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# L-Proline catalyzed selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles☆

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**Abstract**—L-Proline (10 mol %) was found to be a versatile organocatalyst for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from a wide range of substituted *o*-phenylenediamines and aldehydes in moderate to excellent isolated yields (32–95%) under mild conditions using chloroform as a solvent at ambient temperature.


Interest in benzimidazole-containing structures stems from their widespread occurrence in molecules that exhibit significant activity against several viruses such as HIV, herpes (HSV-1), RNA, influenza and human cytomegalovirus (HCMV).[1] In addition, benzimidazole derivatives have been used as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin II inhibitors, 5-$HT_3$ antagonists in isolated guinea pig ileum, potential antitumour agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, a treatment for interstitial cystitis, as factor Xa inhibitors, and in diverse areas of chemistry.[2] In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as 'privileged sub-structures' for drug design.[3] Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.

The traditional synthesis of benzimidazoles involves the reaction between an *o*-phenylenediamine and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.[4] Benzimidazoles have also been prepared on solid-phase to provide a combinatorial approach.[5] The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct N-alkylation of an unsubstituted benzimidazole.[6] A number of synthetic protocols that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support.[7] Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions.[8,9] However, many of these methods have several drawbacks such as low yields, use of expensive reagents, a special oxidation process or long reaction times, tedious work-up procedures, co-occurrence of several side reactions and poor selectivity. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, economic viability and in particular, with greater selectivity.

Recently, the commercially available and inexpensive amino acid L-proline has been elegantly used to catalyze many reactions such as the Mannich reaction and the direct asymmetric aldol reaction.[10] The proline function has been proposed to act like a 'microaldolase' that facilitates each step of the mechanism, including the formation of the intermediate imine and the carbon–carbon bond. Very recently, L-proline has also been effectively used as a versatile organocatalyst in various organic transformations.[11] In continuation of our recent efforts to develop novel synthetic routes for carbon–carbon and carbon–heteroatom bonds and heterocycles,[12] in the present study, we extend the scope of the L-proline-catalyzed synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles and the results from our study are presented herein. Obviously the chirality of the catalyst is not necessary for the described procedure, but the cheapness of L-proline in comparison with the corresponding racemic amino acid (D,L-proline) makes it the catalyst of choice.

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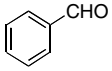
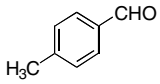
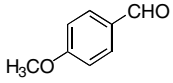
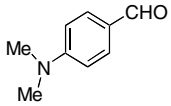
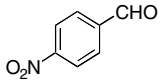
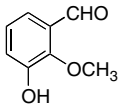
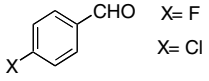
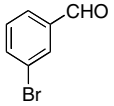
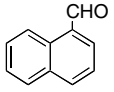
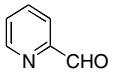
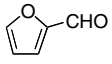
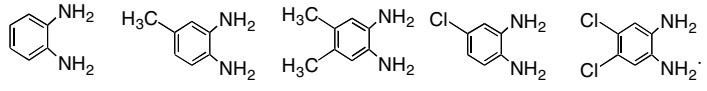
Initially, we studied the efficacy of proline (20 mol %) for the model reaction using *o*-phenylenediamine (*o*-PD) (1 mmol) and benzaldehyde (2 mmol) in chloroform with stirring at ambient temperature to afford the corresponding 1,2-disubstituted benzimidazole in 95% yield in 5 h (Table 1, entry **3a**). Chloroform was the best among the solvents tested ($THF–H_2O$, acetone, $CH_3CN$, MeOH, DMSO and chloroform). The optimum yields of the product were obtained when a ratio of aldehyde to *o*-PD (2:1) was used.

Further studies revealed that even 10 mol % of the catalyst was sufficient to carry forward the reaction (95% yield, 5 h). Using optimized reaction parameters, we obtained exclusively N-alkylated products **3** and no 2-substituted products **4** were observed (Scheme 1).

This selectivity could be useful in synthesizing a small library of 2-aryl-1-arylmethyl-1*H*-benzimidazoles in moderate to excellent yields. To the best of our knowledge, there are no earlier reports on the preparation of benzimidazoles using L-proline as an organocatalyst.

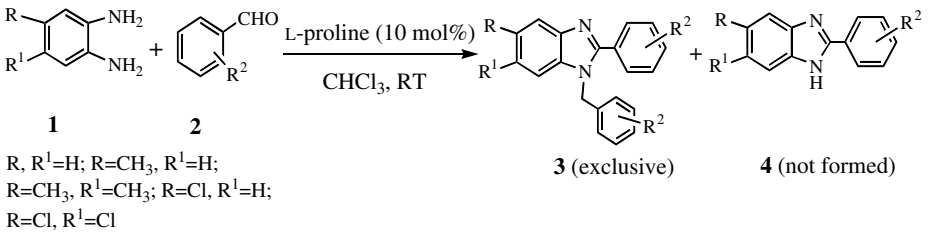
**Table 1.** L-Proline catalyzed selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from *o*-PDs and various aldehydes

| Compound (**3**) | *o*-PD (**1**) | Aldehyde (**2**) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| **3a** | **1a** |  | 5.0 | 95 |
| **3b** | **1b** | | 4.5 | 82 |
| **3c** | **1c** | | 15 | 32 |
| **3d** | **1d** | | 12 | 58 |
| **3e** | **1e** | | 4.5 | 72 |
| **3f** | **1a** |  | 5.0 | 85 |
| **3g** | **1a** |  | 5.5 | 72 |
| **3h** | **1a** |  | 7.5 | 80 |
| **3i** | **1a** |  | 6.0 | 83 |
| **3j** | **1a** |  | 6.0 | 78 |
| **3k** | **1a** |  X= F | 4.5 | 80 |
| **3l** | **1a** | X= Cl | 6.0 | 72 |
| **3m** | **1a** |  | 8.5 | 88 |
| **3n** | **1a** |  | 4.5 | 90 |
| **3o** | **1a** |  | 6.0 | 92 |
| **3p** | **1a** |  | 5.0 | 85 |

*o*-PD: 

**1a** **1b** **1c** **1d** **1e**

[a] Yields refer to isolated pure products.




**Scheme 1.**

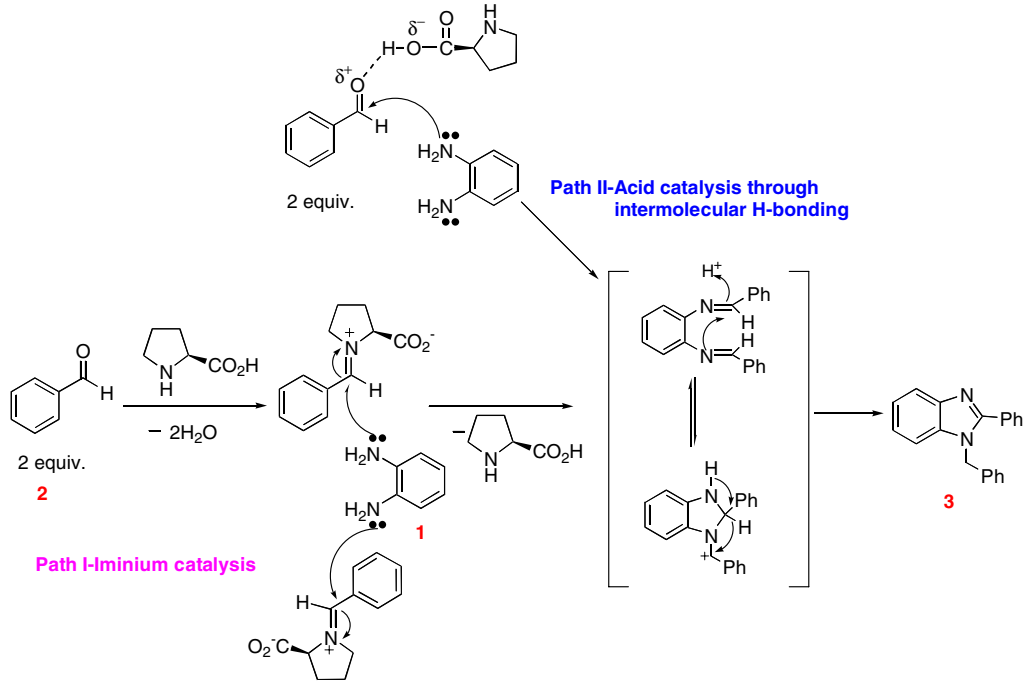
We studied the scope of the reaction by varying the *o*-PDs (**1a**–**e**) for condensation with benzaldehyde under the optimized conditions and the results are shown in Table 1.

Among the various *o*-PDs tested, the order of reactivity in terms of yields and reaction times towards benzaldehyde was as follows: **1a** > **1b** > **1e** > **1d** > **1c**. Intrigued by the results observed, we next studied the scope and generality of the L-proline catalysis, for the condensation of electronically divergent aromatic aldehydes with *o*-PD to afford the corresponding 1,2-disubstituted benzimidazoles selectively. In all cases, the reactions were clean and complete within 4.5–15 h. All products (entries **3a**–**p**) were characterized by IR, $^1$H NMR, MS and elemental analyses.[13] The 1,2-disubstituted benzimidazoles were the only products obtained and the remainder of the material was essentially starting material. The present protocol is equally effective for aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents (entries **3f**–**m**).

In a similar fashion, α-naphthaldehyde (entry **3n**) and heteroaromatic aldehydes (entries **3o**,**p**) also reacted well with *o*-PD to furnish the corresponding benzimidazoles in good yields.

The proposed mechanism for the L-proline-catalyzed synthesis of 1,2-disubstituted benzimidazoles may tentatively be visualized to occur via a tandem sequence of reactions as depicted in Scheme 2 involving **Path I** (i) formation of dibenzylidene-*o*-PD via iminium catalysis,[14] (ii) protonation of the dibenzylidene-*o*-PD and ring closure leading to a five-membered ring either in a sequential or concerted manner, (iii) 1,3-hydride transfer and (iv) deprotonation or via **Path II** involving the activation of the aldehydic carbonyl oxygen by the acid part of L-proline through intermolecular hydrogen bonding,[15] and subsequent condensation with *o*-PD to form dibenzylidene-*o*-PD, followed by steps (ii)–(iv) as above to form 1,2-disubstituted benzimidazoles.

In conclusion, we have developed a practical and novel procedure for the selective synthesis of 1,2-disubstituted benzimidazole derivatives using commercially available, inexpensive L-proline as an organocatalyst in chloroform. The present protocol has several advantages: mild reaction conditions (at room temperature), operational and experimental simplicity. We believe that this L-proline promoted methodology will be a valuable addition to the existing processes in the field of 1,2-disubstituted benzimidazole synthesis.




**Scheme 2.** The proposed mechanism for L-proline catalyzed 1,2-disubstituted benzimidazole synthesis.

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13. *Representative procedure is as follows:* To a suspension of L-proline (10 mol %) in chloroform (5 mL) were added successively *o*-phenylenediamine (1 mmol) and aldehyde (2 mmol) at room temperature for the time specified in Table 1. After the reaction was complete, the reaction mixture was washed with water, extracted with ether and the combined organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure to furnish the crude product, which was further purified by silica gel chromatography using EtOAc/hexane (1:5), to afford the corresponding product. All compounds gave satisfactory spectroscopic data in accordance with their proposed structures. *Spectral data for 1-benzyl-2-phenyl-1H-benzo[d]imidazole* (**3a**). Solid, IR (KBr): $\nu$ 3031, 2947, 1463 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 5.34 (s, 2H), 7.00 (dd, $J = 8$ and 2 Hz, 2H), 7.10–7.26 (m, 6H), 7.32–7.40 (m, 3H), 7.62 (dd, $J = 8$ and 2 Hz, 2H), 7.81 (d, $J = 8$ Hz, 1H); MS (EI): $m/z$ 284 ($M^+$); Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.34; H, 5.69; N, 9.78.
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