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Synthesis of Pyranopyrazole Compounds Using Heterogeneous Base Catalyst Based on 1,3,5-Triazine-2,4,6-Triamine Modified Nano Rice Husk Silica

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ABSTRACT
In the current study, amorphous silica nanoparticles were easily extracted from rice husk ash. The target composite was synthesized by the direct incorporation of chloropropyl groups through the condensation of nanosilica and 3-chloropropyl trimethoxysilane and then grafting of 1,3,5-triazine-2,4,6-triamine (Melamine) onto the propyl groups by the simple nucleophilic substitution reaction (RHA@Melamine). The resulting solid catalyst was characterized by infrared spectroscopy, scanning electron microscope and thermogravimetric analysis. The catalytic activity of this solid acid nanocomposite was probed through one-pot synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole via four-component couplings of aldehydes, hydrazine hydrate, ethyl acetoacetate and malononitrile under solvent-free conditions. In this reaction, RHA@Melamine shows good catalytic nature, easy to handle procedure, recycle exploitation and excellent isolated yields of products.

Keywords: *Rice husk silica; Heterogeneous catalyst; Pyranopyrazole; Melamine catalyst*

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INTRODUCTION

Compare to the solid acid catalysts, solid base catalysts are much less frequently used in heterogeneous catalysts [1-4]. Herein, organic amines and ammonium salts have been used as base catalysts for many reactions [5-11].

Amino-functionalized inorganic supports are useful for the base-catalyzed reactions [12] or further post-synthesis functionalization [13, 14]. A green approach in heterogenized acid or base catalytic application is supporting or immobilizing of homogeneous acid or bases catalysts [15].

Silica is a common support in the synthesis of inorganic-organic hybrid materials due to its easy availability and low cost [16]. In most published reports, the major silica precursors used were commercially made alkoxysilane compounds such as tetraethylorthosilicate (TEOS), sodium silicate and tetramethylorthosilicate.

The main modification pathway for silica-based material is the incorporation of organic

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components, either into the inorganic solid surface or by trapping them within its porous channels [17]. To expand the applications of silica in catalysis [18-20], separation [21, 22], and sensor design [23], many researchers have focused on the preparation of organic-functioned materials by the direct incorporation of organic groups through co-condensation or by grafting the organic groups into the surface of the silica.

However, many researchers have reported that rice husk is an excellent source of high-grade amorphous silica [24].

Silica from rice husk offers a cheap alternative to commercial silica and at the same time help to solve rice husk disposal problem faced by rice milling industry [25].

RH is composed of 20% ash, 38% cellulose, 22% lignin, 18% pentose and 2% other organic components. The burning of rice husk in the air always leads to the formation of silica ash [26]. The white ash obtained from its combustion or calcination at relatively moderate temperatures produces a main residue containing silica (SiO_2) in the form of an amorphous phase, together with small amounts of impurities of metallic oxides [27].

A reaction between a carbon-halogen functional group and one of the base organic compounds or ligands is a nucleophilic substitution reaction [28, 29]. 1,3,5-triazine-2,4,6-triamine (melamine), is a primary amine with three NH_2 groups. These groups can be utilized for catalysis.

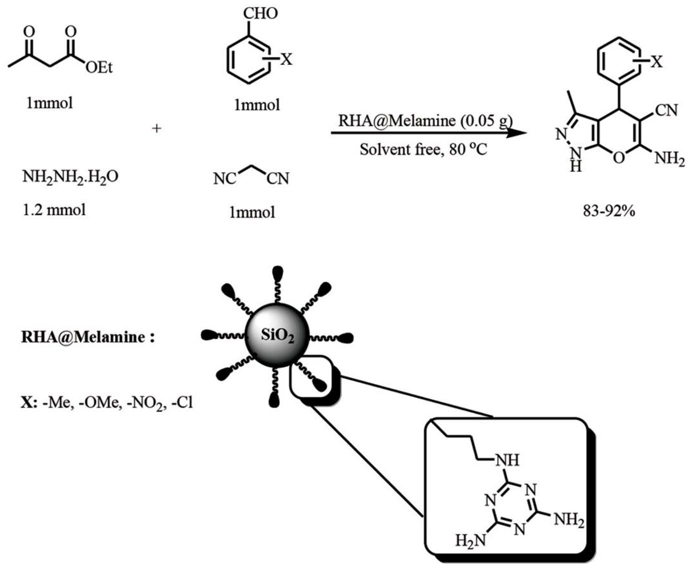
We thought that the grafting of melamine onto the silica surface could afford a catalyst having a unique catalytic activity and selectivity due to the three NH_2 groups.

Pyranopyrazoles are an important class of fused heterocyclic compounds, that are known for their wide range of biological activities such as fungicidal [30], bactericidal [31] and they act as anticancer agents [32]. Furthermore, compounds containing pyrano[2,3-*c*]pyrazole moiety have been reported to exhibit enzyme inhibition [33], anticancer [34] and antifungal [35] activity apart from being significant intermediates for the construction of complex heterocycles. In view of the biological significance, there has been extensive attention toward the development of synthetic routes for the synthesis of compounds containing pyrano[2,3-*c*]pyrazole core [36].

These high profile applications and variety of biological activities have promoted extensive studies for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives through a two-component or three-component reaction.

The use of melamine as a homogeneous or a heterogeneous catalyst has not been reported for synthesis of pyranopyrazole compounds to the best of our knowledge.

This paper reports a systematic study on the synthesis and characterization of a high surface area catalyst prepared by chemically bonding melamine into rice husk ash silica (RHA@Melamine) and its use in the synthesis of pyranopyrazole compounds (Scheme 1).



Scheme. 1. Synthesis of pyranopyrazole compounds.

EXPERIMENTAL

General

Chemical materials were purchased from Fluka and Merck companies and used without further purification. Rice husk (RH) was collected from a rice mill in Khozestan-Baghmalek (Iran). The products were characterized by a comparison of their physical data, IR and 1H NMR and 13C NMR spectra with known samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. NMR spectra were recorded in CDCl3 on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. Fourier transmission infrared (FT-IR) spectra of the powders (as pellets in KBr) were recorded using a fourier transmission infrared spectrometer (BOMEM MB-Series 1998 FT-IR spectrometer).

The TGA curve of the RH@Melamine was recorded on a BAHR, SPA 503 at heating rates of 10°C min-1. The thermal behavior was studied by heating 1-5 mg of samples in aluminum-crimped pans under nitrogen gas flow, over the temperature range of 25-1000°C. The particle size and external morphology of the particles were characterized by scanning electron microscopy, SEM (Philips XL30 scanning electron microscope).

Synthesis of RHA@Melamine

First, rice husk was washed with tapwater and rinsed with distilled water to remove dirt. After drying at room temperature, the rice husk was stirred with 1.0 M nitric acid at room temperature for about 24 h. It was thoroughly washed with distilled water until the pH of the rinse became constant. The wet RH was subsequently dried in an oven at 100°C for 24 h. The cleaned RH was burned in a muffle furnace eat 800°C for 6 h. Silica extraction from RH was carried out by stirring the rice husk in 500 ml, 1.0 M sodium hydroxide for 24 h at room temperature. Then the mixture was filtered to remove the undissolved residues. The extracted sodium silicate was titrated with 3.0 M HNO_3. The acid solution was added at a slow rate of ca. 1.0 mL min-1 with constant stirring. Silica gel started to precipitate when the pH decreased to less than 10. The titration was continued until the solution pH reached 5.0. The silica gel/precipitate was aged for 24 h. The silica gel/precipitate was filtered, washed thoroughly with distilled water and dried at 100°C for 18 h.

About 3.0 g of the nanosilica (obtained from RH) was stirred in350 mL of 1.0 M NaOH at room temperature. The solution was filtered to remove undissolved particles and 3.0 mL solution of 3-chloropropyl trimethoxysilane (CPTMS) was added to the resulting sodium silicate. The solution was then titrated slowly (1.0 mL min-1) with 3.0 M nitric acid with constant stirring. The change in pH was monitored by using a pH meter. A white gel started to form when the pH decreased to less than 11.0. The titration was done slowly until pH 5 was reached. The gel obtained was aged for 24 h. Then the gel was separated by centrifuge. The separation process was repeated 6 times with distilled water. The final washing was done with acetone. The sample was then dried at room temperature.

Then, 3 g of obtained powder was added to a flask containing 40 mL of anhydrous acetone and 3 mmol of melamine. The reaction mixture was refluxed with stirring for 24 h. Then, the mixture was cooled to room temperature, transferred to a vacuum glass filter, and washed with water and acetone. The rice husk ash chemically bonded with melamine (RHA@Melamine) was dried at 50°C.

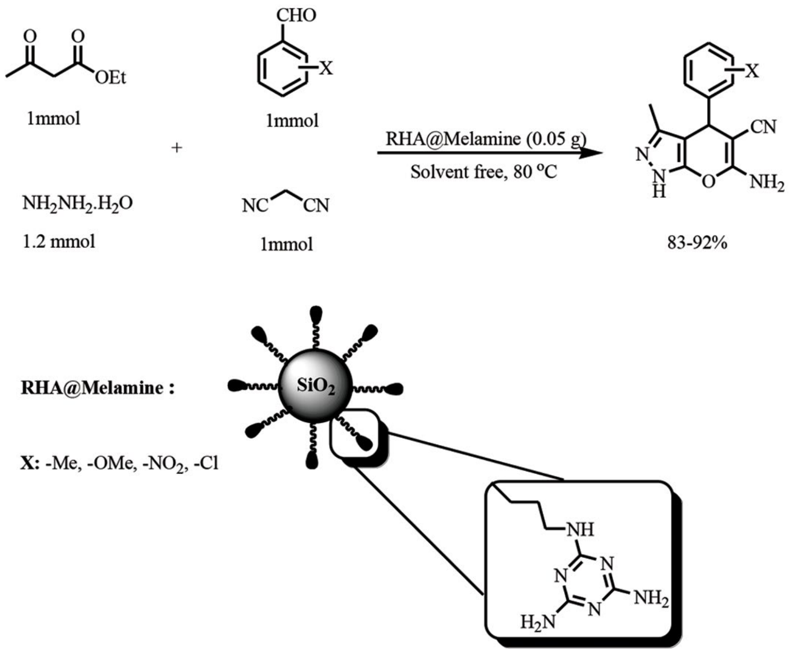
General Procedure for the Synthesis of the Pyranopyrazoles

In a 25 mL round-bottom flask, RHA@Melamine (0.05 g), hydrazine hydrate (1.2mmol), ethyl acetoacetate (1mmol) stirred for 5 min at 80°C. Then, aldehyde (1 mmol) and malononitrile (1mmol) was added and stirred the reaction mixture at the same temperature. After completion of reaction, the reaction mixture was washed with hot ethanol and the catalyst was filtered. The crude product was purified by recrystallization in aqueous ethanol to afford the pure product.

RESULT AND DISCUSSION

There were few studies regarding the preparation of silica supported basic catalyst and its application for multi-component reactions (MCRs). Herein, amorphous nanosilica was successfully extracted from rice husk (RH-SiO_2), functioned with melamine and used as a basic catalyst for the synthesis of pyranopyrazole compounds. Scheme 2 shows the schematic representation of the synthetic pathway for RHA@Melamine solid base catalyst.

The catalyst structure was demonstrated with IR spectroscopy. The FT-IR spectra of the RHA@Melamine sample is shown in Fig. 1. The strong peak at 1097 cm^{-1} is due to the asymmetric stretching vibration of the structural siloxane bond, Si-O-Si. The presenters of peaks at 466 and 771 cm^{-1} were most probably due to the symmetric and asymmetric stretching vibrations of framework and terminal Si-O groups. The characteristic peaks around 1555 cm^{-1} and 1652 cm^{-1} could be clearly observed, which were attributed to C=C, C=N is stretching vibrations of the melamine ring, respectively, and also the presence of peaks at 3332-3469 cm^{-1} is most probably due to the NH and NH_2 groups.



Scheme 2. Synthesis of RHA@Melamine.

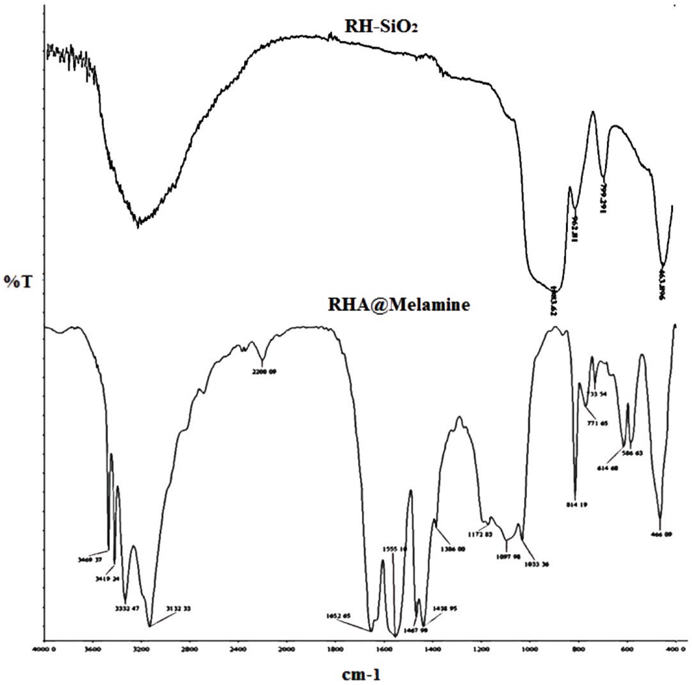


Fig. 1. FT-IR spectra of RH-SiO_2 and RHA@Melamine.

The morphological features of extracted nano silica and RHA@Melamine were studied by SEM. According to Fig. 2, samples have spherical shape with nano dimension ranging from 40-90 nm.

The thermal stability of nanocomposite was also investigated by the TGA and DTA. Weight loss through the changing temperature was measured to estimate the rate of thermal degradation. Fig. 3 indicates TGA-DTA thermogram of the RHA@Melamine composite. The thermal analysis further demonstrates that the propyl and melamine groups are successfully grafted on the RH-nanosilica structure. TGA curve demonstrated high thermal stability, with decomposition starting at around 300°C under a nitrogen atmosphere. The decomposition is complete at about 650-700°C to form the constituent inorganic oxides.

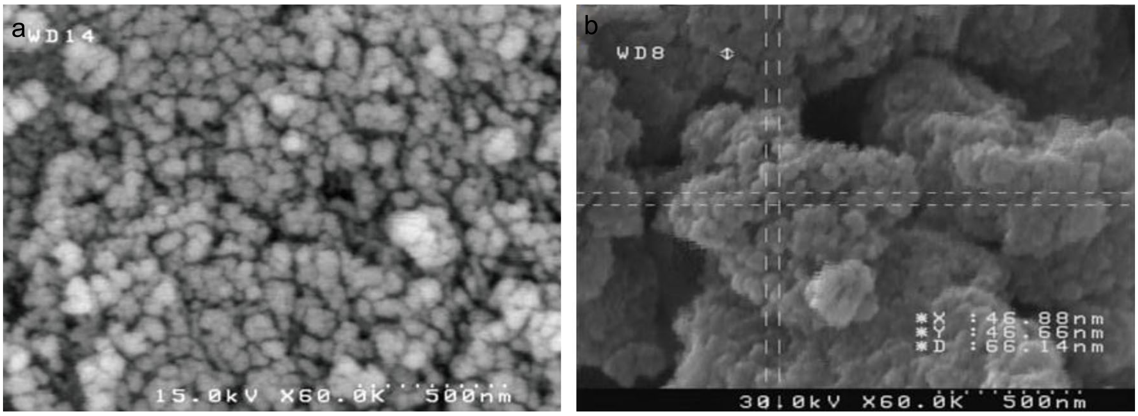


Fig. 2. SEM images of (a) RH-SiO_2 and (b) RHA@Melamine.

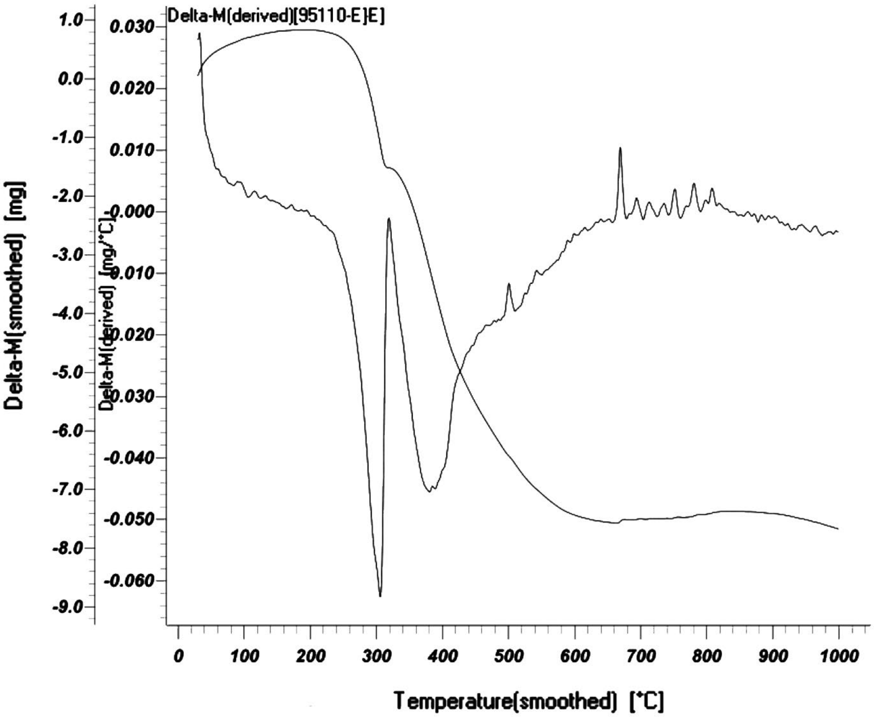


Fig. 3. TGA-DTA thermogram of the RHA@Melamine composite.

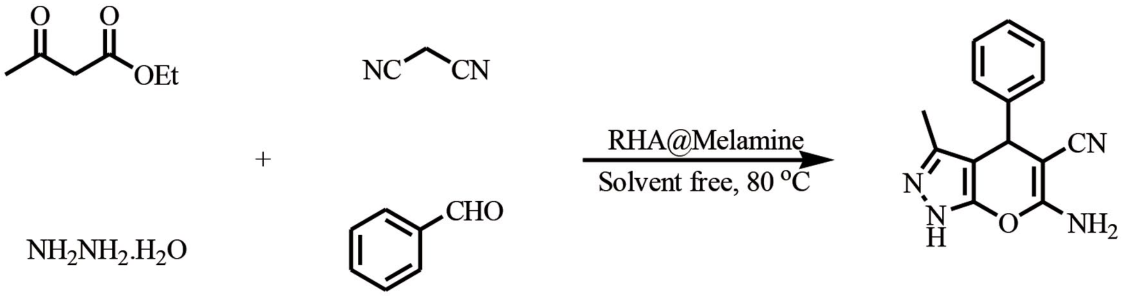
To investigate the catalytic activity of RHA@Melamine in the one-pot multicomponent synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole heterocyclic compounds, in the preliminary stage of investigation, we focused on a four-component process for the model reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile and benzaldehyde. After some experiments (Table 1), it was found that the use of hydrazine hydrate (1.2 mmol) ethyl acetoacetate (1 mmol), malononitrile (1mmol) and benzaldehyde (1mmol) in the presence of RHA@Melamine (0.05 g) under solvent-free conditions at 80°C where the best condition (Scheme 3).

To study the generality of this protocol, we extended our study with different aromatic and aliphatic aldehydes to prepare a series of pyranopyrazoles. A variety of aromatic aldehydes bearing both electron-donating groups (such as alkyl, alkoxyl, and hydroxyl) and electron-withdrawing groups (such as halide, Nitro) were reacted with ethyl acetoacetate, hydrazine hydrate and malononitrile in the presence of a catalytic amount of RHA@Melamine (0.05 g) at 80°C, in order to give the corresponding products in good to excellent yields. The results are summarized in Table 2.

The structures of products were determined from their analytical and spectral (IR,1H &13C NMR) data and by direct comparison with authentic samples. Formation of the products was also confirmed by the comparison of their melting points with the products prepared by reporting methods.

Table 1. The one-pot four component reaction of hydrazine hydrate (1.2 mmol) ethyl acetoacetate (1 mmol), malononitrile (1mmol) and benzaldehyde (1mmol) under different conditions

Entry	Solvent	T(°C)	Catalyst (g)	Time (min)	Yield (%)
1	-	25	0.05	50	55
2	-	60	0.05	40	70
3	-	80	0.05	12	91
4	-	90	0.05	12	88
5	-	100	0.05	12	88
6	-	80	0.01	50	65
7	-	80	0.03	30	80
8	-	80	0.07	15	90
9	Ethanol	Reflux	0.05	60	75
10	Acetonitrile	Reflux	0.05	60	55
11	H_2O	Reflux	0.05	60	70
12	Ethyl Acetate	Reflux	0.05	60	65



Scheme. 3. The one-pot, four-component reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile and benzaldehyde.

Table 2. The one-pot four component synthesis of 1,4-dihydropyrano[2,3-c] pyrazoles catalyzed by RHA@Melamine

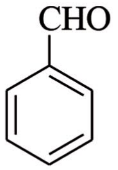
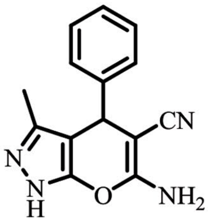
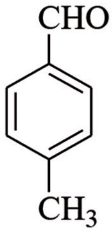
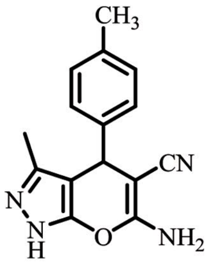
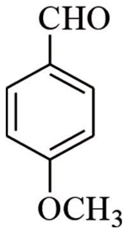
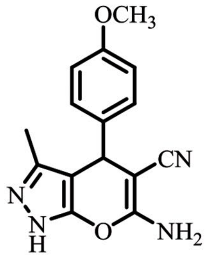
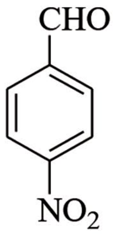
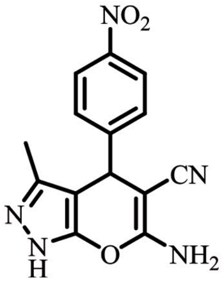
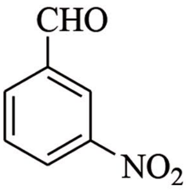
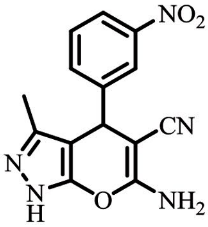
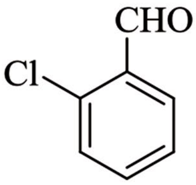
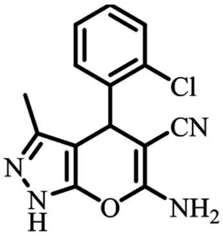
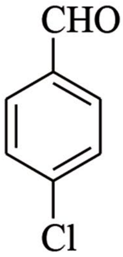
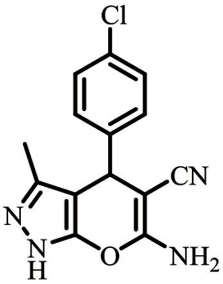
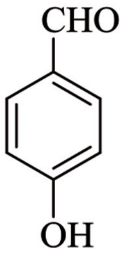
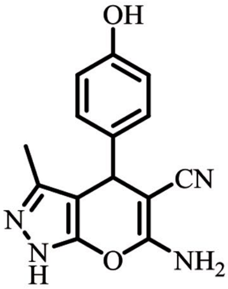
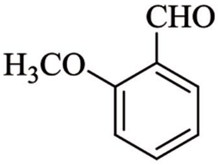
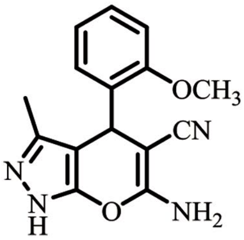
Entry	Aldehyde	Product	Time (min)	Yield (%)
a			12	91
b			18	87
c			17	90
d			10	92
e			12	89

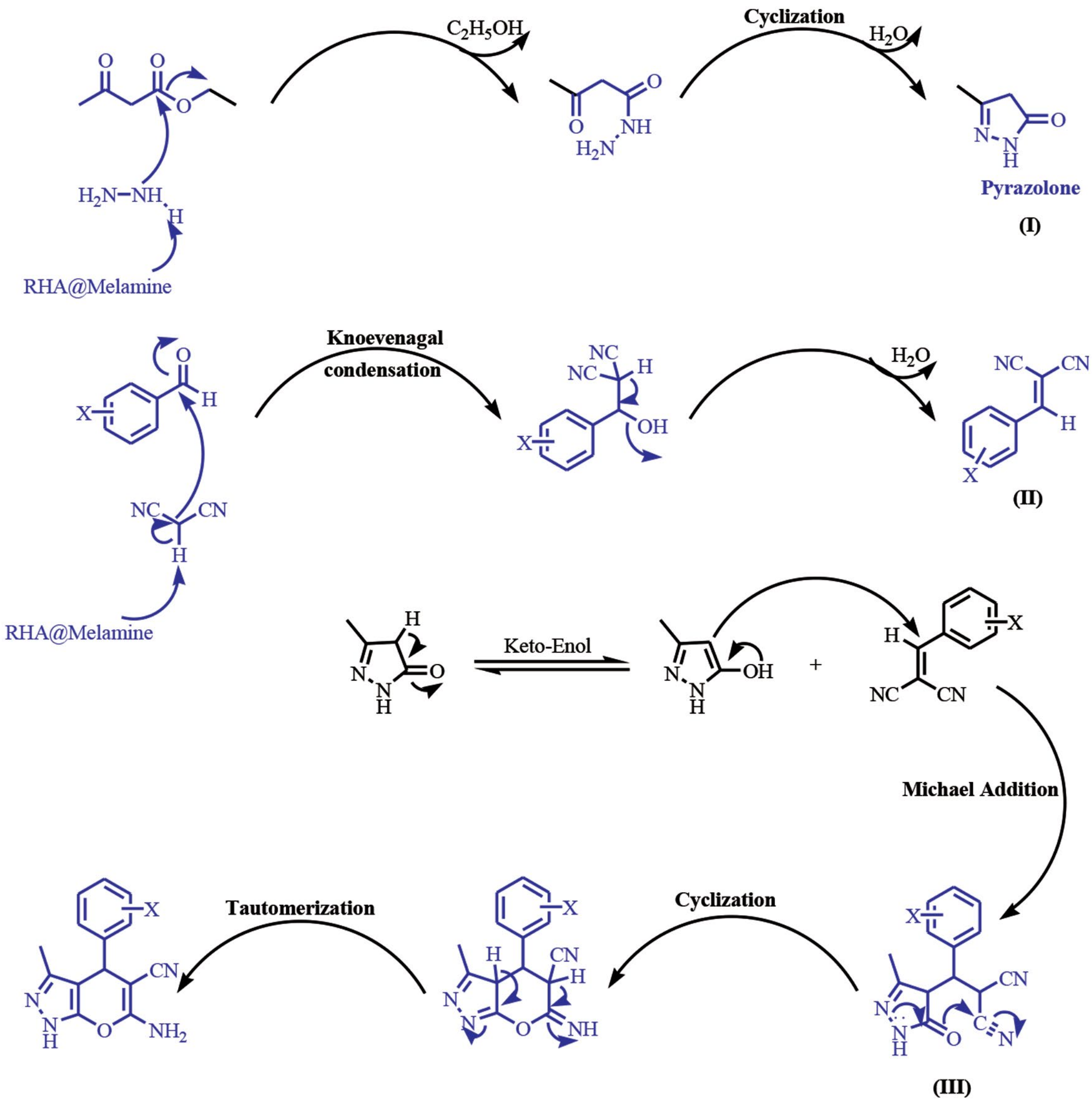
Table 2. Continued

Entry	Aldehyde	Product	Time (min)	Yield (%)
f			18	88
g			15	90
h			22	85
i			24	83

Scheme 4 shows a plausible mechanism indicating the role of the catalyst in the formation of the final product.

In order to show the merit of the presented protocol in pyranopyrazoles synthesis, we have compared the results of RHA@Melamine catalyst with some of those reported in the literature. The model reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile and benzaldehyde was considered as a representative example (Table 3).

To investigate the activity constancy of the catalyst, the catalyst was reused six times in the one-pot multicomponent condensation of benzaldehyde, malononitrile, hydrazine hydrate and ethylacetoacetate under solvent-free condition. The catalyst was magnetically recovered after each run, washed with ethanol, dried in an oven at 80°C for 10 min prior to use and tested for its activity in the subsequent run (Fig. 4). As shown in Fig. 4, smooth loss of catalytic activity of RHA@Melamine was observed.



Scheme. 4. Plausible mechanism for synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole heterocyclic compounds.

Table 3 Comparison of the efficacy of RHA@Melamine catalyst with some of those reported in the literature

Entry	Catalyst	Time (h)	Yield (%)	Ref
1	TEBA	6 h	99%	[37]
2	DBSA	3 h	88%	[38]
3	$H_4[SiW_{12}O_{40}]$	10 min	95%	[39]
4	Isonicotinic acid	25 min	90%	[40]
5	A: Cl_3COOH	5 min	80%	[41]
	B:$Ce(SO_4).4H_2O$	5 min	85%	
6	RHA@Melamine	12 min	91%	This work

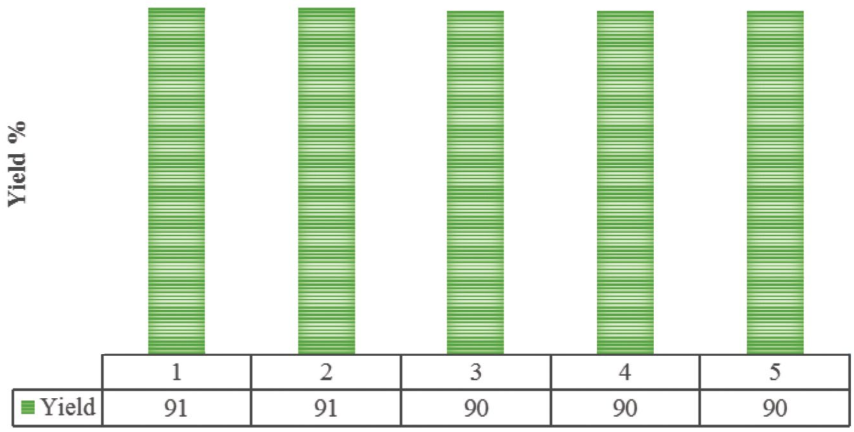


Fig. 4. Recyclability of catalyst.

CONCLUSION

In this paper, chloro propyl-functioned rice husk silica was first synthesized by the direct incorporation of chloropropyl groups through co-condensation of rice husk silica and CPTMS precursors. Melamine was then grafted onto the surface of the silica by a simple nucleophilic substitution reaction. The prepared catalyst (RH@Melamine) was characterized by physicochemical methods such as FT-IR, SEM, TGA and DTA. The catalytic activity of RH@ Melamine was studied for one-pot synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole via three-component couplings of aldehydes, hydrazine hydrate, ethyl acetoacetate and malononitrile under solvent-free conditions. The catalytic reactions proceeded with excellent yields in very short reaction times. Furthermore, high reaction rates, no side reactions, ease of preparation and handling of the catalyst, simple, mild and environmentally friendly method under solvent-free conditions open to this process suggest good prospects for its industrial applicability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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