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Simple, Efficient, and Convenient One-Pot Synthesis of Imidazole Derivatives in the Presence of Nanosilica-supported Imidazolium Ionic Liquid as a Catalyst

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An efficient and simple synthesis of 2,4,5-trisubstituted imidazoles is achieved by three-component cyclocondensation of benzil, aldehyde, and ammonium acetate by using nanosilica-supported imidazolium ionic liquid as a catalyst under solvent-free conditions. The key advantages of this process are high to excellent yields, short reaction time, easy work-up, and the reusability of the catalyst.

Keywords: Imidazole; Nanosilica-supported imidazolium ionic liquid; Cyclocondensation; Solvent-free conditions.

INTRODUCTION

Multicomponent reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation.¹ The developing of new MCRs² and improving known multicomponent reactions is an area of considerable current interest. Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems.³ Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes.⁴ 2,4,5-Trisubstituted imidazoles are used as fungicides, herbicides, plant growth regulators, inhibitors of IL-1 or p38 MAP kinase, CB1 cannabinoid receptor antagonists,⁵ and antibacterial,⁶ antitumor,⁷ and glucagon receptors.⁸

There are several methods for the synthesis of 2,4,5-triarylimidazoles using ZrCl₄,⁹ zeolites HY/silica gel,¹⁰ NaHSO₃,¹¹ sulfanilic acid,¹² iodine,¹³ ceric ammonium nitrate,¹⁴oxalic acid,¹⁵ ionic liquids (ILs),¹⁶ and also by microwave irradiation using acetic acid.¹⁷

Furthermore, some of these procedures suffer from disadvantages including the requirement for an expensive catalyst, poor yield, long reaction time, difficult work-up, and effluent pollution. Therefore, the development of a new mild method to overcome these disadvantages still remains a challenge for organic chemists.

Supported solid nanocatalysis has been the subject of immense interest in catalysis science and technology, because of its potential and wide applications in the chemical industry and environmental protection.^{18,19}

In recent years, ILs have been shown to have attractive properties and are widely used as an alternative to conventional organic solvents and corrosive acid catalysts.^{20–22} Despite their utility and extensive applications, they endure some limitations, such as difficulties in catalyst recovery and product isolation and also requiring large amounts of catalyst, that make them economically and environmentally unfavorable. Recently, immobilization processes involving acidic ILs on solid support have been designed. Immobilized ILs combine the benefits of ILs and heterogeneous catalysts, such as high design ability, ease of handling, separation, and recycling based on economic criteria. It is desirable to minimize the amount of IL utilized in a potential process. Immobilized acidic ILs have been used as novel solid catalysts. These immobilized acidic ILs have been widely applied in esterification, nitration,²³ Baeyer-Villiger reactions,²⁴ acetal formation,²⁵ and the hydrolysis of cellulose²⁶ as novel solid catalysts.

As part of our continuing studies of immobilized ILs as catalyst, we report herein, a simple synthesis of 2,4,5-trisubstituted imidazoles (Scheme 1.) in high to excellent yield using nanosilica-supported imidazolium IL(NSIIL) as a catalyst for the first time.

RESULTS AND DISCUSSION

In the continuation of our studies on the applications of NSIIL catalysts in chemical transformations, herein, we wish to describe the preparation of new silica-bonded (1-imidazolium) propyl chloride as

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Scheme 1. Synthesis of imidazole derivatives in the presence of nanosilica supported imidazolium IL as a catalyst.

illustrated in Scheme 2, and its use as a catalyst for the synthesis of imidazole derivatives.

Figure 1 shows scanning electron micrograph of NSIIL sample. The NSIIL was prepared with mean size of 35 nm. Figure 2 shows the TGA analyses of nanocrystalline sample that estimated the amount of loading IL (0.46 mmol/g).

The reaction conditions were standardized for the representative example of the preparation of 2,4,5-triphenyl-1H-imidazole from benzil, ammonium acetate, and 4-chlorobenzaldehyde in different solvents and solvent-less condition and various amounts of NSIIL as a catalyst (Table 1). The results showed that the highest yield product and lower reaction time was obtained in solvent-free condition at 120 $^{\circ}$ C.

We next investigated the other amounts of NSIIL for this reaction. The optimum amount of catalyst was obtained when 0.005 g (0.2 mol%) of NSIIL was used and we compared this result with nanosilica as a catalyst under the same condition (Table 2).

To understand the role of catalyst, the reaction was performed in its absence when the desired product was isolated only in 30% yield after 40 min (Table 2, entry 5). When the reaction was performed in the presence of simple imidazole, lower yield of the



Fig. 1. FE-SEM micrographs of synthesized NSIIL nanoparticle.

product was obtained in the reaction time compared with reaction in the presence of NSIIL (Table 2, entry 6).

The recyclability of the catalyst was investigated. After washing solid products with dichloromethane, recyclability of the catalyst was tested at least thrice and the desired product was isolated in high to excellent yields in each run (Table 2, entry 4).

To explore the scope, we extended the cyclocondensation of benzil (1 mmol), aldehydes (1 mmol), and ammonium acetate (4 mmol) in the presence of NSIIL (0.005 g, 0.2 mol%) as a catalyst at 120°C under solvent-free condition and the results are summarized in Table 3.

As shown in Table 3 when strong electronwithdrawing substituents are present in benzaldehyde, the reaction time increases (entries 10–16), whereas the effect is reverse in the case of benzaldehyde with strong electron-donating substituents such as -OMe and -OH



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Table 1. Optimization of the reaction conditions^a

Entry	Solvent/t°C	Time (min)	Yield (%) ^b
1	EtOH/reflux	180	20
2	CH ₃ CN/reflux	180	10
3	Dioxan/reflux	180	10
4	H ₂ O/reflux	180	
5	Ethylene glycol/reflux	60	85
6	Solvent free/120°C	40	98
7	Solvent free/100°C	65	95
8	Solvent free/80°C	180	48

^a Reactions were carried out with benzil, ammonium acetate, and aldehyde derivatives in 1:4:1 molar ratio.

^b Yields refer to isolated pure products.

Table 2. Optimization amount of catalyst in the reaction of
benzil with 4-cholorobenzaldehyde and ammonium
acetate in the presence of NSIIL^a

Entry	Catalyst (g)	Time (min)	Yield (%) ^b
1	NSIIL (0.02)	40	98
2	NSIIL (0.005)	40	98, 98, 95, 91
3	NSIIL (0.002)	55	98
4	SiO ₂ (0.005)	40	55
5	_	40	30
6	Imidazole	40	45

^a Reactions were carried out with benzil, ammonium acetate, and 4-chlorobenzaldehyde in 1:4:1 molar ratio.

^b Yields refer to isolated pure products.

(entries 4, 5, and 9). Aliphatic aldehydes do not react efficiently and do not afford yields of the corresponding imidazoles (Table 3, entries 19 and 20). Conjugated aldehydes such as cinnamaldehyde react well with benzil and ammonium acetate, leading to a good yield of the expected product (Table 3, entry 18).

A probable mechanism for the synthesis of imidazoles may be postulated as shown in Scheme 3. As can be seen in Scheme 3, NSIIL can activate the carbonyl group of aldehyde to decrease the energy of transition state. Then the nucleophilic attack of ammonium acetate on the activated carbonyl of aldehyde resulted in the formation of imine, and it was followed by nucleophilic attack of the in situ-generated ammonia from ammonium acetate on the imine, giving the intermediate I. The last one reacts with the activated benzil leading to the formation of intermediate II, followed by loss of two water molecules, to form the final product.

Table 3.	Synthesis of 2,4,5-trisubstituted imidazoles using
	NSIIL as a catalyst

Entry	Aldehyde	Time (min)	Yield (%) ^b	m. p. (°C)	Ref.
1	СНО	65	95	271–273	15
2	сі—	40	98	261–263	17
3	ВгСНО	50	98	262–263	16
4	МеО-СНО	20	98	229–231	17
5	но-Сно	10	98	232–233	16
6	OMe	65	98	210	16
	СНО				
7	Ме-СНО	60	98	231–233	15
8		40	94	195–197	16
9	OH	15	88	204–206	15
10	СІ	90	98	286–288	16
	СНО				
11	МеО	90	98	260–262	
12	Br	80	92	200–202	16
13	СНО	100	98	248–250	18
14		80	90	260–262	16
15		95	88	201–202	16
16	сно	50	96	290–291	16

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Table 3. Continued

Entry	Aldehyde	Time (min)	Yield (%) ^b	m. p. (°C)	Ref.
17	СНО	90	90	241–242	16
18	СНО	90	60	196–198	27
19	CH ₃ CH ₂ CH ₂ CHO	90	N.R.		
20	(CH) CHCHO	00	NP		

^a Reactions were carried out with benzil, ammonium acetate, and aldehyde derivatives in 1:4:1 molar ratio.

^b Yields refer to isolated pure products.



Scheme 3. Probable mechanism for the synthesis of imidazoles derivatives in the presence of NSIIL as a catalyst.

An efficient synthesis of 2,4,5-trisubstituted imidazoles through a three-component reaction of benzil, aldehyde, and ammonium acetate by nanosilica-supported imidazolium ionic liquid as a suitable catalyst. Advantages of this method are the recyclability of the catalyst without a significant loss of catalytic activity, an easy procedure and work-up, broad substrate applicability, and high yields in short reaction times. Finally, this approach could make a valuable contribution to existing processes in the field of 2,4,5-trisubstituted imidazoles synthesis.

EXPERIMENTAL

General

All reagents were purchased from (Merck, Darmstadt, Germany) and (Aldrich, St. Louis, Missourti, Unites States) and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (¹H NMR and ¹³C NMR spectra). The NMR spectra were recorded on a (Bruker, Billerica, Massachusetts, USA) Avance 500 MHz instrument. The spectra were measured in DMSO relative to TMS (0.00 ppm). The NSIIL were characterized by FE-SEM and TGA techniques.

Preparation of NSIIL

The catalyst was prepared by covalent attachment of the IL onto the surface of the nanosilica (Scheme 2). First, nanosilica (1 g) was treated with 3-chloro propyltrimethoxysilane (0.149 g) to give 3-(3-trimethoxysilylpropyl)imidazole (a) which reacted with imidazole (0.06 g), and refluxed for 24 h to produce the IL@nano-SiO₂ catalyst (b) (Scheme 2). The IL@nano-SiO₂ catalyst was characterized by elemental analysis, FT-IR spectroscopy, SEM, and TGA. Based on this value, the amount of IL which is supported on the nanosilica is about 0.46 mmol/g.

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

A mixture of benzil (1 mmol), benzaldehyde (1 mmol), ammonium acetate (4 mmol), and 0.005 g (0.2 mol%) of NSIIL was heated in an oil bath at 120°C for the appropriate time reported in Table 3. The reaction process was monitored by TLC (n-hexane: EtOAc, 17:3), the mixture was washed with CH_2Cl_2 , and pure product was obtained. All of the desired products were characterized by comparison of their physical data with those of known compounds. Some

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characterization data for selected known products are given below.

Data of selected products are represented as follows:

4-(4,5-Diphenyl-1H-imidazol-2-yl)benzonitrile (Table 1, Entry 4). ¹H NMR (400 MHz, DMSO): $\delta = 13.03$ (s, 1H), 8.25 (d, 2H, J = 8.4 Hz), 7.94 (d, 2H, J = 8.4 Hz), 7.50–7.56 (m, 4H), 7.46 (t, 2H, J = 7.2Hz), 7.39–7.42 (m, 1H), 7.32 (t, 2H, J = 7.2Hz), 7.23–7.26 (m, 1H); ¹³C NMR (100 MHz, DMSO): $\delta = 144.15$, 138.51, 135.14, 134.72, 133.26, 131.06, 130.06, 129.20, 128.98, 128.73, 128.62, 127.56, 127.30, 125.98, 119.37, 110.56.

2-(4-Methoxyphenyl)-4,5-diphenylimidazole (Table 1, Entry 5). ¹H NMR (400 MHz, DMSO): δ = 12.52 (s, 1H), 8.02 (d, 2H, *J* = 5.2 Hz), 7.34–7.55 (m, 7H), 7.30 (t, 2H, *J* = 6.8HZ), 7.19–7.23 (m, 1H), 7.05 (d, 2H, 4.8); ¹³C NMR (100 MHz, DMSO): δ = 159.86, 146.07, 137.19, 135.74, 131.65, 129.10, 128.80, 128.63, 128.09, 127.50, 127.15, 126.88, 123.54, 114,55, 55.66.

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