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ORIGINAL PAPER

One-pot synthesis of 1,2,4,5-tetrasubstituted and 2,4,5-trisubstituted imidazoles by zinc oxide as efficient and reusable catalyst

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Abstract ZnO is an efficient, readily available, and reusable catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted and 2,4,5-trisubstituted imidazoles. This procedure is very simple and affords excellent yields.

Keywords Multicomponent reactions · Multisubstituted imidazoles · Biological activity · Environmentally friendly procedure

Introduction

There has been a long-standing desire in preparative chemistry to avoid wastage, to substitute benign chemicals for toxic ones, and to use solvent-free reactions. Multicomponent reactions have proved to be notably successful in generating products in a single synthetic operation [1, 2]. The development of new MCRs [3] and improvement of known multicomponent reactions are an area of considerable current interest. One such reaction is the synthesis of imidazoles. Multisubstituted imidazoles, an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activity such as anti-inflammatory [4], antiallergic [5], antibacterial [6], antitumor [7], and analgesic [8] activities. Furthermore, they act as inhibitors of p38 MAP kinase [9] and glucagon receptors [10].

Because of their wide range of biological, industrial, and synthetic applications, multisubstituted imidazoles have recently received a great deal of attention. There are numerous classical methods for the synthesis of multisubstituted imidazoles [11–41]. Despite their tremendous success, however, some of their drawbacks still remain. For example, some of the catalysts employed are expensive, toxic, complex, or unavailable and organic solvents are always used. Hence the challenge for a sustainable environment calls for the use of alternative procedures avoiding the use of harmful solvents and catalysts.

Zinc oxide, a very economical, safe, and easily available Lewis acid catalyst, has been widely used in organic transformations [42–46], but it has not been studied as a catalyst in the synthesis of 1,2,4,5-tetrasubstituted imidazoles until now. In continuation of our work on solvent-free conditions [47–50], we present here, for the first time, a simple, mild, and efficient synthesis of 1,2,4,5-tetraarylimidazoles in excellent yields using ZnO as an extremely efficient and reusable catalyst (Scheme 1).

Results and discussion

To optimize the reaction conditions, the reaction of benzaldehyde, aniline, benzil, and ammonium acetate was used as a model reaction. Reactions at different temperatures and various molar ratios of substrates in the presence of ZnO showed that the best conditions were solvent-free at 110 °C and a molar ratio of aryl aldehyde/amine/benzil/ammonium acetate/ZnO of 1:1:1:1:0.1. An increase in the reaction temperature and time did not improve the yields significantly. The results are depicted in Table 1.

The reusability of the ZnO catalyst was also examined under the optimized conditions, and the desired product

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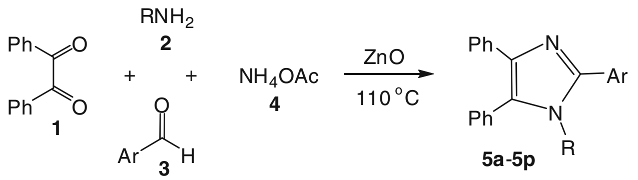


Scheme 1

Table 1 Effect of increasing amount of ZnO on the preparation of 1,2,4,5-tetraarylimidazoles at different reaction temperatures

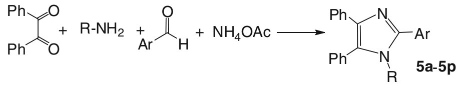
Entry	ZnO (mmol)	*T* (°C)	Yield (%)[a]
1	0	110	Trace
2	0.05	90	60
3	0.05	110	70
4	0.1	100	87
5	0.1	110	98, 95, 94[b]
6	0.2	110	98

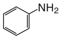
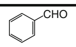
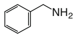
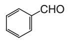
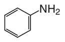
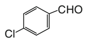
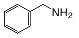
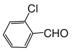
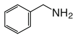
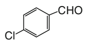
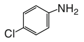
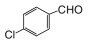
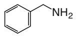
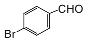
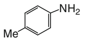
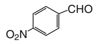
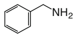
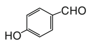
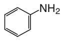
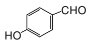
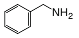
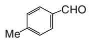
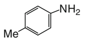
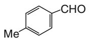
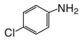
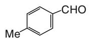
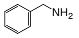
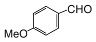
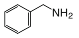
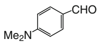
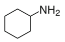
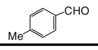
Reaction conditions The reactions were performed with benzaldehyde (1 mmol), aniline (1 mmol), benzil (1 mmol), and ammonium acetate (1 mmol) for 20 min under solvent-free conditions

[a] Isolated yields

[b] Catalyst was reused three times

Table 2 ZnO-catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles



Entry	Amine	Aldehyde	Product	Yield (%)[a] *t* (min)	M.p. (°C)	Ref.
1			**5a**	98 (20)	218–220	[29]
2			**5b**	98 (20)	166	[30]
3			**5c**	95 (25)	140–151	[29]
4			**5d**	95 (30)	139–141	[30]
5			**5e**	97 (27)	163–164	[31]
6			**5f**	90 (30)	187	[32]
7			**5g**	95 (23)	171–172	[32]
8			**5h**	99 (20)	220	[32]
9			**5i**	95 (24)	134–136	[30]
10			**5j**	94 (22)	280	[31]
11			**5k**	94 (22)	167	[31]
12			**5l**	99 (13)	188–190	[32]
13			**5m**	95 (20)	168	[32]
14			**5n**	98 (15)	159–161	[30]
15			**5o**	98 (15)	151–152	[30]
16			**5p**	98 (25)	161–162	[31]

The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures

[a] Isolated yields

was obtained in 98, 95, and 94% yields after one to three runs, respectively (Table 1, entry 5).

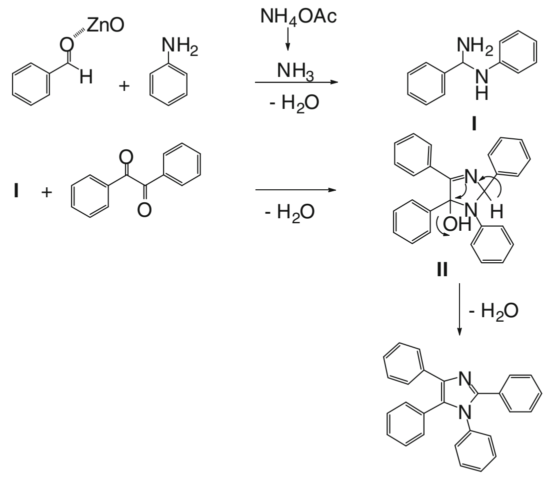
The substrate scope of the reaction was then evaluated by using a variety of structurally diverse aldehydes and primary amines. The results obtained are illustrated in Table 2.

Both aromatic aldehydes and primary amines could be subjected successfully to this protocol. Aromatic aldehydes carrying either electron-donating groups (such as *N*,*N*-dimethylamino, methyl, hydroxy, and methoxy) or electron-withdrawing groups (such as nitro and halides) reacted efficiently and gave excellent yields of 1,2,4,5-tetrasubstituted imidazoles. Steric effects did not influence the yield significantly; for example, in the reaction of 2- and 4-chlorobenzaldehyde (Table 2, entries 4 and 5) the corresponding condensation products were obtained in 95 and 97% yields, respectively. Cyclohexylamine, an aliphatic amine, produced excellent yield of the corresponding imidazole (Table 2, entry 16). In general, the reactions were clean and no side products were detected. With aliphatic aldehydes, for example hexanal and decanal, only trace amounts of imidazoles were observed and could not be isolated.

In accordance with the mechanism proposed by Srinivasan et al. [23], the ZnO catalyst increases the electrophilicity of the carbonyl group of the aryl aldehyde. Nucleophilic attack of the nitrogen atoms of ammonia, obtained from NH_4OAc, and aniline on the activated carbonyl group resulted in formation of intermediate **I**. This intermediate in the presence of ZnO condenses with benzil to form intermediate **II**, which in turn releases a H_2O molecule to form the tetrasubstituted imidazole (Scheme 2).

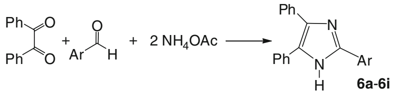
The same reaction conditions were applied for the synthesis of 2,4,5-trisubstituted imidazoles via the one-pot, three-component condensation of benzil (1 mmol), an aryl aldehyde (1 mmol), and ammonium acetate (2 mmol). Aromatic aldehydes bearing electron-donating (Table 3, entries 5–8) and electron-withdrawing (Table 3, entries 2–4) substituents undergo this reaction to furnish excellent yields of 2,4,5-trisubstituted imidazoles in high purity. Acid-sensitive aldehydes such as furfural worked well without the formation of any side products, which are normally observed either in the presence of protic or Lewis acids (Table 3, entry 9). The limitations on the use of the aldehydes were similar to those for the formation of tetrasubstituted imidazoles.

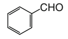
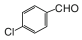
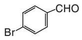
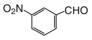
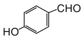
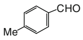
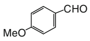
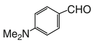
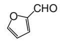
As shown in Tables 2 and 3, aryl amines and ammonium acetate undergo this reaction with benzil and aryl aldehydes



Scheme 2

Table 3 ZnO-catalyzed synthesis of 2,4,5-trisubstituted imidazoles



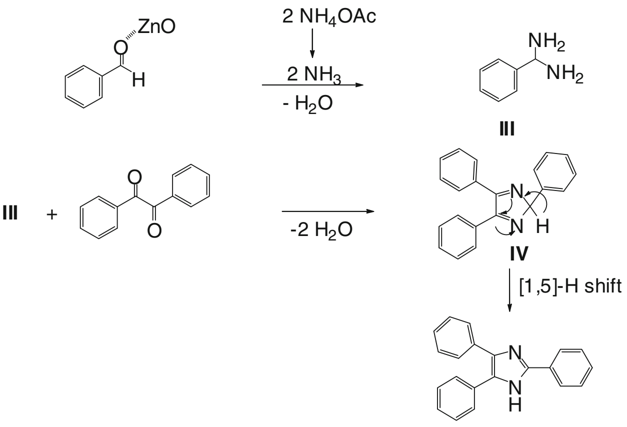
Entry	Aldehyde	Product	Yield (%)[a] *t* (min)	M.p. (°C)	Ref.
1		**6a**	99 (15)	271–272	[29]
2		**6b**	98 (23)	260–262	[33]
3		**6c**	98 (20)	241–244	[33]
4		**6d**	95 (25)	264–266	[29]
5		**6e**	96 (15)	261–262	[29]
6		**6f**	99 (14)	226–228	[33]
7		**6g**	98 (15)	221–224	[29]
8		**6h**	99 (15)	256–258	[34]
9		**6i**	98 (20)	231–234	[41]

The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures

[a] Isolated yields

in equal efficiency. For example, 1,2,4,5-tetraphenyl-1*H*-imidazole was produced in 98% yield in 20 min (Table 2, entry 1) and 2,4,5-triphenyl-1*H*-imidazole in 99% yield in 15 min (Table 3, entry 1).

In a similar manner, a plausible mechanism for the synthesis of the trisubstituted imidazole is presented in Scheme 3. As shown, the reaction of aryl aldehyde and ammonium acetate in the presence of ZnO produces intermediate **III**. This intermediate condenses with benzil to form intermediate **IV**, which in turn rearranges itself to the trisubstituted imidazole by a [1,5]-H shift.



Scheme 3

In conclusion, we have described a simple and efficient method for the synthesis of 1,2,4,5- and 2,4,5-substituted imidazoles using ZnO as a reusable catalyst. Excellent yields, environmentally friendly procedure, short reaction times, simple work-up procedure, and easy isolation and recycling of the catalyst are some advantages of this method. Hence, it is a useful addition to the existing methods.

Experimental

Zinc oxide, ammonium acetate, amines, and all aldehydes employed are commercial products (Merck) and were used without further purification. Melting points were determined in a capillary tube. ^{1}H NMR spectra were recorded on a Bruker 200 MHz NMR spectrometer using TMS as internal standard.

General procedure for synthesis of 1,2,4,5-tetrasubstituted and 2,4,5-trisubstituted imidazoles

Benzil (1 mmol), amine (1 mmol), aryl aldehyde (1 mmol), ammonium acetate (1 mmol), and ZnO (0.1 mmol) were heated at 110 °C under stirring for the time indicated in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. Then, 15 cm^3 ethanol was added to the reaction mixture and it was stirred for 5 min at 80 °C. The reaction mixture was filtered to remove the catalyst and the filtrate was poured into cold water. The solid was filtered by suction to afford crude product. The crystalline pure tetrasubstituted imidazoles were obtained by further recrystalization from acetone/water. An otherwise identical procedure was employed for the synthesis of 2,4,5-trisubstituted imidazoles by using benzil (1 mmol), aryl aldehyde (1 mmol), ammonium acetate (2 mmol), and ZnO (0.1 mmol) (Table 3).

All products were characterized by ^{1}H NMR and their melting points were identical to those of the known compounds reported in the literature.

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