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A new laccase-catalyzed domino process and its application to the efficient synthesis of 2-aryl-1*H*-benzimidazoles

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ABSTRACT

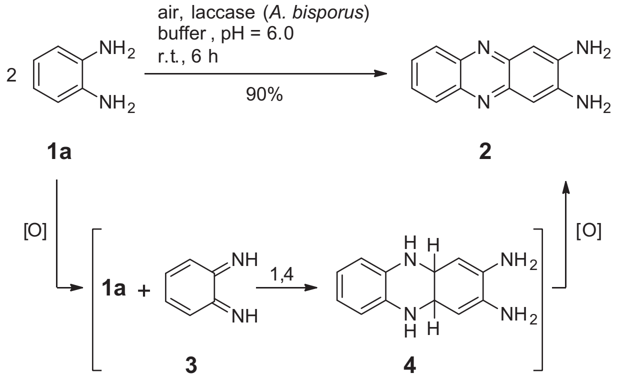
The laccase-catalyzed domino reaction of *o*-phenylenediamine and benzaldehydes with aerial oxygen as the oxidant exclusively yields 2-aryl-1*H*-benzimidazoles in good to very good yields. It is easy to perform under very mild reaction conditions.

Laccases are multicopper oxidases which are able to catalyze the selective oxidation of a number of substrates using oxygen as an oxidant under mild reaction conditions. The oxidation of the substrate is accompanied by the reduction of oxygen to give water as the only side product.[1] Over the last few years the interest in laccase-catalyzed transformations has increased.[2] It has been demonstrated that laccases can be used for the oxidation of aromatic methyl groups,[3a] benzylic, allylic, and aliphatic alcohols,[3b] ethers,[3c] benzyl amines and hydroxylamines.[3d] Laccases have also been employed for the oxidation of catechols and hydroquinones to the corresponding benzoquinones and related transformations.[4] Also, there is ample evidence that laccases catalyze the oxidative coupling of several phenolics using oxygen as the oxidant.[5] In a number of contributions we have reported that laccase initiated domino reactions between catechols and several 1,3-dicarbonyls can be employed for the synthesis of a number of heterocyclic systems, including 1*H*-pyrano[4,3-*b*]benzofuran-1-ones,[6b,c] 3,4-dihydrodibenzofuran-1(2*H*)-ones,[6b] and benzofuro[3,2-*c*]pyridin-1(2*H*)-ones.[6a]

As part of our studies of the laccase-catalyzed domino processes we have observed that the oxidative transformation of *o*-phenylenediamine (**1a**) with air as the oxidant in the presence of catalytic amounts of laccase from *Agaricus bisporus* exclusively delivers 2,3-diaminophenazine (**2**) in 90% yield (Scheme 1).

It is assumed that the oxidative dimerization of **1a** starts with the laccase-catalyzed oxidation of one molecule of the substrate to the corresponding diimine **3**, which reacts with a second molecule *o*-phenylenediamine (**1a**) by means of an inter- and an intramolecular 1,4-addition to yield a tetrahydrophenazine **4**. The last step is the oxidation of this intermediate to afford the 2,3-diaminophenazine (**2**). On an analytical scale this reaction has been employed for determining the activity of laccases.[7c] Alternatively, this transformation can also be performed on a preparative scale using either $FeCl_3$[7a] or hydrogen peroxide in the presence of catalytical amounts of peroxidases.[7b]

The oxidative dimerization of **1a** has caught our attention for two reasons: (a) it allows the preparation of **2** with very high yields, and (b) during the course of the reaction a laccase-catalyzed aerobic oxidation of a C–N-single bond to a C=N-double bond takes place. Since transformations of this type play a central role in heterocyclic chemistry we have studied whether the



Scheme 1. Preparation of 2,3-diaminophenazine (**2**) by laccase-catalyzed aerobic dimerization of **1a**.

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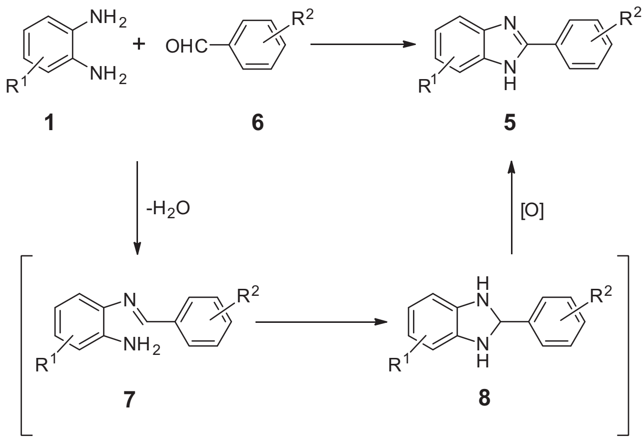
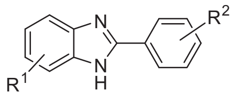


Scheme 2. Reaction of *o*-phenylenediamines **1** with aromatic aldehydes **6** to yield benzimidazoles **5**.

laccase-catalyzed imine formation can be applied to the synthesis of other heterocycles as well.

No doubt, substituted benzimidazoles and structurally related compounds occupy a pivotal position in medicinal chemistry.[8] These compounds have been studied in great detail because many of them exhibit remarkable biological activities, resulting in their use as anti-ulcerative, antitumor, antihypertensive, antifungal, and antihistaminic agents in therapy. This is why the efficient synthesis of 2-aryl-1*H*-benzimidazoles **5** and their derivatives is a highly important and rewarding target for synthetic organic chemists.[9]



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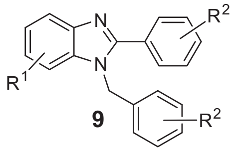
One of the standard methods for the preparation of 2-aryl-1*H*-benzimidazoles **5** starts with the condensation of an *o*-phenylenediamine **1** with an aromatic aldehyde **6** to yield a Schiff base **7**. Cyclization of **7** yields a benzimidazoline derivative **8**, which is then oxidized to give the corresponding benzimidazole **5** (Scheme 2).

Numerous oxidants have been used for this transformation, including nitrobenzene,[10a] 1,4-benzoquinone,[10b] H_2O_2/ceric ammonium nitrate,[10c] (bromodimethyl)sulfonium bromide,[10d] oxone,[10e] iodine,[10f] and cupric acetate.[10g] Meanwhile a number of methods have been developed by making use of the highly attractive oxidant oxygen.[11] However, most of these methods require organic solvents, high reaction temperatures, or the presence of additional reagents, considerably limiting their attractiveness. It has also been established that the synthesis of 2-aryl-1*H*-benzimidazoles **5** by reaction of an *o*-phenylenediamine **1** and an aromatic aldehyde **6** can also be accomplished in aqueous solvent systems.[10f,g,11b,e]

With a number of these methods the formation of the required 2-aryl-1*H*-benzimidazole **5** is accompanied by the occurrence of 1-benzylated 2-aryl-1*H*-benzimidazoles **9** as side products,[11g] and sometimes this type of compounds has been isolated as the main product.[12]



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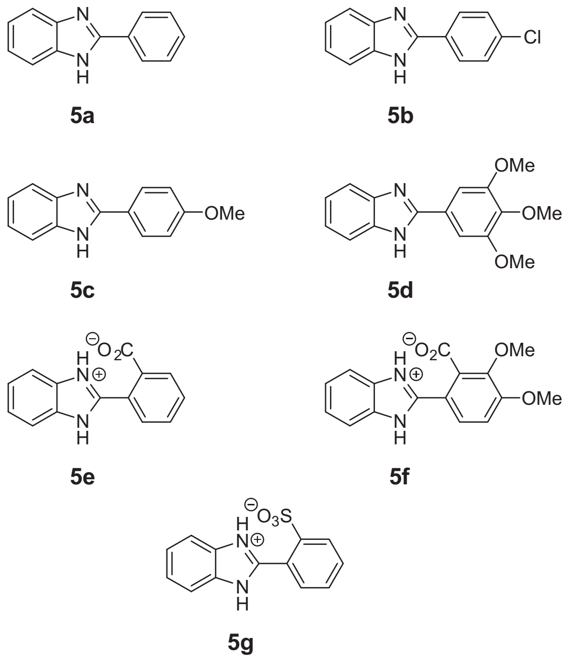
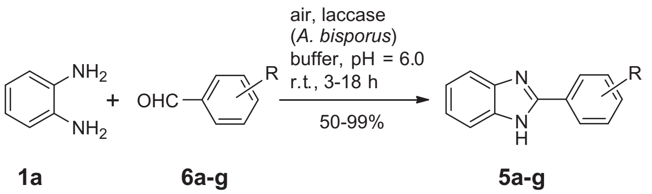


Figure 1. Products **5a–g** of the laccase-catalyzed domino reaction between **1a** and **6a–g**.



Scheme 3. Laccase-catalyzed aerobic synthesis of 2-aryl-1*H*-benzimidazoles **5**.

Therefore, we felt that it was worth to study whether 2-aryl-1*H*-benzimidazoles **5** can be obtained by a laccase-catalyzed domino reaction of *o*-phenylenediamine (**1a**) with aromatic aldehydes **6** using air as the oxidant. The model reaction chosen was the transformation of *o*-phenylenediamine (**1a**) and benzaldehyde (**6a**). We found that the laccase-catalyzed reaction of **1a** and **6a** affords the 2-phenyl-1*H*-benzimidazole (**5a**) (Fig. 1) in 74% yield when performed under aerobic conditions at pH 6.0 (0.2 M phosphate buffer) and at room temperature (Scheme 3, Table 1, entry 1). A commercially available laccase from *Agaricus bisporus* was used as the catalyst.[13] The selectivity of this reaction is quite remarkable for its exclusive formation of the 1*H*-benzimidazole ring system. The dimerization of *o*-phenylenediamine (**1a**) to the 2,3-diaminophenazine (**2**) does not take place under the reaction conditions chosen.

These encouraging findings prompted us to conduct a new benzimidazole synthesis with a number of substituted benzaldehydes (**6b–g**). In all cases the laccase-catalyzed domino process was achieved using equimolar amounts of *o*-phenylenediamine (**1a**) and benzaldehydes **6a–g** at room temperature.[14] The 2-aryl-1*H*-benzimidazoles **5b–g** (Fig. 1) were isolated with yields ranging from 50% to 99% (Scheme 3, Table 1, entries 2–7).[15]

Due to their limited solubility in water the reactions with the aldehydes **6b–d** required the addition of some methanol to the phosphate buffer. All reactions could be performed in a most simple manner by shaking the reaction mixture using a liquid phase synthesis system 'Synthesis 1'. Using this experimental setup sufficient aeration was ensured. The reactions could also be performed using a magnetic stirrer at high stirring speed. The workup of the