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An efficient facile and one-pot synthesis of 2-arylsubstituted benzimidazole derivatives using 1-methyl-3-(2-oxyethyl)-1H-imidazol-3-ium-borate sulfonic acid as a recyclable and highly efficient ionic liquid catalyst at green condition

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Abstract

1-Methyl-3-(2-oxyethyl)-1H-Imidazol-3-ium-Borate Sulfonic Acid ([MOEI]-BSA) was easily prepared and used as a new and highly efficient solid acid catalyst for the synthesis of benzimidazole derivatives with high isolated yields. Various substituted benzimidazoles were synthesized by a combination of *o*-phenylenediamines and aldehydes in the presence of [MOEI]-BSA with excellent yields in water and under a mild and green reaction conditions. This method is also applicable for precursors such as aromatic and unsaturated aldehydes and *o*-phenylenediamines. Addition of organic part to BSA and synthesis of [MOEI]-BSA as a new Bronsted acidic ionic liquid (BAIL) improved the efficiency of this catalyst.

Keywords: 1-Methyl-3-(2-oxyethyl)-1H-imidazol-3-ium-borate sulfonic acid; [MOEI]-BSA; BAIL; solid acid; benzimidazole synthesis; green chemistry.

Introduction

Benzimidazole moieties are classified under several classes of drugs [1],based on the possible substitution at different positions of the benzimidazole nucleus.Benzimidazole derivatives exhibit significant activity against several viruses such as HIV, human cytomegalovirus (HCMV) [2], herpes (HSV-1) [3], RNA [4] and influenza [5]. Furthermore, they have been also used to act as topoisomerase inhibitors [6], selective neuropeptide YY1 receptor antagonists [7], angiotensin II inhibitors [8], potential antitumor agents [9] and smooth muscle cell proliferation inhibitors [10]. In addition, benzimidazoles are very important precursors in organic synthesis. Vitamin B_{12} constitutes a milestone in the chemistry of benzimidazoles. Bisbenzimidazole is DNA-minor grove binding agents possessing anti-tumour activity [11].

A number of methods have been reported for the synthesis of benzimidazoles such as the condensation of o-aryldiamines and

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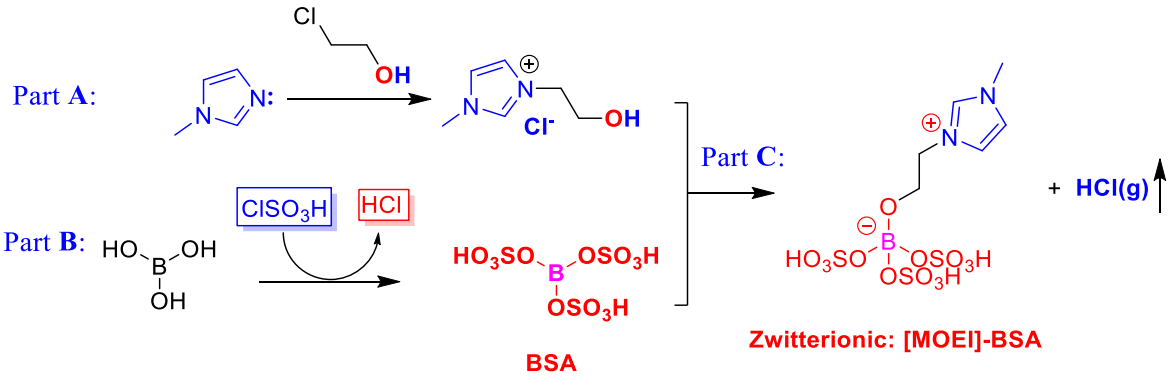
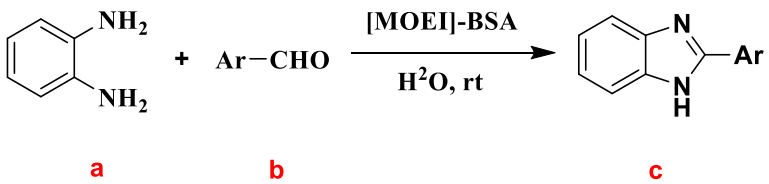
aldehyde in refluxing nitrobenzene [12]. One of the methods is the coupling of phenylenediamines and carboxylic acids[13] or their derivatives (nitriles, imidates, or orthoesters) [14], which often requires strong acidic conditions[15], and sometimes combines with very high temperatures or microwave irradiation [16]. The other route 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 aldehydes. Direct condensation of o-aryldiamines and aldehydes is not a good synthetic reaction, as it is well known to yield a complex mixture, being 1,2-disubstituted benzimidazoles, the bis anil and dihydrobenzimidazoles as the main side products [17]. However, the addition of transition metal, namely copper (II) acetate [18], Tribromo melamine [19] mercury oxide [20] or lead tetracetate [21] allows a partial selective synthesis of benzimidazoles. Benzimidazole derivatives can be synthesized by different catalysts and condition [22]. Unfortunately, many of these processes suffer some limitations, such as drastic reaction conditions, low yields, tedious work up procedures and co-occurrence of several side reactions. In this article, we report a simple and efficient method for the synthesis of benzimidazole derivatives using SBSA as a catalyst under mild reaction conditions. We used water as a green solvent. Water, as a green reaction medium, is highly appreciated. As a solvent, water possesses the following distinct advantages of being safe, nonflammable, readily available in large quantities, operationally very simple and devoid of any carcinogenic effects. Therefore, water mediated organic reactions for the preparation of biologically active molecules constitutes a major challenge for chemists involved in organic synthesis.

In continuation of our study in application and characterization of BSA in organic reactions [23-34], we recently reported the synthesis of [MOEI]-BSA (Scheme 1) as a novel and efficient solid acid catalyst-promoted green synthesis of quinoxaline derivatives[28].



Scheme 1. Synthesis of [MOEI]-BSA



Scheme 2. Prepartion of 2-substituted benzimidazole derivatives

Experimental

General

IR spectra of the compounds were obtained on a Shimadzu IR-435 spectrometer using a KBr disk. The ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz in dimethyl sulfoxide (DMSO-d6) using tetramethylsilane as an internal standard. The progress of reaction was followed with thin-layer chromatography (TLC) using silica gel SILG/UV 254 and 365 plates.All the products are known compounds and were characterized by comparing the IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data and their melting points with the literature values. All chemicals were purchased from Merck or Fluka Chemical Companies.

Preparation of catalyst ([MOEI]-BSA)[22-36]

A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through water adsorbing solution and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged in the flask and chlorosulfonic acid (8.74 g, ca. 5 mL, 75 mmol in 5 mL CH_2Cl_2) was added dropwise over a period of 1 h at room temperature under N_2(g). Hydrogen chloride evolved immediately. After completion of the addition, the mixture was shaken for 85 min, while the residual HCl was eliminated by suction. Then, the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid (^{1}H NMR of SBSA in Acetone-D6 show δ=12.218) and then the liquid form of 1-methyl-3-(2-hydroxyethyl)-1H-imidazol-3-ium chloride (40 mmol) was added to the mixture within a 45-60 minute. Afterwards, a grayish solid material was obtained in 99% yield. Finally, we added silica gel and stirred the mixture. The mixture dried and grayish solid material was obtained.

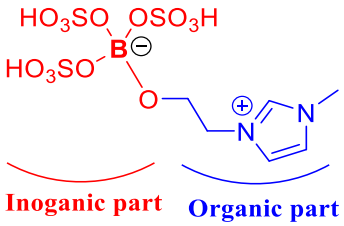
Typical procedure for the synthesis of benzimidazoles

A mixture of *o*-phenylenediamine derivatives 1 (1 mmol), aromatic aldehyde 2 (1 mmol), and [MOEI]-BSA (0.05g, 5 mol %) in 10 mL of water, was stirred in a round bottomed flask at room temperature for 30 minutes (Table 3). The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was added dropwise with vigorous stirring into a mixture of Na_2CO_3 (0.106g, 0.1 mmol) and H_2O (20 mL). In cases where the product precipitated as a free flowing solid, it was collected by filtration, washed with H_2O and dried. In cases where gummy material precipitated the product was extracted into EtOAc, the organic phase was washed with H_2O and dried with Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by column chromatography over silica gel (*n*-hexane:ethyl acetate, 5:1) to afford the corresponding benzimidazole.All of the compounds are known compounds identified by their ^{1}H NMR spectroscopic data and by comparing their melting points with those reported in the literature.

Results and discussion

In continuation of our study on application of BSA and its acidic derivatives in organic reactions, we firstly added organic part to BSA. [MOEI]-BSA was easily prepared by addition of 1-methyl-3-(2-(hydroxy) ethyl)-1H-imidazol-3-ium chloride to boron sulfonic acid at room temperature. This reaction was easy and clean and the

HCl gas evolved from the reaction vessel immediately (Scheme 1).



Scheme 3. Structure f [MOEI]-BSA

We decide to use 1-Methyl-3-(2-Oxyethyl)-1H-Imidazol-3-ium-Borate Sulfonic Acid ([MOEI]-BSA) for the synthesis of 2-substituted benzimidazole derivatives. Firstly, condensation of *o*-phenylenediamine and benzaldehyde was performed with different molar ratio of ([MOEI]-BSA, solvents and temperatures to optimize the reaction conditions. Various solvents with a good range of molar ratios of the catalyst were employed and the results are depicted in Table 1. As shown in Table 1, a mixture of 5 mol% of [MOEI]-BSA in H_2O (10 mL) created the best reaction media and afforded the benzimidazole 3c with optimum yields among the conditions tested (Entry 11, Table 3). In order to find a suitable catalyst ratio for the synthesis of benzimidazoles from 1,2-diamines and aldehydes, the condensation of benzene-1,2-diamine with 4-chlorobenzaldehyde was chosen as a model to provide compound 2-(4-chlorophenyl)benzimidazole (Scheme 2).

Table 1. Optimization of catalyst in synthesis of 2-(4-chlorophenyl)benzimidazole at room temperature

Entry	Catalyst %	Time(min)	Yield %
1	1	45	65
2	3	30	80
3	5	15	98
4	10	25	85
5	15	45	77

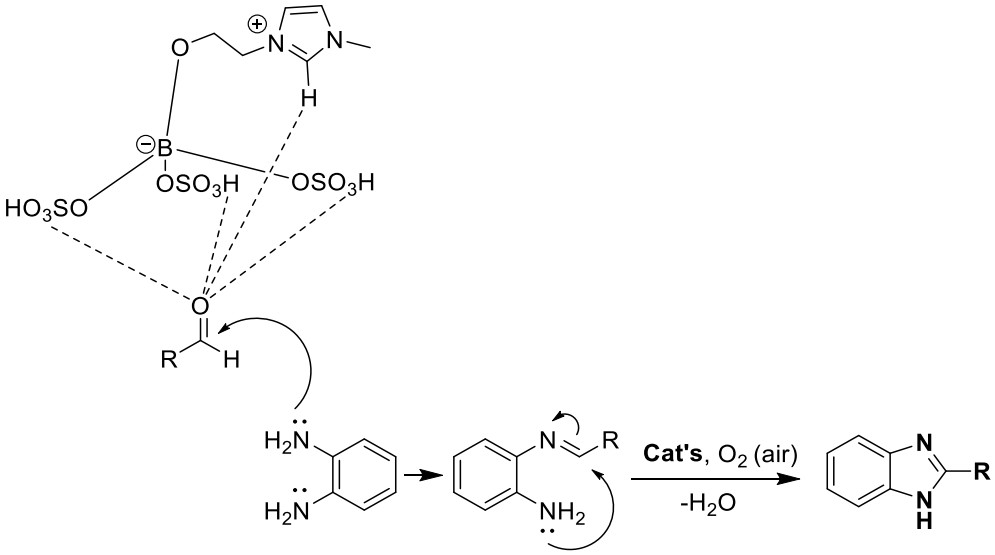
The solvent effect on the model reaction was also investigated. According to the results in Table 2, water was found to be the best solvent for this purpose.

Table 2. Optimization of various solvents in synthesis of 2-(4-chlorophenyl)benzimidazole 11c in presence of [MOEI]-BSA at room temperature

Entry	Solvent	Time (min)	Yield%
1	H_2O (10 mL)	15	98

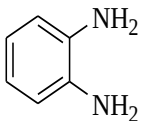
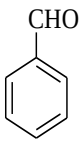
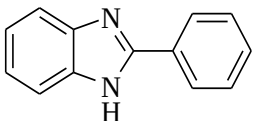
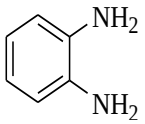
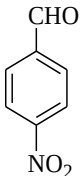
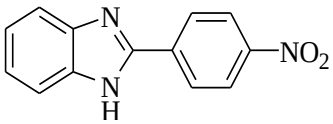
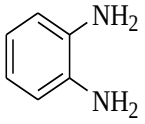
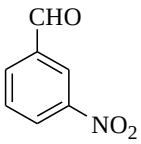
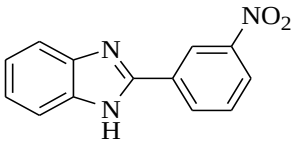
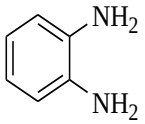
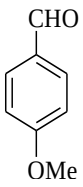
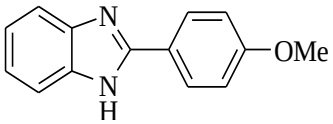
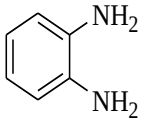
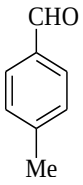
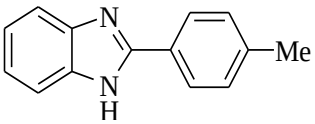
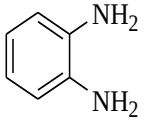
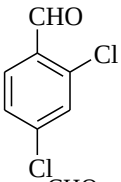
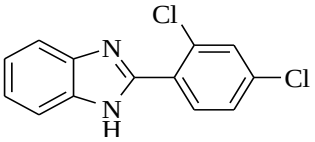
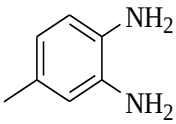
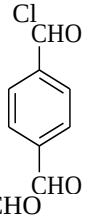
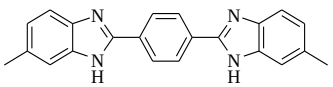
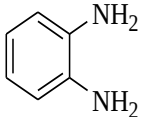
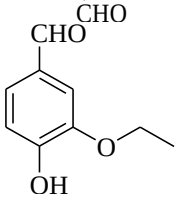
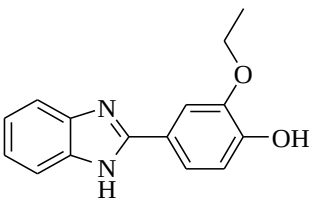
2	EtOH (10 mL)	15	85
3	H_2O:EtOH (1:1, 10 mL)	20	75
4	H_2O:EtOH (2:8, 10 mL)	20	78
5	Solvent-free (80 ^{0}C)	50	69
6	CH_2Cl_2	25	56

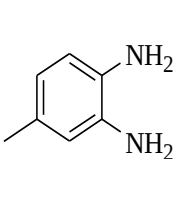
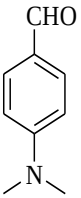
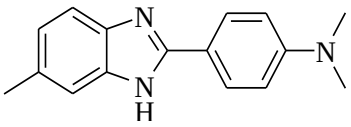
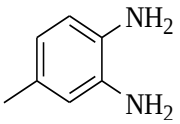
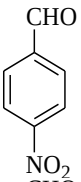
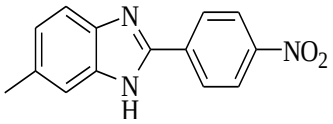
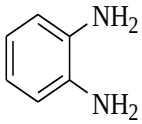
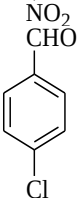
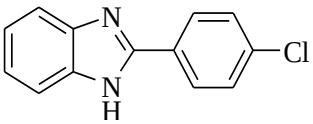
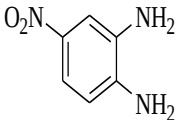
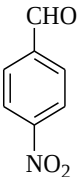
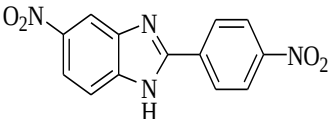
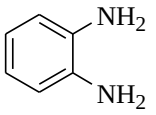
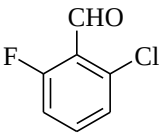
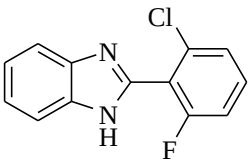
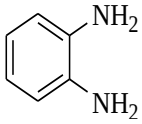
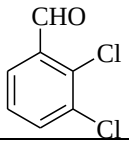
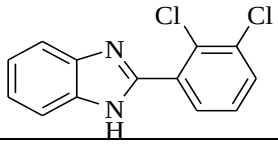
Herein, we wish to report a new protocol for the rapid synthesis of a variety of biologically significant benzimidazoles using a catalytic amount of [MOEI]-BSA under mild aqueous conditions. The reaction was carried out in neat condition at room temperature for 15 minutes, using o-phenylenediamine (1 mmol) and aldehyde (1 mmol) in the presence of [MOEI]-BSA (0.05 mmol). Thus, under the optimized reaction conditions, the reaction was performed using various 1,2-diamines and aldehydes compounds. As shown in Table 3, various aldehydes bearing electron-donating or electron-withdrawing groups reacted with different diamines to afford their corresponding benzimidazoles in good to excellent yields. The reasonable mechanism ~~as~~ is shown below (Scheme 4).



Scheme 4. Mechanisms for the synthesis of 2-alkyl-1,3-benzimidazoles (**c**) *via* condensation reaction of phenylenediamine (**1a**) with different aldehydes(**b**)

Table 3. Synthesis of benzimidazole derivativess catalyzed by ([MOEI]-BSA

Entry	Diamine 1 (a)	Aldehyde 2 (b)	Product (c)	Yield %	Time (min)
1				91	20
2				93	25
3				95	30
4				91	35
5				94	15
6				85	20
7				80	30
8				91	40

9				85	25
10				93	20
11				94	15
12				85	30
13				80	30
14				93	20

[a]Isolated Yield

Conclusion

In conclusion, a new, heterogeneous, strong and highly effective acid catalyst for the synthesis of benzimidazole derivatives *via* the reaction of various 1,2-diamines with various aldehydes has been reported. The advantages of this method are efficiency, generality, excellent yield, short reaction time, cleaner reaction profile, simplicity, easy work up and reusability. The catalyst can be recycled from the reaction mixture by a simple filtration and reused within several runs as a green catalyst.

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