**3j**, 88% yield), CN (**3k**, 91% yield), CF_3 (**3l**, 87% yield), NO_2 (**3m**, 88% yield), and CO_2Me (**3n**, 92% yield) groups were well tolerated in this system, enabling further possible functionalization at these positions. Notably, sensitive hydroxyl (**3o**, 87% yield; **3p**, 65% yield), carboxyl (**3q**, 82% yield) and amine (**3r**, 85% yield) groups, which are easily affected in metal-promoted reactions by chelation, were found to be compatible in this reaction as well. Alkynyl group that is vulnerable under the oxidative conditions was also amenable in

Table 2. Metal- and Additive-Free Condensation Reactions of Catechols with Various Aldehydes and NH_4OAc[a)]





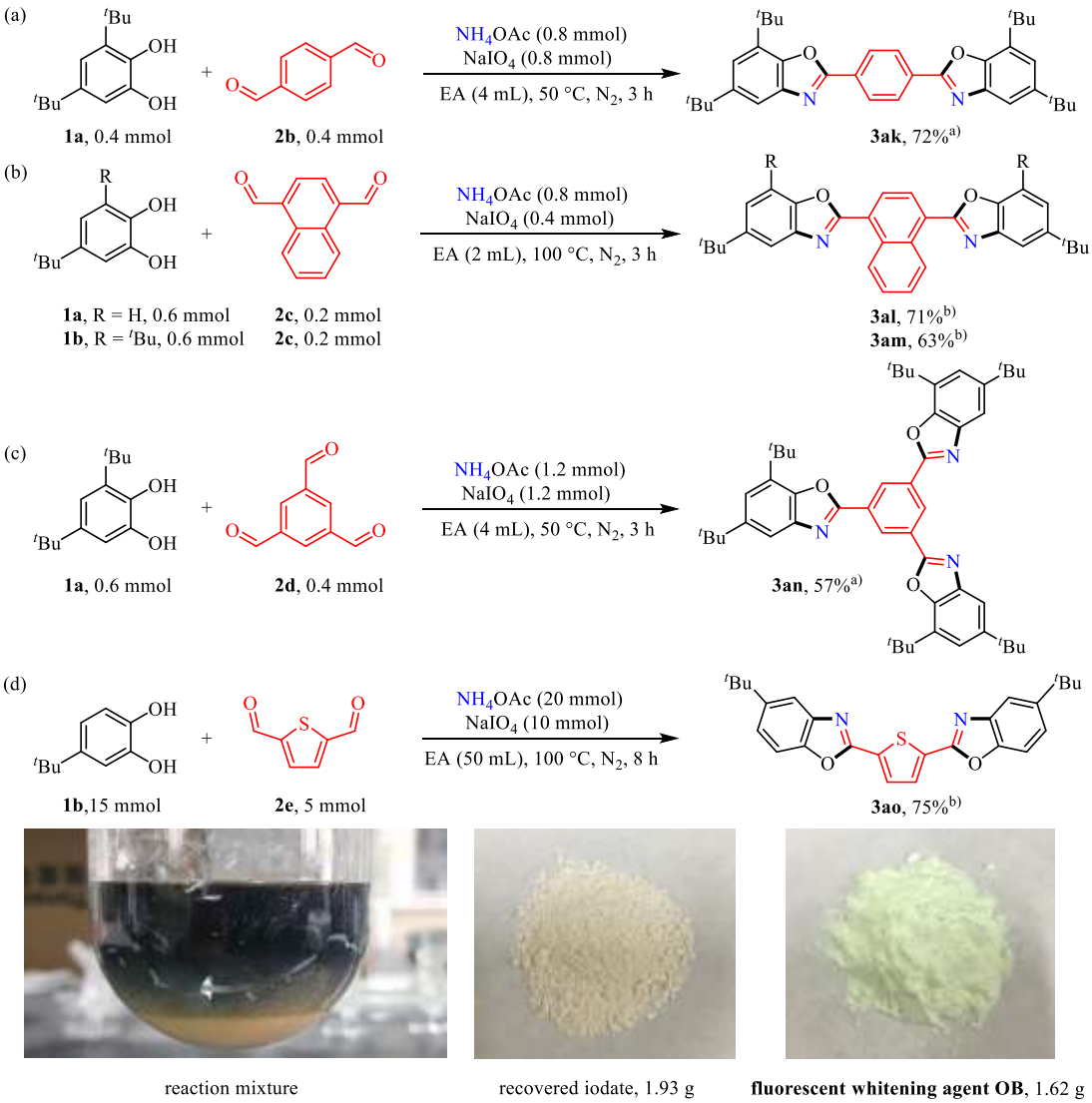
a) Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $NaIO_4$ (2.0 equiv) and NH_4OAc (2.0 equiv) in the EA (2 mL) at 50 °C under N_2 for 3 h. Isolated yields. b) 5 mmol scale. c) Using paraformaldehyde as substrate. d) 100 °C.

this protocol, giving the product (**3s**) in excellent yield (91%). Besides simple aryl aldehydes, 1-naphthaldehyde (**3t**) and 1,4-benzodioxin-6-carboxaldehyde (**3u**) were also good substrates for the reaction, which gave the corresponding products in 91% and 83% yields, respectively. Expectedly, heteroaryl aldehydes, such as furyl (**3v**, 90% yield), thienyl (**3w**, 88% yield), pyridyl (**3x**, 74% yield) and carbazolyl (**3y**, 80% yield) were all tolerable in the metal-free system. Alkyl aldehydes such as *n*-hexanal (**3z**, 74% yield), isovaleraldehyde (**3aa**, 65% yield), phenylpropanal (**3ab**, 75% yield), cyclohexyl formaldehyde (**3ac**, 69% yield), and pivalaldehyde (**3ad**, 95% yield) all gave the desired products in good to excellent yields. In addition, the reaction of catechol **1a** with paraformaldehyde could also furnish the desired product (**3ae**) in 63% yield.

Because of outstanding functional group tolerance and the widespread presence and easy availability of aldehydes, this protocol provides a possibility for the synthesis of a broad range of functional molecules containing benzoxazole skeletons without functional group restrictions, which cannot be easily obtained in aliphatic amines-involved reactions.[11,14-17]

Catechols with different substituted groups were also synthesized and investigated. 3,5-Disubstituted catechols could be well tolerated and gave the desired benzoxazole derivatives (**3af** and **3ag**) in 95% and 91% yield, respectively. Also, 4-(*tert*-butyl)-5-methylbenzene-1,2-diol could react with benzaldehyde and NH_4OAc, affording the corresponding benzoxazole **3ah** in 85% yield. Mono-substituted catechols with *tert*-butyl and methoxy were tested and proved to be applicable to this reaction (**3ai**, 87% yield; **3aj**, 56% yield). The low yield of **3aj** may be attributed to its low reactivity and stability of 3-methoxycatechol. Unfortunately, catechols with electron-withdrawing groups (such as *p*-Br and *p*-NO_2), 1,2,4-trihydroxybenzene and 2-mecaptophenol were ineffective in this reaction.

Besides, polyaldehydes such as terephthalaldehyde, 1,4-naphthalenedicarboxyaldehyde, and benzene-1,3,5-tricarbaldehyde also showed good reactivity, which furnished the corresponding bi- and trimeric benzoxazoles in good to high yields (**3ak**–**an**,



Scheme 2. Cyclization of Polyaldehydes. [a)] Yield based on catechols **1**; [b)] Yield based on aldahydes **2**.

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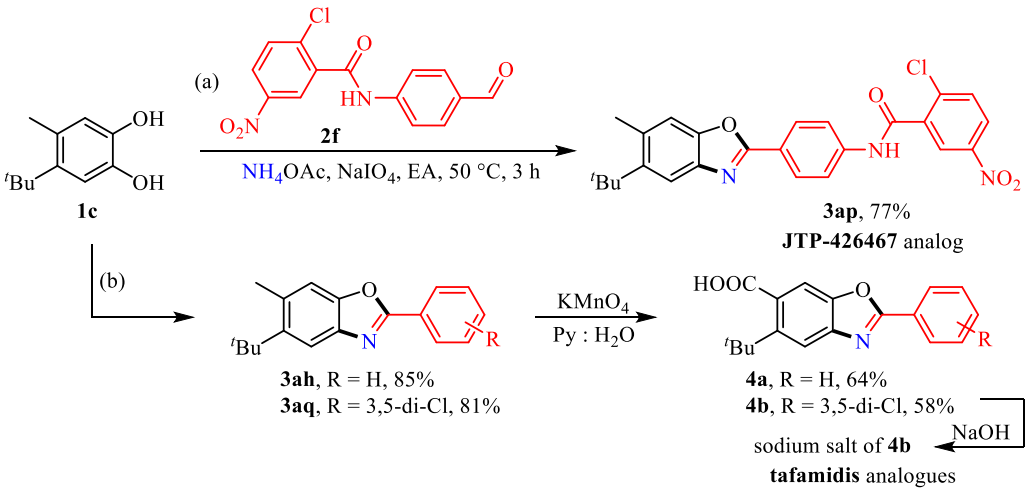
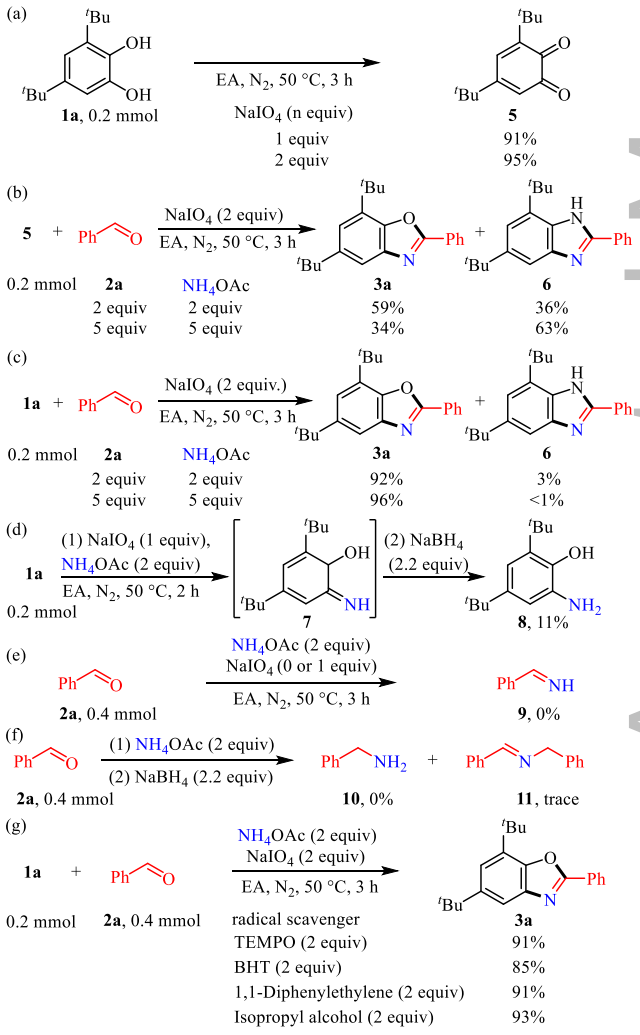


Scheme 3. Synthesis of JTP-426467 and Tafamidis Analogues

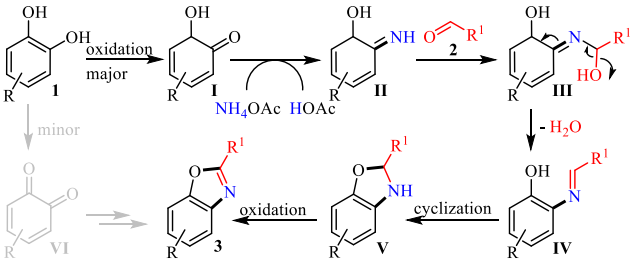
Scheme 2a-c). As far as we know, this is the first report for the synthesis of trimeric benzoxazole skeletons like **3an**. Notably, these structures hold special fluorescent properties, which have been utilized as fluorescent whitening agents and in the preparation of hole-transporting protective layers.[19] To further explore the utility of this mild protocol, the one-pot condensation reaction was carried out at gram scale. As shown in Scheme 2d, the commercial fluorescent whitening agent OB (**3ao**) could be easily prepared in 75% yield (1.62 g) at 5 mmol scale using 4-*tert*-butyl catechol, NH_4OAc and 2,5-thiophenedicarboxaldehyde as substrates. Notably, this procedure avoided the utility of *o*-aminophenol, which requires nitration of phenol and followed reduction in its preparation. In addition, the resulted iodate was easily recovered due to its insolubility in the reaction system. Thus, it is a good alternative to the synthesis of fluorescent whitening agent OB.

Finally, the current methodology was applied to synthesize pharmacologically active drug analogues. JTP-426467 is a selective antagonist for the peroxisome proliferator-activated receptor. When catechol **1c** was reacted with **2f** under the optimized conditions, JTP-426467 analog **3ap** was obtained in 77% yield (Scheme 3a). Additionally, tafamidis analogues **4a** and **4b** could also be synthesized by oxidation of the corresponding condensation products (**3ah** and **3aq**) in 64% and 58% yields, respectively (Scheme 3b). The above results well demonstrated the synthetic value of this method in organic synthesis, as well as chemical and pharmaceutical industry.

To gain an insight into the reaction mechanism, several control experiments were carried out (Scheme 4). Generally, the oxidative condensation of catechols proceeds via cyclohexa-3,5-diene-1,2-diones.[11,14,16-19] And 3,5-di-*tert*-butyl catechol **1a** could be easily oxidized to 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (**5**) in the presence of $NaIO_4$ (Scheme 4a). However, direct reaction of **5** with NH_4OAc and benzaldehyde gave **3a** in 59% yield, with concomitantly producing 5,7-di-*tert*-butyl-2-phenyl-1*H*-benzo[*d*]imidazole (**6**) in 36% yield. Higher loading of NH_4OAc and benzaldehyde led to the higher selectivity of **6** (63% yield, Scheme 4b). In sharp contrast, compound **6** was detected in trace



Scheme 4. Control Experiments



Scheme 5. Possible Reaction Mechanism

(3%) in the reaction system. And the higher loading of NH_4OAc and benzaldehyde (5 equiv) gave the lower yield of **6** (<1%, Scheme 4c). Thus cyclohexa-3,5-diene-1,2-dione was not the main intermediate.

To trap the possible intermediate, a reductant ($NaBH_4$, 2.2 equiv) was added to the reaction system portionwise over a period of 30 minutes (6 times) after stirring the reaction mixture for 2 h, and 2-amino-4,6-di-*tert*-butylphenol (**8**) was observed in 11% yield (Scheme 4d). Therefore, the *o*-iminocyclohexa-diene alcohol (**7**) that was probably formed by the condensation of mono-quinone with NH_4OAc may serve as an intermediate. Phenylmethanimine (**9**) that is formed by the condensation of benzaldehyde with NH_4OAc was a possible intermediate for the reaction,[15a] but it was not detected in the reaction system, nor its reduction product benzylamine (**10**, Scheme 4e and f). These results suggested that *o*-iminocyclohexa-diene alcohol (**7**) rather than phenylmethanimine (**9**) may serve as an intermediate for this reaction. Notably, this type intermediate is unprecedented in the synthesis of benzoxazoles. Radical inhibitors, such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), 1,1-diphenylethylene, and isopropyl alcohol, could hardly block this reaction, suggesting that the free-radical mechanism wasn't involved in this reaction (Scheme 4g).

On the basis of the experimental results above and literature precedent, a possible mechanism is illustrated in Scheme 5. Initially, mono-quinone **I** is formed by oxidation of catechols **1** in the presence of $NaIO_4$, which is condensed with NH_4OAc to generate *o*-iminocyclohexa-diene alcohol **II**. Then, the nucleophilic attack of **II** at aldehydes **2** leads to the formation of intermediate **III**. Imine intermediate **IV** is produced by the dehydration of **III** and followed an intramolecular cyclization of **IV** affords intermediate **V**. Finally, the desired benzoxazole **3** is produced via the oxidative dehydrogenation of **V**. Additionally, the reaction may involve a very minor path by the condensation of cyclohexa-3,5-diene-1,2-dione **VI** with NH_4OAc and aldehydes **2**.

In summary, we have successfully developed an method for the synthesis of benzoxazoles using catechols, aldehydes, and NH_4OAc as the substrates under metal- and additive-free conditions. A broad range of benzoxazoles, as well as bi-, and trimeric benzoxazoles, fluorescent whitening agent OB, JTP-426467 analog and tafamidis analogues are synthesized in 56–95% yields. Due to the very simple and mild reaction conditions, this reaction exhibits sensitive functional group tolerance. Many functional groups, such as NO_2, CF_3, OH, NHR, COOH, and alkynyl groups, furyl, thienyl, pyridyl, and carbazolyl are transferred to the desired products. In addition, aliphatic aldehydes are also good substrates for the reaction. These features cannot be easily achieved for other methods. Mechanistically, an interesting *o*-iminocyclohexa-diene alcohol intermediate is probably involved in the reaction, which avoids pollution and safety problems caused by the nitrification process. The advantages of this protocol, such as green and easily available starting materials, mild conditions, outstanding functional groups tolerance, scale-up operation and easily recyclable iodate, as well as compatibility of drug analogues and fluorescent whitening agents, highlight the broad applicability of the strategy. Therefore, it provides an alternative to the known ones.

Experimental Section

General experimental procedure for the synthesis of benzoxazoles: An oven-dried 25 mL Schlenk tube, which was equipped with a magnetic stir bar and charged with catechol **1** (0.2 mmol), NH_4OAc (0.4 mmol), and $NaIO_4$ (0.4 mmol), was evacuated and backfilled with N_2 three times. Then, premixed solution of EA (2 mL) and aldehyde **2** (0.4 mmol) were added. The reaction mixture was stirred at 50 ºC for 3 h and monitored by GC or GC-MS. Upon completion, the reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel with petroleum ether / ethyl acetate to afford the corresponding benzoxazole **3**.

Acknowledgements

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Metal-Free Oxidative Condensation of Catechols, Aldehydes and NH_4OAc towards Benzoxazoles

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