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A Highly Efficient Synthesis of 2,4,5-Trisubstituted Imidazoles Catalyzed by Composite Magnetic Nanoparticle Under Mild Reaction Conditions

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Abstract: A novel urea-functionalized silica-base magnetic hybrid nanoparticle with a core-shell structure was prepared and found to be a highly efficient and recoverable heterogeneous nanocatalyst for the one-pot three-component condensation reaction between benzil or benzoin with various substituted aldehydes and ammonium acetate to afford the corresponding imidazoles under mild conditions. This procedure is a clean and environmentally friendly approach that offers many advantages including short reaction times, high to quantitative yields, low cost and straightforward workup.

Keywords: Multicomponent reactions (MCRs), Imidazole, Benzil, Benzoin, Urea, Magnetite nanocatalyst

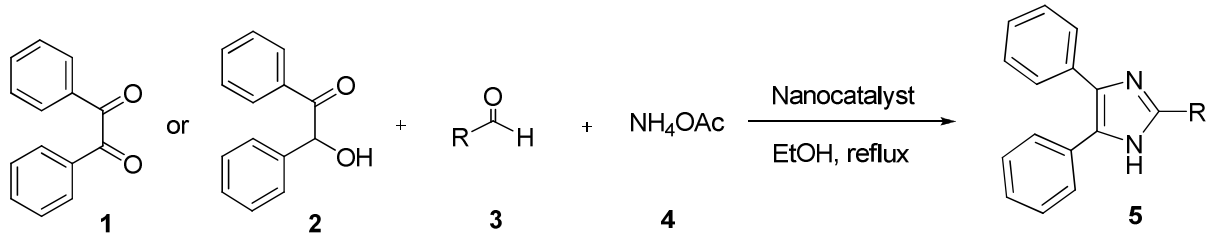
Introduction

The use of environmentally benign, maintainable, and efficiently reusable catalysts provides both economic and ecological advantages [1]. During the past years, advances in nanotechnology have pushed forward the synthesis of functional magnetic nanoparticles (MNPs), which is one of the most active research areas in advanced materials, MNPs that have unique magnetic properties and other functionalities have enabled a wide spectrum of applications [2]. Fe_3O_4-supported

catalysts can be simply separated from the reaction mixture by an external permanent magnet. This strategy is typically more effective than filtration or centrifugation [3]. Coating iron oxides with silica to form core–shell structures is rather simple because of the presence of surface FeOH groups.

Research in multicomponent reactions (MCRs) is an encouraging and hot topic of organic chemistry, because of their advantageous in preparation of small molecule heterocyclic libraries and in drug discovery procedures [4]. Multi-substituted imidazoles are an important class of pharmaceutical compounds and attractive targets in medicinal chemistry as the antiulcerative agent cimetidine, the proton pump inhibitor omeprazole, the fungicide ketoconazole, the benzodiazepine antagonist flumazenil and anticancer agents [5]. Recently, the synthesis of 2,4,5-trisubstituted imidazoles has been performed by condensation of benzil or benzoin, aldehyde and ammonium acetate in the presence of $ZrCl_4$ [6], I_2 [7], proline [8], $InCl_3.3H_2O$ [9] Nano-crystalline magnesium oxide [10]. Some of these synthetic methods are associated with one or more disadvantages such as using expensive reagents, long reaction time, complex work-up and purification and generation of large amount of toxic waste. Therefore, the development of simple, effective, unpolluted, high-yielding, and environmentally friendly approaches using new catalysts for the synthesis of highly substituted imidazoles is an important task for organic chemists.

In continuation of our research on the introduction of novel catalysts in organic synthesis [11], in the present work, we describe that a versatile and useful process for the synthesis of a recoverable Fe_3O_4/SiO_2-supported urea nanocatalyst that can be used as a novel magnetic nanocatalyst for the synthesis of substituted imidazoles **5**.



Scheme 1. Synthesis of 2,4,5-trisubstituted imidazoles catalyzed by nanocatalyst.

Experimental

General

High-purity chemical reagents were purchased from Merck. All reactions and the purity of the products were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate and *n*-hexane as eluents. The spots were detected either under UV light or by placing in an iodine chamber. Melting points were determined in open capillaries using an Electrothermal 9100.

General procedure for the preparation of 2,4,5-trisubstituted imidazoles derivatives

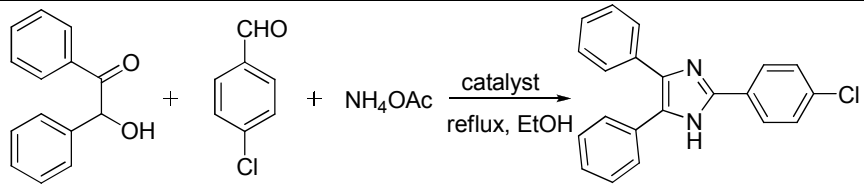
MNPs-SiO_2-urea (0.0088 g) was added to a mixture of benzil or benzoin (1.0 mmol), various substituted aldehydes (1.0 mmol) and NH_4OAc (4.0 mmol) in refluxing ethanol and stirred for the appropriate times. The progress was monitored by TLC. After completion of the reaction the catalyst was separated by an external magnet and the simple product was isolated by filtration of the reaction mixture. Pure products were obtained via re-crystallization by EtOH.

Results and discussion

The catalytic ability of the magnetite nanoparticle-supported urea was evaluated in catalyzing a reaction for the efficient synthesis of trisubstituted imidazoles by condensing benzil or benzoin, aldehydes and ammonium acetate in refluxing EtOH (Table 1). The results were evaluated qualitatively through TLC. It was found that the quantitative yield can be achieved when the reaction was carried out in the presence of 0.0088 g catalyst for 50 min in refluxing EtOH.

MNPs-urea was tested as basic magnetically separable heterogeneous nanocatalyst for the synthesis of the imidazole (**5a-j**) from reaction of benzil **1** or benzoin **2**, wide range of aromatic aldehyde **3** and ammonium acetate **4** in refluxing ethanol. After completion of the reaction, the catalyst was easily separated by a magnet and the solid product was purified by recrystallization from ethanol. The results are summarized in Table 2.

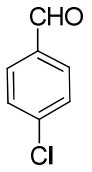
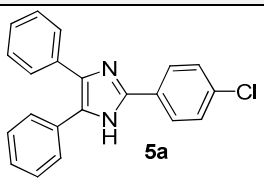
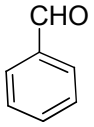
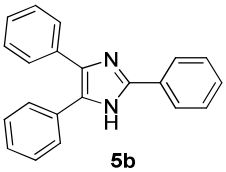
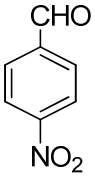
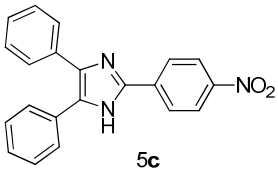
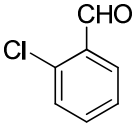
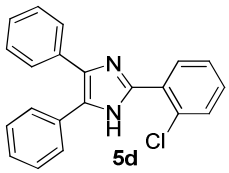
Table 1. Optimization of the amount of Fe_3O_4/SiO_2/urea nanocatalyst.

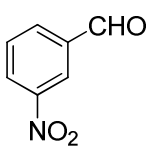
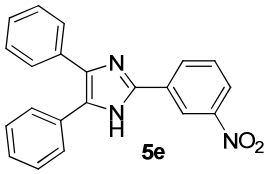
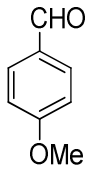
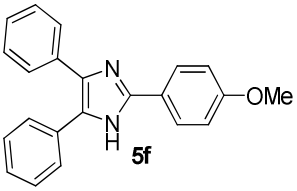
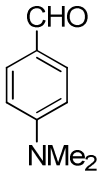
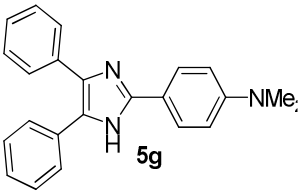
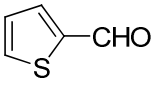
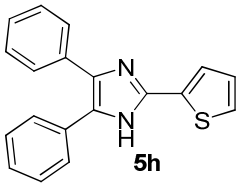
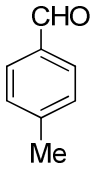
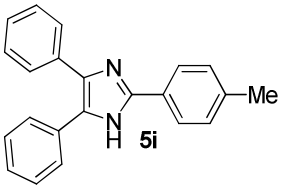
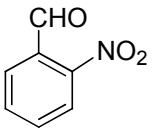
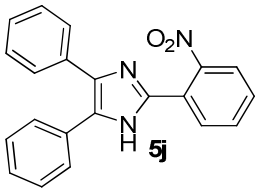


Entry	Catalyst (g)	Time (min)	Yield[b] (%)
1	0.0017	150	70
2	0.0035	70	87
3	0.0088	50	95
4	0.0176	50	86

[a]Reaction conditions: benzoin (1 mmol), 4-chlorobenzaldehyde (1 mmol), ammonium acetate (4 mmol), refluxing EtOH. [b]Yields of the isolated products.

Table 2. Synthesis of imidazole derivatives **5a-j** in the presence of Fe_3O_4/SiO_2/urea.[a]

Entry	RCHO (**3**)	Product (**5**)[b]	Time (min)		Yield[c] (%)		Mp (ºC)	
			1	**2**	**1**	**2**	Found	Reported
1		 **5a**	40	50	98	95	260-261	260-262[12]
2		 **5b**	60	75	95	91	272-274	272-273[13]
3		 **5c**	55	60	98	94	199-201	200-202[14]
4		 **5d**	80	95	75	68	196-198	196-198[15]

5		 **5e**	65	75	89	85	298-301	301-302[16]
6		 **5f**	140	150	80	71	163-165	165-167[17]
7		 **5g**	120	150	79	72	255-257	256-258[15]
8		 **5h**	150	180	75	68	261-262	261-263[18]
9		 **5i**	75	90	90	86	231-234	231-233[12]
10		 **5j**	100	115	80	73	231-233	230-233[19]

[a]Reaction conditions: benzoin or benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (4 mmol), EtOH (reflux) and Fe_3O_4/SiO_2/urea (0.0088 g).

[b]All compounds were known and their structures were established from their spectral data and melting points as compared with literature values. [c]The yields refer to isolated products.

The Fe_3O_4/SiO_2-urea nanoparticles were easily separated with an external magnet and the recovered catalyst was reused for at least six runs without significant degradation in catalytic activity and performance (Fig. 1).

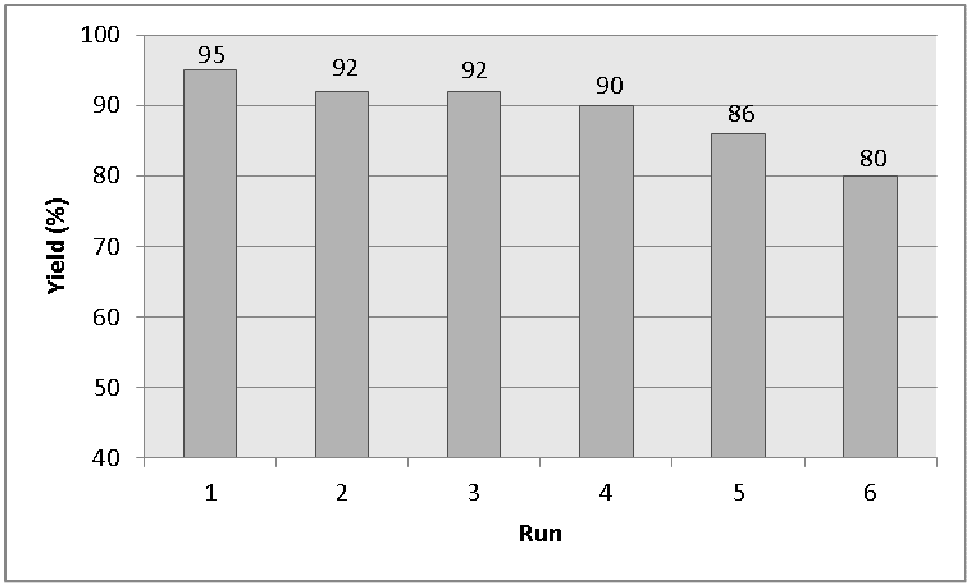


Figure 1. The recycling of the Fe_3O_4/SiO_2-urea (0.0088 g) carried out under reflux conditions using a model reaction of 4-chlorobenzaldehyde, benzoin and ammonium acetate.

Conclusions

In summary, a novel urea-functionalized magnetite nanoparticle has been synthesized through the facile and simple synthetic procedures starting from commercially available starting materials. It was found that the urea functionalized magnetite nanoparticle can be utilized as efficient heterogeneous catalyst for the condensation reaction of benzil or benzoin with various substituted aldehydes and ammonium acetate in refluxing ethanol under mild reaction conditions in suitable time and excellent yields.

Acknowledgements

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