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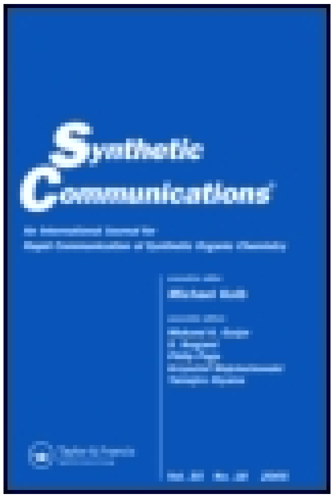

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# Synthesis of Benzimidazoles via Iron-Catalyzed Aerobic Oxidation Reaction of Imine Derivatives with *o*-Phenylenediamine

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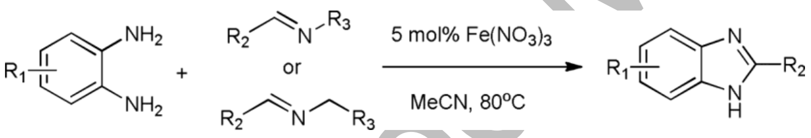
## Abstract

A simple and efficient protocol for preparing benzimidazoles via $Fe(NO_3)_3{\cdot}9H_2O$ catalyzed aerobic oxidation reaction of imine derivatives with *o*-phenylenediamine. This procress uses air as the economic and green oxidant, tolerates a wide range of substrates, and affords the targeted benzimidazoles in moderate to excellent yields.



## INTRODUCTION

Synthesis of privileged benzimidazoles through an economical and environmental friendly method is always desirable because benzimidazole moieties are of paramount interest in medicinal chemistry due to their significant pharmacological and biological activities such as anticonvulsant, anticancer, antiulcer, antihypertensive, antibacterial, and antihistaminic properties. Moreover, benzimidazole and its derivatives are important building blocks for the construction of pharmaceuticals, natural products, functional materials, and agrochemical compounds.[1-5] Over the past few decades, there are two main methods for the synthesis of benzimidazoles. One method involves the condensation reactions of *o*-phenylenediamine with carboxylic acids or their derivatives (nitriles, imidates, orthoesters).[6-10] Another method involves the oxidative cyclo-dehydrogenation of aniline Schiff's base, which is often generated in situ from the condensation of *o*-phenylenediamines and aldehydes.[11-17] Although the reaction was efficiently carried out by the above methods, these methods suffer from one or more disadvantages, such as strong acidic conditions, high temperature conditions, stoichiometric or excess amounts of strong oxidant, high cost of the catalyst, and generate the environmentally hazardous/toxic by-products. In recent years, there have been a number of simple and straightforward methods on the synthesis of benzimidazoles through the coupling of aldehydes with o-phenylenediamine, such as using a nanoporous aluminosilicate catalyst,[18] using simple air oxidation without catalyst,[19] and using ammonium chloride as the catalyst.[20]

Despite the condensation of *o*-phenylenediamine with aldehydes is the most widely used, the method of oxidative condensation of *o*-phenylenediamine and imines seems very attractive, compared to aldehydes, imines are usually less toxic, more stable and easier to handle.

Recently, the aerobic oxidative reactions have attracted increasing attention, which are comparatively green, preferable, and practical processes, due to the use of pure oxygen or air as the economic and green oxidant, much more easily disposable catalysts, and milder reaction conditions, along with generating water as the by-product. In our previous work, we have developed aerobic oxidative synthesis of benzimidazoles direct from aromatic alcohols or amines with *o*-phenylenediamine under the corresponding oxidation conditions.[21-23] So based on our previous work, herein, we report a general and efficient procedure for aerobic oxidative synthesis of benzimidazoles from imines and *o*-phenylenediamine catalyzed by $Fe(NO_3)_3 \cdot 9H_2O$. (Scheme 1)

## RESULTS AND DISCUSSION

In our initial studies, the reaction of *o*-phenylenediamine with *N*-benzylidenebenzylamine was chosen as a model to optimize the reaction conditions. The results are shown in Table 1. No product could be obtained when equal amounts of *o*-phenylenediamine and *N*-benzylidenebenzylamine were treated in acetonitrile (MeCN) at 80°C in the absence of catalyst (Table 1, entry 1). Fortunately, the desired product 2-phenylbenzimidazole was obtained in 85% yield by using 5 mol% $Fe(NO_3)_3 \cdot 9H_2O$ as a catalyst (entry 2). Other iron catalyst, such as $FeCl_3$ and $Fe_2(SO_4)_3$, also worked for this reaction (entries 3-4). However, lower yields were resulted when other metal salts were conducted in this reaction, including $Cu(OAc)_2$, $CuCl_2$, $Cu(NO_3)_2$, CuI, and $CoCl_2$ (entries 5-9). Among which, $Fe(NO_3)_3 \cdot 9H_2O$ exhibited the highest activity. In addition, we also investigated the amount of *o*-phenylenediamine in the reaction. It was found that the use of 1.5 equivalent gave the best results (entries 10-12). Further optimization by screening the loading of

$Fe(NO_3)_3 \cdot 9H_2O$ indicated that 5 mol% was the most suitable proportion (entries 13-14). Solvent screening demonstrated that MeCN is the best one compared with all the others (entries 15-17). Reducing the reaction temperature from 80°C to room temperature led to great decrease in the yield (entries 18, 19). Finally, the reaction was equally efficient when proceeding in $O_2$ atmosphere, but less product could be detected in the atmosphere of $N_2$ (entries 20, 21).

With the optimized reaction conditions, we proceeded to explore the substrate scope of this transformation. As the reaction conditions are mild, we expected that various functional groups would be tolerated. To our delight, we could indeed show that homo-coupled imine with either electron-donating or electron-withdrawing groups on the benzene ring smoothly generated the corresponding products in moderate to good yields under the optimized reaction conditions. Clearly, the reaction conditions were compatible with fluoro, chloro, and bromo substituent groups, giving the desire product in high yields (Table 2, entries 2-4). When the *N*-benzylidenebenzylamines bear electron-withdrawing substituents, the yield of the ortho-position was slightly lower than the para position (entries 3, 5). That may be, in part, due to steric hindrance. *N*-(2-furanylmethylene)-2-furanyl methanamine as a representative of heterocyclic homo-coupled imine used in this transformation. To our surprise, it showed high reactivity to give the corresponding product in good yield (entry 7). In addition, 4-chloro-*o*-phenylenediamine, and 4-nitro-*o*-phenylenediamine were also employed in the reaction, giving the corresponding products in moderate yields (entries 8-9). Besides, *N*-(amylmethylene)-octylamine could successfully be convered to 2-amylbenzimidazole in a yield of 65% (entry 10).

To investigate the scope and limitation of this catalytic system, a series of hetero-coupled imines could also be applied to synthesize benzimidazoles through the reactions of *o*-phenylenediamine and imines. Initially, we investigated the aerobic oxidation reaction of a series of *N*-benzylidene amines with *o*-phenylenediamine to form 2-phenylbenzimidazole. The results show that either *N*-benzylidene aromatic amines or *N*-benzylidene aliphatic amines smoothly generated the corresponding products in moderate to good yields under the optimized reaction conditions. Among them, *N*-benzylideneaniline gave the highest yield (Table 3, entries 1a-1c). The reason may be that aromatic ring easily removed in the reaction condition than aliphatic chain. With these results in hand, we expected that various functional groups would be tolerated. As expected, *N*-benzylideneaniline bearing electron-donating or electron-withdrawing substituents on the aromatic ring under the reaction conditions, giving the corresponding products in moderate yields. It seemed that *N*-benzylideneaniline bearing electron-withdrawing substituents at the *para*-position gave higher yields of products than did those bearing electron-donating substituents (entries 2-8). The reason may be that the strong electron-withdrawing groups ($NO_2$) enhanced the reaction rate.

*N*-heteroaryl anilines such as *N*-(2-furanylmethylene)-aniline, *N*-(5-methyl-2-furanylmethylene)-aniline, and N-(2-pyridinylmethylene)-aniline, were used in the reaction, and the yields were satisfactory (entries 14-16). In addition, 4-chloro-*o*-phenylenediamine and 4-nitro-*o*-phenylenediamine were also employed in the reaction, the results revealed that the electron-donating group enhanced the reaction, meanwhile electron-withdrawing substituent slowed the reaction (entries 17-18). To demonstrate the scope and efficiency of the present method, this catalytic system was then extended for the synthesis of 2-alkylbenzimidazole. We found the *N*-(amylmethylene)-aniline could be converted to 2-amylbenzimidazole in a yield of 59% (entry 19).

## CONCLUSION

In summary, we have described an efficient protocol for preparing benzimidazoles via $Fe(NO_3)_3\cdot 9H_2O$ catalyzed aerobic oxidation reaction of imine derivatives with *o*-phenylenediamine. This procress uses air as the economic and green oxidant, tolerates a wide range of substrates, and affords the targeted benzimidazoles in moderate to excellent yields.

## EXPERIMENTAL SECTION

All starting materials were purchased from commercial sources and used without further treatment. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. All known compounds were identified by appropriate technique such as $^1$H NMR and compared with previously reported data. $^1$H NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent technologies 6110 quadrupole LC/MS equipped with an electrospray ionization (ESI) probe operating in positive ion mode. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). All the products are the known compounds. The spectras were in supporting information.

## TYPICAL PROCEDURE FOR OXIDATIVE SYNTHESIS OF BENZIMIDAZOLES

A mixture of 1.5 mmol *o*-phenylenediamine, and 1 mmol imine, 5mol% $Fe(NO_3)_3 \cdot 9H_2O$, and 5ml MeCN were mixed in a 10 ml three-necked flask, equipped with a condenser and a thermometer, and then stirred rapidiy open to air at 80 °C for 12 hours. The reaction progress was monitored by TLC. After completion of the reaction, the residue was directly purified by column chromatograph on a silica gel using hexane/ethyl acetate (7:3) as eluent to afford the pure product.

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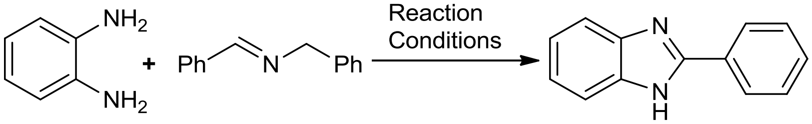
**Table 1.** Reaction Optimization.[a]



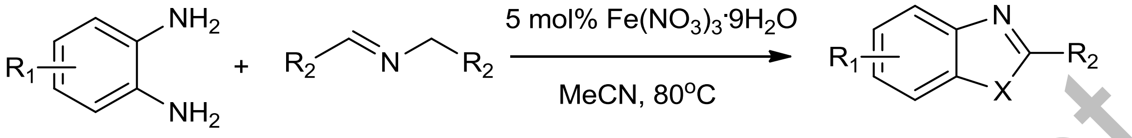
| Entry | Diamine (equiv.) | Catalyst [mol%] | Solvent | T [$^{o}$C] | Gas | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | 1 | - | MeCN | 80 | Air | Trace |
| 2 | 1 | $Fe(NO_3)_3·9H_2O$ (5) | MeCN | 80 | Air | 85 |
| 3 | 1 | $FeCl_3$ (5) | MeCN | 80 | Air | 81 |
| 4 | 1 | $Fe_2(SO_4)_3$ (5) | MeCN | 80 | Air | 78 |
| 5 | 1 | $Cu(OAc)_2$ (5) | MeCN | 80 | Air | 56 |
| 6 | 1 | $CuCl_2$ (5) | MeCN | 80 | Air | 59 |
| 7 | 1 | $Cu(NO_3)_2$ (5) | MeCN | 80 | Air | 62 |
| 8 | 1 | CuI (5) | MeCN | 80 | Air | 71 |
| 9 | 1 | $CoCl_2$ (5) | MeCN | 80 | Air | 48 |
| 10 | 1.2 | $Fe(NO_3)_3·9H_2O$ (5) | MeCN | 80 | Air | 88 |
| 11 | 1.5 | $Fe(NO_3)_3·9H_2O$ (5) | MeCN | 80 | Air | 93 |
| 12 | 0.8 | $Fe(NO_3)_3·9H_2O$ (5) | MeCN | 80 | Air | 74 |
| 13 | 1.5 | $Fe(NO_3)_3·9H_2O$ (1) | MeCN | 80 | Air | 76 |
| 14 | 1.5 | $Fe(NO_3)_3·9H_2O$ (10) | MeCN | 80 | Air | 92 |

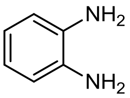
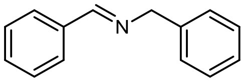
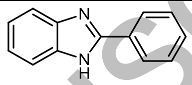
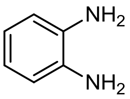
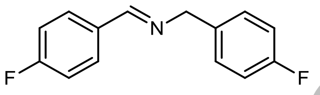
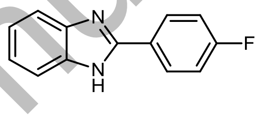
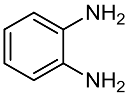
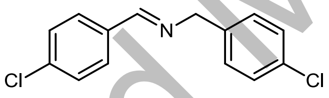
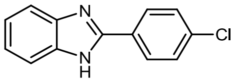
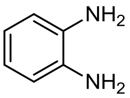
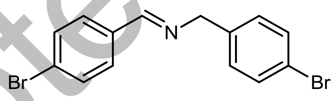
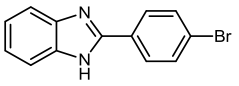
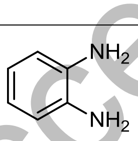
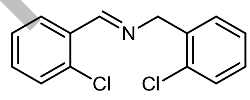
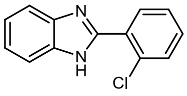
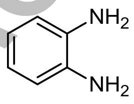
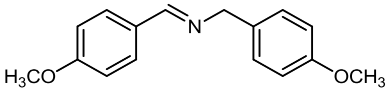
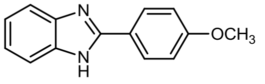
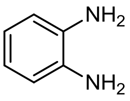
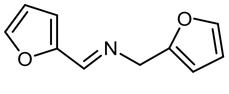
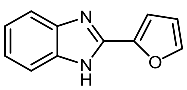
| | | | | | | |
|---|---|---|---|---|---|---|
| 15 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | EtOH | 80 | Air | 87 |
| 16 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | DMSO | 80 | Air | 62 |
| 17 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | Toluene | 80 | Air | 80 |
| 18 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | MeCN | 50 | Air | 55 |
| 19 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | MeCN | RT | Air | Trace |
| 20 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | MeCN | 80 | $O_2$ | 93 |
| 21 | 1.5 | $Fe(NO_3)_3{\cdot}9H_2O$ (5) | MeCN | 80 | $N_2$ | 10 |

[a] Reaction conditions: A mixture of diamine and N-benzylidenebenzylamine, catalyst, 5 ml solvent were mixed in a 10 ml three-necked flask, and then stirred rapidiy for 10 hours. The reaction progress was monitored by TLC.

[b] Isolated yield.

Table 2. Synthesis of 2-substituted benzimidazoles from Homo-coupled imines and diamines.[a]



| Entry | Diamine | Imine | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 93 |
| 2 |  |  |  | 90 |
| 3 |  |  |  | 95 |
| 4 |  |  |  | 95 |
| 5 |  |  |  | 82 |
| 6 |  |  |  | 85 |
| 7 |  |  |  | 80 |

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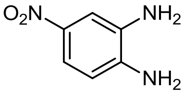
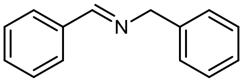
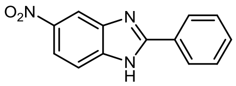
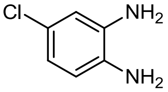
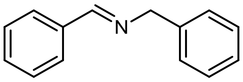
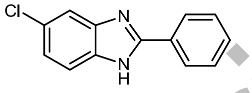
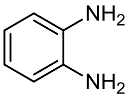
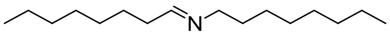
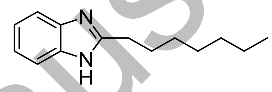
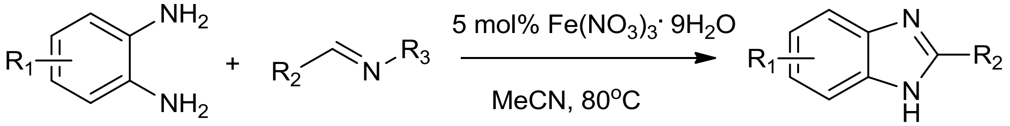
| 8 |  |  |  | 73 |
| 9 |  |  |  | 79 |
| 10 |  |  |  | 65 |

[a] Reaction conditions: 1.5 mmol *o*-phenylenediamine and 1 mmol imine, 5 mol% $Fe(NO_3)_3·9H_2O$, and 5 ml MeCN were mixed in a 10 ml three-necked flask, and then stirred rapidiy in the open air for 12 hours. The reaction progress was monitored by TLC.

[b] Isolated yield.

**Table 3.** Synthesis of 2-substituted benzimidazoles from Hetero-coupled imines and diamines.[a]



| Entry | Diamine | Imine | Product | Yield[b] (%) |
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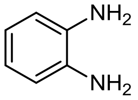
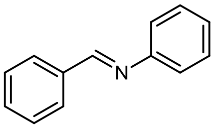
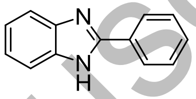
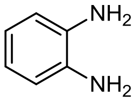
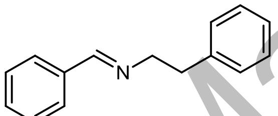
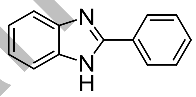
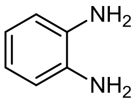
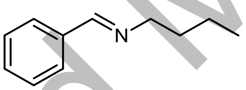
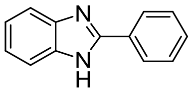
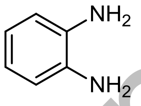
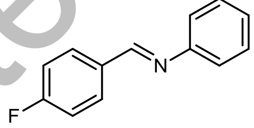
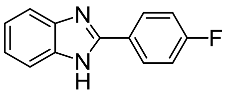
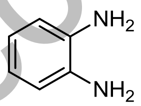
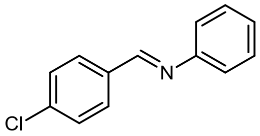
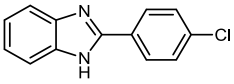
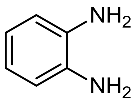
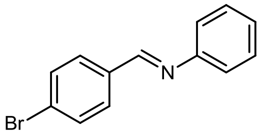
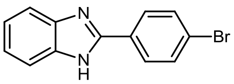
| 1 a |  |  |  | 88 |
| b |  |  |  | 83 |
| c |  |  |  | 79 |
| 2 |  |  |  | 87 |
| 3 |  |  |  | 89 |
| 4 |  |  |  | 89 |

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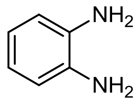
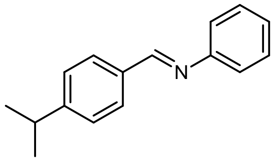
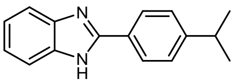
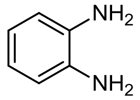
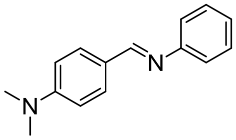
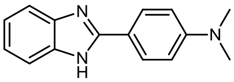
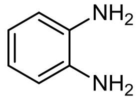
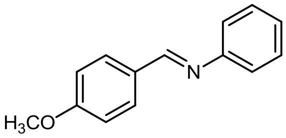
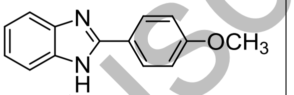
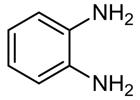
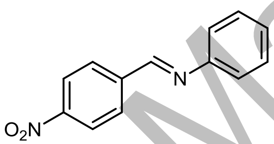
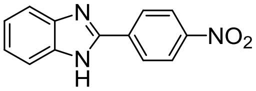
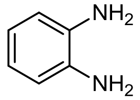
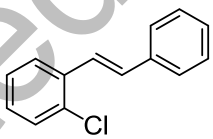
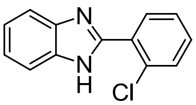
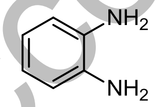
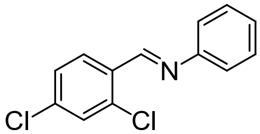
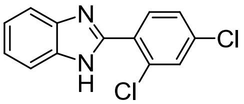
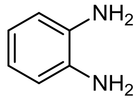
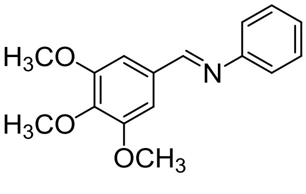
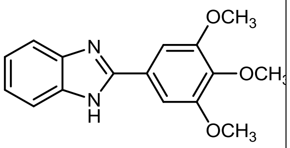
| 5 |  |  |  | 82 |
| 6 |  |  |  | 75 |
| 7 |  |  |  | 79 |
| 8 |  |  |  | 91 |
| 9 |  |  |  | 75 |
| 10 |  |  |  | 81 |
| 11 |  |  |  | 78 |

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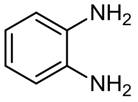
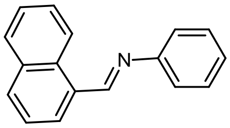
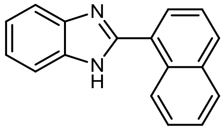
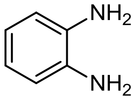
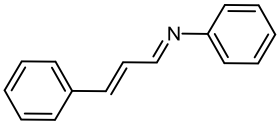
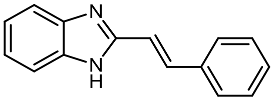
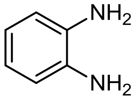
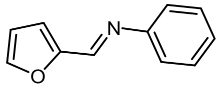
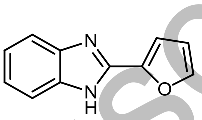
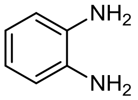
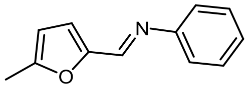
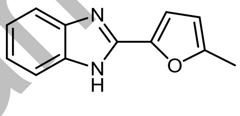
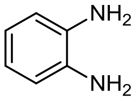
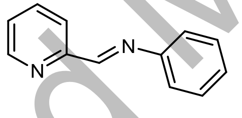
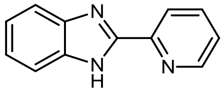
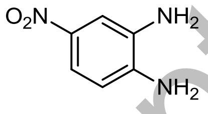
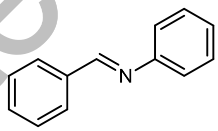
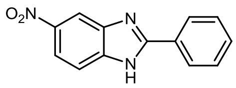
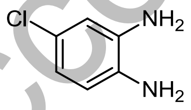
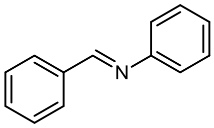
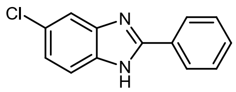
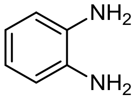
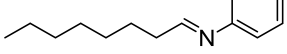
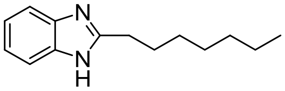
| 12 |  |  |  | 86 |
| 13 |  |  |  | 77 |
| 14 |  |  |  | 84 |
| 15 |  |  |  | 83 |
| 16 |  |  |  | 79 |
| 17 |  |  |  | 65 |
| 18 |  |  |  | 73 |
| 19 |  |  |  | 59 |

[a] Reaction conditions: 1.5 mmol *o*-phenylenediamine and 1 mmol imine, 5 mol% $Fe(NO_3)_3 \cdot 9H_2O$, 5 ml MeCN were mixed in a 10 ml three-necked flask, and then stirred rapidiy in the open air for 12 hours. The reaction progress was monitored by TLC.

[b] Isolated yield.

**Scheme 1.** Methods for the preparing the benzimidazoles.