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Short Communication

Ultrasound-promoted greener synthesis of 2,4,5-trisubstituted imidazoles catalyzed by $Zr(acac)_4$ under ambient conditions

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Abstract

A simple, efficient and green procedure has been developed for the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by zirconium (IV) acetylacetonate using ultrasonic irradiation. The present methodology offers several advantages such as excellent yields, simple procedure, short reaction times and milder conditions.

Keywords: 2,4,5-Trisubstituated imidazoles; $Zr(acac)_4$; Ultrasonic-assisted reaction; Aldehyde; Benzil

1. Introduction

Imidazole and their derivatives, which usually possess diverse biological activities, play important roles as versatile building blocks for the synthesis of natural products and as therapeutic agents [1,2]. In particular, 2,4,5-trisubstituted imidazoles are biologically active and occur in structures of a number of herbicides [3], fungicides [4] or as inhibitors of IL-1 or P38 MAP kinase [5–7]. This core also has been utilized in diverse pharmaceutical applications such as anti-inflammatory [8] and anti-thrombotic [9] activities agents. Therefore, the synthesis of these imidazole derivatives has attracted much attention in organic synthesis. The classical route to 2,4,5-trisubstituted imidazoles involves the multi-component reaction of aldehydes, benzil and ammonium acetate proceed with low yields after many hours in refluxing HOAc [10]. Recently, some modification has been carried out in the presence of protic or Lewis acids such as H_3PO_4 [11], silica sulfuric acid (SSA) [12], I_2 [13], $NiCl_4 \cdot 5H_2O$ [14], $H_4[PMo_{11}VO_{40}]$ [15], $[Hbim]BF_4$ [16] or $[HeMIM]BF_4$ [17] under reflux conditions or microwave irradiation. However, some of these preparations require relatively expensive reagents, harsh reaction conditions, and sometimes tedious work-up with using of toxic reagents or solvents. Additionally, most of the reported methods are only successful with aryl aldehydes and failed to work with aliphatic ones. So the development of a milder, simpler, greener and more efficient procedure for the synthesis of 2,4,5-trisubstituted imidazoles is highly desirable.

As increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures [18]. Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions [19,20]. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [21–23]. However, the use of

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ultrasound in heterocyclic system is not fully explored [24–26]. In order to expand the application of ultrasound in the synthesis of heterocyclic compound, we wish to report a general, efficient and eco-friendly method for the synthesis of 2,4,5-trisubstituted imidazoles.

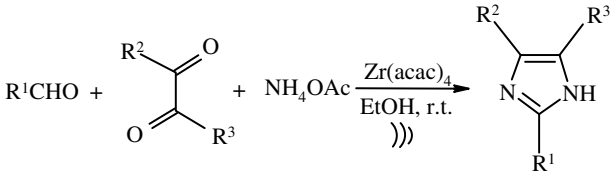
2. Results and discussion

Many recent papers describing the use of $Zr(acac)_4$ in organic transformations pointed out that its use due to low toxicity, low cost, ease of handling and high catalytic activity is a potential green catalyst [27]. In continuation of our work to develop new and eco-friendly synthetic methodologies [28–31], herein we report a green, facile and efficient method for the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by $Zr(acac)_4$ under ultrasonic irradiation at ambient temperature (Scheme 1).

The experimental procedure for this reaction is remarkably simple and requires no toxic organic solvents or inert atmospheres. The reactions were carried out at room temperature for 20–85 min by taking a 1:1:10 mol ratio mixture of aldehyde, benzil and ammonium acetate, respectively in the presence of 20 mol% of $Zr(acac)_4$ using EtOH as solvent at 24 kHz under sonication. To the best of our knowledge no report is available in the literature using ultrasonic-assisted for this transformation.

In an initial study, for examination of the catalytic activity of different catalysts such as ZrO_2, $ZrCl_4$, $Zr(OAc)_3$ and $Zr(acac)_4$ in this condensation reaction, 4-chlorobenzaldehyde was first reacted with benzil and ammonium acetate in ethanol (2 mL) for 35 min under ultrasound irradiation in the presence of each catalysts (0.2 equiv.) separately. In the course of this study we found that $Zr(acac)_4$ was the most effective catalyst in term of yield of the triarylimidazole (91%) while other catalysts formed the product with the yields of 37–82%. In the absence of catalyst, the yield of the product was found to be very low.

To show the effect of ultrasonic irradiation in these reactions, the synthesis of 2-(2-chlorophenyl)-4,5-diphenylimidazole was investigated as a typical example in the presence of 5, 10, 15, 20 and 25 mol% of $Zr(acac)_4$ with and without ultrasonic irradiation (Table 1). In all cases, the experimental results show that the reaction times are shorter and the yields of the products are higher under sonication. The best results were obtained using 20 mol% of the catalyst under both conditions. Based on the results of this study, it seems that the ultrasound irradiation



Scheme 1.

Table 1
Comparison of reaction time and yields with or without sonication for the synthesis of 2-(2-chlorophenyl)-4,5-diphenylimidazole

Entry	mol% $Zr(acac)_4$	With sonication[a]		Without sonication	
		Yield (%)	Time (min)	Yield (%)	Time (min)
1	0	4	45	6[b] (0[a])	210
2	5	16	45	18[b]	210
3	10	53	45	55[b]	210
4	15	69	45	71[b]	210
5	20	88	45	84[b]	210
6	25	89	60	84[b]	240

[a] At ambient temperature.
[b] Reflux condition.

improves the reaction times and yields but has no effect on the catalyst activity.

The generality of this process was demonstrated by the wide range of substituted and structurally divers aldehydes to synthesize the corresponding products in high to excellent yields (Table 2, method A). For more examination of the influence of ultrasound irradiation in this transformation, comparison of the reaction under two methods, ultrasound irradiation at ambient temperature (method A) and reflux conditions (method B) was performed. As illustrated in Table 2, method A in comparison with method B is better in both yields and especially in the reaction times (see Table 3.

The high yield transformations were carried out without any significant amounts of undesirable side products. Unlike some previously reported methods, the present method does not require toxic or anhydrous organic solvents to produce the 2,4,5-trisubstituted imidazole derivatives. All the products were characterized by NMR, IR and mass spectroscopy and also by comparison with authentic samples. A wide range of aromatic aldehydes were employed and all imidazoles were obtained in high to excellent yields (Table 2, method A, entries 1–20), and was observed a general method that tolerates both electron-withdrawing and electron-donating constituents. Another important aspect is that various functionalities such as ether, halide, nitro, etc., survived under the present reaction conditions. Interestingly, we achieved that in the case of 4-(diethoxymethyl)benzenaldehyde (Table 2, entry 9), one-pot deprotection–cyclization reaction was carried out in the reaction conditions. On the other hand, aliphatic aldehydes as well as unsaturated ones (Table 2, entries 21–24), which normally show extremely poor yields in the previous methods, gave the corresponding imidazoles in high yields. The reaction conditions are mild enough not to induce any isomerization for conjugated aldehydes or damage to moieties such as methoxy which often undergoes cleavage in strongly acidic reaction media (Table 2, entries 14–16,18 and 21–23). To evaluate the generality of this method, we also concentrated our study on different benzils (Table 2). The results illustrate the high ability of this method for the synthesis of 2,4,5-triarylimidazoles with different groups.