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Simple, Efficient, and Applicable Route for Synthesis of 2-Aryl(Heteroaryl)-Benzimidazoles at Room Temperature Using Copper Nanoparticles on Activated Carbon as a Reusable Heterogeneous Catalyst

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Abstract A series of 2-(hetero)arylbenzimidazoles were synthesized by the catalytic condensation of (hetero)aryl aldehydes with 1,2-phenylenediamine derivatives at room temperature in the presence of air as the oxidant. Copper nanoparticles on charcoal was employed as an efficient and mild catalyst for this methodology.

Keywords 2-Aryl(heteroaryl)benzimidazoles · Copper nanoparticles · Cu/C · Heterogeneous catalysis

1 Introduction

2-Aryl(heteroaryl)-substituted benzimidazoles have received a considerable amount of attention in diverse areas of chemistry. These compounds exhibit a wide spectrum of biological and pharmacological activities [1–7]. Also, 2-aryl benzimidazole derivatives are fluorescent acid–base indicators [8], dopants for plastic scintillation applications [9] and subunits of polybenzimidazoles as thermally stable polymers [10].

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Because of their importance and wide applications, the synthesis of these benzimidazole derivatives has become a focus of synthetic organic chemistry.

Two main synthetic routes could be observed in all of these reported procedures. One route that is common to the 2-aryl benzimidazoles synthesis typically involves direct coupling of a carboxylic acid or carboxylic acid derivatives with an appropriate 1,2-phenylenediamine under the influence of a strong acid such as hydrochloric acid [11] or polyphosphoric acid [12] at high temperature or under microwave irradiation [13]. The other important way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff bases, which are often generated from the condensation of *o*-phenylenediamines and aryl aldehydes. Various oxidative and catalytic reagents have been employed in the second route [14–35].

Albeit several reports [25–33], the direct condensation of *o*-aryldiamines and aromatic aldehydes at room temperature is less developed because as previously reported [36] this superficially simple reaction is a complex sequence of competing reactions and leads to the formation of a complex mixture of products containing 1,2-disubstituted benzimidazoles and 1,2-disubstituted benzimidazolines as main byproducts. Moreover, most of the catalysts have been used for this purpose are not recoverable and destroyed in the work-up procedure. Therefore, the discovery of such mild and practicable routes for selective synthesis of 2-aryl(heteroaryl)-benzimidazoles continues to attract the attention of researchers.

In the recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. Synthetic organic routes followed by using heterogeneous catalysts have advantages over their counterparts in which, used-catalyst can be easily

Scheme 1

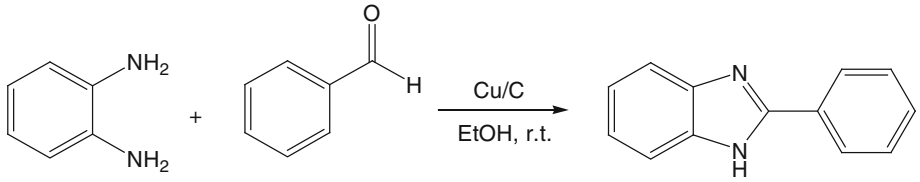


Table 1 Effect of different solvents in the condensation reaction of *o*-phenylenediamine (1.0 mmol) with benzaldehyde (1.0 mmol) at room temperature using Cu/C

Entry	Mol % of catalyst	Solvent	Time (h)	Yield[a] (%)
1	5	Acetonitrile	18	89
2	5	Chloroform	24	18
3	5	Dioxane	24	55
4	5	Ethyl acetate	24	82
5	5	Toluene	24	52
6	5	DMF	4	93
7	5	THF	18	92
8	5	Ethanol	3	92
9	1	Ethanol	3	64
10	3	Ethanol	3	79
11	10	Ethanol	3	93

[a] Isolated yield

recycled [21]. As a part of our continued efforts to utilize heterogeneous catalysts for developing organic reactions [37–50], herein we report on a new and reused catalyst system based on copper on charcoal (Cu/C). This heterogeneous catalyst system exhibits an excellent catalytic performance for the construction of the 2-arylbenzimidazoles framework. Moreover, Cu/C can be repeatedly used for this transformation and subsequently recovered after the reaction.

2 Results and Discussion

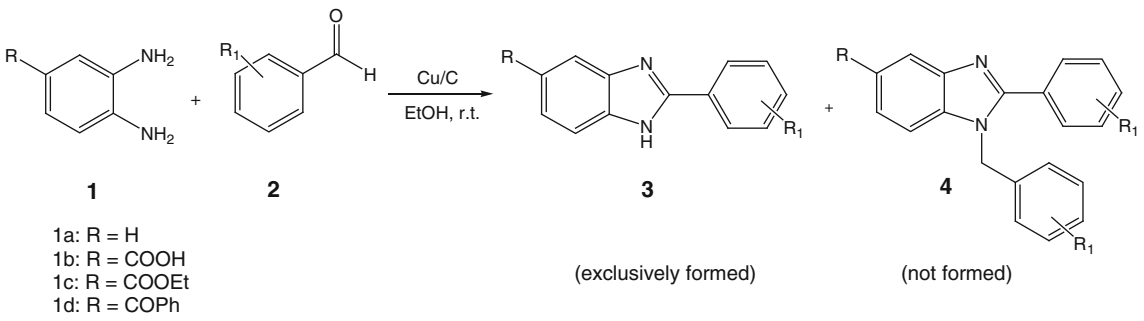
Previously we have reported several practical methods for synthesis of a series of 2-arylbenzimidazoles in high yield at room temperature. The catalyst we used in this project was previously introduced [38], copper nanoparticles on charcoal (Cu/C), as an efficient recyclable heterogeneous catalyst in organic synthesis.

The catalyst was synthesized in two steps. In a general procedure the activated carbon was refluxed with a nitric acid solution for several hours and washed with deionized water until pH 6–7 and then dried in an oven at 110 °C overnight under vacuum. The oxidized activated carbon was refluxed with a solution of CuI under a N_2 atmosphere in absolute EtOH, washed with ethanol and finally dried under vacuum in an oven overnight at 110 °C.

In order to ascertain the optimum conditions of the reaction, we optimized various parameters including the solvent and the amount of catalyst for reaction of *o*-phenylenediamine (1.0 mmol) with benzaldehyde (1.0 mmol) as the model reactants (Scheme 1).

During our optimization studies, various solvents were examined, and it was found that these reactions appeared to be largely dependent on the nature of the solvent. Ethanol appeared as the solvent of choice due to its fast reaction rate, high yield, selectivity, cheapness, and environmental acceptability. The optimal amount of catalyst was found to be 5.0 mol%. A decrease in the amount of catalyst resulted in a significant reduction of the yield while an increased amount of catalyst revealed negligible effect on the efficiency of the reaction (Table 1). The best yield and purity of desired product was obtained in the presence of 5.0 mol% of the catalyst in 10.0 mL of ethanol as the appropriate solvent. The product was isolated by simple washing by ethanol followed by the usual work-up.

Structural assignments of benzimidazole **3a** were made by comparison of the ^{1}H- and ^{13}C NMR spectra with those reported previously.



Scheme 2

Table 2 Condensation reaction of o-phenylenediamines (1.0 mmol) with different aryl(heteroaryl) aldehydes (1.0 mmol) using Cu/C (5.0 mol%) in ethanol at room temperature

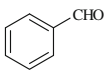
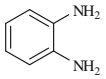
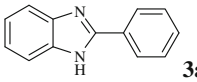
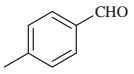
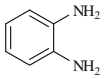
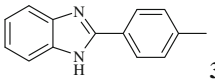
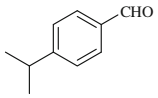
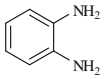
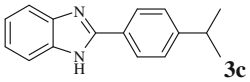
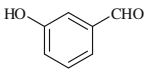
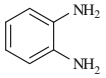
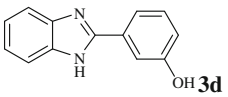
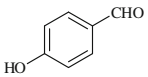
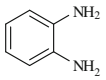
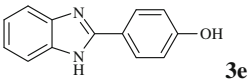
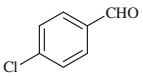
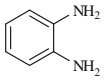
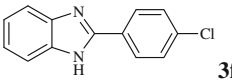
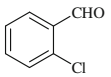
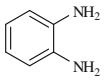
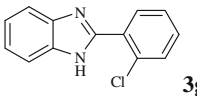
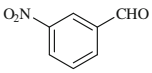
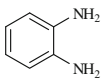
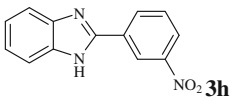
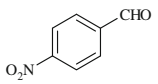
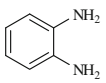
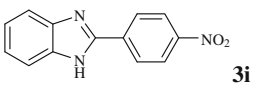
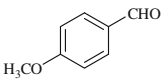
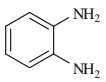
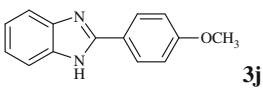
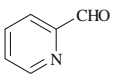
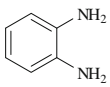
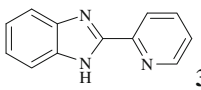
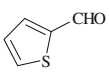
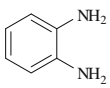
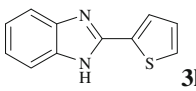
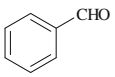
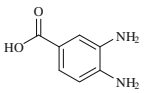
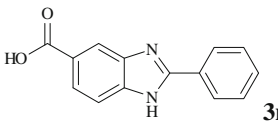
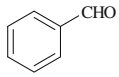
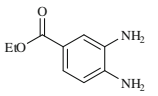
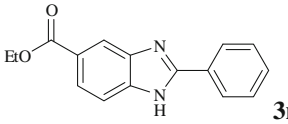
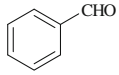
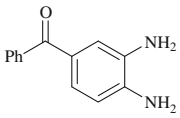
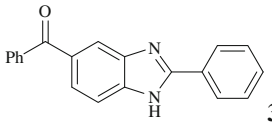
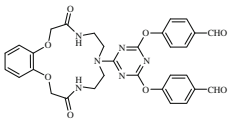
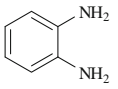
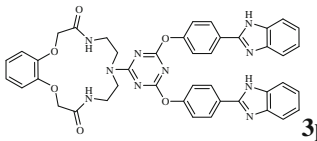
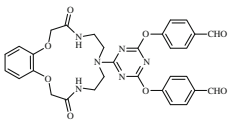
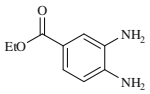
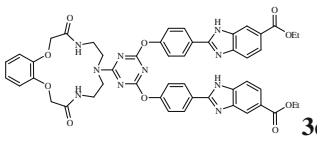
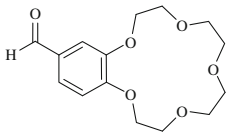
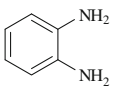
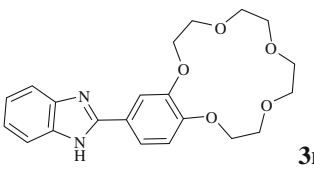
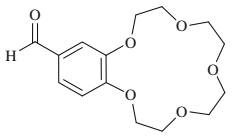
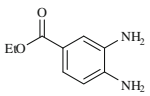
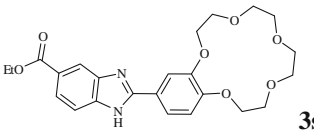
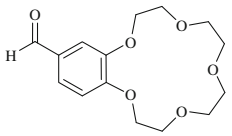
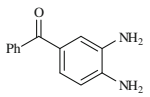
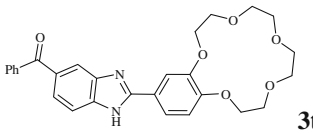
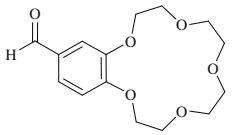
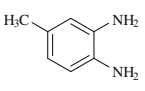
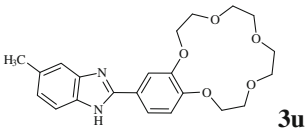
Entry	Aldehyde	Diamine	Product	Time (h)	Yield[a] (%)
1			 **3a**	3	92
2			 **3b**	6	89
3			 **3c**	6.5	91
4			 **3d**	4	93
5			 **3e**	7	94
6			 **3f**	5	90
7			 **3g**	7	97
8			 **3h**	9.5	90
9			 **3i**	7	84
10			 **3j**	6	95
11			 **3k**	3	88
12			 **3l**	18	92
13			 **3m**	3.5	85

Table 2 continued

Entry	Aldehyde	Diamine	Product	Time (h)	Yield[a] (%)
14			 **3n**	3	94
15			 **3o**	4.5	90
16			 **3p**	12	82
17			 **3q**	12	85
18			 **3r**	4	93
19			 **3s**	7	92
20			 **3t**	6	90
21			 **3u**	3	96

[a] Isolated yield

Under the optimized reaction conditions, we obtained exclusively 2-substituted products **3**, and either no *N*-alkylated products **4** were observed or they could be found only in trace amounts in just a few cases (Scheme 2).

To investigate the generality and versatility of this method, the reaction was extended to various structurally diverse aldehydes and *o*-phenylenediamines derivatives. In all cases, reactions were complete in a reasonable time and 2-arylbenzimidazole derivatives were isolated in good to high yields. The use of this methodology in the reaction of the *o*-phenylenediamines with different aldehydes produced only one of the possible regioisomers, as expected (Table 2).

Table 3 Catalyst recyclability studies in ethanol at room temperature

Reaction run	Time (h)	Yield[a] (%)
1	3	92
2	3	92
3	3	92
4	3	92
5	3	91
6	3	91
7	3	91
8	3	90

[a] Isolated yield

As shown in Table 2, the generality and selectivity of this catalysis method is excellent. Electronic variation in the aldehydes or *o*-phenylenediamines was tolerated and did not change the efficiency of the reaction and afforded the desired benzimidazoles in high yields. Heteroaryl aldehydes, such as 2-pyridinyl- and 2-thiophenylcarboxaldehydes (Table 2, entries 11 and 12), also show good results under these conditions.

We felt that this methodology could then be extended to synthesize azacrown ether-containing benzimidazoles. The azacrown ether, which has a 1,3,5-triazine substituent, containing dialdehydes, at the nitrogen position, gave the corresponding dibenzimidazole in good yield (Table 2, entries 16 and 17). We decided to extend the scope of this methodology to the 4′-formyl-benzo-15-crown-5 as starting material; the reaction proceeded with various *o*-phenylenediamine derivatives smoothly in good yield. The structures of the products were determined from their spectral (^{1}H NMR, ^{13}C NMR, IR, and mass) analysis.

In order to assess the feasibility of applying this method on a preparative scale, we carried out the coupling of *o*-phenylenediamine with benzaldehyde in a 30 mmol scale in the presence of the heterogenous catalyst. As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (Table 2, entry 1), and the desired 2-phenylbenzimidazole was obtained in 92% isolated yield in 3 h.

We also studied catalyst recyclability. The Cu/C can be recovered and recycled by simple filtration of the reaction mixture and reused for at least eight consecutive trial runs without significant decrease in the activity (Table 3).

A comparison of the catalytic efficiency of Cu/C with selected previously known catalysts is collected in Table 4 to demonstrate that the present protocol is indeed superior to several of the other protocols.

Most of the listed methodologies suffer from some limitations such as prolonged reaction times, elevated temperatures, or use hazardous materials. For example, preparation of benzimidazole has carried out in CH_2Cl_2 as a solvent and $SOCl_2/SiO_2$ as reagent that both solvent and reagent are hazardous material (Table 4, entry 1).

Additionally, some of protocols require high temperature using previous catalysts (Table 4 entries 2, 3, 4, and 5).

It was also observed that, the preparations of those catalysts and their ligands are very difficult (Table 4, entries 3, 6–11). But the present method shows a new, ligand free, cheap, and easy procedure for preparation of catalyst and introduces a general, simple and efficient synthetic method for preparation of 2-arylben zimidazoles.

Table 4 Comparison of protocols for synthesis of 2-phenylbenzimidazole

Entry	Reagent/catalyst	Solvent	Time (min)	Temperature (°C)	Yield[a] (%)	Ref.
1	$SOCl_2/SiO_2$	CH_2Cl_2	240–360	25	92	15
2	$I_2/KI/K_2CO_3$	H_2O	45	90	75	16
3	$Cu_{3/2}PMo_{12}O_{40}/SiO_2$	1,4-dioxane	15	Reflux	70	20
		Solvent-free	15	25	90	
4	Graphite/TsOH	EtOH	40	75	89	23
5	NH_4OAc	EtOH	270	75	95	24
6	CoxO–Co (salen)	EtOH	25	25	96	25
7	T(*o*-Cl)PPFe^{III}-SiO_2	EtOH	90	25	95	26
8	Cu(BHPPDAH)H_2O	EtOH	120	25	96	27
9	$ZrOCl_2{\cdot}nH_2O$/montmorillonite K10	H_2O	10	25	84	29
10	DMP	1,4-dioxane	10	25	89	31
11	$H_3PW_{12}O_{40}/ZrPO_4$	Solvent-free	15	25	85	33
12	H_2O_2/CAN	Solvent-free	12	50	97	34
13	Cu/C	EtOH	180	25	93	

[a] Isolated yield

3 Conclusion

As a brief statement, we introduced a general, simple, and efficient synthetic method for preparation of 2-arylbenzimidazoles from phenylenediamines and aromatic aldehydes using Cu/C as catalyst. The mild reaction conditions, excellent yields, large-scale synthesis, easy and quick isolation of products, recyclability of the catalyst, employment of atmospheric air as the oxidant, cost-effectiveness, environmentally friendly, high generality, and good selectivity are the main advantages of this procedure. So we believe that it will find wide application in organic synthesis as well as in industry.

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