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Short communication

Thiourea-functionalized magnetic hydroxyapatite as a recyclable inorganic–organic hybrid nanocatalyst for conjugate hydrocyanation of chalcones with TMSCN

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ABSTRACT

an industrially viable and eco-safe catalyst.

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1. Introduction

The nucleophilic 1, 4-addition is one of the most interesting reactions that always has been a significant notice [1]. Michael reaction has many applications in diverse fields such as coating, synthesis of bioactive natural products, and toxicity, but there is always the problem of competition between 1, 4-addition and 1, 2-addition reactions [2,3]. Improvement of organic catalysts for the nucleophilic 1, 4-addition is still an interesting subject in synthetic chemistry. There are a few useful methods for hydrocyanation using various cyanation reagents such as hydrogen cyanide, alkali or earth metal cyanides, organoaluminum cyanide, organosilicon cyanide, and acetone cyanohydrin, which can generate cyanide ion in the presence of a base. Lapworth procedure used potassium cyanide [4] and Nazarov base catalyzed hydrocyanation used acetone cyanohydrin as the cyanide source [5]. Some Lewis acid catalysts have been used for example Et₂AlCN (Nagata's reagent) [6], Et₃Al [7], and AlCl₃[8]. Previously, Ellis used 125 mol% of acetone cyanohydrin and 5 mol% of tetramethyl ammonium hydroxide [9] and Hamana applied MW irradiations without any catalyst [10]. CsF catalyst with water was applied as additive in refluxing dioxane [11]. Recently Lalitha et al. reported scandium(III) triflate with tetraethylammonium cyanide as a cyanide source [12]. In most hydrogenation methods the amount of cyanide source has been applied

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extra, and in some cases the protocols involve the usage of harsh conditions and laborious aqueous work-up leading in the production of the large amount of unwanted products such as hydrogen cyanide. Furthermore the safety worries, the reaction mixture has become highly colored on reaching reflux. Among different cyanide sources, TMSCN has been used as a safer and more effectual cyanide anion source compared

The recoverable nanomagnetic catalyst was manufactured based on thiourea modified magnetic hydroxyapatite.

Magnetic hydroxyapatite (mHAp) as the inorganic-organic hybrid support was fabricated using co-precipitate con-

dition and then modified via the covalently anchoring of 1-(3,5-bis(trifluoromethyl)phenyl-3-propyl)thiourea. The

hybrid nano-catalyst has been identified by TEM, SEM, FTIR, BET, TGA, and XRD. This nanocatalyst appeared efficient

and robust in the 1,4-addition reaction of TMSCN to $\alpha\beta$ -unsaturated aromatic enones in excellent yields (85–96%) under mild reaction condition and simple work-up process. This recoverable organocatalyst has a great potential as

to the above cyanide reagents [13]. Recently nanomagnetic catalysis has emerged as a remarkable issue to create ideal systems for broad biological, medical, and catalytic applications [14–16]. Indeed, owing to the demands of clean technology. there are many reports about the synthesis and applying of recyclable nano-catalysts [17-20]. In spite of these reports, the introduction of novel green catalysts and reagents has still remained as an interesting challenge. In the traditional heterogenization (surface immobilization on inorganic materials) the catalyst recovery was improved, but the high rigidity of the support containing catalytic centers leads to a decrease in the disposal catalytic centers for the reactants [21,22]. Therefore, "inorganic–organic hybrid materials" which are achievable by grafting of flexible organic spacers on the surface, have introduced as applicable tools to overcome this shortcoming. The delicate advantage of these compounds is the favorable germination of the organic and inorganic characteristics such as high reactivity and stability [23–25]. Due to the high stability, surface area, surface manipulation ability and low toxicity, hydroxyapatite (HAp) "Ca₁₀(PO₄)₆(OH)₂" has been used as a robust material for drug and protein delivery agent [26–29] and catalyst supporting material [30–32]. Thiourea derivatives



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Scheme 1. a) Synthesis of organosilane I, and b) thiourea functionalized mHAp.

are regarded as typical and fundamental organo-catalytic compounds and in many kinds of base and hydrogen bond catalyzed reactions has been used for C–C bond formation [33–34]. In this regards, we wish to report a green magnetically recoverable thiourea based organocatalyst for hydrocyanation of chalcone derivatives.

2. Experimental section

2.1. Preparation of catalyst

2.1.1. Synthesis of organosilane I

N'-(3,5-bis-trifluoromethylphenyl) isothiocyanate and trimethylsilyloxypropyl amine in 1:1 mol ratio was refluxed in dry EtOH for 2 h under Ar atmosphere. After evaporation of the solvent and washing with 100 mL Et₂O, the solid was dried under vacuum at 100 °C to give 1-(3,5-bis(trifluoromethyl)phenyl)-3-(3-(trimethoxysilyl)propyl)thiourea (organosilane I). ¹HNMR (500 MHz, MeOD):8.16 (s, 2H), 7.61 (s, 1H), 3.55 (s, 9H), 3.3 (t, 2H), 1.73 (m, 2H), .68 (t, J = 6.0 Hz, 2H).

2.1.2. Synthesis of thiourea functionalized mHAp

1 g of mHAp which was prepared according to the previously reported method was pre-activated by heating under vacuum for 48 h at 120 °C [35]. Then the activated magnetic HAp was suspended in a mixture of 100 mL of dry toluene containing organosilane I (3 mmol, 1.35 g). The mixture was refluxed under Ar atmosphere at 100 °C for 24 h. The resulted solid was separated by an external magnetic device and then washed with Et₂O. Afterwards, It was further purified by soxhlet extraction with EtOH and then dried under vacuum for 24 h at 50 °C to give the thiourea functionalized magnetic nanoparticles at a loading about 0.93 + 0.01 per gram of catalyst (determined by TGA analysis).

2.2. General procedure for the synthesis of beta ketonitrile 3

1.1 mmol of TMSCN was added to a mixture of thiourea functionalized mHAp (5.5 mg, 0.5 mol%) and 1 mmol a chalcone in 4 mL of H₂O and allowed to stir at 50 °C. The reaction progress was monitored by TLC. At the end of the reaction, the nanocatalyst was separated from the reaction mixture by an external magnet. Then the resulting suspension was concentrated on a rotary evaporator. The product was obtained via purification of the residue by recrystallization on EtOH/H₂O (4:1) to afford the pure products. For testing the recovery of catalyst, the separated catalyst was washed with hot EtOH and also acetone or Et₂O to remove the residual product, and dried to reuse in the subsequent runs. All isolated products gave satisfactory spectral data compared with those reported in literature.

3. Results and discussion

To achieve the desired organocatalyst, we synthesized a magnetically recoverable organocatalyst based on thiourea using magnetic hydroxyapatite as a robust supporting material according to the procedure shown in Scheme 1. Afterwards, to achieve the organosilane I, the equimolar amount of N'-(3,5-bistrifluoromethylphenyl) isothiocyanate was reacted



Fig. 1. a) The isotherm plot, and b) VSM curve of mHAp and functionalized mHAp nanoparticles.



Fig. 2. a) TEM, SEM, and c) EDX micrographs of thiourea functionalized mHAp.

with trimethylsilyloxy propyl amine in dry EtOH (Scheme 1a), and was confirmed by FTIR, ¹HNMR and ¹³CNMR. Then the synthesized organosilane I was grafted onto the surface of mHAp to synthesize thiourea functionalized mHAp as a magnetic thiourea-based inorganic–organic hybrid material (Scheme 1b).

The nanoparticles were characterized by different techniques such as FT-IR, TGA, VSM, TEM and SEM. In the FT-IR spectra characteristic absorption bands due to the bending vibration of O–P–O group in the HAp shell were observed at 581 and 617 cm⁻¹ and the stretching of P–O bond appeared at 1063 cm⁻¹. The C=S and C–N stretching bands of thiourea group appeared at 1546 and 1314 cm⁻¹, respectively. Also, the bending vibration modes of O–Si–O and thiourea functional group were observed at 677 cm⁻¹ and 1270 cm⁻¹, respectively. The surface area of the mHAp and thiourea functionalized mHAp was determined utilization BET analysis showed reduction from 224 m²·g⁻¹ to 89 m²·g⁻¹ which revealed the success of the immobilization of thiourea

Table 1

Entry	Catalyst	Solvent	mol%	Time(h)	Yield%				
1	-	CH₃OH	-	24	0				
2	$H_3PW_{12}O_{40}$	CH ₃ OH	10	24	0				
3	Oxalic acid	CH ₃ OH	10	24	0				
4	Guanidine hydrochloride	CH ₃ OH	5	24	0				
5	mHAp	CH ₃ OH	50	24	10				
6	Thiourea functionalized mHAp	CH ₃ OH	0.5	1	86				
7	Thiourea functionalized mHAp	H_2O	0.5	6	90				
8	Thiourea functionalized mHAp	H_2O	1	3	90				

Table	2
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Efficient synthesis of \beta-ketonitriles.

onto the surface of mHAp. The synthetic powder showed a type (IV) nitrogen adsorption–desorption isotherm (Fig. 1a). The synthesized core-shell catalyst possesses sufficient superparamagnetic characteristic for practical applications. Magnetic hysteresis measurements were done in an applied magnetic field at r.t, with the field sweeping from – 8000 to + 8000 Oe using a vibrating sample magnetometer (VSM) as a scientific instrument for measuring magnetic properties. As shown in Fig. 1b, the M (H) hysteresis loop for the samples was completely reversible. The magnetic saturation values of the mHAp and thiourea functionalized mHAp Nanocrystallites are 7.2 and 4.5 emu·g⁻¹ at r.t, respectively. Decreased magnetic saturation of mHAp thiourea functionalized NPs is attributed to the influence of the grafted organic moiety. Both particles show high permeability in magnetization and their magnetization is sufficient for magnetic separation with a conventional magnet.

Quantitative determination of the thiourea-based functionality loading was performed by using TGA analysis. TGA analysis of the catalyst showed a first peak due to desorption of water (centered at 97 °C). This was followed by a second decrease from 337 °C to 592 °C, corresponding to the loss of the organic functional group. With the knowledge of the thermal decomposition of the mHAp and thiourea functionalized mHAp, it was concluded that the loading of the thiourea moiety on the surface was about 0.93 + 0.01 mmol per gram of catalyst. The SEM, EDX, and TEM images of thiourea functionalized mHAp nanoparticles were shown in Fig. 2.

To evaluate the capability of thiourea functionalized mHAp, nucleophilic 1,4-addition of TMSCN to α_{β} -unsaturated aromatic enones was selected as a model reaction. The reaction generally involves the nucleophilic addition of activated cyanide ion **2** to chalcone **1** to form

		+ TMSCN Thiourea functionalized mH H2O, 50 °C R1 6h	Ap Ar R ₁				
	1a-j	2	3a-j				
Entry	Ar	R ₁	Product	Yield (%) ^a			
1	Ph	Н	3a	90			
2	4-MePh	Н	3b	92			
3	Ph	OMe	3c	85			
4	Ph	Br	3d	96			
5	Ph	Ph	3e	89			
6	4-Br-Ph	Н	3f	90			
7	1-Naphtyl	Cl	3g	91			
8	4-Cl-Ph	Н	3h	92			
9	Ph	NO ₂	3i	85			
10	4-NO ₂ -Ph	Н	3j	89			

^a Isolated yield.



Fig. 3. The reusability test of the catalyst.

cyanohydrin trimethylsilyl ether which undergoes in situ desilylation by thiourea functionalized mHAp (Scheme 1). The 1, 4-addition reactions take place smoothly leading to the corresponding β -keto nitriles **3** in excellent to good yields. Initially we set out to investigate solvent, amount of catalyst, and time effects in the reaction of chalcone 1a and TMSCN 2 as a simple model substrate (Table 1). The results showed that the presence of a catalyst is required to achieve the products. The effect of solvent was studied using various solvents, with MeOH and H₂O providing the highest yields and short reaction times. With respect to the green chemistry goals and the mol% of catalyst, time and solvent, the best optimized condition is: thiourea functionalized mHAp (0.5 mol%), H₂O as solvent (4 ml) at 50 °C for 6 h (Table 1, Entry 7). As shown in Table 2, in this method we have seen only the desired product 1, 4-adduct and the 1, 2-adduct was not seen. The products were satisfactorily characterized by its ¹HNMR, ¹³CNMR and melting points.

With regard to the success of the above reaction, various chalcones were subjected to this reaction (Table 2). The reactions proceed in the presence of thiourea functionalized mHAp under optimal condition. Through this protocol the 1,4-addition reaction of TMSCN to α , β -unsaturated aromatic enones was accomplished in excellent yields (85–96%) under mild reaction condition and simple work-up process. Notably, no undesirable side reactions (1, 2-addition) were observed under this reaction condition. Spectral analysis of the β -ketonitrile products clearly indicated the formation of **3a-j**.

We have also tried to evaluate the recyclability of the nanocatalyst at least ten times. To this purpose, the separated catalyst was thoroughly washed with hot EtOH and also acetone or Et_2O to remove traces of the previous reaction mixture and then dried also no preconditioning step was used. The obtained results are shown in Fig. 3. Additionally no significant decrease was observed in the magnetic saturation values of the 1th and 10th reused thiourea functionalized mHAp NPs (please see the Supplementary data file).

In addition, to rule out any contribution of homogeneous organothiourea catalysis, we tested the reaction leached. Firstly, the model reaction started with a catalytic amount of catalyst and then the catalyst was removed and allowed the reaction resumed in the later condition without catalyst. The reaction did not show any progress without the catalyst, even after 24 h. This result clearly confirmed that no catalytic active species were present in the supernatant. Also mHAp was examined as catalyst in the aforementioned reaction, and it was found that the reaction did not carry out with mHAp as catalyst after 24 h.

4. Conclusions

In conclusion, thiourea functionalized magnetic HAp nano-framework has been demonstrated as a convenient organocatalyst due to its biocompatibility. We found that thiourea functionalized mHAp can be applied as a novel and simple magnetic separable heterogeneous organocatalyst for selective and highly efficient 1, 4-addition reaction of chalcones and related enones with TMSCN. Based on these observations, it can be concluded that the operational simplicity, practicability, easy approachability of reactive centre and environmentally benefits are the worthy advantages of this green and cost-effective catalyst. The introduced thiourea functionalized mHAp is in particular highly stable and can be reused in ten successive runs with no significant structural change and loss of catalytic activity. This method proposes several advantages such as high yields, simple work-up condition, high selectivity and straightforward starting from easily accessible starting materials, which makes it a useful and attractive strategy for the preparation of betaketonitriles.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.catcom.2015.08.016.

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