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A simple protocol for the synthesis of 2-arylbenzoxazoles by oxidation with *o*-iodoxybenzoic acid (IBX) and its application in the synthesis of arylbenzoxazole-containing amino acids

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This paper is dedicated with gratitude to our friend Professor Harry H. Wasserman on the occasion of his 90th birthday

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ABSTRACT

A simple protocol for the preparation of 2-arylbenzoxazoles has been developed based on the oxidation of phenolic Schiff bases with *o*-iodoxybenzoic acid (IBX), wherein the oxidant can be recycled. The robustness of this new protocol has been demonstrated in the synthesis of arylbenzoxazole-containing amino acids.

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2-Arylbenzoxazoles are an important group of target molecules by virtue of their special photophysical properties[1–3] and biological activities, including antitumor, antimicrobial, and antiviral properties.[4–6] It has also been reported that arylbenzoxazole-containing amino acids have high fluorescence quantum yields and can be engineered into convenient fluorescent probes.[7–13] Recently, it has been reported that 2-arylbenzoxazoles are novel cholesteryl ester transfer protein inhibitors,[14] and some 2-arylbenzoxazoles are highly selective amyloidogenesis inhibitors.[15] Generally, the synthesis of 2-arylbenzoxazoles can proceed by two strategies. One is the coupling of 2-aminophenol with carboxylic acid derivatives by dehydration, which can be catalyzed by a strong acid,[16] assisted by microwave condition,[17–21] or mediated by hexachloroethane and triphenylphosphine.[22] The other is the oxidative cyclization of phenolic Schiff bases, which are derived from the condensation of 2-aminophenols and aldehydes. In the latter case, various oxidants have been used, such as DDQ,[23] O_2 (promoted by activated carbon or catalyzed by Cu-nanoparticle),[24,25] $Mn(OAc)_3$,[26] $PhI(OAC)_2$,[27,28] $Th^{+\cdot}ClO_4^-$,[29,30] $BaMnO_4$,[31] NiO_2,[32] $Pb(OAc)_4$,[33] Deoxo-Fluor reagent,[34] $[Cp^*IrI_2]_2$,[35] Dess-Martin Periodinane,[36] and *tert*-butyl hypochlorite.[37] Preparation of 2-arylbenzozaxoles from phenolic Schiff bases in the presence of base and phototrigger have also been reported.[38] In the research on the preparation of arylbenzoxazole-containing amino acids, $Pb(OAc)_4$ was reported as the best oxidant,[11] though it is toxic and deleterious to the environment. Herein we report a simple protocol for the synthesis of 2-arylbenzoxazoles with *o*-iodobenzoic acid (IBX)[39] as the oxidant (Scheme 1), wherein the oxidant can be recycled.

IBX is an old hypervalent iodine reagent, but previously it has rarely been used in reactions due to its insolubility in most organic solvents.[39] In recent years, IBX has been rediscovered as a versatile oxidant in dimethyl sulfoxide (DMSO) and dimethyl formaldehyde (DMF) to oxidize alcohols to carbonyl compounds,[40,41] secondary amines to imines,[42] saturated carbonyl compounds to α,β-unsaturated carbonyl compounds,[43,44] phenols to *o*-quinones,[45] and so on.[46–48] Other than DMSO and DMF, it has also been reported that IBX can oxidize alcohols to aldehydes in ethyl acetate (EtOAc) at 80 °C.[49] This is an important improvement for the oxidative reactions with IBX, since the new protocol is very clean and the oxidant can be easily recycled. Therefore, we proposed the use of IBX for oxidizing phenolic Schiff bases to arylbenzoxazole in EtOAc.

The preparation of arylbenzoxazoles through the oxidative cyclization of phenolic Schiff bases involves three steps (Scheme 2). The first step is the condensation between aromatic aldehyde **1** and *o*-aminophenol **2** to form Schiff base **3**. The second step is the five-membered-ring formation from **3** to **4**. The third step is the oxidation of **4** to arylbenzoxazole **5**. In steps 1 and 3, water is produced, and in the presence of water, the equilibrium of the reaction moves backwards. Thus, part of the Schiff base **3** is hydrolyzed to form *o*-aminophenol **2**, which is in turn oxidized by IBX to form side products and results in a decrease in reaction yield. Therefore, removing water and increasing the stability of **2** under oxidative condition would be beneficial to the reaction yield. In

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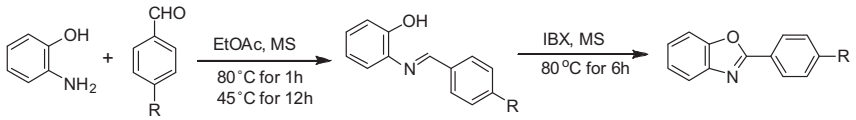
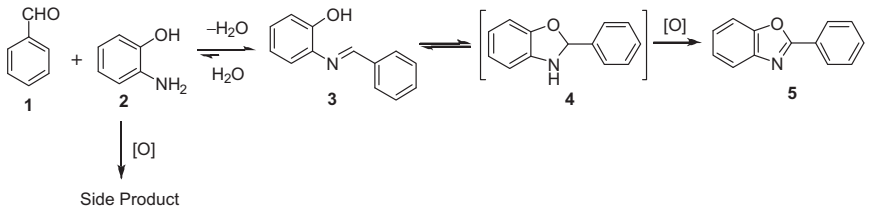


Scheme 1. Synthesis of 2-arylbenzoxazoles by IBX oxidation.



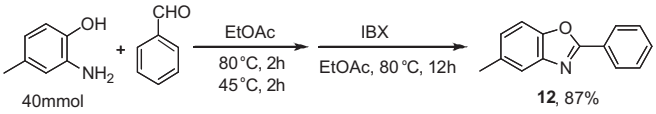
Scheme 2. Pathway for the synthesis of 2-arylbenzoxazole.

the reaction system, a Schiff base was generated from the condensation between *o*-aminophenol and aromatic aldehyde (1:1) in EtOAc. 4 Å molecular sieves (MS) were added to absorb water and 2 equiv of IBX was used as the oxidant.[50] A comparison between the yields of the reactions with or without the addition of MS is made in Table 1 (Scheme 1). With the addition of MS, in the case of benzaldehyde, the yield was improved from 69% to 73%. In the case of *p*-fluorobenzaldehyde, the yield was improved from 63% to 73%. Therefore, the addition of MS leads to improvement of the reaction yield. We also tried to mix *o*-aminophenol, benzaldehyde, IBX, and MS together in a one-pot reaction, but the yield was found to be low according to TLC analysis, which probably resulted from the fact that *o*-aminophenol is not stable under oxidative condition.

Then, we screened various *o*-aminophenols and aromatic aldehydes to explore the scope of the reaction. The reaction yields

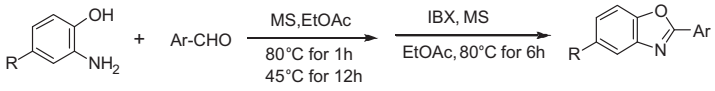
Table 1
Yields of the synthesis of 2-arylbenzoxazoles with or without MS

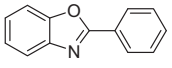
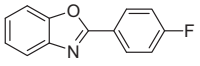
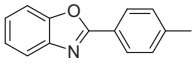
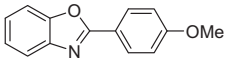
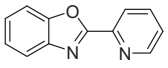
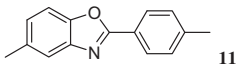
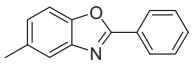
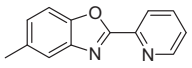
Entry	R	Yield (without MS)	Yield (with MS)
1	H	69%	73%
2	F	63%	73%

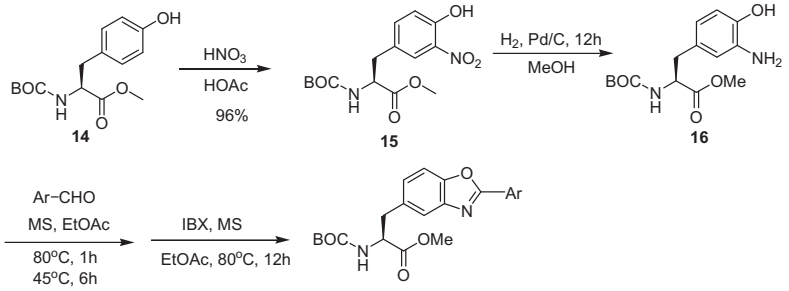


Scheme 3. Large-scale synthesis of **12**.

Table 2
Synthesis of 2-arylbenzoxazoles by oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-aminophenols and aldehydes



Entry	R	Ar	Product	Yield (%)
1	H	Ph	 **6**	73
2	H	*p*-F–C_6H_4	 **7**	73
3	H	*p*-Me–C_6H_4	 **8**	74
4	H	*p*-OMe–C_6H_4	 **9**	70
5	H	2-Pyridine	 **10**	70
6	Me	*p*-Me–C_6H_4	 **11**	78
7	Me	Ph	 **12**	88
8	Me	2-Pyridine	 **13**	98



Entry	Ar	Product	Yield/%
1	2-pyridine	**17**	79
2	Ph	**18**	81
3	p-Me-C_6H_4	**19**	71

Scheme 4. Synthesis of derivatives of arylbenzoxazole-containing amino acids.

are listed in Table 2. When *o*-aminophenol was used (entries 1–5), 70–74% yields of the desired products were obtained, regardless of the electronic properties of aromatic aldehydes. The substituents on aromatic aldehydes seem to have no major impact on the yield. When 4-methyl-2-aminophenol was used (entries 6–8), the yields were higher than those of the cases where *o*-aminophenol was used, probably because 4-methyl-2-aminophenol is more stable than *o*-aminophenol under oxidative condition. In addition, the reaction yield increased markedly with the electron deficiency of the aromatic rings of the aldehydes, among which 2-pyridinecarboxaldehyde gave the highest yield (98%). One possible reason is that the electron-withdrawing group on the aldehyde can deter the reversible hydrolysis of imine formed in the first step, thus suppressing byproduct formation from the oxidation of *o*-aminophenol (Scheme 2).

We then raised the scale of the reaction to 40 mmol (Scheme 3). In this large-scale reaction, Dean-Stark trap was used instead of MS to remove water and the amount of IBX was reduced to 1.5 equiv. The yield of the reaction reached 87% and the byproduct IBA from IBX could be easily recovered by filtration after the reaction.[44] The collected IBA was reoxidized to IBX by the standard procedure[51] in 80% yield.

This new protocol for 2-arylbenzoxazole synthesis was subsequently applied to the synthesis of arylbenzoxazole-containing amino acids. Three different arylbenzoxazole groups, that is, 2-pyridinyl (**17**), phenyl (**18**), and *p*-methylphenyl (**19**) benzoxazoles, were introduced in good yields (71–81% from **15**; Scheme 4). Compound **15** was synthesized from **14** by nitration with nitric acid in acetic acid.[52] Then, it was reduced to **16** by hydrogenation catalyzed by palladium (Pd) on activated carbon in methanol. After filtration and solvent removal, **16** was used directly in the next step. The arylbenzoxazole-containing amino acids **17**–**19** with sensitive BOC and CO_2Me protecting groups were successfully synthesized with our new protocol.

In summary, a simple protocol is developed for the synthesis of 2-arylbenzoxazoles from *o*-aminophenols and aromatic aldehydes with IBX as a recyclable oxidant. This protocol has been successfully employed in the synthesis of arylbenzoxazole-containing amino acids with interesting fluorescent properties.

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50. *Typical experimental procedure (see entry 1 in* Table 2*)*: A mixture of 2-aminophenol (423 mg, 4.0 mmol), benzaldehyde (435 mg, 4.0 mmol), and 4 Å molecular sieves (0.40 g, 0.1 g/mmol 2-aminophenol) in anhydrous ethyl acetate (10 mL) was placed in a 25 mL flask, stirred at 80 °C for 1 h, and kept at 45 °C for 12 h. Then, IBX (2.233 g, 2 equiv) and 4 Å molecular sieves (0.4 g, 0.1 g/mmol 2-aminophenol) were added. The mixture was stirred at 80 °C for 6 h. The reaction mixture was then filtered through Celite. After the filtrate was concentrated, the product was isolated by silica gel chromatography to give compound **6** as a white crystalline solid (569 mg, 73% yield).
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