Research Article

Boric Acid Catalyzed Convenient Synthesis of Benzimidazoles in Aqueous Media

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Synthesis of benzimidazoles has been developed by the *o*-phenylenediamine with aldehydes using boric acid an efficient catalyst under mild reaction conditions in aqueous media. The product is applicable to aryl and heteroaryl aldehydes. This reaction led to the formation of benzimidazoles new derivatives in good yields. The FT-IR, ^{19}F -NMR, ^1H -NMR, ^{13}C -NMR spectra and elemental analysis confirm the structure of compounds.

1. Introduction

Benzimidazole and its derivatives have been the area of much research interest due to their importance in various applications and its widespread biochemical significance [1]. Benzimidazole structure is found in several classes of drugs based on the substituents present at different positions [2]. Benzimidazole derivatives find many applications in several therapeutic areas such as antimicrobial agents, [3] antiviral agent against several viruses such as HIV, [4] influenza [5], and herpes (HSV-1) [5], antitumor, [6] anti-inflammatory, [7] anthelmintic agents, [8] as well as antiprotozoal agents [9]. The amino ketone derivatives of imidazo [1,2-*a*]-benzimidazoles are potent adrenoblockers, spasmolytics, antiarrhythmogens, and antimicrobial agents [10]. Benzimidazoles are also important intermediates in organic synthesis [11, 12]. A number of methods have been adopted for the synthesis of benzimidazoles from different reactants and reaction conditions such as reaction between *o*-phenylenediamine and aldehyde under oxidative conditions, [13, 14], *o*-phenylenediamine and carboxylic acid [15–17] in the presence of catalyst such as $\text{H}_2\text{O}_2/\text{HCl}$ [18], $\text{Sc}(\text{OTf})_3$ [19, 20], $\text{Cu}(\text{OTf})_2$ [21], KHSO_4 [22], ionic liquids [23], *p*-TsOH [24], and SiO_2 as solid support [25] and under microwave irradiation using polyphosphoric acid as catalyst [26]. However many

of these methodologies suffer one or more disadvantages like low yields, lack of easy availability of the starting materials, prolonged reaction time, high temperature, excess requirement of catalysts, special apparatus, harsh reaction conditions, extraction of product, formation of byproduct, and so forth. Thus there is a need for simple and efficient protocol for the synthesis of benzimidazole derivatives. Organic synthesis in aqueous media is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. Since the pioneering studies by Breslow [27], on Diels-Alder reactions, there have been profound research activities in the development of organic reactions in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration. Also, in the context of green chemistry, aqueous media is acting as a stepping stone in the greener synthesis of bioactive heterocyclic compounds.

Boric acid is a water soluble catalyst and has been found to be effective in various organic transformations such as esterification of hydroxycarboxylic acids [28], aza Michael [29], thia Michael [30], addition, and bromination [31]. Herein, we report a method for the synthesis of benzimidazole derivatives by using boric acid catalyst to obtain product with high yield in moderate reaction time and easy work-up.

2. Experimental

2.1. Materials and Instruments. Melting point was recorded on a Barnstead/Electro thermal/9200 (England) instrument. All reagents were purchased from Merck. Aldehydes were distilled before use. NMR spectra were recorded using either a Bruker DRX500 machine at room temperature. ^1H , ^{13}C NMR, and ^{19}F NMR spectra were measured using DMSO- d_6 as solvent. CHN analyses were performed on Exeter Analytical Inc. Model C-400 CHN Analyzer. Mass spectra were obtained using a Micro Mass LCT machine in ES or EI mode. Infrared spectra were measured on a Perkin Elmer Paragon 100 FT-IR spectrometer. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60F₂₅₄) UV indicator.

2.2. Typical Procedure for Synthesis of 2-Phenyl-1H-benzo[d]imidazole (3a). A mixture of *o*-phenylenediamine (107 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), and boric acid (10 mol%) in water (5 mL) was stirred at room temperature for 30 min. After completion of reaction, as monitored by TLC (ethyl acetate/*n*-hexane, 1:5) the solid product was collected by simple filtration and washed with water. The crude product (3a) was purified by recrystallization from ethanol.

Spectroscopic Data

2.2.1. 2-(4-Fluorophenyl)-1H-benzo[d]imidazole (3m). White powder; 201 mg (95%); mp 237°C; IR (KBr): 3043, 1408, 1289, 973, 732 cm^{-1} ; ^1H NMR (DMSO- d_6 , 500 MHz): δ 13.06 (s, 1H, NH), 8.11 (d, 2H, J = 8.5 Hz, ArH), 7.77-7.43 (m, 6H, ArH); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 151.54, 135.09, 134.54 (d, J_{CF} = 253.58 Hz), 129.87, 129.23, 127.89, 124.54, 119.33; ^{19}F NMR (DMSO- d_6 , 470 MHz): -72.54; MS (EI), m/z (%) = 212 (M^+ , 76), 116 (32); HRMS (EI) Found: M^+ , 212.0706. $\text{C}_{13}\text{H}_9\text{FN}_2$ requires M^+ , 212.0701; Anal Calcd for $\text{C}_{13}\text{H}_9\text{FN}_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.51; H, 4.31; N, 4.32.

2.2.2. 2-(4-(Trifluoromethyl)phenyl)-1H-benzo[d]imidazole (3n). Yellow powder; 248 mg (95%); mp 221°C; IR (KBr): 3095, 2199, 1625, 1451, 810, 726 cm^{-1} ; ^1H NMR (DMSO- d_6 , 500 MHz): δ 12.91 (s, 1H, NH), 8.09 (d, 2H, J = 8.4 Hz, ArH), 7.89-7.53 (m, 6H, ArH); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 159.12, 139.14, 135.98, 126.89 (q, J = 283.5 Hz, CF_3), 125.45, 122.43, 121.48, 120.09, 116.25; ^{19}F NMR (DMSO- d_6 , 470 MHz): -43.25; MS (EI), m/z (%) = 382 (M^+ , 15), 292 (65); HRMS (EI) Found: M^+ , 267.0713. $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$ requires M^+ , 267.0720; Anal Calcd for $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$: C, 64.12; H, 3.46; N, 10.68. Found: C, 64.16; H, 4.52; N, 10.71.

3. Results and Discussion

In continuation of our research work using boric acid in organic synthesis here we are pleased to report that a mixture of aldehyde, *o*-phenylenediamine in the presence of boric acid (10 mol%) in H_2O at room temperature furnished benzimidazoles in good yields (Scheme 1).

TABLE 1: Model reaction of *o*-phenylenediamine (1.0 mmol) with benzaldehyde (1.05 mmol) by using different amounts of catalyst boric acid in water at room temperature.

Entry	Amount of catalyst (%)	Reaction time (min)	Yield (%) ^a
1	0	60	0
2	5	60	60
3	10	30	95
4	15	90	90
5	20	90	85

^aIsolated yield.

SCHEME 1: Synthesis of benzimidazoles using boric acid as catalyst in H_2O .

The reaction was optimized by varying amount of catalyst. We chose the reaction between *o*-phenylenediamine 1 and benzaldehyde 2a as the model reaction. First we carried out model reaction in the presence of a catalyst (Table 1, entry 1) and found that the reaction did not proceed. Next, the amount of catalyst was varied with respect to 1 (Table 1, entries 2–5). It was found that only 65% and 88% yields were obtained by taking 5% and 20% amounts of catalyst boric acid (Table 1, entries 2 and 5), respectively. The best result (95% yield of product 3a) was obtained by using 10% amount of catalyst (Table 2, entry 3). By using these optimized conditions, various benzimidazole derivatives 3a-o were synthesized in shorter time as well as in high yields using boric acid as the catalyst.

A wide range of aromatic and heteroaryl aldehydes were subjected to prove the general applicability of our present procedure which is summarized in Table 2. It was observed that the aromatic aldehyde bearing an electron donating substituent underwent the conversion smoothly as compared to that bearing an electron withdrawing substituent (Table 2). We have synthesized compounds 3a-o bearing an electron withdrawing substituent ($-\text{NO}_2$) 3j in 10 min with high yields were as compounds 3f & 3i bearing an electron donating substituent ($-\text{OCH}_3$ & $-\text{OH}$, resp.) in 60 min.

In ^1H NMR spectra of compounds 3a-o, the N-H proton of benzimidazole moiety resonates in more down field region, that is, around δ 13 ppm. The plausible mechanism for the formation of benzimidazole derivative is suggested in Figure 1.

4. Conclusion

In conclusion, we have demonstrated a very simple, efficient, and practical method for the synthesis of benzimidazoles with boric acid as catalyst in aqueous media, from readily available *o*-phenylenediamines and aromatic aldehydes,

TABLE 2: Synthesis of benzimidazole **3a–o** by using boric acid in water.

Entry	Diamine	Aldehydes	Products	Time (min)	Yield (%) ^a
1			3a	30	95
2			3b	40	90
3			3c	45	89
4			3d	60	89
5			3e	60	89
6			3f	60	88
7			3g	60	88
8			3h	60	86
9			3i	60	85
10			3j	10	98

TABLE 2: Continued.

Entry	Diamine	Aldehydes	Products	Time (min)	Yield (%) ^a
11				10	95
12				15	90
13				5	95
14				5	95
15				20	90

^a Isolated yield.

FIGURE 1: Plausible mechanism for the formation of benzimidazoles.

under simple and convenient conditions. The conditions are mild, and a wide range of functional groups can be tolerated. The main features of our new reaction are as follows: (1) the simplicity of the system; (2) the condensation reaction could be performed exclusively using cheap, commercially available chemicals; (3) easy separation of products from the reaction mixture; (4) the method is cost-effective and environmentally benign.

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