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Synthesis of 2-arylbenzoxazoles via DDQ promoted oxidative cyclization of phenolic Schiff bases—a solution-phase strategy for library synthesis

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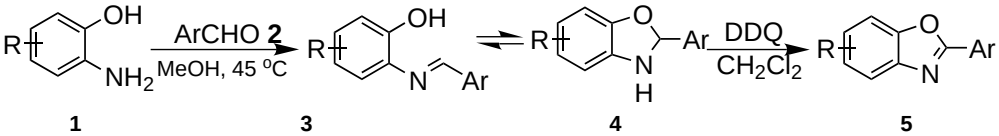
Abstract—The Schiff base derived from the condensation of *o*-aminophenol with benzaldehydes was induced to undergo oxidative cyclization in the presence of DDQ. The resulting 2-arylbenzoxazoles were separated from the reduced DDQ byproduct by treatment of reaction mixture with a strongly basic ion-exchange resin. The applicability of this chemistry to spatially separate library synthesis is demonstrated by the preparation of a 352-member library.

2-Arylbenzoxazoles posses the important biaryl pharmacophore and have exhibited a variety of biological activities, including antimicrobial and antitumor properties.[1] For example, a 2-arylbenzoxazole, AJI9561, was recently isolated as a cytotoxic metabolite from the extract of *Streptomyces* sp.[2] The two most popular methods for synthesizing 2-substituted benzoxazoles are: (1) coupling of carboxylic acids with 2-aminophenols by dehydration catalyzed by a strong acid;[3] and (2) the oxidative cyclization of phenolic Schiff bases, derived from the condensation of 2-aminophenols and aldehydes, using various oxidants such as $PhI(OAc)_2$,[4] $Mn(OAc)_3$,[5] $Th^+ClO_4^-$,[6] $Ba(MnO_4)_2$,[7] NiO_2,[8] and $Pb(OAc)_4$.[9] The first method has been used for making large quantities of pharmaceutical intermediates but typically requires activation of carboxylic acids under strongly acidic conditions at high temperature. The second method usually involves the use of transition metals that require purification by filtration or aqueous treatments to remove the metal byproducts.

Recently, both solution- and solid-phase methods for the synthesis of combinatorial libraries have gained tremendous popularity in pharmaceutical and academic institutions.[10,11] The preparation of compound libraries requires the development of superb methods for both the synthesis and purification in order to final products in a form suitable for biological testing. Although there have been several reports describing the solid-phase synthesis of benzoxazoles,[12] there have yet to appear any publications describing solution-phase libraries of benzoxazoles presumably due to the lack of any robust procedure for synthesis and purification. Herein, we will describe a mild and efficient protocol for the synthesis of 2-arylbenzoxazoles and the application to the synthesis of a 352-member compound library.

A solution-phase library approach is an attractive choice if reactions can be found that are high yielding and that generate byproducts that can be readily removed. Schiff base formation between 2-aminophe-



Scheme 1.

Keywords: 2-arylbenzoxazoles; DDQ; oxidation; ion-exchange resin; solution phase; library.
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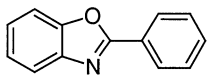
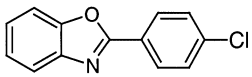
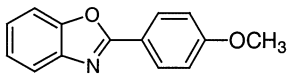
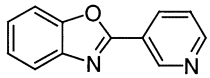
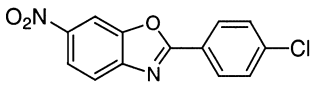
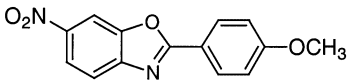
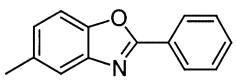
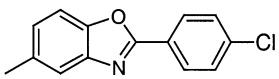
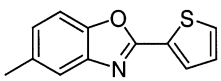
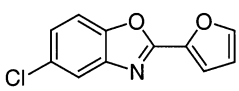
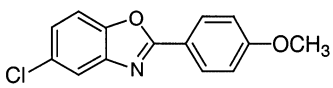
nols and aldehydes generates only water as a byproduct and conversion to the final products can be achieved with the appropriate selection of oxidants. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a versatile reagent for the oxidation of alcohols and selected amino groups. DDQ has also been described for the synthesis of benzoimidazoles from corresponding *o*-phenylenediamines and aldehydes.[13] Li and coworkers have also reported the DDQ oxidation of hydroxylamine groups to the corresponding isoxazolines.[14] We envisioned that DDQ would also be an efficient reagent for the oxidative cyclization of phenolic Schiff bases to produce 2-substituted benzoxazoles. Furthermore, we expected that 4,5-dichloro-3,6-dihydroxy-phthalonitrile (DDP), the reduced product of DDQ, could be easily removed from the reaction mixture by basic ion-exchange resins thereby enabling the solution-phase synthesis of the desired library.

We first examined whether 2-arylbenzoxazoles would result from the treatment of the phenolic Schiff bases **3**, preformed via the condensation of 2-aminophenols **1** and aromatic aldehydes **2** in methanol, with 1.1 equiv. DDQ in CH_2Cl_2 (Scheme 1). As shown in Table 1, 2-arylbenzoxazoles were produced in high to excellent yields by this method (Isolation A).[15] The desired oxi-

Table 1. Results of DDQ-promoted synthesis of 2-arylbenzoxazoles

Entry	Product	Isolation A % Yield[a]	Isolation B % Yield[b]	Isolation B % Purity[c]
1		93	75	94
2		95	84	94
3		83	63	87
4		74	57	97
5[d]		92	85	>99
6[d]		91	82	>99
7		89	89	97
8		96	90	91
9		94	85	97
10		81	55	86
11		82	76	>99

[a] Isolated yields by flash column chromatography;
[b] Crude yields after ion-exchange resin treatment;
[c] HPLC purities of Isolation B were determined by integration of peak areas at 255 nm without calibration;
[d] Refluxing in ethanol for the formation of **3**.

dation presumably occurred after the cyclization of phenolic Schiff bases with the phenol hydroxy moiety to give the corresponding oxazolines **4**. The 2-aminophenols with electron-withdrawing groups, which were predicted to be less reactive toward aldehydes, gave comparable results (entries 5–6, 10–11). It is noteworthy that the nitro compound needs higher reaction temperature (reflux in ethanol) for the formation of Schiff base to fulfill the final products in excellent yields. This method can employ aldehydes with both electron-donating (entries 3, 6 and 11) and electron-withdrawing groups (entries 2, 5 and 8). In addition, heterocyclic aldehydes can also be used for efficient preparation of various 2-heterocyclic substituted benzoxazoles (entries 4, and 11–12). These results have shown that DDQ is an efficient oxidation agent for the one-pot synthesis of benzoxazole-containing biaryl structures.

Encouraged by these preliminary results, we continued to explore the possibility of generating a library of this class of biaryl compounds. One prerequisite is to remove the DDP in a highthroughput format. Among various purification methods available for solution-phase combinatorial synthesis, the treatment of reaction solutions with ion exchange resins has proven effective in the removal of some acidic or basic byproducts,[16] and there is a recent report demonstrating applicability to a 96-well format.[17] We assumed that basic ion-exchange resins could be a good option to neutralize and absorb acidic DDP. Amberlite® IRA-900, which is a macroreticular resin with benzyltrialkylammonium functionality, proved to be the most efficient in this respect. The results are summarized in Table 1 as Isolation B.[18] Thus, 4 g of the aforementioned resin was freshly washed by methanol and used for the purification of each reaction on a 0.2 mmol scale, and this simple treatment gave the desired products in excellent purities. Since we used exactly equal amount of DDQ in the reaction leading to the comparable results as aforementioned 1.1 equiv. of DDQ being used, there was no need to use a polymer-bound scavenger resin for removing DDQ from the reaction solutions.[19]

A 352-member library was then prepared by this solution-phase strategy. Thus, 8 2-aminophenols and 44 arylaldehydes were prepared as 0.1 M stock solutions in methanol. They were then mixed in four 2 mL 96 (8×12) deep-well plates (0.2 mL of 2-aminophenol and 0.2 mL of aldehyde in each well). The resulting plates were heated in a oven at 45°C for 12 h. The methanol was then removed by a plate rotatory evaporator and the resulting residue was redissolved in 0.2 mL of 1,2-dichloroethane (DCE) in each well which was subsequently treated with 0.2 mL of 0.1 M DDQ in 10% THF in DCE. It was noteworthy that exactly equal amount of DDQ was used in order to facilitate subsequent purification. The addition of THF is to increase the solubility of DDQ. The reaction plates were agitated at room temperature for 2 h before the solutions were transferred to the corresponding filter bottom plates loaded with 0.4 g of freshly washed (MeOH) and dried Amberlite® IRA-900 in each well. Additional 0.4 mL of DCE was added to each well. The plates were clamped and rotated slowly for 2 h before filtering the solution into collection plates. The higher freezing temperature of DCE allowed the reaction solutions to be frozen so that possible leakage during the transfer was avoided. The final removal of solvents using a plate rotatory evaporator gave the desired compounds in the collection plates.

The library was characterized by LC–MS. The purity of the individual compound was determined by LC integration without calibration. As a result, 73% of the library showed purity greater than 80%, while 9% of the compounds with purities less than 50%.

In summary, the preparation of 2-arylbenzoxazoles was efficiently achieved by the condensation arylaldehydes with 2-aminophenols and subsequent DDQ-promoted oxidative cyclization reactions. This one-pot procedure is mild and efficient for producing individual arylbenzoxazole compounds. Moreover, the combination of this procedure with the use of basic ion-exchange resin allows for the combinatorial library synthesis. The current method represents the first example for benzoxazole library synthesis by a solution-phase strategy.

Acknowledgements

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15. Representative experimental procedure: To a solution of 2-aminophenol (0.109 g, 1.0 mmol) in MeOH (5 mL) was added *p*-anisaldehyde (0.136 g, 1.0 mmol). The resulting mixture was heated at 45°C for 12 h. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (10 mL) and DDQ (0.250 g, 1.1 mmol) was then added. After stirring at room temperature for 30 min, the resulting mixture was diluted with additional CH_2Cl_2 (10 mL) and washed sequentially with saturated Na_2CO_3 (10 mL×2) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. After evaporation, the crude was purified by flash column chromatography (10% EtOAc in hexane) to afford the desired product (0.187 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.05 (d, 2H, J=9.0 Hz), 7.34 (m, 2H), 7.58 (d, 1H, 9.1 Hz), 7.76 (d, 1H, 9.0 Hz), 8.22 (d, 2H, 9.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 55.9, 110.8, 114.8, 120.0, 120.1, 124.8, 125.0, 129.8, 142.7, 152.6, 162.8, 164.0.
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18. The material loss, as indicated by crude yields in Table 1, was mainly due to the binding of the product to the resin. In order to keep the same protocol as used in the final library synthesis, we did not use excessive solvent, which was limited by the volume of the collection plate, to wash the resin to improve the yields.
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