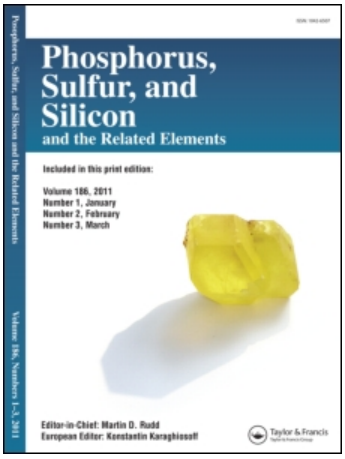


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# An Efficient Procedure for the Synthesis of Benzoxazole and Benzothiazole Derivatives Using a $H_2O_2/SiO_2$-$FeCl_3$ System

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# AN EFFICIENT PROCEDURE FOR THE SYNTHESIS OF BENZOXAZOLE AND BENZOTHIAZOLE DERIVATIVES USING A $H_2O_2/SiO_2$-$FeCl_3$ SYSTEM

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***A series of benzoxazole and benzothiazoles was readily prepared from the reaction of* ortho-*aminophenol/*ortho-*aminothiophenol and aldehydes using solid silica supported ferric chloride ($SiO_2$-$FeCl_3$) as catalyst followed by oxidation with $H_2O_2$ under ambient conditions. Some of advantages of this method are a simple and convenient procedure, easy purification, and shorter reaction times.***

***Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.***

**Keywords** Aldehydes; benzothiazoles; benzoxazoles; $SiO_2$-$FeCl_3$, $H_2O_2$



## INTRODUCTION

Heterocycles containing a nitrogen atom are an important class of heterocyclic compounds, since many of these heterocyclic systems exhibit building blocks and biological activities.[1] A wide spectrum of these properties is displayed by 2-substituted benzoxazoles and benzothiazole skeletons. These find applications in material sciences as melatonin receptor agonist, cyclooxygenase inhibitory, anticancer, antimycobacterial, and antagonist activities.[2] The widespread interest in these structures has prompted extensive studies for their synthesis. Numerous synthetic methods are available for the preparation of 2-arylbenzothiazoles and 2-arylbenzoxazoles. The most important ones include the reaction of *o*-aminophenols and *o*-aminothiophenols with aromatic aldyhydes in a wide set of conditions.[3] 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 introduced a simple and convenient method for the synthesis of 2-substituted benzoxazoles and benzothiazoles via one-pot cyclocondensation-oxidation of *ortho*-aminophenol or *ortho*-aminothiophenol and aldehydes using silica supported ferric chloride ($SiO_2$-$FeCl_3$)[4] as catalyst under ambient conditions (Scheme 1). Among several

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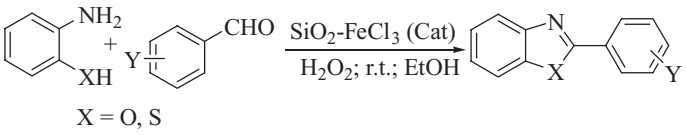



**Scheme 1**

reusable and heterogeneous catalysts designed and used in organic reactions, silica supported ferric chloride ($SiO_2$-$FeCl_3$) is one of the useful examples of them that has performed as an inexpensive catalyst that can be easily separated and reused, and is not contaminated by the products.[4] Also, this catalyst is an active catalyst, nontoxic, safe, easy to handle, and environmentally benign with fewer disposal problems.

## RESULTS AND DISCUSSION

In order to estimate the catalytic efficiency of $SiO_2$-$FeCl_3$ and to determine the most appropriate reaction conditions, at first we carried out the cyclocondensation-oxidation reaction of *ortho*-aminophenol with benzaldehyde as a model reaction under different reaction conditions (Table I).

Among the various tested solvents regarding the amount of the catalyst and temperature, 0.02 g of catalyst in ethanol at room temperature was the best reaction condition for cyclocondensation-oxidation of *ortho*-aminophenol with benzaldehyde (Table I). In order to improve the yields, we performed reaction using different quantities of reagents. The best results were obtained with 1:1.1 molar ratios of *ortho*-aminophenol and aryl aldehyde, respectively. The results are summarized in Table I.

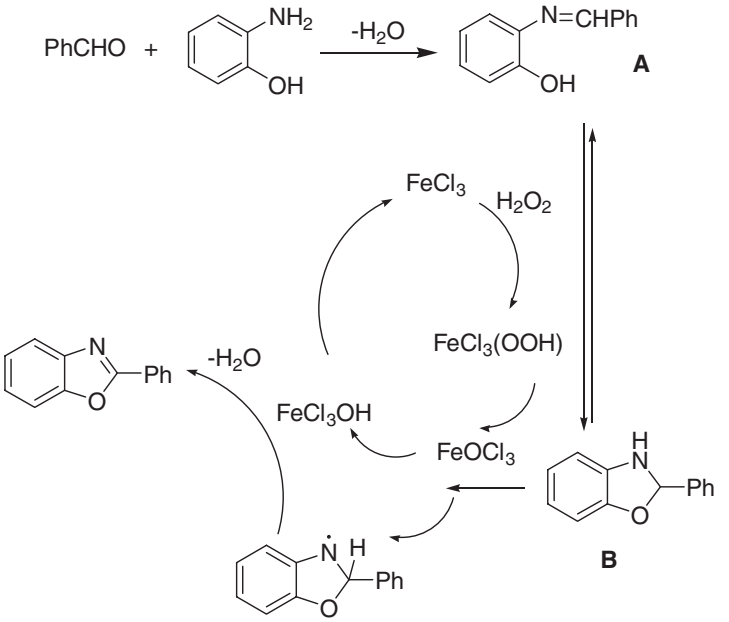


**Table I** Optimization of the reaction conditions

| Entry | Catalyst (g) | Temp. (°C) | Solvent | Time (min) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 0.04 | 150 | — | 23 | 78 |
| 2 | 0.04 | 125 | — | 28 | 76 |
| 3 | 0.04 | 100 | — | 30 | 69 |
| 4 | 0.04 | 80 | — | 48 | 58 |
| 5 | 0.04 | 50 | — | 70 | 42 |
| 6 | 0.04 | Rt | $H_2O$ | 135 | — |
| 7 | 0.04 | Rt | $H_2O$/EtOH (50:50) | 50 | 40 |
| 8 | 0.04 | Rt | EtOH | 22 | 89 |
| 9 | 0.04 | Rt | $CH_2Cl_2$ | 135 | — |
| 10 | 0.04 | Rt | n-Hexane | 135 | — |
| 11 | 0.04 | Rt | EtOAc | 42 | 38 |
| 12 | 0.05 | Rt | EtOH | 15 | 59 |
| 13 | 0.1 | Rt | EtOH | 10 | 63 |
| 14 | 0.025 | Rt | EtOH | 19 | 61 |
| 15 | 0.075 | Rt | EtOH | 13 | 83 |
| 16 | 0.02 | Rt | EtOH | 15 | 88 |

[a]Isolated yields.

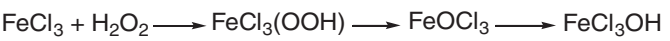
Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for the synthesis of corresponding 2-arylbenzoxazoles (Scheme 2).




**Scheme 2**

Generally, the cyclocondensation-oxidation reaction between *ortho*-aminophenol and aryl aldehydes proceeded well and afforded the desired products (Table II, entries 1–9) in good to high yields. As shown in Table II, the reaction was carried out successfully with a variety of aryl aldehydes having electron-donating and electron-withdrawing substituents.

We further investigated the one-pot synthesis of benzothiazole derivatives from the reaction of *ortho*-aminothiophenol and aryl aldehydes (Scheme 3). We applied the above optimal reaction conditions (Table I) for this reaction. As shown in Table II, a variety of aldehydes was investigated. The reaction of *ortho*-aminothiophenol with aromatic aldehydes containing both electron-donating and electron-withdrawing groups was compatible successfully in good yields (Table II, entries 10–17).




**Scheme 3**

The work-up procedure is very easy; that is, the products were isolated and purified by simple filtration and crystallization from ethanol. An efficient conversion of benzoxazole and benzothiazole derivatives has been achieved in high yield by the use of ambient temperature during the reaction process, making it superior to the previous methods.

The suggested mechanism of the $SiO_2$-$FeCl_3$ catalyzed transformation is shown in Scheme S1 (Supplemental Materials, available online).

**Table II** Synthesis of benzoxazole and benzothiazole derivatives using $SiO_2$-$FeCl_3$ as catalyst

| Entry | Y | X = O, S | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | H | O | 15 | 88 |
| 2 | 2-Nitro | O | 9 | 77 |
| 3 | 4-*N,N*-Dimethylamino | O | 8 | 86 |
| 4 | 2-Bromo | O | 8 | 89 |
| 5 | 4-Bromo | O | 8 | 87 |
| 6 | 2-Chloro | O | 8 | 90 |
| 7 | 4-Chloro | O | 8 | 89 |
| 8 | 3-Nitro | O | 9 | 73 |
| 9 | 4-Nitro | O | 9 | 70 |
| 10 | 2-Nitro | S | 8 | 76 |
| 11 | 4-*N,N*-Dimethylamino | S | 7 | 82 |
| 12 | 2-Bromo | S | 8 | 89 |
| 13 | 4-Bromo | S | 8 | 83 |
| 14 | 2-Chloro | S | 8 | 88 |
| 15 | 4-Chloro | S | 8 | 86 |
| 16 | 3-Nitro | S | 9 | 71 |
| 17 | 4-Nitro | S | 9 | 69 |

[a]Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[3]



Upon investigating the reaction mechanism, and in accordance with the reported procedures, the formation of benzimidazoles causes a connection with the formation of intermediate Schiff base **A**, which is equilibrated with the hydrobenzimidazole **B** that is produced by intramolecular participation of the *o*-hydroxyl group (Scheme S1, Supplemental Materials).[4]

The mechanisms of the catalytic decomposition of $H_2O_2$ 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 previous reports, different reactive species are supposed to be formed: free- and bound-hydroxyl radicals, and hypervalent iron species [Fe(IV), Fe(V)] (Scheme 3).[5]

The route of $SiO_2$-$FeCl_3$ can be shown as $SiO_2$-$FeCl_3$(OOH), $SiO_2$-$FeCl_3O$, and $SiO_2$-$FeCl_3$(OH). Finally, the oxidative dehydrogenation of adduct **B** in the presence of the $SiO_2$-$FeCl_3O$ complex affords the desired 2-arylbenzimidazoles (Scheme S1, Supplemental Materials).

**Table III** Comparison results of $SiO_2$-$FeCl_3$ with some catalytic systems reported in the literature[a]

| Entry | Conditions | Time | Yield (%)[Ref] |
|---|---|---|---|
| 1 | $Fe(NO_3)_3$; $H_2O_2$; solvent-free, 50°C | 2 min | 98[3c] |
| 2 | DDQ, MeCN, r.t. | 6 h | 90[3d] |
| 3 | $Me_2S^+BrBr^-$, MeCN, r.t. | 5 h | 85[3e] |
| 4 | Cu-nanoparticles; MeOH, $K_2CO_3$,$O_2$; 80–100°C | 3 h | 90[3f] |
| 5 | Activated carbon(Darco KB); $O_2$, xylene, 120°C | 4 h | 78[3g] |
| 6 | $SiO_2$-$FeCl_3$; EtOH, r.t.; $H_2O_2$ | 15 min | 88 |

[a]Based on the preparation of 2-phenylbenzoxazole.

### Recyclability of the Catalyst

To test its recyclability, the $SiO_2$-$FeCl_3$ catalyst was studied with respect to the preparation of 2-phenyl benzoxazole. After each cycle, the used catalyst was filtered and activated at 100°C before being used for the next cycle. There was no significant change in the activity and selectivity, even after three cycles (Figure S1, Supplemental Materials).

To show the merit of the present work in comparison with reported results in the literature, we compared results of $SiO_2$-$FeCl_3$ with some catalytic systems reported in the literature used in the synthesis of 2-phenyl benzoxazole (Table III). As shown in Table III, $SiO_2$-$FeCl_3$ is an effective catalyst with respect to reaction times, yields, and the obtained products.

## CONCLUSION

In conclusion, we have demonstrated that $SiO_2$-$FeCl_3$ is an efficient and heterogeneous catalyst for synthesis of a variety of benzoxazole and benzothiazole derivatives using aryl aldehydes and *ortho*-aminophenol/*ortho*-aminothiophenol under ambient conditions. The reactions were carried out at room temperature with short reaction time and produced the corresponding product in good to high yields.



## EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and were used without further purification. All yields refer to isolated products after purification. $SiO_2$-$FeCl_3$ was prepared according to the reported procedure.[4] Products were characterized by spectroscopic data (IR, NMR spectra), and melting points were compared with authentic samples. The NMR spectra were recorded on a Bruker Avance DEX 300 MHz instrument. The spectra were measured in DMSO-$d_6$ relative to TMS (0.00 ppm). IR spectra were recorded on a Jasco FT-IR 460plus spectrophotometer. All of the compounds are solids, 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.

### General Procedure

To a mixture of *ortho*-aminophenol/*ortho*-aminothiophenol (1 mmol), aryl aldehydes (1.1 mmol), and aq. 30% $H_2O_2$ (7 mmol) in ethanol (5 mL), $SiO_2$-$FeCl_3$ (0.02 g) was added, and the mixture was stirred at room temperature for the appropriate time shown in Table II. 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 dissolved in $CH_2Cl_2$ (10 mL). The catalyst was separated, and the organic layer was washed with water (2 × 10 mL). Then the combined extracts were dried under $MgSO_4$. The filtrate was evaporated, and the corresponding benzoxazoles/benzothiazoles were obtained as the only product after recrystallization in ethanol (Table I).

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