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Orginal Research Article

Tribromo melamine (TBM) as an efficient and inexpensive catalyst for the one-pot synthesis of benzimidazoles and benzoxazole derivatives

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ABSTRACT

In this work, a simple and facile method for the preparation of tribromo melamine (TBM or melamine-Br_3) as an environmentally friendly homogeneous catalyst is described as it is used for the one-pot synthesis of benzimidazoles and benzoxazole derivatives *via* condensation reactions between aromatic aldehydes and ortho-phenylenediamine or ortho-aminophenol in aqueous media conditions. This green method offers significant advantages in terms of its simplicity, high catalytic efficiency, good to excellent product yields, use of ethanol as a green solvent, mild conditions, eco-friendly, and in acceptable reaction times.

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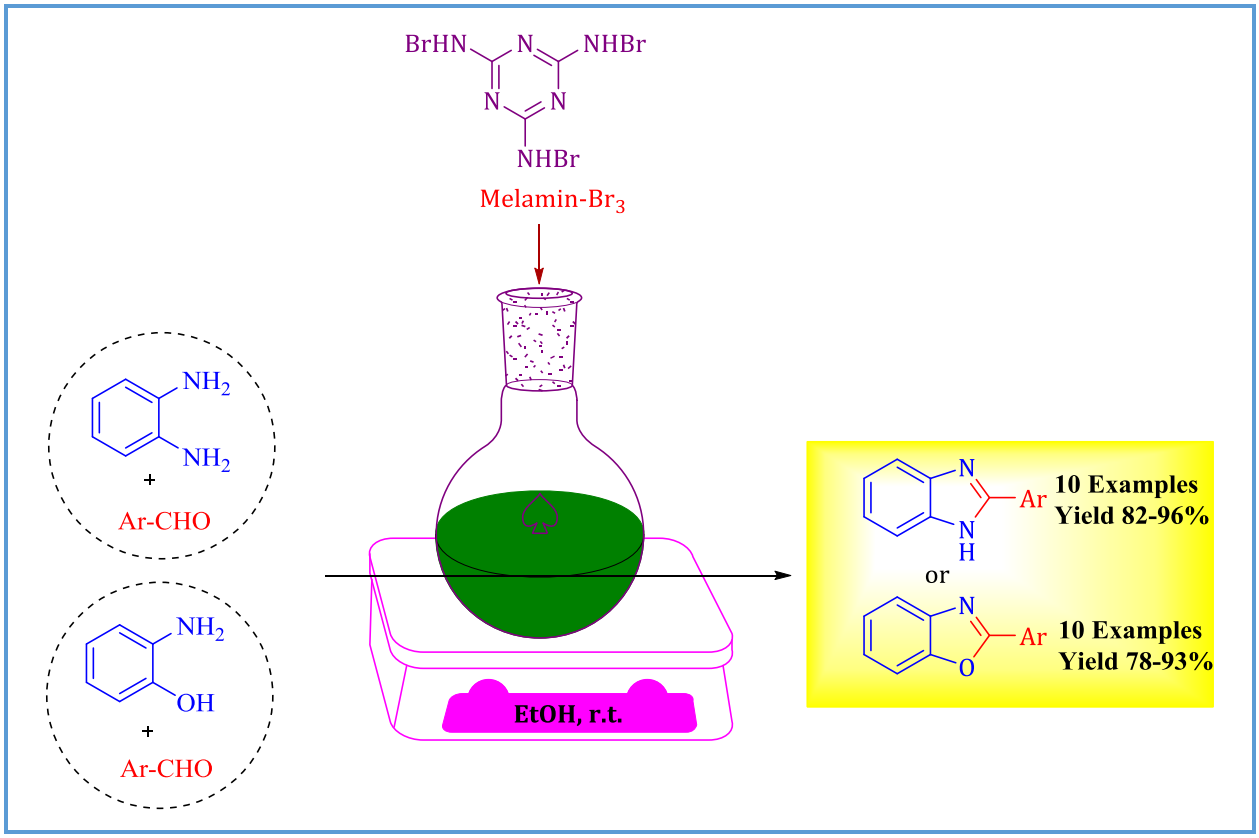
Graphical Abstract



Introduction

The challenge in chemistry is to develop practical methods with convenient conditions and reagents. Besides, the concept of "green chemistry" is becoming ever important in the scientific community and is emerging as a high-priority guiding principle for organic synthesis.

A large number of benzimidazole moieties are found in various biologically active and naturally occurring compounds having antiviral [1], antiulcer [2], antihypertensive [3], antihistaminic [4], and anticancer properties [5]. Moreover, some benzimidazole derivatives have been demonstrated to be potent antiparasitic agents [6], potential antitumour agents [7], selective neuropeptide Y Y1 receptor antagonists [8], inhibitors of HCMV replication [9], angiotensin II (AII) inhibitors [10], topoisomerase I inhibitors [11], antimicrobial agents [12], and inhibitors of the hepatitis C virus RNA polymerase [13]. Therefore, their preparations have received an increasing attention to synthetic organic chemists and biologists. The widespread interest in benzimidazole-containing structures has prompted extensive studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles; the first one which is the coupling of ortho-phenylenediamines and carboxylic acids [14] often requires strong acidic conditions, very high temperatures or the use of

microwave irradiation [15]. The other one involves a two-step procedure that includes the oxidative cyclodehydrogenation of aniline Schiff's bases which are often generated in situ from the condensation of ortho-phenylenediamines and aldehydes. Various oxidative and catalytic reagents such as sulfamic acid [16], $Yb(OTf)_3$ [17], *N*-halosuccinamide (X = Cl, Br, I) [18], sulfur/ultrasonic [19], polyaniline-sulfate [20], phospho sulfonic acid (PSA) [21], L-praline [22], $SOCl_2/SiO_2$ [23], $I_2/KI/K_2CO_3/H_2O$ [24], $In(OTf)_3$ [25], and (bromodimethyl)sulfonium bromide [26] have been employed. However, some of the reported methods tolerate disadvantages including expensive reagents, long reaction times, low yields, the use of an excess of reagents/catalysts, or the use of toxic organic solvents. Therefore, to avoid these limitations, a new and efficient catalyst with high catalytic activity, short reaction time, and simple reaction working-up for the preparation of benzimidazoles and benzoxazole derivatives is still favored.

The aim of this study is to utilize melamine-Br_3 as an efficient, novel, and homogeneous catalyst for the synthesis of benzimidazoles and benzoxazole derivatives under green solvent and room temperature (Scheme 1).

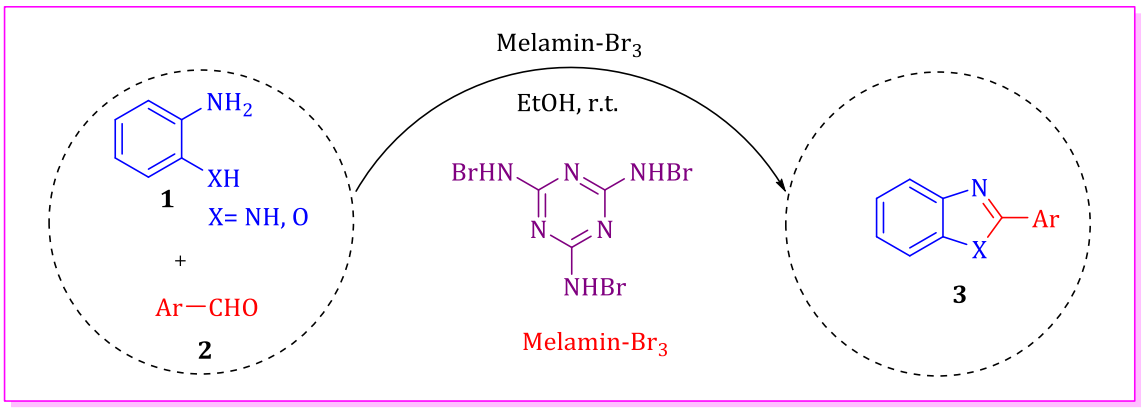
Experimental

Materials and methods

All reagents were purchased from Aldrich (USA) or Merck Fine Chemicals (Germany) and were used without further purification. Products were separated and purified by different chromatographic techniques and were identified by the comparison of their Melting point and NMR with those reported for the authentic samples. The IR spectra of the compounds were obtained using a Perkin-Elmer spectrometer (USA), version 10.03.06 using a KBr disk. ^1H NMR spectra were recorded on a Bruker DRX-300 AVANCE (Germany) spectrometer in $CDCl_3$ as a solvent and chemical shift values are given as parts per million (δ) relative to TMS as an internal standard. Thin-layer chromatography (TLC) was performed on pre-coated aluminium plates (Silica-gel 60 F254, Merck, Germany). The chromatographic spots on the plates were visualised under UV light and iodine vapour. Melting points were recorded on an electrothermal capillary melting point apparatus (UK) and are uncorrected.

General procedure for synthesis of benzimidazole derivative

Aldehyde (1 mmol), ortho-phenyldiamine/ortho-aminophenol (1.1 mmol) and 10 mol% melamine-Br_3 were stirred in methanol (10 mL) as solvent at room temperature for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated and the residue was purified by column chromatography on a silica-gel



Scheme1. Synthesis of benzimidazole derivatives

using *n*-hexane/ethyl acetate (70:30) as eluent to afford the pure product. All the products were characterized by Melting point, ^{1}H NMR and ^{13}C NMR.

Characterization of selected compounds

2-Phenyl-1H-benzo[d]imidazole (Table 2, entry 1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 12.87 (broad s, 1H), 8.20-8.16 (m, 2H), 7.60-7.46 (m, 5H), 7.23-7.18 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 116.0, 124.0, 127.9, 130.2, 131.1, 131.5, 140.3, 153.5.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (Table 2, entry 3)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-8.02 (m, 2H), 7.54-7.57 (m, 2H), 7.20-7.22 (m, 2H), 7.03-7.08 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 56.0, 115.6, 123.5, 123.7, 129.5, 153.6, 163.0.

2-Phenylbenzo[d]oxazole (Table 2, entry 11)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21-8.27 (m, 2H), 7.75-7.79 (m, 1H), 7.48-7.58 (m, 4H), 7.31-7.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.8, 120.2, 124.7, 125.3, 127.3, 127.8, 129.1, 131.7, 142.3, 150.9, 163.2.

Result and discussion

In continuation of our ongoing effort to apply cheap and ecofriendly materials as catalysts for the development of new synthetic methodologies [27, 28], we became interested in the synthesis of melamine-Br_3 *via* reaction of melamine with bromine in alkali media (Scheme 2).

In the present paper, a simple, efficient and high-yielding method has been reported for the synthesis of benzimidazoles and benzoxazole derivatives by treatment of various aldehydes with

ortho-phenylenediamine or ortho-aminophenol catalyzed by melamine-Br_3 as an eco-friendly catalyst in ethanol as green solvent at room temperature (Scheme 1).

To find the optimal conditions, the reaction between ortho-phenylenediamine **1** (1 mmol) and benzaldehyde **2** (1.1 mmol) was used as a model in order to develop a protocol for the optimization of the reaction conditions (Table 1). To improve the yield of the target product, we carried out the test reaction in the presence of various solvents such as ethanol, acetonitrile, dichloromethane, toluene, and chloroform. The results are presented in Table 1. As shown in Table 1, in the absence of the catalyst, the reaction was not complete after 24 h (Table 1, entry 1). On the optimized amount of the catalyst, we found that 10 mol% of melamine-Br_3 could effectively catalyze the reaction for the synthesis of the desired product. With inclusion of 5 mol%, the reaction took longer time and low yield (Table 1, entry 2). A higher percentage of loading of the catalyst neither increased the yield nor shortened the conversion time (Table 1, entries 3 and 4). Use of acetonitrile (Table 1, entry 6) and dichloromethane (Table 1, entry 7) as solvents was much better than the other solvents including toluene (Table 1, entry 8) and chloroform (Table 1, entry 9). When the reaction was performed in solvent-free conditions, the reactions proceeded slowly and resulted in reduced product yields (Table 1, entry 10). Hence, performing the reaction in ethanol as green solvent and in the presence of 10 mol% of melamine-Br_3 at room temperature was determined as the optimal condition (Table 1, entry 3). Using the optimized reaction condition, the scope and limitations of this methodology were evaluated using a variety of aromatic aldehydes (Table 2).

Scheme 2. Synthesis of melamine-Br_3

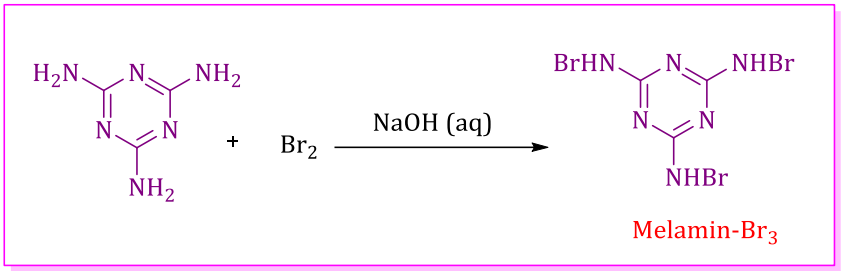


Table 1. Optimization of the melamine-Br_3 catalyzed model reaction[a]

Entry	Catalyst (mol%)	Solvent	Time (h)	Yields (%)
1	No catalyst	Ethanol	1	Not complete
2	5	Ethanol	1.5	78
3	10	Ethanol	1	94
4	15	Ethanol	1.5	85
5	20	Ethanol	1.5	65
6	10	Acetonitrile	2	71

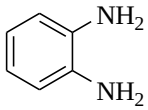
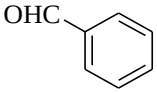
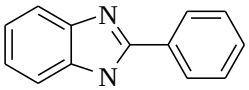
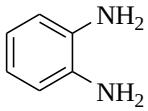
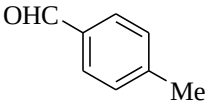
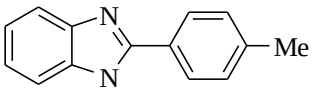
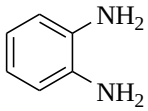
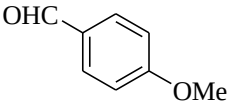
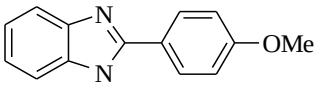
7	10	Dichloromethane	2	65
8	10	Toluene	3	35
9	10	Chloroform	3	48
10	10	Solvent-free	2	51

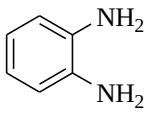
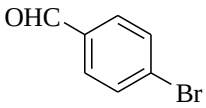
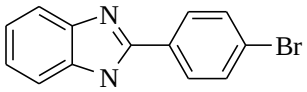
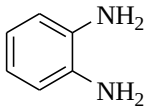
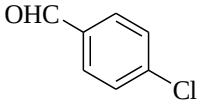
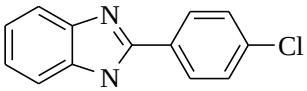
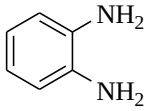
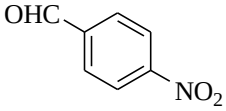
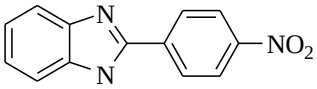
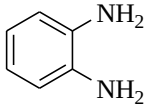
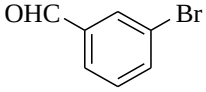
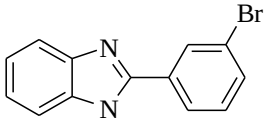
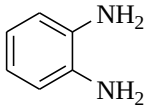
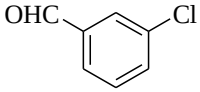
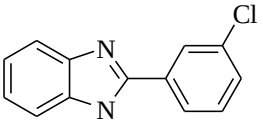
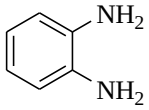
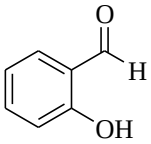
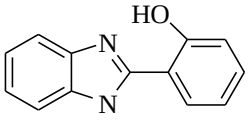
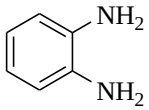
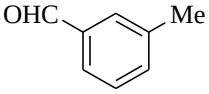
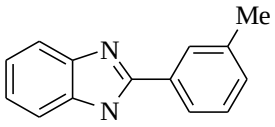
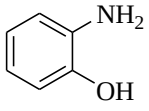
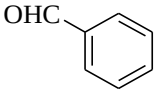
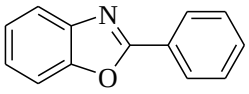
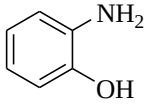
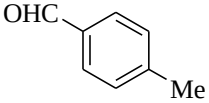
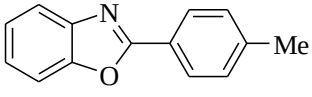
[a] Model reaction: ortho-phenylenediamine **1** (1 mmol), benzaldehyde **2** (1.1 mmol), melamine-Br_3 (10%) at room temperature

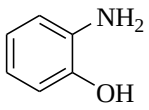
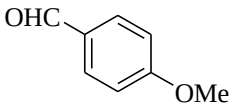
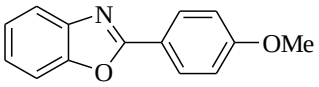
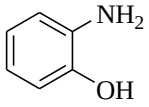
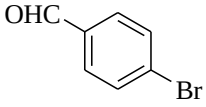
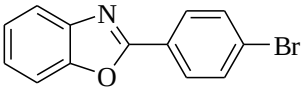
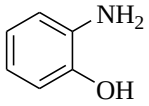
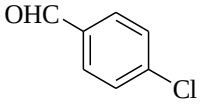
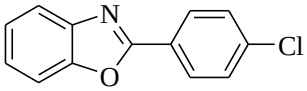
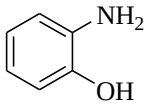
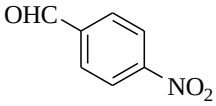
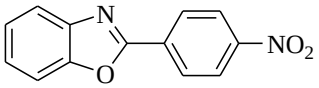
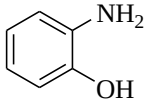
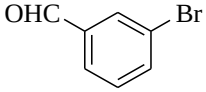
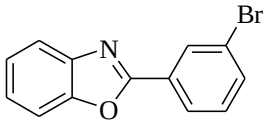
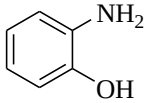
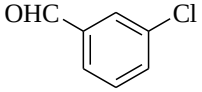
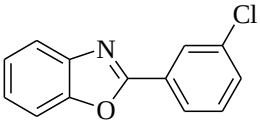
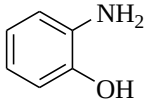
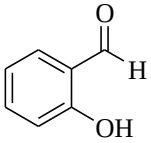
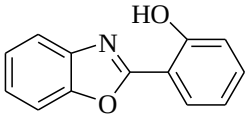
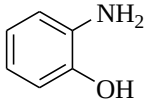
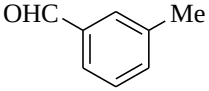
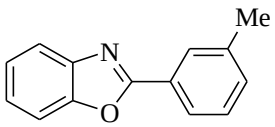
All products were identified by ^1H NMR and ^{13}C NMR spectroscopic methods and the results were confirmed by comparison with those available in the literature. In general, the results given in Table 2 show that good to excellent yields of Benzimidazole and Benzoxazole derivatives were obtained under mild conditions in acceptable reaction times (1–2.5 hours). Furthermore, it was observed that this protocol permitted the use of aryl aldehydes containing electron-withdrawing and electron-donating groups.

In order to show the merit of the present work in comparison to the reported results in the literature, we compared results of melamine-Br_3 with that of Cu-np/SiO_2 [29], silica sulfuric acid [30], iron(III) sulfate-silica [31], and ceric ammonium nitrate [32] in the synthesis of benzimidazole derivatives. Thus, it is evident that melamine-Br_3 can act as an effective catalyst with respect to reaction times and yields.

Table 2. Melamine-Br_3 catalysed synthesis of benzimidazoles and benzoxazoles

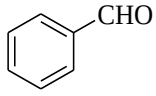
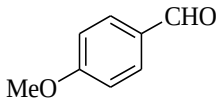
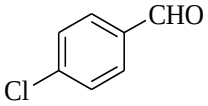
Entry	Diamines	Aldehyde	Product	Time (h)	Yield (%)[a]
1				1	94
2				2	91
3				1.5	91

4				1	96
5				1	94
6				1	89
7				2	84
8				2	82
9				2	87
10				1	92
11				2	93
12				2	89

13				2.5	89
14				1	87
15				1	85
16				2	86
17				2	80
18				2	78
19				2.5	90
20				2	92

[a] Isolated yields

Table 3. Comparison result ofmelamine-Br_3 with Cu-np/SiO_2, silica sulfuric acid, iron(III) sulfate-silica, and ceric ammonium nitrate in the synthesis of benzimidazole derivatives

Substrate	Catalyst	Condition	Yield (%)
	Cu-np/SiO_2	Methanol/ room temperature/ 4h	93
	Silica sulfuric acid	Water/ room temperature/ 2 h	71
	Iron(III) sulfate-silica	solvent-free/ 30 °C/ 2h	89
	Ceric ammonium nitrate	PEG/ 50 °C/ 2 h	98
	Melamine-Br_3	Ethanol/ room temperature/ 1h	94
	Cu-np/SiO_2	Methanol/ room temperature/ 6h	85
	Silica sulfuric acid	Water/ room temperature/ 2.5 h	78
	Iron(III) sulfate-silica	Solvent-free/ 30 °C/ 2h	85
	Ceric ammonium nitrate	PEG/ 50 °C/ 2 h	94
	Melamine-Br_3	Ethanol/ room temperature/ 1.5 h	91
	Cu-np/SiO_2	Methanol/ room temperature/ 1.5 h	87
	Silica sulfuric acid	Water/ room temperature/ 2 h	82
	Iron(III) sulfate-silica	Solvent-free/ 30 °C/ 1.5 h	87
	Ceric ammonium nitrate	PEG/ 50 °C/ 1.5 h	94
	Melamine-Br_3	Ethanol/ room temperature/ 1 h	94

Conclusions

In summary, an efficient, green and simple procedure for the one-pot synthesis of benzimidazole and benzoxazole derivatives from various aldehydes and ortho-phenylenediamine or ortho-aminophenol under green solvent at room temperature was described. The reactions were carried out using 10 mol% of melamine-Br_3, in acceptable reaction times, affording good to excellent yields of the products.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at http://www.ajgreenchem.com/article_57683.html.

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