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Graphical Abstract

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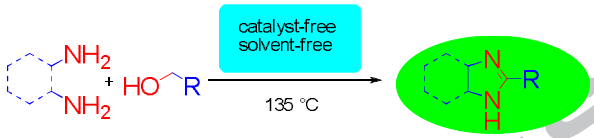

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Catalyst-free one-pot synthesis of benzimidazoles from 1,2-diaminoarenes and alcohols

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ABSTRACT

A new and efficient protocol is described for the one-pot synthesis of benzimidazoles from a variety of aryl alcohols and 1,2-diaminoarenes. The yields ranging from moderate to excellent. Moreover, the present method is utilizing alcohols instead of aldehydes and the reactions are carried out under solvent- and catalyst-free conditions, offering an environmentally benign process.

The development of new strategies that present high synthetic efficiency and atom economy has been an important task for synthetic organic chemists. Tandem reactions are good candidates for this target and are a rapidly growing area.[1] Tandem reactions complete several chemical transformations in a single step and offer a powerful approach for rapidly increasing molecular complexity from simple starting materials. The main advantages of tandem reactions are reduction of overall steps by avoiding isolation of often highly reactive intermediates, minimization of waste compared to stepwise reactions, the amount of solvents, reagents, adsorbents and energy can be dramatically decreased.

Benzazoles, such as benzimidazoles are studied as privileged motifs in the field of medicinal chemistry.[2] Benzimidazole derivatives have been found to possess enormous therapeutic applications including antiviral, antihypertensive, antiulcer, antifungal, antihistaminic, anticancer activities[3] and are also very useful intermediates in organic synthesis.[4] Moreover, benzimidazole derivatives exhibit significant activity against several viruses such as HIV, herpes (HSV-1) and influenza.[5] Due to their interesting properties and applications, various synthetic methods have been developed for the synthesis of benzimidazoles. Among these methods, the most common method being the heterocyclization of 1,2-diaminoarenes with carboxylic acids or their derivatives,[6] which requires strong acidic conditions and sometimes combines high temperatures or use of microwave. The other method is condensation of 1,2-diaminoarenes and aldehydes followed by oxidation to give benzimidazoles.[7] This process needs oxidizing agents and unstable aldehydes as reactants. Recently, Nguyen *et al*.[8] reported the formation of benzimidazoles from amines and 1,2-diaminoarenes under oxidative conditions.

An alternative environmentally-benign approach to the synthesis of benzimidazole is a one-pot multi-step process using inexpensive and readily available alcohols and 1,2-diaminoarenes as starting materials. Until now, many transitional metal complexes/salts/supported catalysts such as, iron,[9] ruthenium,[10] platinum-titanium,[11] manganese[12] and aurum-cerium[13] have been reported for the synthesis of benzimidazoles from alcohols. A couple of transition metal-free[14] (I_2 and IBX mediated) protocols have also been reported using alcohols. However, many of these methods have several limitations such as low yields, tedious work-up procedures, use of expensive catalysts and reagents.

Today the world is facing major problems from global pollution. To overcome this issue, chemical waste should be reduced. This would be especially significant on the industrial scale. In this context, metal-free reactions appear to be greatly desirable to maximize atom-economy and to avoid chemical waste. Herein, we report a novel straightforward method for the preparation of benzimidazoles from aryl alcohols and 1,2-diaminoarenes without employing any oxidant/catalyst.

Initially, we studied the reaction of 1,2-phenylenediamine (1 equiv.) with benzyl alcohol (1.5 equiv.) as a model reaction to optimize the best reaction conditions (Table 1). The reaction was remarkably accelerated by varying the reaction temperature from 100 to 135 °C (Table 1, entries 1-4) and yield gradually improved

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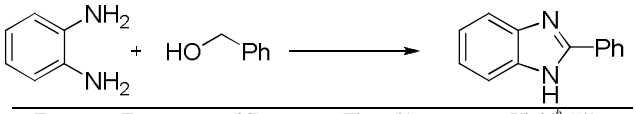
Table 1

Optimization of reaction conditions for the synthesis of benzimidazole[a]



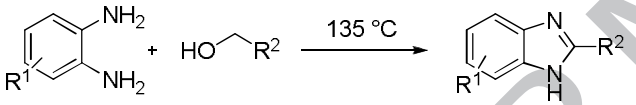
Entry	Temperature (°C)	Time (h)	Yield[b] (%)
1	100	24	31
2	110	24	39
3	120	24	55
4	135	24	78
5[c]	135	24	61

[a] Reaction conditions: Benzyl alcohol (3 mmol), 1,2-Phenylenediamine (2 mmol), open atmosphere.

[b] Products were characterized by NMR, Mass spectra and isolated yields calculated based on 1,2-Phenylenediamine.

[c] Benzyl alcohol (2 mmol), 1,2-Phenylenediamine (2 mmol).

from 31 to 78%. The effect of mole ratio of amine to alcohol was then investigated at 135 °C. When decreasing the mole ratio of amine to alcohol (1:1.5 to 1:1.0), the yield of the desired product was decreased from 78% to 61% (Table 1, entries 4 and 5). The above results revealed that 1:1.5 mole ratio of 1,2-phenylenediamine and benzyl alcohol at 135 °C showed to be the optimum reaction conditions for synthesis of 2-phenyl-1*H*-benzimidazole (Table 1, entry 4).

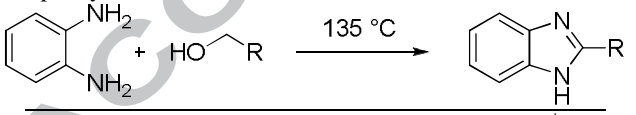


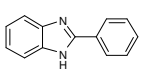
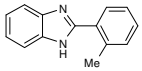
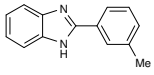
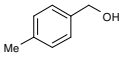
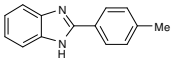
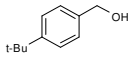
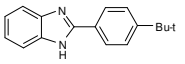
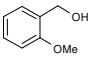
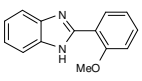
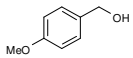
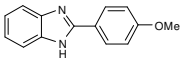
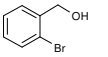
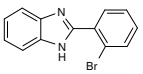
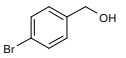
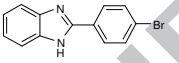
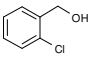
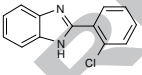
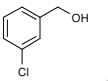
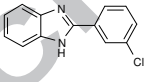
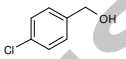
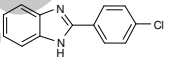
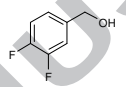
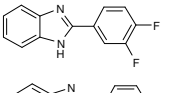
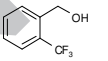
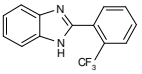
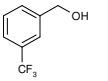
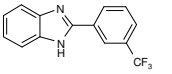
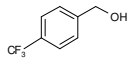
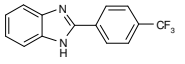
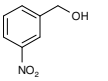
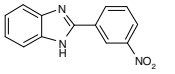
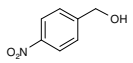
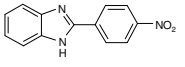
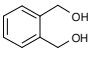
Scheme 1. Synthesis of benzimidazoles from 1,2-diaminoarenes and alcohols.

Under the optimized conditions, next we explored the scope and generality of the reaction with various combinations of substrates (aryl alcohols and 1,2-diaminoarenes) and results are summarized in Table 2 and 3 (Scheme 1). As shown in Table 2, various aryl alcohols successfully reacted with 1,2-phenylenediamine to afford moderate to excellent yields of the corresponding benzimidazoles.

Table 2

Synthesis of benzimidazole derivatives from aryl alcohols and 1,2-phenylenediamine[a]



Entry	Alcohol	Product	Yield[b] (%)
1			78
2			82
3			72
4			71
5			76
6			74
7			61
8			81
9			60
10			71
11			72
12			82
13			91
14			89
15[c]			85
16[c]			78
17[d]			78
18[d]			91
19[d]			55
20[d]			70
21			89
22			–
23			–
24			–

[a] Reaction conditions: Alcohol (3 mmol), 1,2-Phenylenediamine (2 mmol), 135 °C, 24 h, open atmosphere.

[b] Products were characterized by NMR, Mass spectra and isolated yields calculated based on 1,2-Phenylenediamine.

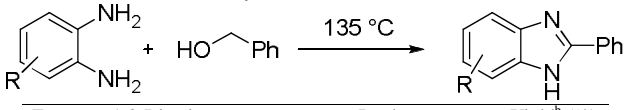
[c] 12 h.

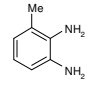
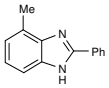
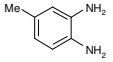
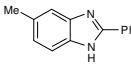
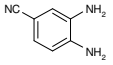
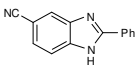
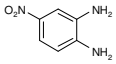
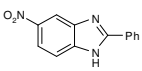
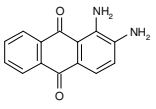
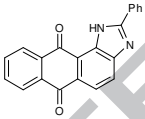
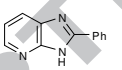
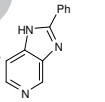
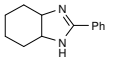
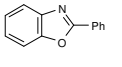
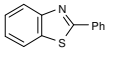
[d] Reaction temperature 150 °C.

In order to determine the influence of substitution on the aromatic ring of benzyl alcohol on the reaction path we carried out the reaction of different substituted benzyl alcohols with 1,2-phenylenediamine under optimized conditions. It was noticed that there is not much difference in reactivity between the electron-donating and electron-withdrawing groups and the reaction proceeded well to give the corresponding products in moderate to excellent yields (Table 2, entries 2-18). The position of substitution on the phenyl ring of benzyl alcohol affects the reaction yield. Interestingly, methyl (Table 2, entries 2 and 4), methoxy (Table 2, entries 6 and 7), bromo (Table 2, entries 8 and 9) and trifluoromethyl (Table 2, entries 14 and 16) groups at *ortho* position furnished higher yield compared to *para* position.

Table 3

Synthesis of benzimidazole derivatives from different 1,2-diaminoarenes and benzyl alcohol[a]



Entry	1,2-Diaminoarene	Product	Yield[b] (%)
1[c]			75
2			73
3[d]			58
4[d]			71
5[d]			83
6[d]			70
7[d]			88
8			–
9			–
10			–

[a] Reaction conditions: Benzyl alcohol (3 mmol), 1,2-Diaminoarene (2 mmol), 135 °C, 24 h, open atmosphere.

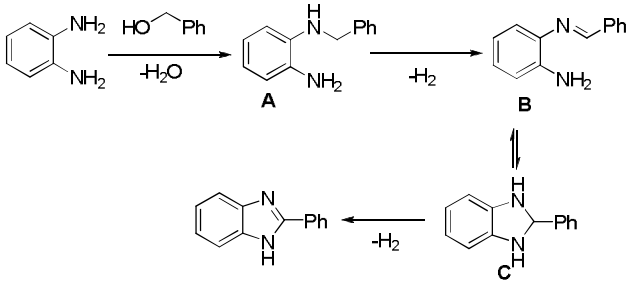
[b] Products were characterized by NMR, Mass spectra and isolated yields calculated based on 1,2-Diaminoarene.

[c] mixture of tautomers.

[d] Reaction temperature 150 °C.

However chloro group at *ortho* position provided lesser yield than *para* position (Table 2, entries 10 and 12). Notably, the reaction was also effective with nitro substituted benzyl alcohols (Table 2, entries 17 and 18) under slightly higher temperature (150 °C). Moreover, 1,2-benzenedimethanol and polyaromatic alcohol i.e. 1-naphthalenemethanol reacted with 1,2-phenylenediamine to give the respective benzimidazoles selectively in 55% and 70% yields, respectively, at higher temperature (150 °C) (Table 2, entries 19 and 20). Also, the reaction with 2-pyridinemethanol did not reduce the yield of the corresponding product (Table 2, entry 21). However, the reaction of 2-phenylethylalcohol and aliphatic alcohols with 1,2-phenylenediamine was not quite successful (Table 2, entries 22-24). This method can be well tolerated by many valuable functional groups such as methyl, methoxy, bromo, chloro, fluoro, trifluoromethyl and nitro groups in the present reaction conditions.

To further examine the scope of this reaction, various substituted 1,2-diaminoarenes were employed to react with benzyl alcohol under the optimized conditions to provide the corresponding benzimidazole products in moderate to excellent yields (Table 3). 1,2-Phenylenediamine bearing electron-donating groups were successfully converted into the respective benzimidazole derivatives in excellent yields (Table 3, entries 1 and 2). However, strongly electron-withdrawing groups such as cyano and nitro groups present on 1,2-phenylenediamine yielded the respective benzimidazole derivatives in 58% and 71% yields, respectively (Table 3, entries 3 and 4) at 150 °C. It is noteworthy that, 1,2-diaminoanthraquinone furnished the corresponding benzimidazole in 83% yield (Table 3, entry 5) at 150 °C, which is used as colorimetric and ratiometric fluorescent chemosensors for fluoride.[15] The heterocyclic 1,2-diamines such as 2,3-diaminopyridine and 3,4-diaminopyridine were also shown to be effective (at 150 °C) in this reaction conditions and afforded corresponding benzimidazole derivatives in 70% and 88% yields, respectively (Table 3, entries 6 and 7). Unfortunately, 2-aminophenol, 2-aminothiophenol and 1,2-diaminocyclohexane failed to give any product under similar conditions (Table 3, entries 8-10).



Scheme 2. Plausible reaction mechanism for the synthesis of benzimidazole.

To obtain an insight into the reaction mechanism for the formation of benzimidazoles from 1,2-diaminoarenes and aryl alcohols, a couple of experiments were carried out using our standard reaction conditions. The reaction of benzyl alcohol with 1,2-phenylenediamine under inert atmosphere also provided the respective benzimidazole in excellent yield. To confirm the *N*-benzylated product **A** as an intermediate, we performed the reaction with **A** in benzyl alcohol at 135 °C to give the corresponding benzimidazole. Based on above experimental observations, we propose a possible reaction mechanism for the formation of benzimidazoles from amines and alcohols are illustrated in Scheme 2.

It is assumed that, the reaction of amine with benzyl alcohol gave the corresponding *N*-benzylated product **A**. This then dehydrogenated to imine **B**, which remain in equilibrium with the

cyclized product **C**. Finally, the cyclized product dehydrogenated to desired product.

In summary, an effective and green protocol has been developed for the one-pot synthesis of benzimidazoles from easily available aryl alcohols and 1,2-diaminoarenes without using catalyst or additive under solvent-free conditions. Notable advantages offered by this strategy are broad substrate scope, solvent-free, catalyst- and additive-free conditions, high atom-economy (only water and H_2 are by-products), environmentally benign, higher yields of the desired products and simple work-up procedure, which make it an attractive and useful alternative to the existing methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xx.xxxx/j.tetlet.2014.xx.xxx.

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