

## H<sub>2</sub>O<sub>2</sub>/SiO<sub>2</sub>-FeCl<sub>3</sub> 계를 이용한 Benzimidazoles의 효율적인 합성

Abbas Fazlinia\*, Mohammad Hossein Mosslemin, and Hesamaddin Sadoughi

Department of Chemistry, Islamic Azad University- Yazd Branch, Yazd, Iran

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## An Efficient Procedure for the Synthesis of Benzimidazoles Using H<sub>2</sub>O<sub>2</sub>/SiO<sub>2</sub>-FeCl<sub>3</sub> System

Abbas Fazlinia\*, Mohammad Hossein Mosslemin, and Hesamaddin Sadoughi

Department of Chemistry, Islamic Azad University- Yazd Branch, Yazd, Iran

\*E-mail: fazlinia@gmail.com

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**요약.** Solid silica supported ferric chloride (SiO<sub>2</sub>-FeCl<sub>3</sub>) 촉매를 이용하여 다양한 benzimidazoles의 one-step 합성을 수행하였으며, 합성 방법이 간단하며, 화합물의 분리가 용이하며, 반응시간이 짧다.

**주제어:** SiO<sub>2</sub>-FeCl<sub>3</sub>, Benzimidazole, Aryl aldehyde, *o*-Phenylenediamine

**ABSTRACT.** Solid silica supported ferric chloride (SiO<sub>2</sub>-FeCl<sub>3</sub>) catalyzed one-step synthesis of various benzimidazoles from *o*-phenylenediamine and aldehydes using H<sub>2</sub>O<sub>2</sub> as the oxidant. The salient features of this method are simple and convenient procedure, easy purification and shorter reaction times.

**Keywords:** SiO<sub>2</sub>-FeCl<sub>3</sub>, Benzimidazole, Aryl aldehyde, *o*-Phenylenediamine

### INTRODUCTION

Nitrogen compounds are basic building blocks in animal biology and life.<sup>1</sup> Nitrogen heterocycles are of special interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities.<sup>1</sup> A series of heterocycles containing nitrogen atom is benzimidazole. Substituted benzimidazoles have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics to name only a few.<sup>2</sup> The widespread interest in benzimidazole containing structures has prompted extensive studies for their synthesis. Thus a number of routes have been developed for synthesis of 2-substituted benzimidazoles.<sup>3</sup> But some of these procedures have certain limitations such as tedious process, long reaction times, harsh reaction conditions, and low yields.

In our program, we targeted a simple and convenient

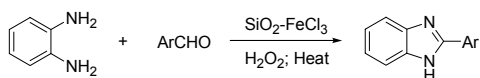
method for the synthesis of 2-substituted benzimidazoles via one-pot cyclocondensation-oxidation of *o*-phenylenediamine and aldehydes using silica supported ferric chloride (SiO<sub>2</sub>-FeCl<sub>3</sub>) as catalyst under thermal conditions (Scheme 1).

### EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by spectroscopic data (IR, NMR spectra) and melting points with authentic samples. The NMR spectra were recorded on a Bruker Avance DEX 300 MHz instrument. The spectra were measured in DMSO-d<sub>6</sub> relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. All of the compounds were solid and solid state IR spectra were recorded using the KBr disk technique. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates.

#### Preparation of SiO<sub>2</sub>-FeCl<sub>3</sub>.

In a 250 mL flask, ferric chloride hexahydrate (FeCl<sub>3</sub>·6H<sub>2</sub>O) (1 g) was dissolved in acetone (50 mL) and silica gel



Scheme 1. Preparation of 2-aryl benzimidazole derivatives

(10 g) ( $\text{SiO}_2$  for column chromatography; 70 - 230 mesh) was added to this mixture and was vigorously stirred under vacuum until acetone was evaporated. A pale yellowish powder was obtained. This powder was kept in oven at  $100^\circ\text{C}$  for 1 h to give the active catalyst.<sup>4</sup>

## GENERAL PROCEDURE

To a mixture of *o*-phenylenediamine (1 mmol) and aryl aldehydes (1 mmol) aq. 30%  $\text{H}_2\text{O}_2$  (7 mmol) and  $\text{SiO}_2\text{-FeCl}_3$  (0.1 g) were added and the mixture was heated at  $150^\circ\text{C}$  in a sand bath for the 30 min. The progress of the reaction was monitored by TLC (eluent: *n*-hexane-EtOAc, 7:3). When the starting materials had completely disappeared the mixture was cooled at room temperature, and then the solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL). The catalyst was separated and the organic layer was washed with water ( $2 \times 10$  mL) and dried under  $\text{MgSO}_4$ . The filtrate was evaporated and the corresponding benzimidazole was obtained as the only product after recrystallization in aq. Ethanol (25%) (Table 1).

## RESULTS AND DISCUSSION

As summarized in Table 1, several different aromatic aldehydes and *o*-phenylenediamine were reacted in the presences of  $\text{SiO}_2\text{-FeCl}_3$  as catalyst under thermal solvent-free conditions resulting the corresponding 2-substituted benzimidazoles in good to high yields (Scheme 1 and Table 1). The reactions were performed with benzaldehyde containing electron withdrawing groups as well as electron-donating

**Table 1.** Synthesis of benzimidazole derivatives using  $\text{SiO}_2\text{-FeCl}_3$  as catalyst

Entry	Aldehyde	Time (min)	Yield (%) <sup>a</sup>
1	Benzaldehyde	30	95
2	2-Nitrobenzaldehyde	30	75
3	4-Methoxybenzaldehyde	30	89
4	4-Hydroxybenzaldehyde	30	87
5	2-Bromobenzaldehyde	30	90
6	4-Bromobenzaldehyde	30	87
7	2-Chlorobenzaldehyde	30	91
8	4-Chlorobenzaldehyde	30	90
9	3-Chlorobenzaldehyde	30	93
10	3-Nitrobenzaldehyde	30	72
11	4-Methylbenzaldehyde	30	89
12	4-Methoxybenzaldehyde	30	85

<sup>a</sup>Yields refer to pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.<sup>3</sup>

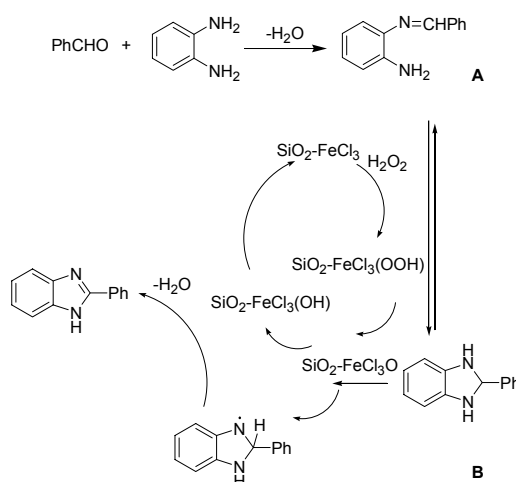
groups and gave the desired products at short reaction times with excellent yields (Table 1).

The work-up procedure is very clear-cut; that is, the products were isolated and purified by simple filtration and extraction from  $\text{CH}_2\text{Cl}_2$ . Our protocol avoids the use of dry media during the reaction process, making it superior to the previous methods.

In a typical experiment, after completion of the reaction  $\text{CH}_2\text{Cl}_2$  was added into the reaction mixture until solid crude product was dissolved. Then, the  $\text{SiO}_2\text{-FeCl}_3$  as catalyst was isolated from the reaction mixture by simple filtration. In continuation of work-up, the organic layer was washed with water and dried under  $\text{MgSO}_4$ . The filtrate was evaporated and the corresponding benzimidazole was obtained after recrystallization in ethanol (Table 1).

The suggested mechanism of the  $\text{SiO}_2\text{-FeCl}_3$  catalyzed transformation is shown in Scheme 2.

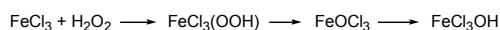
Mechanism:



**Scheme 2**

On investigating the reaction mechanism and in accordance to the reported procedures, the formation of benzimidazoles cause to be connected with the formation of intermediate Schiff base **A** which is equilibrated with the hydrobenzimidazole **B** that is produced by intra-molecular participation of the *o*-hydroxyl group (Scheme 2).

The mechanisms of the catalytic decomposition of  $\text{H}_2\text{O}_2$  by Fe(III) in homogeneous aqueous solution have been the subject of numerous studies. The mechanisms involved may be quite complex and are not clearly established. According to previously reports, different reactive species are supposed to be formed: free- and bound-hydroxyl radicals, hyper-valent iron species (Fe(IV), Fe(V)) (Scheme 3).



### Scheme 3

The route can be shown as SiO<sub>2</sub>-FeCl<sub>3</sub>(OOH); SiO<sub>2</sub>-FeCl<sub>3</sub>O and SiO<sub>2</sub>-FeCl<sub>3</sub>(OH).<sup>5</sup> Finally, the following oxidative dehydrogenation of adduct **B** in the presence of the SiO<sub>2</sub>-FeCl<sub>3</sub>O complex affords the desired 2-arylbenzimidazoles (Scheme 2).

### CONCLUSION

In conclusion, we have demonstrated that SiO<sub>2</sub>-FeCl<sub>3</sub> is an efficient and heterogeneous catalyst for the synthesis of a variety of benzimidazole derivatives using aryl aldehydes and *o*-phenylenediamine under solvent-free conditions. The reactions were carried out under thermal conditions with short reaction time to produce the corresponding product in good to high yields.

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