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A versatile synthesis of bis[2-(2′-hydroxylphenyl)benzoxazole] derivatives as zinc sensors†

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A versatile synthetic route has been developed to prepare 2, 5-bis(benzoxazole-2-yl)benzene-1,4-diol derivatives **2**. Although one of the derivatives (**2b**) has recently been shown to exhibit an excellent response to Zn^{2+} cations, the low yielding synthetic route will likely prevent its wide application. This report describes an improved synthetic procedure to obtain **2**, thereby making this class of compounds available for biologically relevant studies. An effective synthesis has been developed for 2-aminophenol derivative **6**, which bears a carboxylate group in the desired position. The strategy allows construction of bis(benzoxazole) compound **5**, where the built-in ester group can be easily converted to either a hydroxymethyl or a bromomethyl group to introduce the zinc-chelating ligand.

Introduction

In recent years, fluorescent sensors have emerged as useful tools for molecular imaging.[1] Among the optical imaging technologies, near infrared (NIR) fluorescence (700-1000 nm) has received immense attention owing to its low absorption and autofluorescence from organisms and tissues in the NIR spectral range.[2] The attractive features of NIR fluorescence dyes include minimized background interference, improved tissue depth penetration and image sensitivity,[3–5] which enables the detection of molecular activity for *in vivo* applications.[6] An ideal NIR probe should exhibit a large Stokes shift, in order to minimize interference between excitation and emission signals. Additionally, a desirable NIR probe should be integrated with a suitable chemical event that can generate a large optical response when responding to a specific analyte of interest.[2] Our recent studies show that 2, 5-bis(benzoxazole-2-yl)benzene-1,4-diol derivatives **2** [2,5-bis(HBO)] can exhibit a remarkable optical response upon zinc binding, giving the turn-on emission in both the visible (at ~550 nm) and NIR regions (at ~750 nm).[7–9] The fluorescence properties of the sensor appear to be quite sensitive to the substituents present on benzoxazole moiety **B** (Fig. 1). Although sensor **2b** exhibits better performance than **2a**,[9] the current synthetic route to **2** suffers from low yields (total yield <1%). It is, therefore, highly desirable to develop an efficient synthesis of **2**, in order to facilitate its application in various studies.

One of the essential components in bis(HBO) sensor **2b** is the di-2-picolylamine (DPA) group, which is used to selectively bind the zinc cation to trigger the subsequent NIR emission from the zinc complex **3b**.[9] In the previous report, bromination of the methyl group (on benzoxazole **A** of compound **1**) was the bottleneck for the synthesis of bis(HBO) system due to the low yield (12.1%). In addition, bromination *via* a radical mechanism makes it a synthetic challenge to include any primary or secondary alkyl groups on benzoxazole **B**, which hampers the study of substitution effects on the optical properties. In order to overcome the drawback of the existing approach, we decided to explore the alternative routes to introduce the DPA group. Herein, we report a versatile and efficient synthesis of the bis(HBO) system, which not only provides bis(HBO) **2a** and **2b**, but also new derivatives.

In the previous design, the low yield of bromination step was introduced at the late stage of synthesis. Part of the problem is that functionalization of the Ar–CH_3 moiety is difficult. In the new molecular design, benzoxazole fragment **A** of bis(HBO) **4** includes a more reactive benzylic hydroxy group, which could be transformed to DPA group in high yield. The synthetic design is based on the following knowledge: (a) bromination and tosylation of benzylic hydroxyl group can be accomplished in more than 90% yield;[10,11] (b) replacement of Br or OTs with a chelating group, such as DPA, has also been reported in up to 99% yield.[10,11] As shown in Scheme 1, the efficient synthesis is dependent on the construction of key intermediate **4**, which could be obtained by reduction of ester **5** or direct coupling between **8** and **7**.

Our initial attention was directed to the synthesis of 2-aminophenol derivatives **6** and **8** (Scheme 2). First, direct nitration of **9** with nitric acid failed to produce the desired

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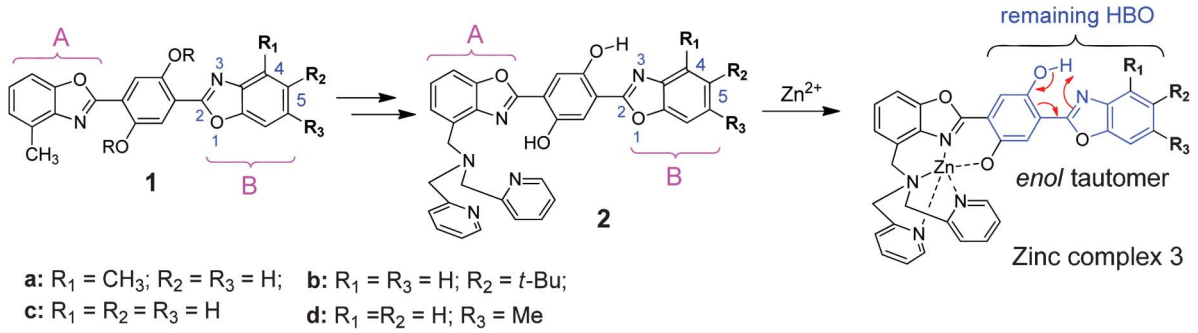


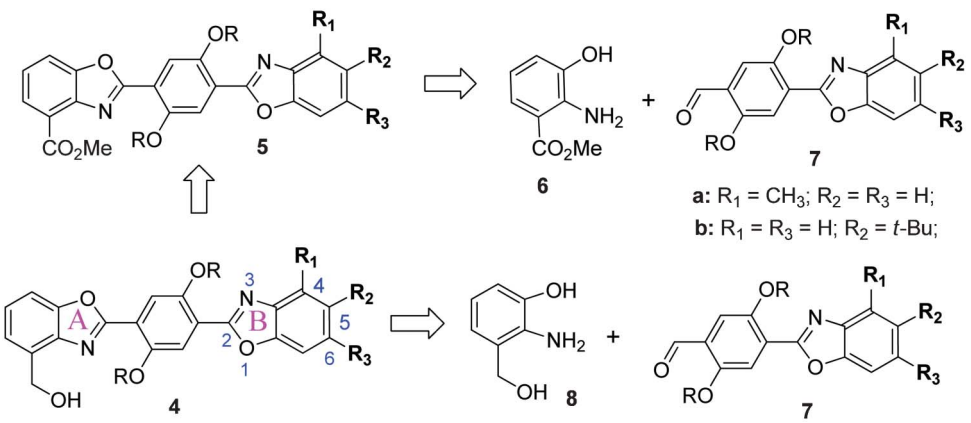
Fig. 1 Structure of bis[2-(2′-hydroxylphenyl)benzoxazole] and their zinc complexes.

nitro compound **12** in a reasonable yield, because the nitration of phenol led to precipitation of a mixture of nitro products which were hard to separate from each other. Therefore, the phenol **9** was converted to **10**, which could be completely dissolved in nitric acid solution. Interestingly, nitro compound **11** precipitated out as a white solid, which could be easily separated from the other nitro by-products by filtration. The nitro compound **11** could be further purified by recrystallization in MeOH or EtOAc–hexane to give large colorless square crystals of the pure product in 50–60% yield. Deprotection of the methoxy group was successful with $AlCl_3$ in DCM to give **12** in almost quantitative yield, and the deprotection could be carried out on a gram scale.[12] Selective reduction of the nitro group using Pd/C gave the desired compound **6** in quantitative yield.

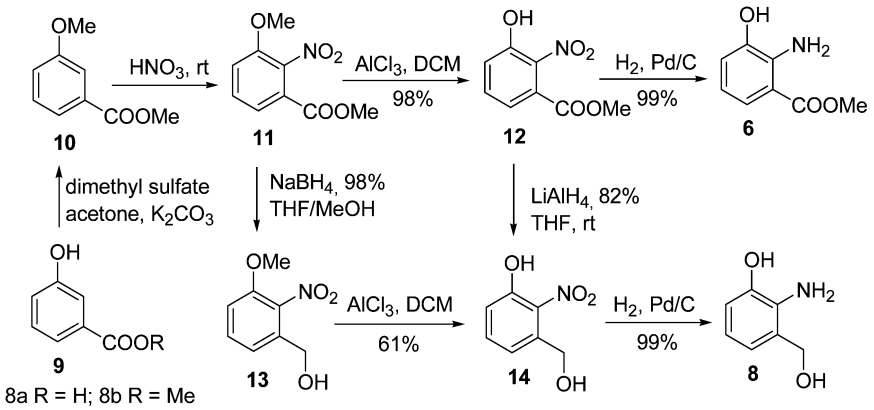
Our next target was the synthesis of 2-aminophenol derivative **8**, which was desirable for the construction of **4** (Scheme 1). Selective reduction of carboxyl ester **11** with $LiAlH_4$ in dry THF or $NaBH_4$ in THF–MeOH gave **13** in 92–98% yield (Scheme 2). The deprotection of the methoxy group of **13** by $AlCl_3$, however, gave **14** in only 61% yield, along with some unreacted **13**. Deprotection of **13** by BBr_3 also gave **14**, although the reaction mixture contained several unidentified by-products. Selective reduction of ester **12** with $NaBH_4$ in THF–MeOH did not proceed. We finally found that **12** could be reduced by $LiAlH_4$ in anhydrous THF to afford **14** in about 82% yield. Then, the desired product **8** was prepared by hydrogenation of **14** catalyzed by Pd/C.

With the convenient synthesis of 2-aminophenol derivatives **6** and **8** in hand, our attention then turned to the construction of the benzoxazole **A** from aminophenol **6** (or **8**) and aldehyde **7b** (Schemes 1 and 3). To our surprise, the reported catalysts and methods,[13] such as $Mn(OAc)_3$,[13d] $KAl(SO_4)_2$,[13e] $Pb(OAc)_4$,[13f] $Ba(MnO_4)_2$,[13g] and DDQ[4–6] did not work at all in this case. When the reaction of **6** and **7b** was monitored carefully by TLC, we found that the imine intermediate **I** was not formed after the reaction mixture was refluxed in EtOH or toluene overnight. A likely reason for this is the large steric hindrance. After exhaustive exploration, we were happy to find that Tagawa's method using O_2 with activated carbon worked very well in this case,[14] resulting in formation of bis(HBO) **5b** in as high as 78% yield. The coupling of **8** and **7b** was also carried out with Tagawa's method, however it gave **4b** in only 42% yield. Thus, the reaction of **6** and **7** was adopted to obtain the key intermediate **5**.

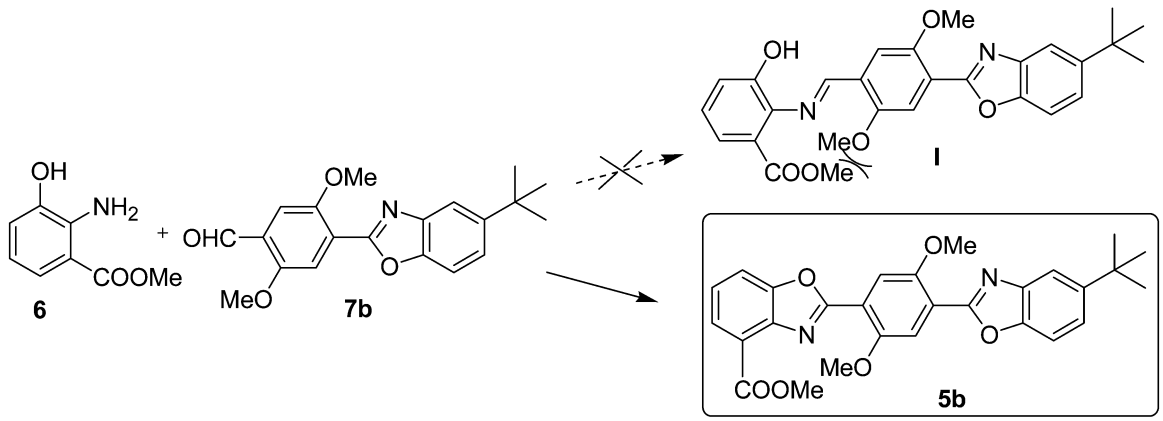
The reduction of the carboxylic ester group of **5** was then studied using different methods (Scheme 4). Though $LiAlH_4$ is



Scheme 1 Synthetic design for bis(HBO).



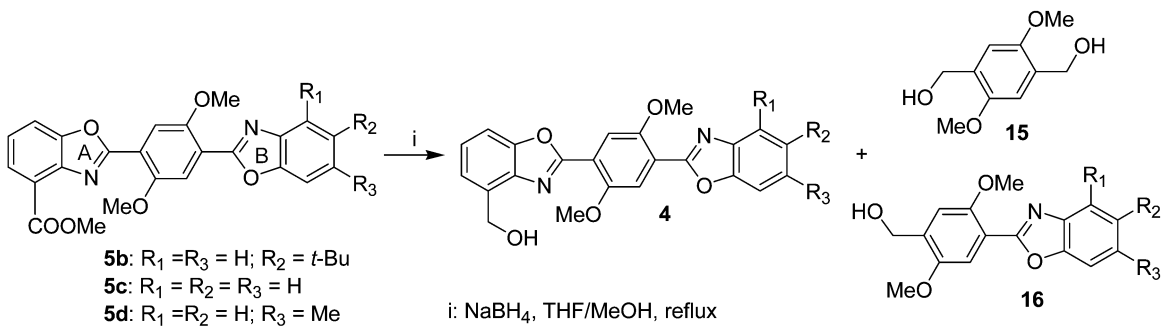
Scheme 2 Synthesis of the key intermediates **6** and **8**.



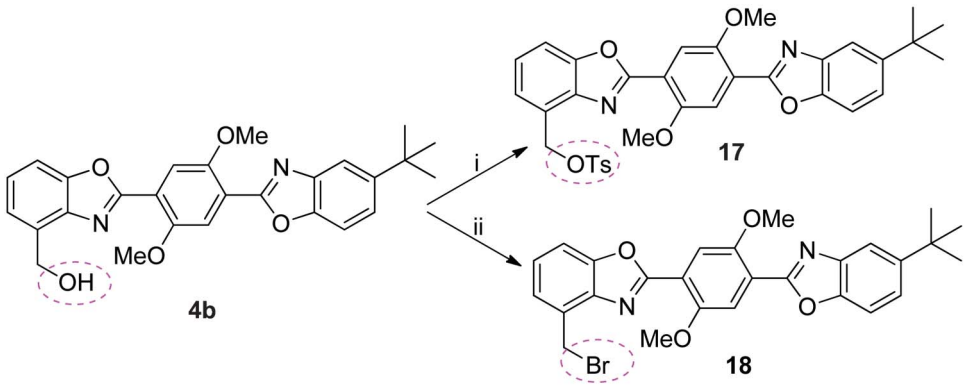
Scheme 3 Construction of the benzoxazole **A**.

well-known to be an efficient reducing reagent for esters, both benzoxazole rings **A** and **B** could not survive the harsh reaction conditions, resulting in the isolation of compound **15** as the major product. Furthermore, reduction by $NaBH_4$ in MeOH also resulted in partial decomposition of the benzoxyl rings as well, but a small amount of **16** was observed in the reaction mixture (see **16d** in SI). Finally, we found that in anhydrous THF with $NaBH_4$, both benzoxyl rings were stable even under reflux conditions. Careful reduction by $NaBH_4$ in THF and treatment with MeOH at the end of the reaction resulted in 82–88% yield of compound **4** (see details in SI).

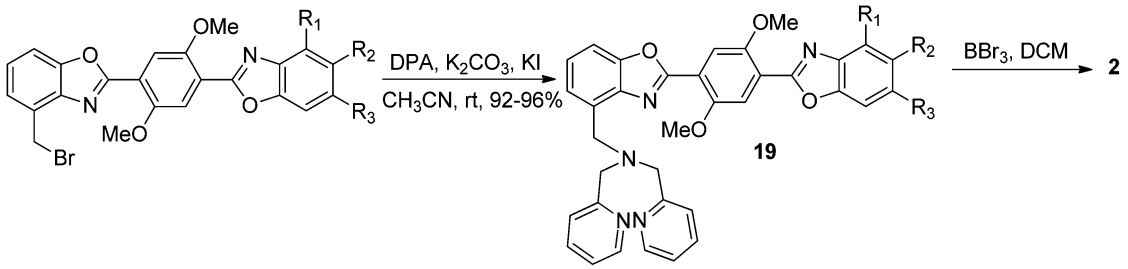
Subsequently, transformation of the benzylic hydroxyl to a better leaving group was studied (Scheme 5). When using pyridine, TEA or Na_2CO_3, the tosylation of **4b** did not proceed at all. Treatment of **4b** with NaH (a stronger base) in THF, however, afforded tosylation product **17** in only about 30%



Scheme 4 Reduction of the carboxylic ester.



Scheme 5 Transformation of the benzylic hydroxyl group to better leaving groups.



Scheme 6 Synthesis of bis[2-(2′-hydroxylphenyl)benzoxazole] zinc sensor **2**.

yield, along with several unidentified byproducts, which made subsequent purification a very difficult task. The results suggested that the benzoxazole rings were not stable under strongly basic conditions. Fortunately, bromination of **4** by PBr_3 in acetonitrile gave **18** in excellent yield (up to 99%). The replacement of bromide by DPA was also found to proceed smoothly in acetonitrile in the presence of K_2CO_3 at room temperature (1–2 h). Subsequent deprotection of the methoxy group using BBr_3 was successful as reported[7,15] to give the final product **2** (Scheme 6).

Conclusions

In summary, a versatile and efficient synthetic route to bis[2-(2′-hydroxylphenyl)benzoxazole] derivatives has been developed. The developed synthetic procedure greatly improved the production yields of sensor **2b**, thereby making the compound available for various applications. In addition, the method can be used to obtain more derivatives with different functional groups, which are necessary to examine the substitution impact on the fluorescence sensor properties. As an example, **2d** was synthesized, which would be difficult to accomplish using the reaction sequence for **1** → **2**, because both methyl groups are reactive. Since bis(HBO) sensor **2** has attractive characteristics for zinc detection (large Stokes shift and NIR emission), the developed synthetic method for **2** thus makes this material accessible for use in relevant fields. In addition, the developed methodology could be used for synthesis of a wide range of benzoxazole compounds and materials.

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