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# Highly Efficient, Four Component, One-pot Synthesis of Tetrasubstituted Imidazoles Using a Catalytic Amount of $FeCl_3 \cdot 6H_2O$

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**Summary.** An efficient and improved procedure for the synthesis of tetrasubstituted imidazoles by $FeCl_3 \cdot 6H_2O$ catalyzed four-component one-pot synthesis in refluxing ethanol is described.

**Keywords.** Multi component reactions; Highly substituted imidazoles; Ferric chloride.

## Introduction

In recent years, considerable interest has been devoted to finding a new methodology for the synthesis of highly substituted imidazoles [1, 2]. These five-membered heterocycles belong to an important class of compounds due to their biological activities [3, 4]. Numerous methods for the synthesis of highly substituted imidazoles have been reported. Widely used methods are: (a) condensation of diones, aldehydes, primary amines, and ammonia [5]; (b) *N*-alkylation of trisubstituted imidazoles [6]; (c) condensation of benzoin or benzoin acetate with aldehydes, primary amines, and ammonia in the presence of copper acetate [7]; (d) cyclization of sulfonamides with mesoionic 1,3-oxazolium-5-olates [8]; (e) four-component condensations of diones, aldehydes, primary amines, and ammonium acetate in refluxing acetic acid [9]; (f) condensation of $\beta$-carbonyl-*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing HO*Ac* [10]; and (g) conversion of *N*-(2-oxo)amides with ammonium trifluoroacetate under neutral conditions [11]. In the classic approach for the synthesis of tetrasubstituted imidazoles, cyclocondensations proceed with low yields after many hours in refluxing HO*Ac* [9]. Other methods also need special and complex reagents. Therefore the development of clean, high-yielding, and environmentally friendly approaches is still desirable and much in demand.

In recent years, the use of solid acid catalysts [12] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction times, simple workup, and recoverability of the catalysts.

Following our previous work on the synthesis of tri/tetrasubstituted imidazoles [13, 14], in view of the importance of solid acids as reusable catalysts in organic synthesis, and in continuation of our work on catalytic properties of solid acids [15–25] here we report the four-component condensation of benzil, benzaldehyde derivatives, primary amines, and ammonium acetate catalyzed by $FeCl_3 \cdot 6H_2O$, as an efficient and facile one-pot synthesis of tetrasubstituted imidazoles (Scheme 1).

## Results and Discussion

The synthesis is based on the condensation of benzil (**1**) with aldehydes (**2**) and amines (**3**) resulting in 1,2,4,5-substituted imidazoles using ammonium acetate (**4**) as the ammonia source and $FeCl_3 \cdot 6H_2O$ as the catalyst (Scheme 1). The multi-component nature of the synthesis of 1,2,4,5-substituted imida-

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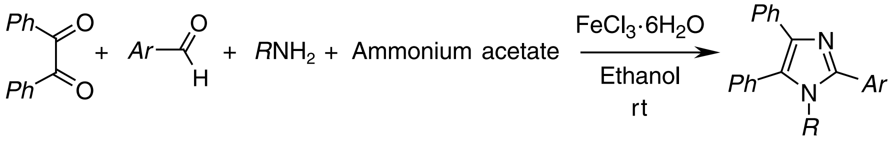

1 2 3 4 5a–5h

Scheme 1

zoles together with the existence of a wide variety of commercially available aldehydes and amines makes this reaction an ideal candidate for the combinatorial synthesis technology.

Preliminary optimization of reaction conditions was done using the pair benzil/benzaldehyde and benzylamine ($R^1 = R^2 = Ph$). Comparison of two solvents and solvent-free conditions (Table 1) showed that ethanol was the most suitable solvent for the synthesis of **5a**, and therefore it was used in all subsequent experiments.

**Table 1.** Synthesis of 1,2,4,5-tetraphenylimidazole (**5a**) in the presence of $FeCl_3 \cdot 6H_2O$ in different solvents

| Entry | Solvent ($T$/°C) | $t$/min | Yield/%[a] |
|---|---|---|---|
| 1 | *Et*OH (78.3) | 90 | 80 |
| 2 | $CHCl_3$ (61) | 180 | 75 |
| 3 | solvent-free (70) | 180 | 70 |

[a] Yields were determined by GC

**Table 2.** Synthesis of 1,2,4,5-tetraphenylimidazole (**5a**) in the presence of $FeCl_3 \cdot 6H_2O$ in ethanol and at different temperatures

| Entry | $T$/°C | $t$/min | Yield/%[a] |
|---|---|---|---|
| 1 | 25 | 90 | 60 |
| 2 | 45 | 90 | 70 |
| 3 | 78 | 90 | 80 |

[a] Yields were determined by GC

The effect of temperature was studied by carrying out both reactions at different temperatures (room temperature, 45, and 78°C). It was observed (Table 2) that yield is a function of temperature and it was increased as the reaction temperature was raised. Thus, in the subsequent studies all reactions were carried out using refluxing ethanol.

The optimal conditions were then applied for the preparation of a series of 1,2,4,5-substituted imidazoles **5a–5h**. The product yields are shown in Table 3. The results show that this method provides an efficient way to access diverse, highly functionalized imidazoles.

As could be expected, $FeCl_3 \cdot 6H_2O$ is not soluble in ethanol and all of the reactions are heterogeneously catalyzed, so it could be easily recovered by a simple filtration and reused in another reaction after washing with chloroform.

In order to show the advantages of $FeCl_3 \cdot 6H_2O$ as a catalyst in this reaction, the obtained results for 1-(2-naphtyl)-2,4,5-triphenylimidazole (**5h**) were compared with those obtained in refluxing ethanol and refluxing acetic acid [9] without any catalyst, and results are summarized in Table 4.

**Table 3.** Synthesis of tetrasubstituted imidazoles using a catalytic amount of $FeCl_3 \cdot 6H_2O$

| Product | *Ar* | *R* | $t$/min | Yield/%[a] | mp/°C | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported [Ref.] |
| **5a** | *Ph* | *Me* | 40 | 95 | 144–145 | 143–144 [26] |
| **5b** | *Ph* | *Ph* | 90 | 80 | 218 | 216–218 [26] |
| **5c** | *Ph* | *Ph*$CH_2$ | 60 | 98 | 165 | 158–160 [26] |
| **5d** | 4-*MePh* | *Me* | 90 | 80 | 221–223 | 218–220 [26] |
| **5e** | 4-*MePh* | *Ph* | 40 | 98 | 189 | 185–188 [26] |
| **5f** | 4-*MePh* | *Ph*$CH_2$ | 60 | 90 | 165–166 | 165–166 [26] |
| **5g** | 4-Br*Ph* | *Me* | 90 | 80 | 201–202 | 199–200 [26] |
| **5h** | 2-naphtyl | *Ph* | 90 | 85 | 244 | 240–241 [9] |

[a] Yields were determined by GC

**Table 4.** Comparison of the synthesis of 1-(2-naphtyl)-2,4,5-triphenylimidazole (**5h**) under different conditions

| Entry | Solvent (catalyst) | $t$/h | Yield/% | Ref. |
|---|---|---|---|---|
| 1 | *Ac*OH | 2 | 45 | [9] |
| 2 | *Et*OH | 5 | 60[a] | this work |
| 3 | *Et*OH ($FeCl_3 \cdot 6H_2O$) | 1.5 | 80[a] | this work |

[a] Yields were determined by GC

## Experimental

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. $^1H$ NMR spectra were recorded on a Bruker AC-80 MHz spectrometer using *TMS* as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC spectra were carried out on a Network GC System-Agilent 5973 spectrometer. All products were known and characterized by comparison of their physical and spectroscopic data with those already reported [26].

*Synthesis of Tetrasubstituted Imidazoles: General Procedure*
A mixture of 10 mmol benzil, 10 mmol amine, 10 mmol aldehyde, 10 mmol ammonium acetate, and 5 mol% $FeCl_3 \cdot 6H_2O$ was refluxed in 10 $cm^3$ ethanol. After completion of the reaction (monitored by *TLC*) the mixture was filtered to separate the catalyst, then cooled to room temperature, and the precipitated products were separated by filtration. The resulting solid residue was purified by recrystallization from *Et*OH.

The recycled catalyst could be washed with chloroform and reused in another reaction. Such procedure applied for **5a** in a second run resulted in 75% yield.

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