Reports

Diversity Oriented Synthesis of Benzimidazole and Benzoxa/(thia)zole Libraries through Polymer-Supported Hypervalent Iodine Reagent

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The development of new therapeutic agents, as well as the identification of molecular probes for the study of the chemical/biological interfaces, is one of the major goals in biomedical research. In this context, the availability of large libraries of small organic molecules, covering as much chemical space as possible, is seen as the only means which guarantees potential modulation of the many biological targets that are ultimately being unveiled by genomics.[1] Therefore, advances in drug discovery depend heavily on the availability of synthetic transformations that allow the rapid assembly of complex molecular frameworks providing maximum diversity.

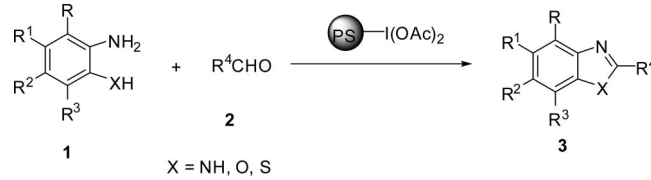
Low molecular weight nitrogen containing heterocycles are securing their place among the most highly recognized pharmacophores.[2] Among them, the benzo fused imidazoles, oxazoles, and thiazoles are of particular interest, since they are well-known to exhibit a broad range of biological activities.[3] They are also showing interesting utility in advanced material science such as nonlinear optics (NLO),[4] organic light-emitting diodes (OLED),[5] and liquid crystals.[6] Consequently, benzimidazoles and benzoxa/(thia)zoles are prized as potential drug candidate and biological probes (Figure 1).

The retro-synthesis of these heterocycles suggests that they could be synthesized by coupling of the amine component **1** and aldehyde or acid derivative component **2** (Figure 2).

Polymer-supported combinatorial chemistry is an efficient methodology for the construction of compound libraries and has been applied to drug discovery, catalyst development, and material science.[7] The use of a polymeric support in combinatorial chemistry facilitates handling and purification of polymer-bound intermediates and separation of products.[8] Another important advantage of using solid supported reagents is that the solid support can easily be filtered off, recovered, and reused. This is environmentally safe.

There are a few reports related to the synthesis of functionalized benzimidazoles, benzoxazoles, and benzothiazoles by combinatorial synthesis. In most of the combinatorial approaches for the synthesis of scaffold **3**, either the carboxylic acid derivative **2** or the amine **1** has been attached to a resin and then it has been fused to its complement (**1** or **2**) under strongly acidic conditions.[9] Attaching either the amine **1** or the aldehyde/acid derivative **2** to the solid support restricts the diversity of the libraries. For example, in the combinatorial synthesis of bezimidazoles and benzoxa(thia)zoles reported by Hioki et al.,[10] the substitution R^2 at the 2-position is limited to only benzoic acid derivatives.

Scheme 1



In order to improve the diversity in the libraries of scaffold **3** via a combinatorial approach, we attempted to couple amine **1** with an aldehyde **2** in the presence of a solid supported hypervalent iodine reagent, poly[4-diacetoxyiodo] styrene (PDAIS) (Scheme 1). PDAIS was synthesized according to our reported procedure.[11] The use of PDAIS in the combinatorial synthesis of benzimida(oxa/thia)zoles gives the benefits of solid support and the extra advantage of the diversity not being lost in the libraries from any point as in the case of earlier reports.

The direct coupling of *o*-phenylenediamine **1a** with benzaldehyde **2a** in absence of PDAIS resulted to the formation of a complex mixture from which 2-phenyl benzimidazole **3a** (30%), 1-benzyl-2-phenyl-1*H*-benzo[d]imidazole **4a** (29%), and 2-phenyl-2,3-dihydro-1*H*-benzo[d]imidazole **5a** (15%) were isolated (Scheme 2). A detail mechanistic study on direct coupling of *o*-phenylenediamine and benzaldehyde was carried out by Smith and Ho.[12] When we carried out the reaction using 1.5 equiv of poly[4-diacetoxyiodo] styrene only **3a** was isolated in 95% yield. The presence of PDAIS accelerates the synthesis of benzimidazoles by fast oxidation of in situ generated intermediate **5a**. PDAIS is highly selective as it does not oxidize the aldehyde present in the reaction mixture.

Thus, we propose here a general mechanism for PDAIS mediated synthesis of benzimidazoles, benzoxazoles, and benzothiazoloes (Scheme 3). Reaction of amine **1** with aldehyde **2** generates an imine **6** which undergoes intramolecular cyclization to form **5**. PDAIS abstracts the two hydrogen selectively from **5** to generate the final product **3**.

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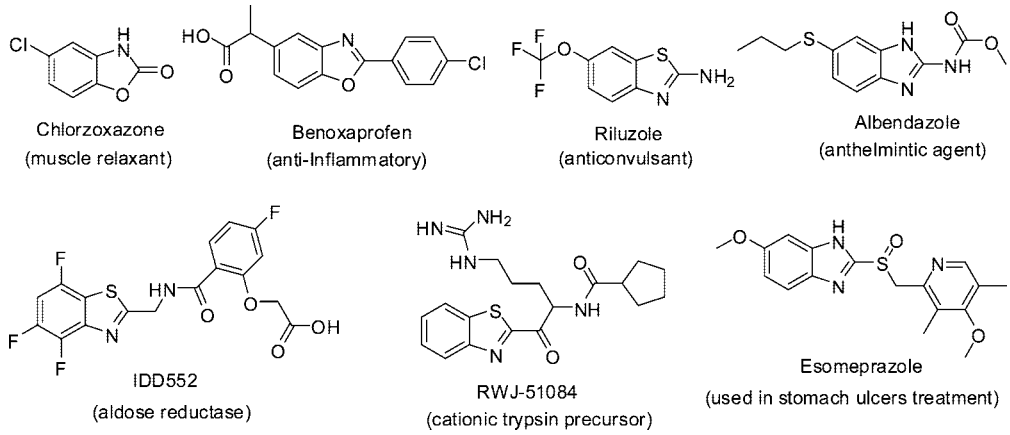


Figure 1. Benzimidazole, benzoxazole, and benzothiazoles drugs.

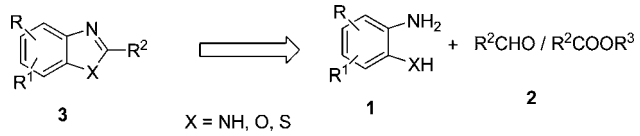


Figure 2. Synthetic approach for benzimidazoles and benzox-a(thia)zoles.

The amine component could be substituted *o*-phenylene-diamine but with aliphatic diamines like ethylene diamine the desired products were not formed (Figure 3). The reaction gives excellent yields of products with *o*-arylenediamines. From the diversity point of view, the aldehyde could be aliphatic, aromatic and heterocyclic (Figure 4). We have synthesized a PDAIS mediated library of benzimidazoles (Figure 5).

The reaction is quite general and could be equally applied for the synthesis of benzoxazoles and benzothiazoles. We synthesized the PDAIS mediated synthesis of benzoxazoles (Figure 6) and benzothiazole (Figure 7) using the similar protocol. High yields of products were obtained in just a few minutes.

Typical Experimental Procedure for the Synthesis of Benzimidazoles (3a−j)/Benzoxazoles (7a−m)/Benzothia-

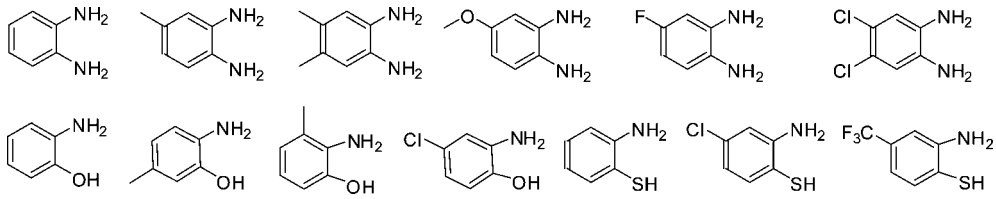


Figure 3. Sublibrary of amines.

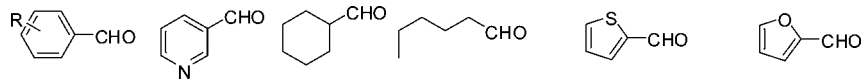
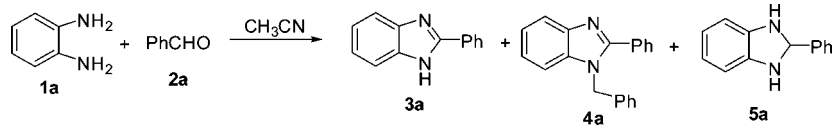
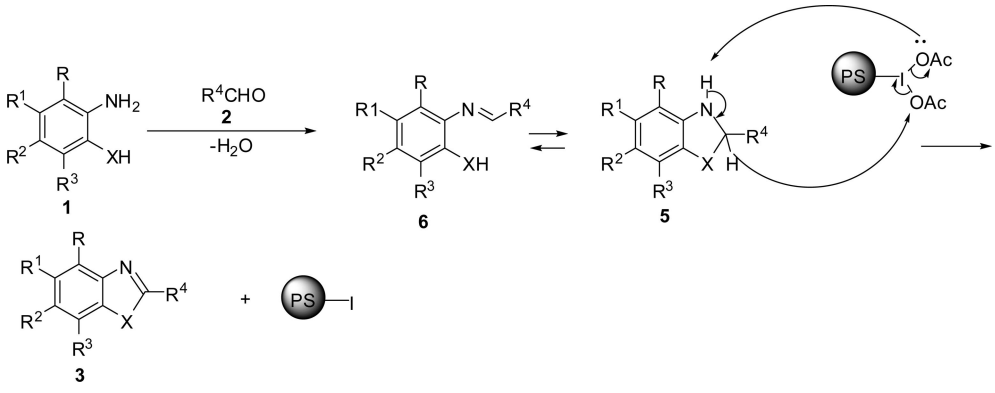


Figure 4. Sublibrary of aldehydes.

Scheme 2. Coupling of *o*-Phenylenediamine with Benzaldehyde



Scheme 3. PDAIS Mediated Oxidative Coupling of *o*-Arylenediamine/2-Aminophenol(thiol) with Aldehyde



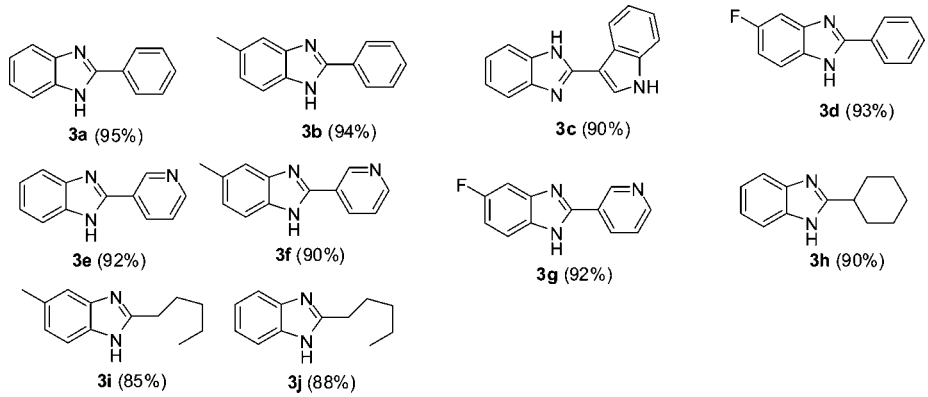


Figure 5. PDAIS mediated synthesis of a library of benzimidazoles.

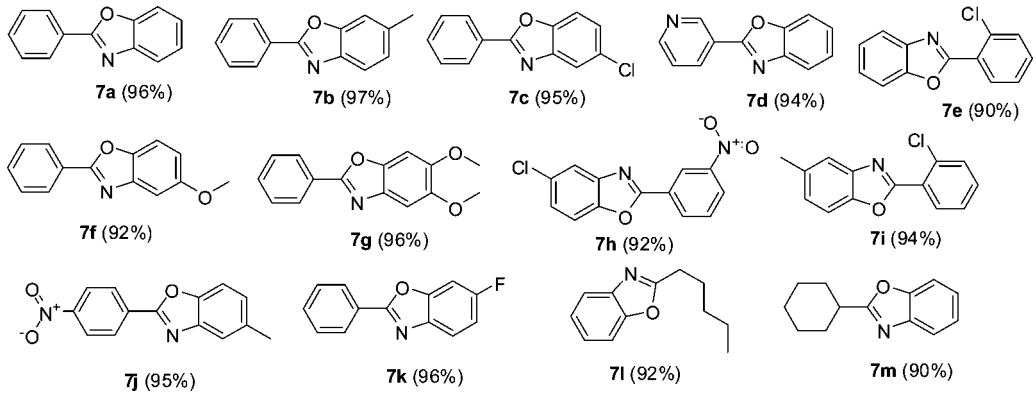


Figure 6. Library of benzoxazoles.

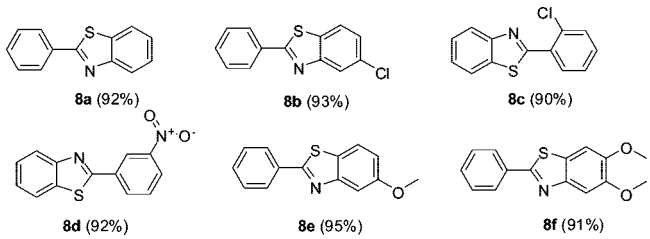
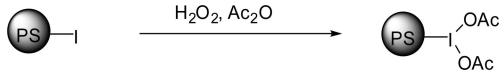


Figure 7. Library of benzothiazoles.

Scheme 4. Regeneration of PDAIS



zoles (8a−f). Aldehyde (1.0 mmol), amine (1.0 mmol), and PDAIS (1.5 mmol) were dissolved in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 5−10 min. After completion, the reaction mixture was diluted with methanol and the precipitate was filtered off. The filtrate was concentrated and purified by silica-gel column chromatography to yield pure benzimidazoles/benzoxazoles/benzothiazoles.

Recovery, Regeneration, and Reuse of PDAIS. After reaction, PDAIS was converted to polyiodostyrene, which was recovered by simple filtration. The regeneration of PDAIS was achieved by reaction of polyiodostyrene in acetic anhydride with dropwise addition of 32 mL of cold hydrogen peroxide (30% solution) (Scheme 4). The reaction mixture was stirred at room temperature for 16 h. The above reaction mixture was kept overnight at room temperature. The PDAIS product was precipitated with diethyl ether and then dried for use.

In summary, we have demonstrated a combinatorial synthesis of 2-substituted benzimidazoles, benzoxazoles, and benzothioazoles using PDAIS. In the present methodology, there is no diversity restriction in the libraries of 2-substituted benzimidazoles, benzoxazoles, and benzothioazoles as in the cases of previous reports.[10] Other important benefit is that after reaction PDAIS is converted to polymer supported iodobenzene which is recovered by filtration, converted to PDAIS and reused. This reusing can be done many times without loss of activity of the PDAIS.

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