An Efficient and Inexpensive Synthesis of 2-Substituted Benzimidazoles in Water Using Boric Acid at Room Temperature

ZAHED KARIMI-JABERI and MOHAMMAD AMIRI

Department of Chemistry, Firoozabad Branch
Islamic Azad University, Firoozabad, Fars, Iran
zahed.karimi@yahoo.com

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Abstract: 2-Substituted benzimidazoles have been synthesized in a one-pot reaction from *o*-phenylenediamine and aldehydes in the presence of boric acid in water at room temperature. The method was proved to be eco-friendly, convenient and the products were isolated with good yields.

Keywords: Benzimidazoles, Boric acid, *o*-Phenylenediamine, Inexpensive synthesis

Introduction

The preparation of benzimidazoles has gained considerable attention in recent years. The benzimidazole is found in a variety of naturally occurring compounds and is of significant importance in medicinal chemistry. Their diverse applications include as potential antitumor agents¹, antimicrobial agents², angiotensin II inhibitors³, inhibitors of HCMV replication⁴, selective neuropeptide YY1 receptor antagonists⁵. In addition, benzimidazoles are very important intermediates in organic reactions⁶.

Several methods have been reported for the synthesis of benzimidazoles⁷. The traditional synthesis of benzimidazole involves the reaction between *o*-phenylenediamine and a carboxylic acid or their derivatives at elevated temperature in the presence of strong acids such as polyphosphoric acid⁸ or mineral acids⁹ and thermal or acid promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines¹⁰. Recently direct condensation of *o*-aryldiamines and aldehydes is the most convenient method for the preparation of these compounds. In this context some methods and catalysts have been reported such as indium triflate¹¹, iodine¹², cetylpyridinium bromide¹³, PEG 400¹⁴, (bromodimethyl)sulfonium bromide¹⁵ and ammonium acetate¹⁶. Although, these approaches are satisfactory for synthesis of benzimidazoles, the harsh reaction conditions, expensive reagents, use of toxic organic solvents and long reaction times limit the use of these methods.

In recent years, water-mediated organic synthesis without using organic solvents has become one of the most important aspects in organic chemistry in order to meet the environmental demands. Carrying out organic synthesis in aqueous phase is highly challenging both from the synthetic view point and also from the impact of the environmental pollution¹⁷.

During the course of our systematic studies directed towards the development of environmentally friendly procedures for several important organic transformations¹⁸⁻²⁰, we now describe a simple, general and efficient protocol for the synthesis of 2-substituted benzimidazoles using boric acid in water at room temperature (Scheme 1).

Scheme 1

Boric acid (H_3BO_3) is a useful and environmentally benign catalyst which has been successfully utilized in numerous reactions, for example, the aza Michael addition²¹, Biginelli reaction²² transesterification of ethyl acetoacetate²³, mannich reaction²⁴ and synthesis of α -aminophosphonates and dibenzoxanthenes by our group²⁵⁻²⁶. It offers milder conditions relative to common mineral acids. Boric acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture. Thus, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the reaction of diamines with aldehydes.

Experimental

A mixture of aldehyde (2 mmol), *o*-phenylenediamine (2 mmol), boric acid (0.1 g) and water (1 mL) was stirred at room temperature for the appropriate time indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/petroleum ether=1/4). After completion of the reaction, water (5 mL) was added and the mixture was stirred for 10 min. The obtained solid was collected by filtration and purified by recrystallization from ethanol. Spectral data for selected products: Entry 4: mp 291-293 °C; ¹HNMR (250 MHz, DMSO-*d*₆): δ 12.98 (1H, br s), 8.17, (2H, d, *J* = 8.5 Hz), 7.53-7.63 (4H, m), 7.19-7.21 (2H, m).

Results and Discussion

To optimize the reaction conditions, the reaction of *o*-phenylenediamine with benzaldehyde was used as a model reaction. Reactions at different conditions in the presence of boric acid revealed that the best conditions were using water as solvent at room temperature. After completion of the reaction, the catalyst (boric acid) can easily be separated from the reaction mixture by washing the product with water.

To show the generality of this method the optimized system was used for the synthesis of other derivatives. Several examples illustrating this novel and general method for the synthesis of dibenzoxanthenes are summarized in Table 1.

These data clearly show that different aromatic aldehydes were successfully converted into the corresponding benzimidazoles in high yields at room temperature. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring makes no difference to the course of the reaction. Various functionalities present in the aryl aldehydes, such as halogen, methoxy and nitro groups were tolerated (Table 1). Furthermore, unsaturated aldehydes, such as cinnamaldehydes (Entry 9), gave the corresponding benzimidazoles without any polymerization or conjugate addition to the α,β -unsaturated carbonyl group under the above reaction conditions. Moreover, heteroaromatic (Entries 10-12)

were effective substrates to successfully execute couplings by boric acid. All products are known compounds and structures of them were confirmed by comparison with their known physical and spectral (NMR and IR) data^{11–16}.

Table 1. Synthesis of 2-substituted benzimidazoles in the presence of boric acid

Entry	Aldehyde	Product	Time, min	Yield, % ^a
1			30	92
2			15	90
3			20	91
4			15	93
5			15	90
6			15	92
7			30	84
8			15	92
9			20	95
10			35	70
11			15	70
12			30	93
13			25	75
14			15	98 ^b

^aIsolated yield, ^bconditions: *o*-phenylenediamine (2 mmol) terphthaldehyde (1 mmol)

Conclusion

In conclusion this paper describes a convenient and efficient process for the synthesis of 2-substituted benzimidazoles by one-pot reaction of *o*-phenylenediamine with aldehydes in the presence of boric acid in water. This method offers some advantages in terms of simplicity of performance, using water as solvent, low reaction times, low cost and it follows along the line of green chemistry. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. We believe that this procedure is convenient, economic and a user-friendly process for the synthesis of substituted imidazoles of biological and medicinal importance.

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