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Nano-SiO_2/hexamethylenetetramine promoted synthesis of pyrano[2,3-*c*] pyrazoles under solvent-free conditions

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ABSTRACT

In this study, the nano-SiO_2/hexamethylenetetramine as a new basic heterogeneous nanocatalyst was prepared and used for the synthesis of pyranopyrazole *via* the four-component reaction. Various aldehydes, hydrazine hydrate, ethyl acetoacetate and malononitrile were reacted at room temperature under solvent-free and grinding conditions. The morphology and structure of nano-catalyst were investigated by techniques such as FT-IR spectroscopy, FESEM, TEM, XRD, CHNS elemental analyzer and TGA. The structure of pyranopyrazoles was determined by spectroscopic data of FTIR and NMR. The principal affairs of this procedure are easy work-up, high yields, mild conditions and short reaction times.

Keywords: *Nano-SiO_2/hexamethylenetetramine, Multicomponent reactions, Pyrano[2,3-c]pyrazole, Basic nanocatalyst, Reusable catalyst.*

1. Introduction

Multicomponent reactions (MCRs) have selectivity, simplicity and effectiveness compared with the conventional multistep synthesis [1,2]. For economic reasons and preventing environmental pollution, solvent-free methods are used to correct classical methods for the synthesis of materials in a clean and safe condition [3-5].

In recent years, the use of heterogeneous catalysts has received great consideration in the organic synthesis because of its easy separation [6,7]. Nano sized solid-supports such as SiO_2 and Al_2O_3 have possessed very attention owing to their versatile physical surface [8].

Hexamethylenetetramine (HMTA) is known as a basic material with antibacterial property [9]. It is mainly applied as the curing agent of plastic, resin and chloramphenicol synthesis in the pharmaceutical industry [10].

Pyranopyrazole have drawn high importance due to their biological, pharmaceutical and agrochemical activities such as analgesic [11,12], antitumor [13], antimicrobial [14], antiinflammatory [15-17], antiplatelet [18], vasodilator [19], molluscicidal [20], human Chk1 kinase inhibitoring [21], anticancer [22] and cholinesterases inhibitory activity [23]. The most general procedure for synthesis of pyranopyrazole is the multi-component reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile and aldehyde. Recently, several catalysts such as per-6-amino-β-cyclodextrin (per-6-ABCD) [24], molecular sieves [25], cetyltrimethyleammonium chloride (CTACl) [26], isonicotinic acid [27], morpholine triflate (MorT) [28], γ-alumina [29], glycine [30], ionic liquid [31], meglumine [32], triethylamine [33], $Ba(OH)_2$ [34], urea [35], SnO_2 quantum dots [36] and β-Cyclodextrin-epichlorohydrin [37], triethylamine [38,39], DABCO [40], Fe_3O_4@SiO_2-HMTA-SO_3H [41] have been used for this reaction. In this work, we have synthesized and characterized nano-SiO_2/hexamethylenetetramine (Nano-SiO_2/HMTA) as a novel basic heterogeneous nano-catalyst. Nano-SiO_2/HMTA was used for the synthesis of pyrano[2,3-*c*]pyrazole via the four-component reaction of aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate.

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2. Experimental

2.1. General

All compounds were purchased from Merk, Aldrich and Fluka chemical companies and used without any additional purification. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 and DRX-250 Avance) NMR was used to record the ^{1}H NMR and ^{13}C NMR spectra. X-ray diffraction (XRD) pattern was obtained by a Philips Xpert MPD diffractometer equipped with a Cu Kα anode (k = 1.54 Å) in the 2θ range from 5 to 80°. Field Emission Scanning Electron Microscopy (FESEM) and Transmission Electon Microscopy (TEM) images of catalysts were obtained on a Mira 3-XMU and Philips CM120 with a LaB6 cathode and the accelerating voltage of 120 Kv, respectively. The Elemental analyses (C,H,N,S) were performed by the Elemental Vario EL analyzer.

2.2. Preparation of nano silica chloride

In a good-ventilated system, thionylchloride (4 mL) was added dropwise to nano-silicagel (1g) in a round-bottomed flask. The mixture was stirred for 48 hours under reflux conditions. Then, the suspension obtained is filtered, washed with dichloromethane and dried at room temperature. This silica chloride can be stored for months without decreasing its activity [42].

2.3. Preparation of nano-SiO_2/HMTA

In a round-bottomed flask, a mixture of nano Si-Cl (0.5 g), HMTA (0.5 g) and 1,2 dichloroethane (5 mL) was added. Then, the mixture was stirred for 15 hours at room temperature. The product was filtered, washed with dichloromethane and dried at room temperature.

2.4. General procedure for synthesis of pyrano [2,3-c]pyrazole derivatives

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) in the presence of nano-SiO_2/HMTA (0.04 g) was ground at room temperature under solvent-free conditions. The progress of reaction was monitored by TLC (*n*-hexane: EtOAc, 4:1). After completion of the reaction, the reaction mixture was dissolved in hot ethanol. The catalyst was separated by adding hot ethanol and then filtered. Subsequently by adding water to the filtrate, the product was appeared as a pure solid.

3. Results and Discussion

Nano-SiO_2/HMTA was prepared in a two-step reaction. First, nano silica chloride (Si-Cl) was synthesized from the reaction of nano silica-gel and thionylchloride under reflux conditions, then, the nano silica chloride was used for the synthesis of nano-SiO_2/HMTA. The heterogeneous basic catalyst, nano-SiO_2/HMTA, is characterized by FT-IR, FESEM, TEM, XRD, TGA and CHNS analysis. The FT-IR spectra of HMTA, nano-SiO_2, and nano-SiO_2/HMTA are shown in Fig. 1. In the FT-IR spectrum of nano-SiO_2/HMTA (Fig. 1(c)), the signal relating to the Si-N stretching vibrations appeared at 815 cm^{-1}.

The existence of each element in the structure of the nano-SiO_2/HMTA was proved by the CHNS analysis. The percentage of N, C and H in catalyst are 4.40, 5.39 and 0.716 respectively. The particles size of nano-SiO_2 and nano-SiO_2/HMTA were investigated by the field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM). According to FESEM and TEM, the particle size for nano-SiO_2 and nano-SiO_2/HMTA are 20 nm and 70 nm respectively (Figs. 2 and 3). The XRD patterns of nano-SiO_2 and nano-SiO_2/HMTA are shown in Fig. 4. By comparing them, it can be found that in 2θ equal to 23, a broad signal is seen in the nano-SiO_2 pattern, it also appeared in nano-SiO_2/HMTA pattern. The HMTA is an organic compound and cannot be determined using the XRD spectrum. To investigate the thermal stability of nano-SiO_2/HMTA, the thermo-gravimetric analysis (TGA) of catalysts was done in a range of 45-813 ℃ (Fig. 5). According to the TGA curve, at 150-300 ℃, about 10 % of the catalyst weight decreased. According to the DTA curve, an endothermic process was acquired at 150-300 ℃. The first region displayed a mass loss that was attributed to the loss of adsorbed solvent or trapped water from the catalyst. This catalyst is stable till 150 ℃ and is suitable for promotion of some organic reactions.

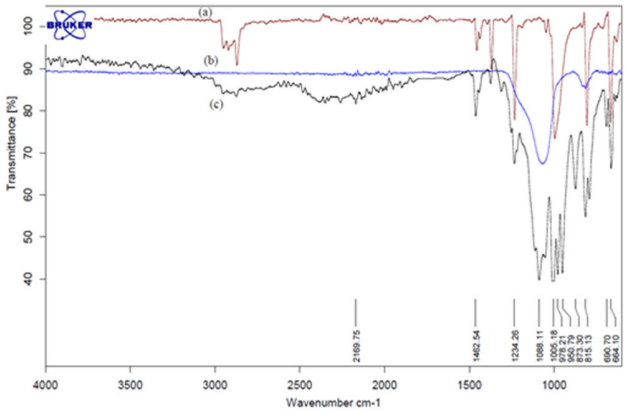


Fig. 1. FT-IR spectra of (a) HMTA, (b) Nano-SiO_2 and (c) Nano-SiO_2/HMTA.

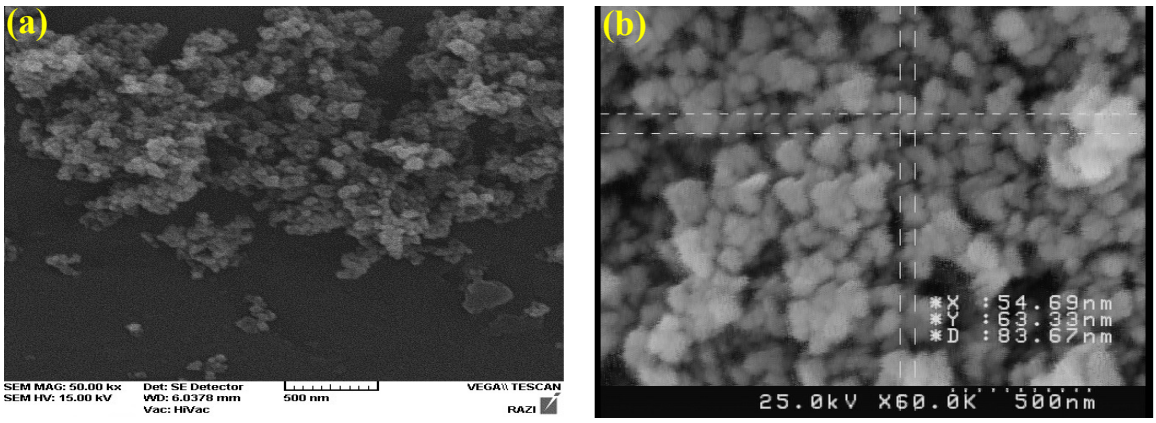


Fig. 2. FESEM image of a) Nano-SiO_2 and b) Nano-SiO_2/HMTA.

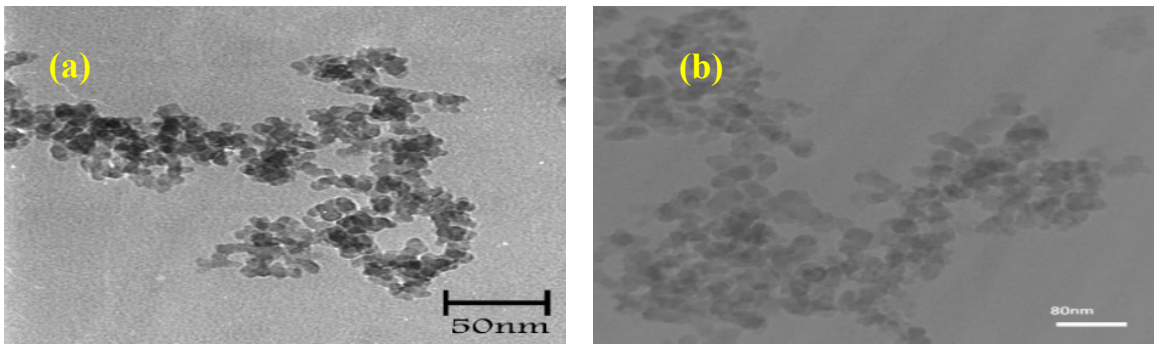


Fig. 3. TEM image of a) Nano-SiO_2 and b) Nano-SiO_2/HMTA.

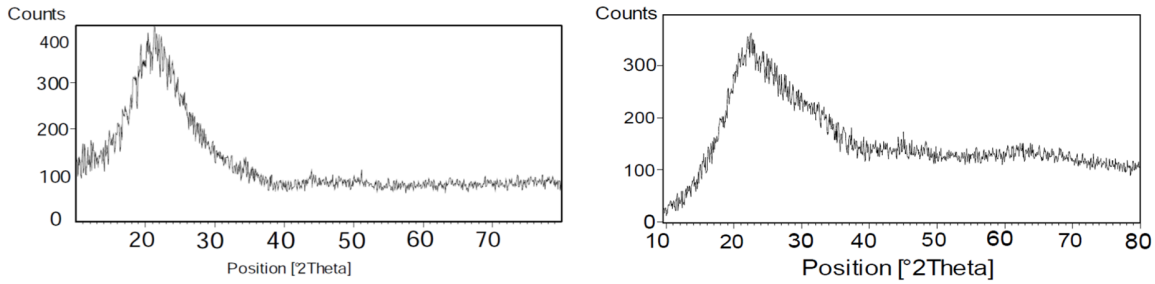


Fig. 4. XRD image of a) Nano-SiO_2 and b) Nano-SiO_2/HMTA.

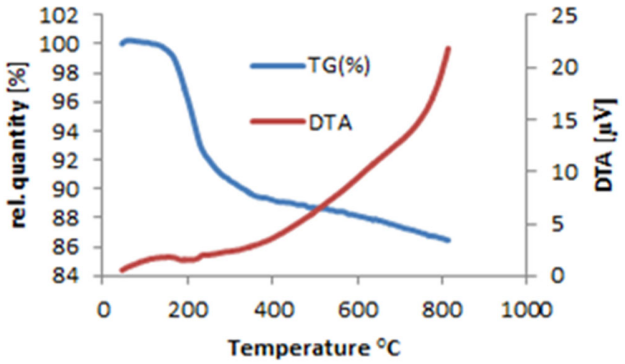
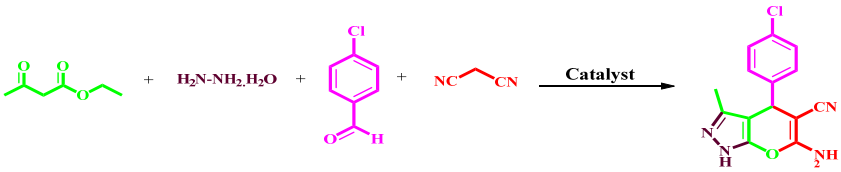


Fig. 5. Thermal gravimetric analysis pattern of nano-SiO_2/HMTA.

The catalytic activity of nano-SiO_2/HMTA was investigated for the synthesis of pyrano[2,3-*c*] pyrazole derivatives via one-pot four- component reactions of aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate. In order to optimize the reaction conditions, initially, the condensation among 4-chlorobenzaldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate, as a model reaction, was investigated in the presence of various conditions (Table 1). In the best reaction condition, we used 0.04 g of the catalyst for 1 mmol of any substrates under solvent-free grinding conditions (Table 1, Entry 2).

Table 1. The comparison among yields of model reaction under various catalysts and conditions.[a]



Entry	Catalyst (mol % or g)	Solvent	Conditions	Time (min)	Yield (%)[b]	Ref.
1	Nano-SiO_2/HMTA (0.04)	EtOH	r.t.	45	85	-
2	Nano-SiO_2/HMTA (0.04)	-	r.t., grinding	20	97	-
3	Nano-SiO_2/HMTA (0.04)	EtOH/H_2O	r.t.	20	72	-
4	Nano-SiO_2/HMTA (0.04)	H_2O	r.t.	50	75	-
5	Nano-SiO_2/HMTA (0.06)	-	r.t., grinding	15	89	-
6	Nano-SiO_2/HMTA (0.02)	-	r.t., grinding	30	75	-
7	CTACl (20 mol %)	H_2O	90 °C	240	88[24]	[26]
8	Isonicotinic acid (10 mol %)	-	85 °C	10	90[25]	[27]
9	MorT (10 mol %)	EtOH/H_2O	Reflux	540	92[26]	[28]
10	γ-Alumina (30 mol %)	H_2O	Reflux	35	90[27]	[29]
11	$Ba(OH)_2$ (10 mol %)	H_2O	Reflux	90	93[32]	[34]
12	Meglumine (10 mol %)	EtOH/H_2O	r.t.	15	95[30]	[32]
13	Nano MgO	Acetonitrile	r.t.	5	97[35]	[43]
14	Et_3N[c]	-	grinding	5	82[36]	[44]

[a]One mmol of any substrate was used.
[b]Isolated yields after recrystallization from ethanol.
[c]4-bromobenzaldehyde was used.

According to the best condition obtained, several pyranopyrazole derivatives were synthesized and the results are summarized in Table 2. The structure of these products was identified by physical and spectroscopic data such as the melting point, FT-IR, ^{1}H NMR and ^{13}C NMR. In addition, the reusability of the catalyst was studied on the model reaction. After completing the reaction, the catalyst was separated from products, washed with hot ethanol and reused in the model reaction three times without a significant loss of its catalytic activity.

A mechanism proposed for the synthesis of pyrano [2,3-*c*]pyrazole derivatives in the presence of nano-SiO_2/HMTA is displayed in Scheme 1. Initially, the reaction of ethyl acetoacetate and hydrazine hydrate formed pyrazolone as an intermediate (3). Then, the Knoevenagel condensation between aromatic aldehyde and malononitrile, in the presence of catalyst produced the compound 6. Finally, In the presence of nano-SiO_2/HMTA, Michael addition reaction between 3 and 6, intramolecular cyclization, and aromatization, leads to pyrano[2,3-*c*]pyrazole.

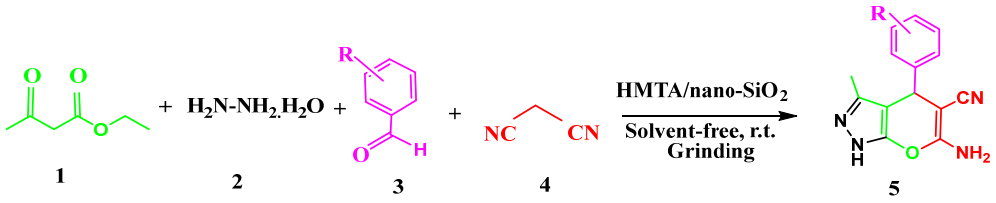
4. Conclusions

In this research, we have synthesized and characterized nano-SiO_2/HMTA as a heterogeneous new basic catalyst. This catalyst was used for synthesis of pyrano[2,3-*c*] pyrazoles under grinding conditions at room temperature *via* the condensation of hydrazine hydrate, ethyl acetoacetate, malononitrile and aromatic aldehyde. This method includes some main advantages such as solvent-free conditions, good to excellent yields, room temperature, short reaction time, non-toxic, easy workup and reusability of catalyst.

Acknowledgements

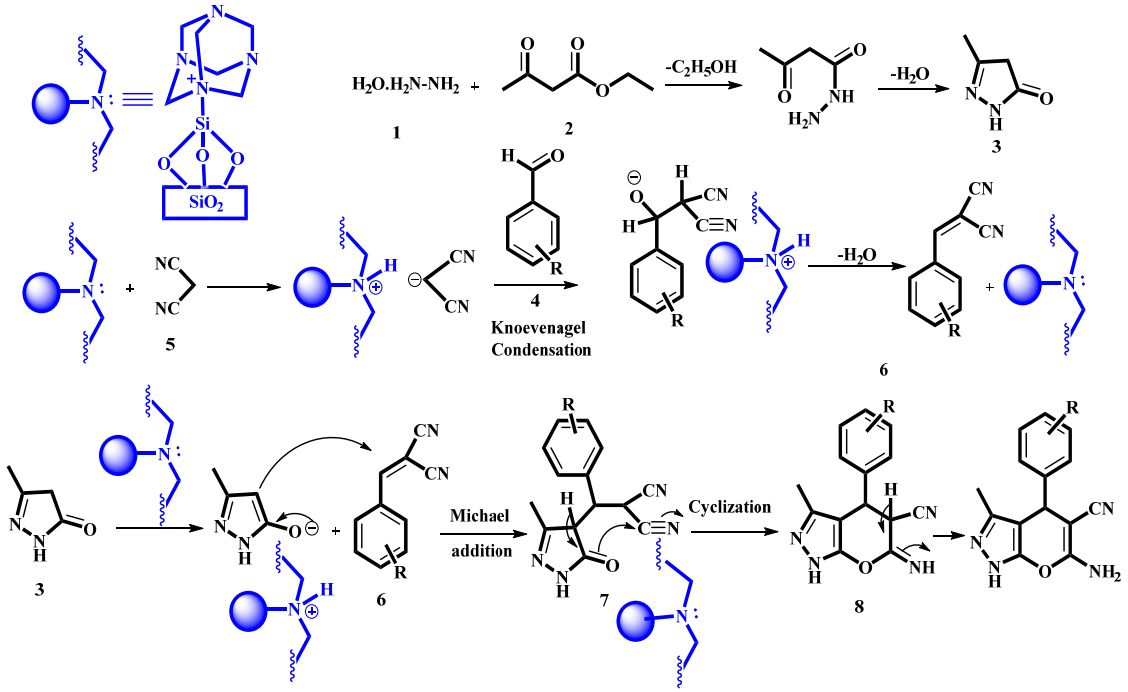
The Research Council of Yazd University gratefully acknowledged for the financial support for this work.

Table 2. Synthesis of pyrano[2,3-*c*] pyrazole derivatives (5a-m) in the presence of nano-SiO_2/HMTA under solvent-free conditions at room temperature.[a]



Entry	R	Product	Time (min)	Yield (%)[b]
1	4-Cl	5a	20	97
2	2-Furyl	5b	30	72
3	Ph	5c	40	94
4	2-OMe	5d	75	70
5	2,4-$(Cl)_2$	5e	35	80
6	3-NO_2	5f	25	75
7	3,4-$(OH)_2$	5g	45	82
8	4-OH	5h	30	70
9	4-OH-3-OCH_3	5i	50	80
10	4-CH_3	5j	75	81
11	4-NO_2	5k	20	73
12	4-Br	5l	10	80
13	4-F	5m	40	83

[a]1 mmol of 1,2,3,4 and 0.04 g of catalyst were used.
[b]Isolated yields after recrystallization from ethanol.



Scheme 1. A mechanism proposed for the synthesis of pyrano[2,3-*c*]pyrazole derivatives.

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