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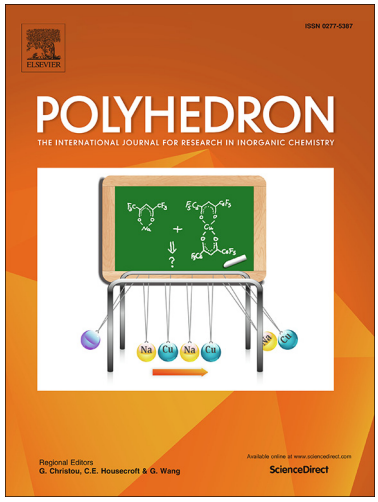

Efficient One-Pot Synthetic Methods for the Preparation of 3,4-Dihydropyrimidinones and 1,4-Dihydropyridine Derivatives using $BNPs@SiO_2(CH_2)_3NHSO_3H$ as a Ligand and Metal Free Acidic Heterogeneous Nano-catalyst

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Efficient One-Pot Synthetic Methods for the Preparation of 3,4-Dihydropyrimidinones and 1,4-Dihydropyridine Derivatives using BNPs@$SiO_2(CH_2)_3NHSO_3H$ as a Ligand and Metal Free Acidic Heterogeneous Nano-catalyst

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Abstract

Heterocyclic compounds with biological and pharmacological activates like 3,4-dihydropyrimidin-2-(1H)-ones and 1,4-dihydropyridines have attracted great interest. Boehmite nanoparticles functionalized with silylpropyl sulfamic acid (BNPs@$SiO_2(CH_2)_3NHSO_3H$) as a metal free and environmentally friendly catalyst has been found to be effective for the one pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and the preparation of 1,4-dihydropyridines derivatives. Some features of this protocol are low cost and available materials, short reaction times, convenient catalyst separation, and no need for a neutral atmosphere. Moreover, the catalyst can be reused for at least five times with only a 7% reduction in yield. This study also shows that BNPs@$SiO_2(CH_2)_3NHSO_3H$ is a sustainable, recoverable and effective heterogeneous catalyst for multicomponent reactions.

Keywords: Boehmite; Acidic heterogeneous nano-catalysts; Biginelli reaction; 1,4-Dihydropyridines.

1. Introduction

In recent years, one of the most important disciplines in synthetic and pharmaceutical chemistry is the chemistry of heterocyclic compounds [1-3]. Today, science and technology have changed to develop eco-friendly and cost-effective methods. To this end, the development of one-pot multi-component reactions under solvent-free conditions and design and synthesis of stable, active, cost-effective and recyclable heterogeneous nano-catalysts are increasingly needed. In addition, one-pot Multicomponent reactions (MCPs) are nowadays highly regarded in organic and medicinal chemistry not only for their time saving, reduce chemical waste,

pot/atom and step economy and higher yields but also, for ease of product separation and purification [4-9].

In the past several years, the functionalized dihydropyrimidone compounds (DHPMs) have known for their multipurpose usages in nature products, chemical building blocks, pharmacy and therapeutic activities such as antiviral, anti-tumor, antibacterial. and anti-inflammatory [10-14], as mitotic kinesin inhibitors [15], antihypertensive agents [16, 17], neuropeptide Y (NPY) antagonists [18], calcium channel blockers [14, 19, 20], as an useful organic intermediates [21, 22] and as a key component in several alkaloids with marine sources. The batzelladine alkaloids including the DHPM structure is a strong HIVgp-120-CD4 inhibitor [13, 23]. Some of these compounds with biological applications were presented in the Fig. 1.

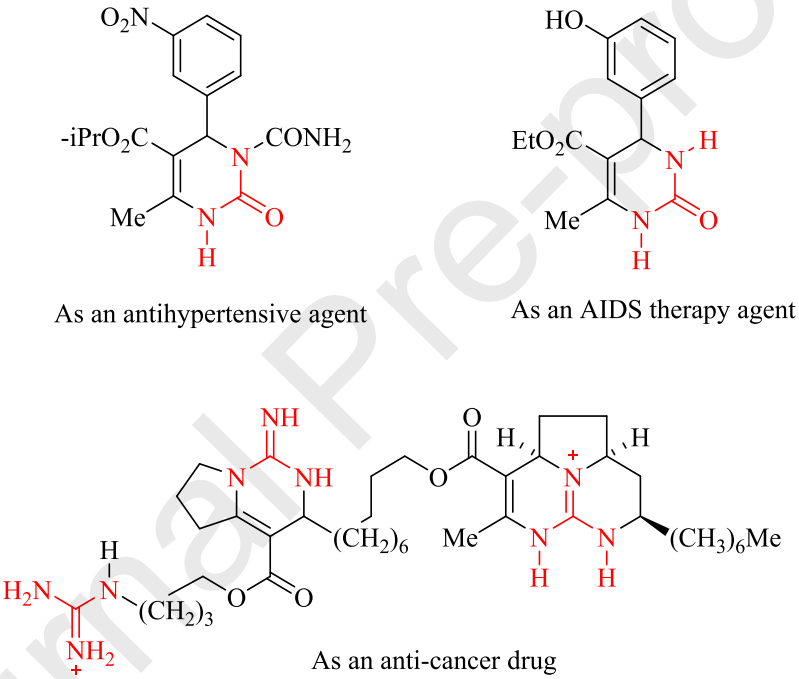


Fig. 1. Examples of biologically active DHPMs

For the first time, in 1893, Italian chemist Pietro Biginelli [14] reported the simple one-pot three component cyclocondensation synthesis of ethyl acetoacetate, benzaldehyde and urea under acidic conditions [24]. In the traditional Biginelli conditions, due to the use of strong acid catalysts, the purification of the products was difficult and the yields were low [25]. In addition, high temperatures, stoichiometric use of catalysts, costly reagents, environmental pollution and long reaction times are the operational drawbacks of the classical protocols [26, 27]. Ionic liquids [28, 29], ultrasound irradiation [30], H_3BO_3 [31], VCl_3 [32], nanomagnetic supported sulfonic acid [33], $KAl(SO_4)_2$-$12H_2O$ supported on silica [34], SiO_2-$CuCl_2$ [35],

(MWCNTs) [36, 37], boehmite nanoparticles [38], graphite [39], silica–sulfuric acid [40], $Mn(OAC)_3$-$2H_2O$,[41] $Ce(NO_3)_3$-$6H_2O$ [42], ytterbium chloride [43] and graphene oxide [44] are some of the different catalysts were used for modified Biginelli reactions.

To resolve the problems of previous methods, nowadays, many approaches have been reported for the synthesis of DHPMs, which in most cases have been attempted to minimize the dangerous reaction conditions and improve the catalyst separation from the reaction medium.

1,4-dihydropyridine compounds (1,4-DHPs) have gained special prominence among researchers due to the widespread use of these compounds in the biological and pharmaceutical fields, such as calcium blocker agents in heart disease, anti-tumour [45], antidiabetic agents [46], antihypertensive [47], antianginal [48], antimicrobial [49] and drugs to treat many other diseases [50] (Fig. 2). Also 1,4-dihydropyridines with optical activity used as valid precursors in various chiral N-heterocycles [51]. More than a century ago, 1,4-DHPs are synthesized by Hantszch, *via* cyclocondensation of aldehyde, *β*-ketoester, and ammonia in EtOH refluxing for a long time [52].

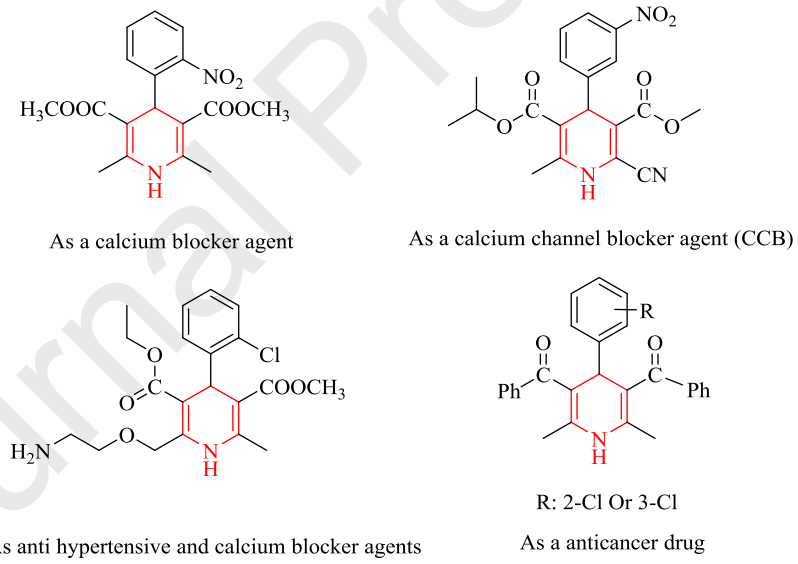
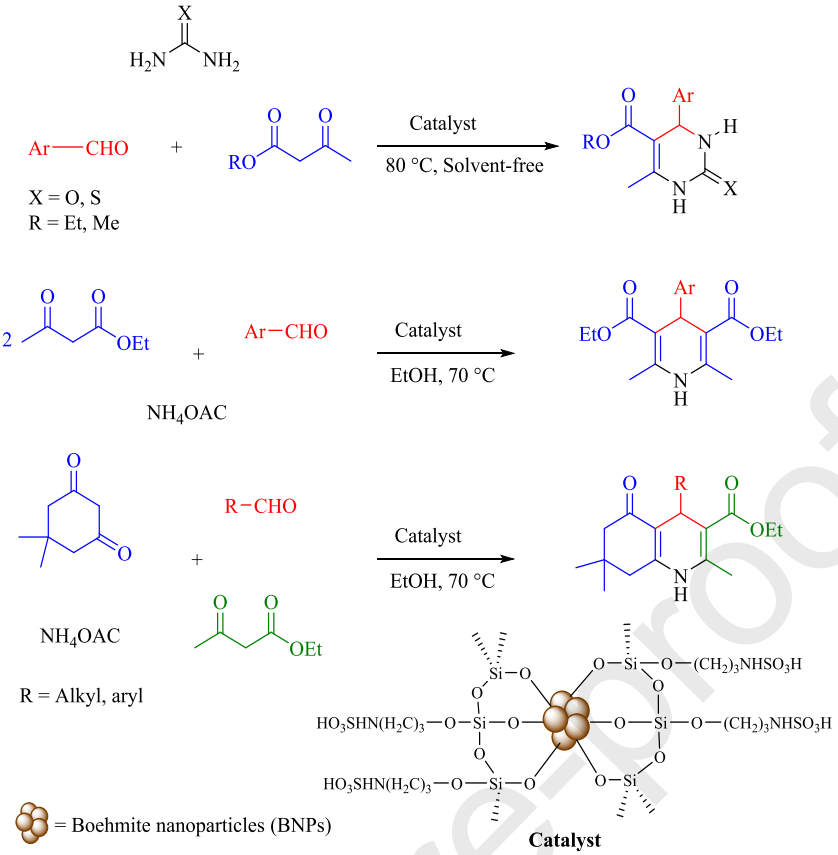


Fig. 2. Examples of biologically active 1,4-dihydropyridine compounds

In the last decades, many researchers have attempted to expand more efficient approaches for the preparation of 1,4-DHPs, because the traditional methods had disadvantages such as the use of strong, toxic and corrosive acids, high temperatures, prolonged reaction times, toxic solvents, low to moderate yields, difficult to work up and tedious reaction conditions.[53, 54] Since in most of the reported methods in the scientific literature, catalysts have been non-recyclable, the development of novel, inexpensive and renewable heterogeneous nano-catalysts

is a fundamental issue. In between, solid-phase catalysts are of particular interest because they have higher yields, easier product purification, catalyst recovery and easier catalytic separation from the environment which form an economic approach for the multi-component reactions. Among various supports, boehmite nanoparticles (BNPs) (γ-AlOOH) is attractive solid-phase catalyst because boehmite has remarkable merits containing high specific surface area, ease of modification due to the many hydroxyl groups on the surface, mechanical, thermal and chemical stability, cheap and commercially available precursors, high dispersity and air and moisture insensibility.

Aiming to develop green chemistry and improve the synthetic methods for the preparation of heterocyclic compounds, in this approach, we introduced a useful acidic metal and ligand free catalyst (BNPs@$SiO_2(CH_2)_3NHSO_3H$**)** for the solvent-free one-pot multicomponent synthesis of DHPMs from reaction of divergent aldehydes with 1,3-dicarbonyl compounds and urea/thiourea at 80 °C with decent yields as well as the one-pot atom-economic multicomponent preparation of 1,4-DHP derivatives *via* condensation reactions of various aldehydes, 1,3-dicarbonyl compounds and ammonium acetate at 70 °C in MeOH with efficient catalytic performance (Scheme 1).



Scheme 1. Synthesis of DHPMs and 1,4-DHPs using BNPs@$SiO_2(CH_2)_3NHSO_3H$ as a catalyst

2. Experimental

This nano-catalyst (BNPs@$SiO_2(CH_2)_3NHSO_3H$) was synthesized according to previously reported procedure [55].

2.1. General

Yields refer to isolated products. The purity of the products and the progress of the reactions were accomplished by TLC. Melting points were determined by a Stuart Scientific SMP2 apparatus. The FT-IR spectra were recorded on Perkin-Elmer 683 spectrometer using pressed KBr pellets. The materials were purchased from Merck Company and used without any purification. TEM and SEM recorded using a TESCAN, Model: MIRA3. X-ray powder diffraction (XRD) was performed on a PANalytical Company X'Pert Pro MPD diffractometer. Thermogravimetric analyis (TGA) was carried out using a STA PT-1000 Linseis (Germany) in the temperature range of 25– 800 °C at a heating rate of 10˚C min^{-1}, under air atmosphere. All yields refer to isolated products after purification by EtOH.

2.2. General Procedure for the Preparation of 3,4-Dihydropyrimidon-2-(1H)-ones using BNPs@SiO$_2$(CH$_2$)$_3$NHSO$_3$H

In a round bottom flask, a mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and BNPs@SiO$_2$(CH$_2$)$_3$NHSO$_3$H (0.05 g, containing 0.07 mmol SO$_3$H) was heated at 80 °C under solvent-free conditions for the appropriate time. When the reaction was complete as monitored by TLC (*n*-hexane/ethyl acetate: 6/4), ethanol was added to the mixture and it was stirred for 5 min at 80 °C. Then, the catalyst was removed by simple filtration. After evaporation of the solvent corresponding product was obtained and further purification was carried out by crystallization in hot ethanol.

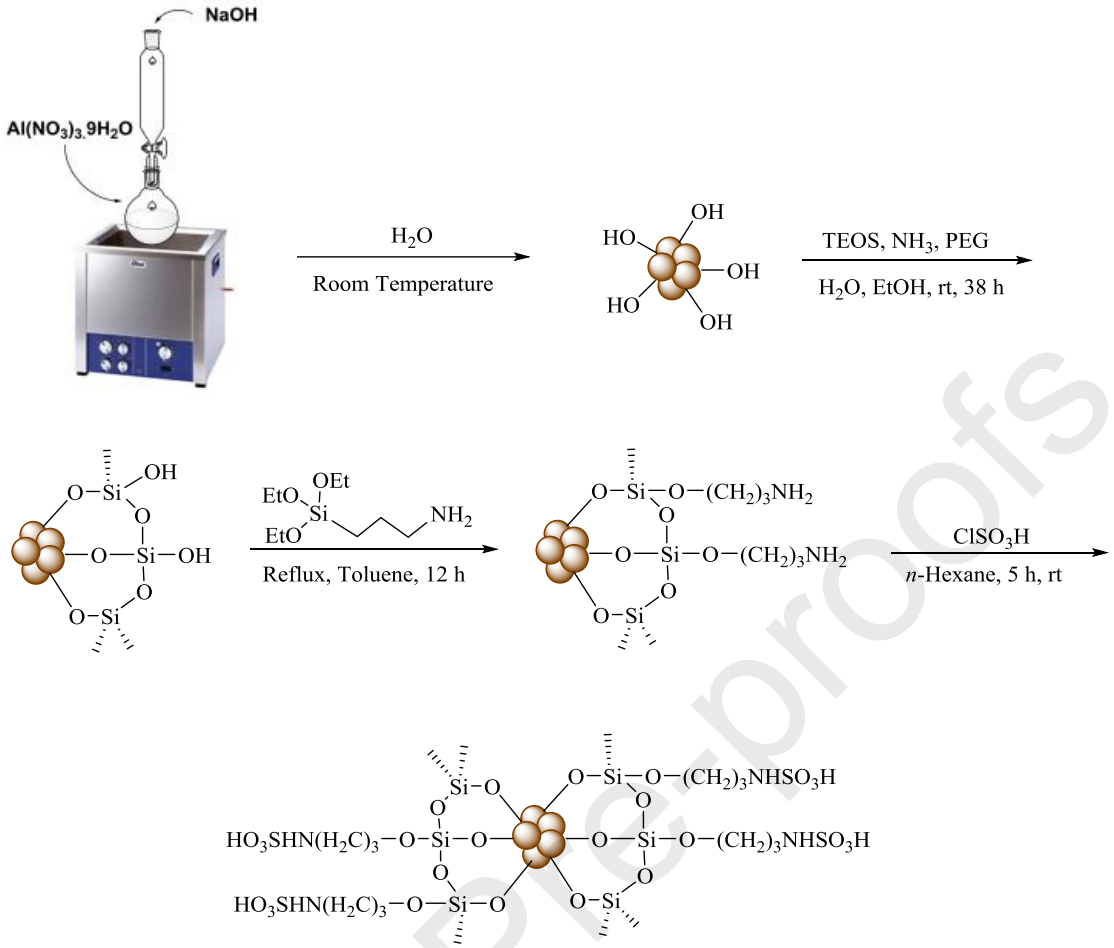
3.3. General Procedure for the Synthesis of 1,4-Dihydropyridines using BNPs@SiO$_2$(CH$_2$)$_3$NHSO$_3$H

A mixture of the aldehyde (1 mmol), 1,3-dicarbonyl compounds (2 mmol) and ammonium acetate (1.5 mmol) in the presence of BNPs@SiO$_2$(CH$_2$)$_3$NHSO$_3$H (0.06 g, containing 0.08 mmol SO$_3$H) was heated at 70 °C in EtOH (7 mL) as a solvent. The progress of the reaction was monitored by TLC (eluent: EtOAc: *n*-hexane = 3/7)). After completion of the reaction, the mixture was cooled to room temperature and then ethanol was added to the resulting mixture and the catalyst was isolated by filtration. After evaporation of solvent, solid product was obtained and recrystallized from ethanol to give the pure products in excellent yields.

3. Results and discussion

3.1. Catalyst characterization

Following the successful synthesis of the BNPs@SiO$_2$(CH$_2$)$_3$NHSO$_3$H and its use for the selective oxidation of sulfides in the previous work, we found this to be a stable and efficient nano-catalyst for the synthesis of heterocyclic compounds including DHPMs and 1,4-DHPs.
The boehmite nanoparticles were synthesized according to the method described in the literature [55, 56] The schematic pathway for the preparation of sulfonic acid-modified silica-coated BNPs are depicted in Scheme 2.



Scheme 2. The schematic route for synthesis of BNPs@$SiO_2(CH_2)_3NHSO_3H$

Catalyst was well identified using different methods including FT-IR, EDX, XRD, mapping, TEM, SEM, TGA-DTA analysis and *p*H analysis.

The bonding of different groups onto the catalyst surface and catalyst synthesis were investigated step by step by the IR technique. FT-IR spectra of a) BNPs b) BNPs-TEOS, c) BNPs@$SiO_2(CH_2)_3NH_2$ and d) BNPs@$SiO_2(CH_2)_3NHSO_3H$ are depicted in Fig. 3. As can be seen, all peaks appearing in Fig. 3a for BNPs are repeated in Fig. 3b, with a slight change in frequency which is due to the grafting of TEOS to the boehmite surface. In addition, in all spectra (Fig. 3a-d), the peaks appearing in 424, 511, 636 and 778 cm^{-1} are related to the Al-O stretching frequency and also the strong peak in 1000-1300 cm^{-1} is related to the hydrogen bond (OH…OH) between the boehmite plates and asymmetric and symmetric stretching vibration of the Si-O-Si band buried below this peak.[55, 57] As can be seen in Fig. 3a,b, OH bending adsorption and OH stretching adsorption appeared in 1605, 1625 cm^{-1} and 3370-3580 cm^{-1} respectively. It should be noted that all Al-O peaks shift to lower frequencies after binding

the acidic groups to the BNPs@$SiO_2(CH_2)_3NH_2$ surface and OH bending frequency shift to higher frequency, which collaborates the successful synthesis of the catalyst.

Also, broad adsorption in 3000–3500 cm^{-1} is prone to the successful attachment of the SO_3-H groups to the catalyst surface [55]. However, in the 3100 to 3500 region, in addition to the acidic groups, there is also the possibility of non-functionalized hydroxyl groups of boehmite.

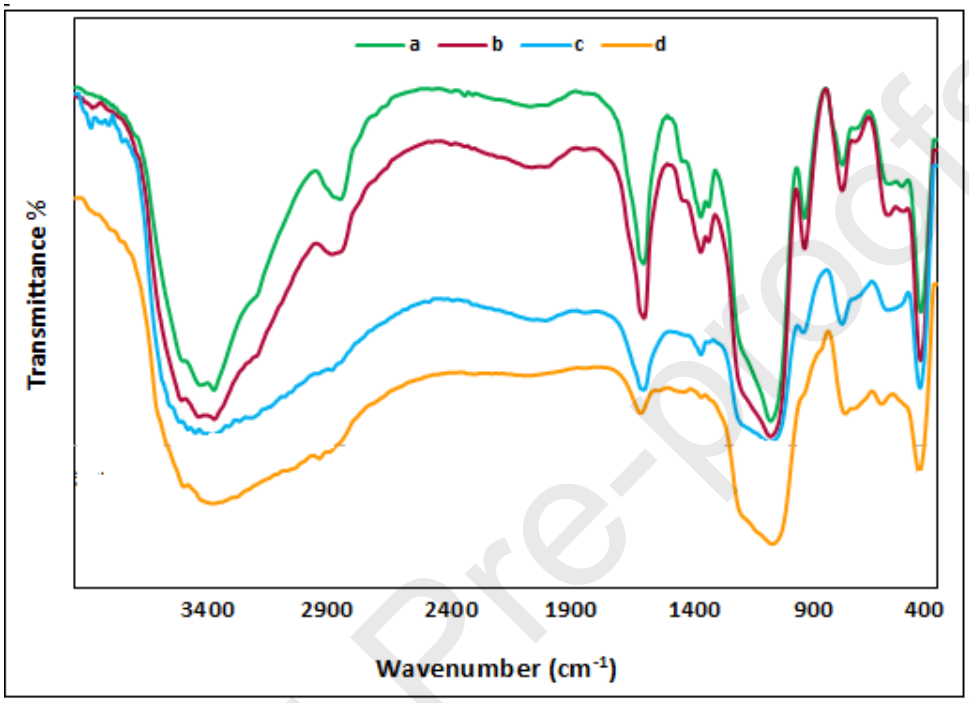


Fig. 3. FTIR spectra of a) BNPs, b) BNPs-TEOS, c) BNPs@$SiO_2(CH_2)_3NH_2$ and d) BNPs@$SiO_2(CH_2)_3NHSO_3H$

TEM and SEM analyzes were used to obtain accurate information on the morphology and particle size of the BNPs@$SiO_2(CH_2)_3NHSO_3H$. According to Fig. 4a, the morphology of acidic boehmite is nearly orthorhombic [8] and the particles are irregularly dispersed and there is little accumulation which is common in bohemite nanoparticles due to hydrogen bonding between the plates. The average particle size of BNPs@$SiO_2(CH_2)_3NHSO_3H$ is between 10-40 nm.

Also, the structure and particle size of the boehmite and BNPs@$SiO_2(CH_2)_3NHSO_3H$ were investigated by SEM, the results of which are in agreement with the obtained results from TEM. SEM images of boehmite and BNPs@$SiO_2(CH_2)_3NHSO_3H$ are shown in Fig. 4b-c. The morphology of the initial boehmite is irregular and accumulates due to the many hydroxyl groups on the boehmite surface (Fig. 4b). It is worth mentioning that, the particle size in the nano-catalyst is between 15-40 nm, which corroborates the particle size obtained from TEM

(Fig. 4c). It is worth noting that after the functionalization of the boehmite surface, the accumulation is reduced and the structure is spherical and regular.

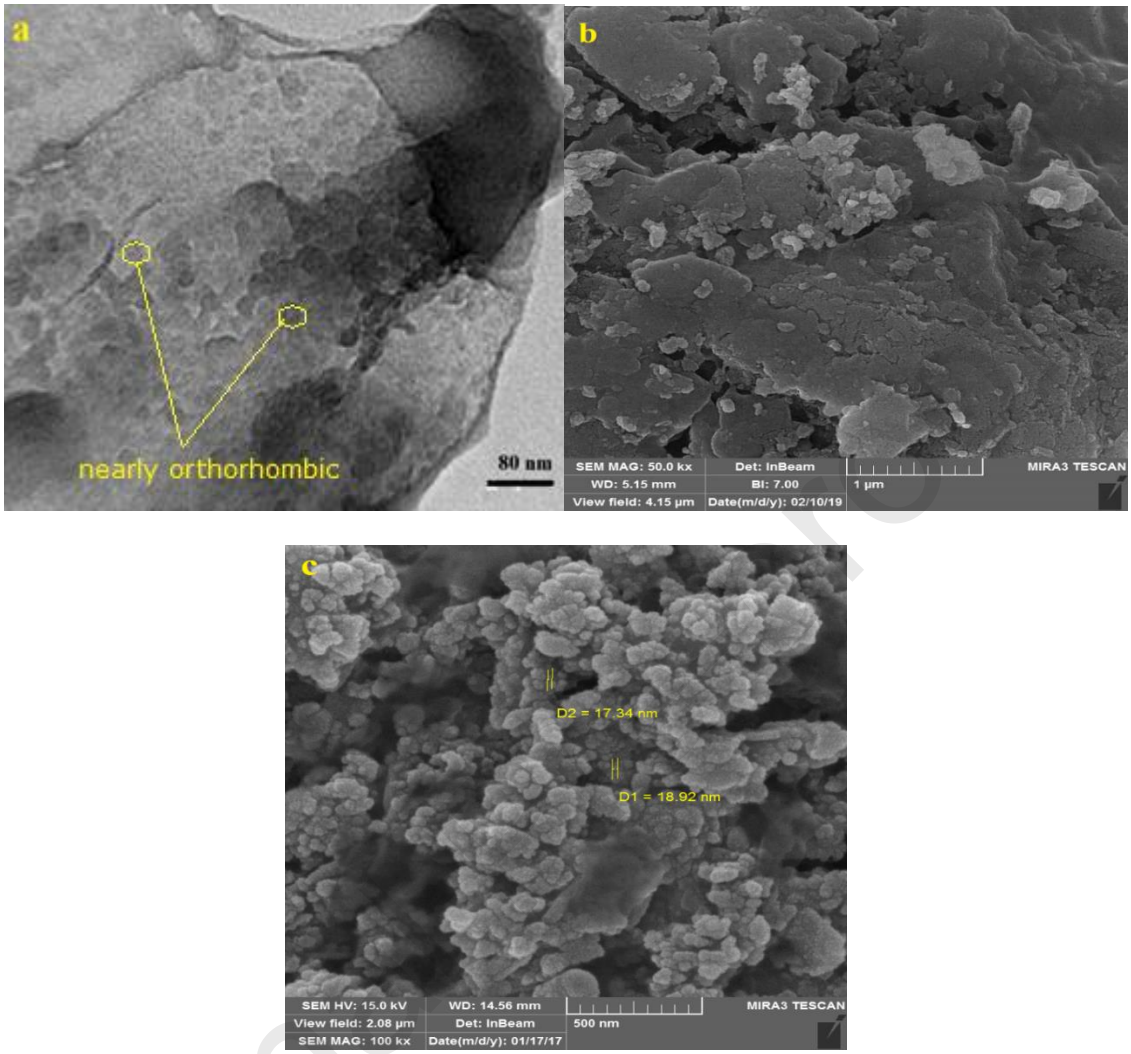


Fig. 4. a) TEM image of BNPs@$SiO_2(CH_2)_3NHSO_3H$, b) SEM image of boehmite and c) SEM image of the BNPs@$SiO_2(CH_2)_3NHSO_3H$

Powerful technique to scrutiny the crystallinity and phase purity of the material is XRD. Fig. 5 showed the XRD pattern of BNPs@$SiO_2(CH_2)_3NHSO_3H$. According to the diffraction peaks at the Bragg angles of 14.40° (020), 28.41° (120), 31.96° (110), 40.46° (060), 45.71° (131), 51.94° (200), 56.02° (151), 65.04° (231) and 68.09° (171), the boehmite crystalline phase is orthorhombic.[55, 58] It is obvious that the boehmite crystalline phase is retained after several modification steps and after the increase of different groups and linkers, the XRD pattern changes and as can be seen in the XRD pattern, several peaks at 20-30° are typical for silica and not seen in the XRD pattern of Boehmitt [59, 60]. Based on the evidence the introduced catalyst was successfully synthesized.

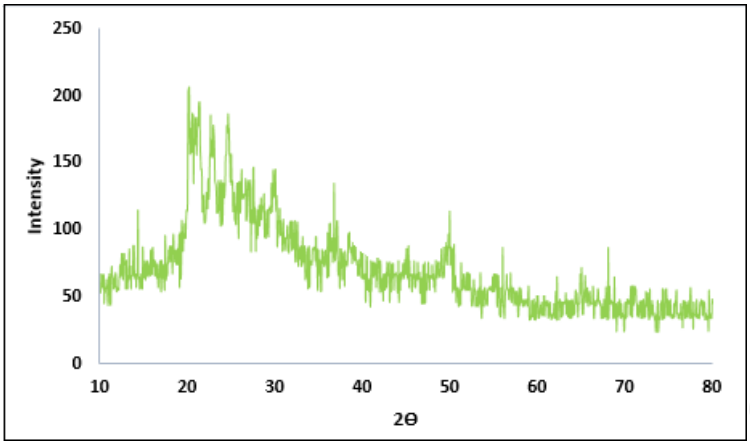


Fig. 5. XRD pattern of BNPs@$SiO_2(CH_2)_3NHSO_3H$

In the following, energy-dispersive X-ray spectrometry (EDX) analysis was used to corroborate the presence of all the elements in the catalyst structure and based on the EDX pattern, the composition of the BNPs@$SiO_2(CH_2)_3NHSO_3H$ was affirmed by the presence of N (5.56%), O (76.28%), Al (6.10%), S (9.22%) and Si (2.83%) (Fig. 6).

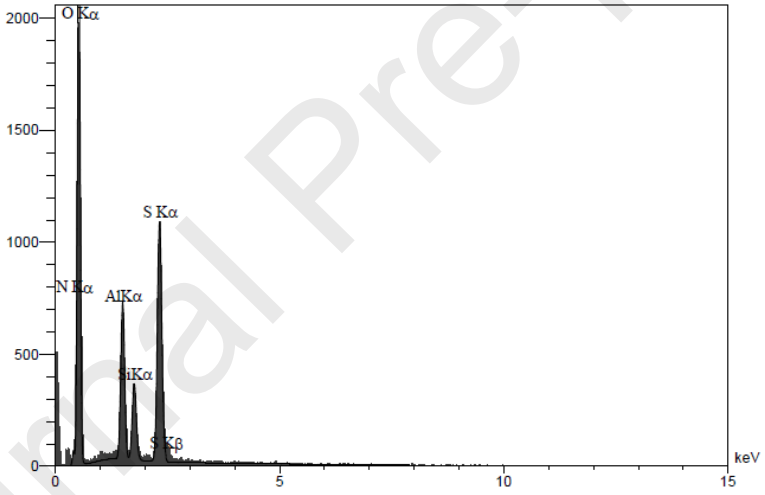


Fig. 6. EDX spectrum of the nano-catalyst

Another useful technique used to illustrate the distribution of elements in the nano-catalyst structure is mapping. The mapping pattern of the BNPs@$SiO_2(CH_2)_3NHSO_3H$ is illustrated in Fig. 7 and the identical distribution of all the elements in the structure of the acidic heterogeneous catalyst is quite evident.

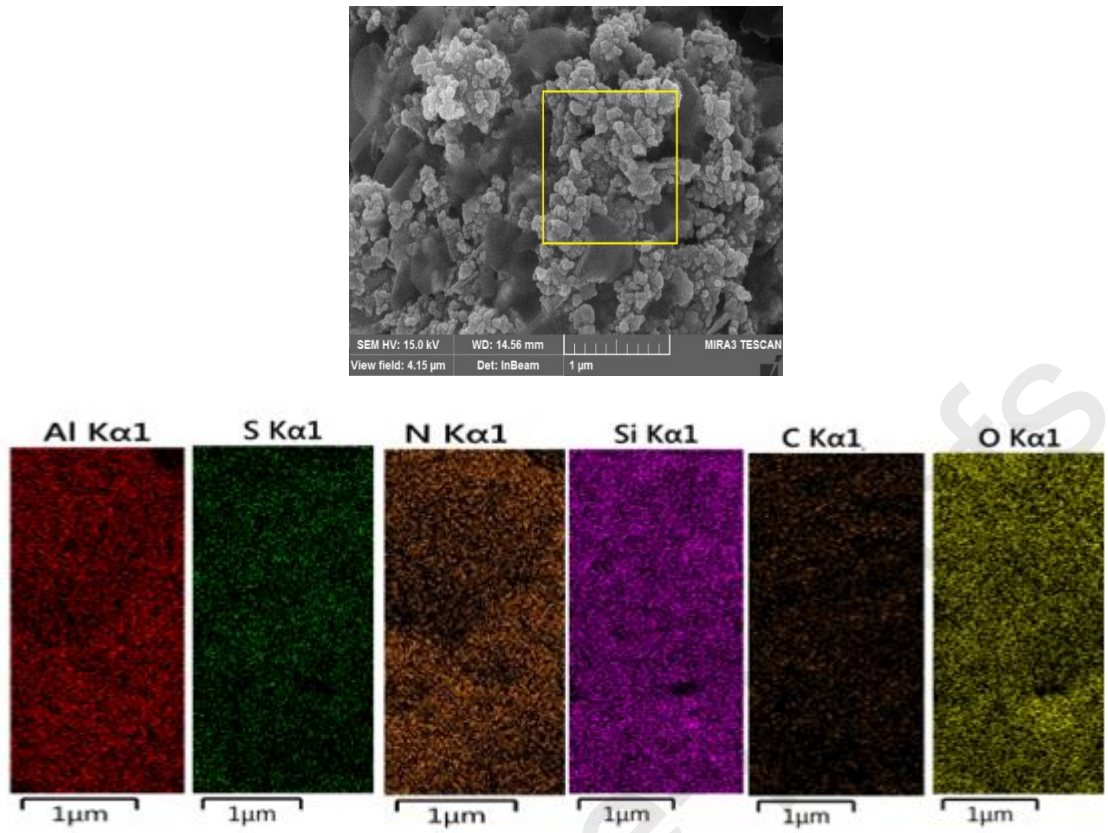


Fig. 7. Mapping pattern of the BNPs@$SiO_2(CH_2)_3NHSO_3H$

Thermogravimetric analysis (TGA) was used for the survey of the thermal behavior of the catalyst. Fig. 8 presents a) TGA curve and b) TGA-DTA diagram of the BNPs@$SiO_2(CH_2)_3NHSO_3H$. Based on the literature, boehmite nanoparticles are stable even at temperatures up to 400 °C and retains approximately 90% of its weight.[61] The first weight losing before 120 °C (3.58%) can be related to the water elimination. A second weight loss (14.54%) in the range of 130-300 °C is ascribed to the thermal decomposition of the $NHSO_3H$ groups and organic solvents. It is worth noting that, a third weight loss that occurred in 300-600 °C is attributed to the APTES and TEOS removal from the boehmite surface. Finally, according to the TGA diagram, the last weight loss which observed between 600 to 800 °C is related to the boehmite crystalline phase change. In addition, based on DTA curve (Fig. 8b), the process of decomposition of inorganic and organic templates is an exothermic process. In the DTA diagram, three exothermic peaks are seen and the first peak at 130 °C might be attributed to the water evaporation and the second peak in 336 °C can be related to the removal of the organosilane and organic groups from the catalyst surface and the last peak at 490 °C is probably corresponding to the catalyst crystalline phase variation.

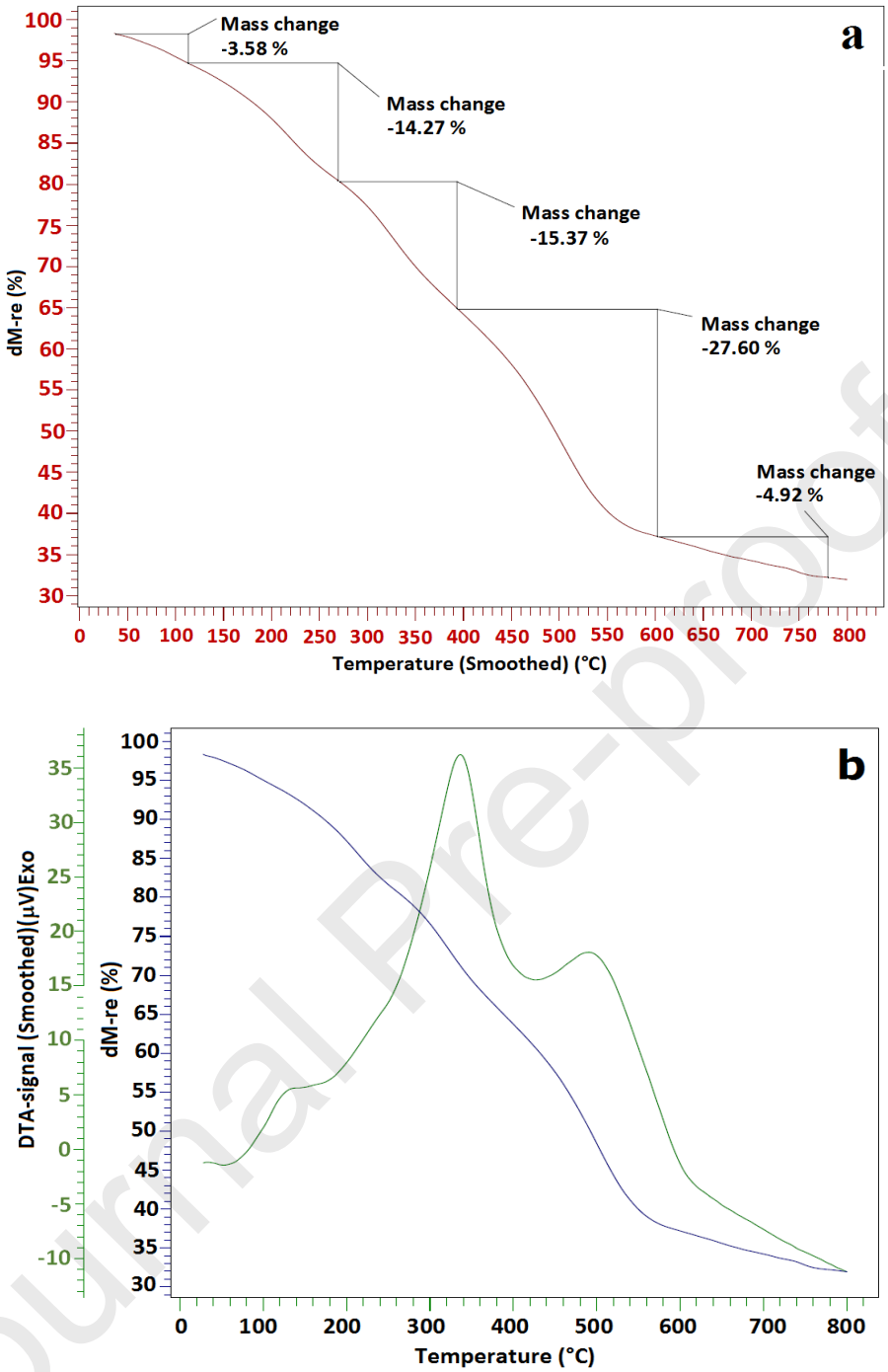


Fig. 8. a) TGA diagram of the catalyst and b) TGA-DTA diagram of the catalyst

3.2. pH analysis of the catalyst

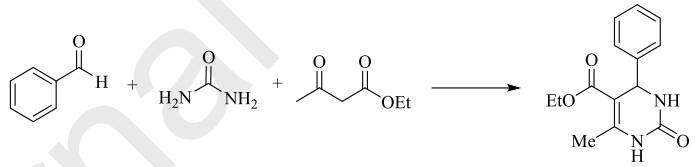
To measure the acidity of the catalyst surface, (0.1 g) of the prepared catalyst was added to the aqueous solution of NaCl (1 M, 10 mL) with an initial pH of 7.62. The mixture was stirred continuously for 30 min during which the *p*H of the mixture diminished to 1.84, denoting an ion exchange between protons of $NHSO_3H$ groups and sodium ions, this represents 1.44 mmol g^{-1} of acidic groups on the boehmite surface [55]. In this way, the acidity was measured for the

catalyst surface after the fifth run (*p*H = 1.95), and the surface acidity of the catalyst 1.12 mmol/g^{-1} was obtained. Also, the acidity of the surface was evaluated by titration with a NaOH (0.1 M), and the acidity was found to be 1.42 mmol per gram of catalyst, which is in good agreement with the value obtained with the PHM apparatus.

3.3. Catalytic studies

To optimize the reaction conditions, as a model, the condensation of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol) was examined in the presence of different quantities of the catalyst under solvent-free conditions at different temperatures. The respective results are summarized in Table 1. The reaction was tested in the presence of 0.02-0.08 g of BNPs@$SiO_2(CH_2)_3NHSO_3H$. The best results regarding the reaction time and yield were achieved in the presence of 0.05 g (0.05 g, containing 0.07 mmol SO_3H) of the catalyst (Table 1, entry 4). Also, using a lower amount of the catalyst resulted in a lower yield, while a higher amount did not affect the reaction time and yield (Table 1, entries 3 and 5). To evaluate the temperature influence, the model reaction was performed in 70, 80 and 100 °C. It was found that 80 °C was the optimal reaction temperature and the reaction was incomplete at lower than 80 °C (Table 1, entry 7).

Table 1. Effect of the catalyst amount and temperature on the reaction between ethyl acetoacetate, urea, and benzaldehyde[a]

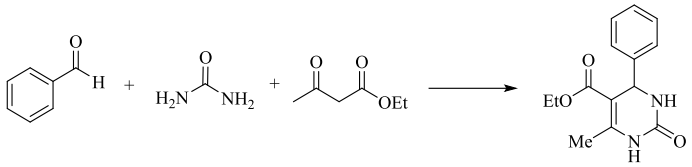


Entry	BNPs@$SiO_2(CH_2)_3NHSO_3H$ (g)	Temp (°C)	Yield (%)[b]
1	-	80	Trace
2	0.02	80	60
3	0.03	80	30
4	0.05	80	97
5	0.08	80	98
6	0.08	100	98
7	0.05	70	80

[a] Reaction conditions: Benzaldehyde (1 mmol), ethylacetoacetate (1 mmol) and urea (1.5 mmol), solvent-free.
[b] Isolated yields.

To survey the solvent effect on the time and reaction yield, we studied varied solvents, containing CH_3CN, H_2O, CH_2Cl_2, DMF and EtOH at 80 °C using 0.05 g (0.07 mmol SO_3H) of the catalyst. The results of these examinations revealed that polar solvents led to a significant decrease in the yield of the desired product compared to solvent-free conditions (Table 2, entries 1–5).

Table 2. Effect of various solvents on the preparation of 3,4-dihydropyrimidinones[a]



Entry	Solvent	Yield (%)[a]
1	H_2O	30
2	EtOH	65
3	CH_2Cl_2	50
4	CH_3CN	60
5	DMF	70
6	-	97

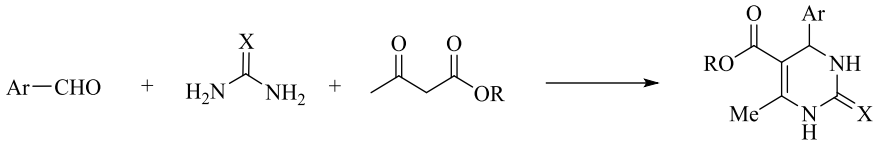
[a]Reaction conditions: Benzaldehyde (1 mmol), ethylacetoacetate (1 mmol) and urea (1.5 mmol), catalyst (05 g) (0.05 g, containing 0.07 mmol SO_3H), 30 min.
[a]Isolated yields.

With optimized conditions in hand, synthesis of 3,4-dihydropyrimidinones with variety of functionalized aromatic aldehydes was performed to explore the scope and the generality of this protocol and the corresponding results are summarized in Table 3. Aromatic aldehydes bearing either electron donating or electron-withdrawing substituents reacted efficiently and gave excellent yields (Table 3, entries 3,5,12-13). Also. furane-2-carbaldehyde and thiophene-2-carbaldehyde as Heterocycle aldehydes, produced corresponding compounds with remarkable yields (Table 3, entries 6,7). It is noteworthy that, BNPs@$SiO_2(CH_2)_3NHSO_3H$ was an efficient and reusable acidic heterogeneous catalyst for the preparation of the 3,4-dihydropyrimidinones. It is noted that the reaction time is shorter in the presence of aldehydes with electron-poor groups.

In addition, to evaluate the efficiency of this approach, comparison of this procedure with previous methods was performed and the results are summarized in Table 4. As the Table demonstrates, BNPs@$SiO_2(CH_2)_3NHSO_3H$ is superior to former methods and has indeed improved the synthesis of 3,4-dihydropyrimidinones.

A plausible mechanism for the synthesis of 3,4-dihidropyrimidones using the BNPs@$SiO_2(CH_2)_3NHSO_3H$ catalyst is as follows: The BNPs@$SiO_2(CH_2)_3NHSO_3H$ as a Bronsted acidic catalyst participates in the reaction by activating the aldehyde **(1)**. This is pursued by nucleophilic addition of urea or thiourea **(2)** forming the intermediate **(4)**. Then, this intermediate interacts with ketoester **(5)** to produce an open chain intermediate **(6)**, which is followed by cyclization and dehydration to produce 3,4-dihidropyrimidone (**8**) (Scheme 3).

Table 3. One pot synthesis of various 3,4-dihydropyrimidinones[a]

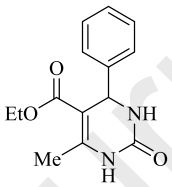


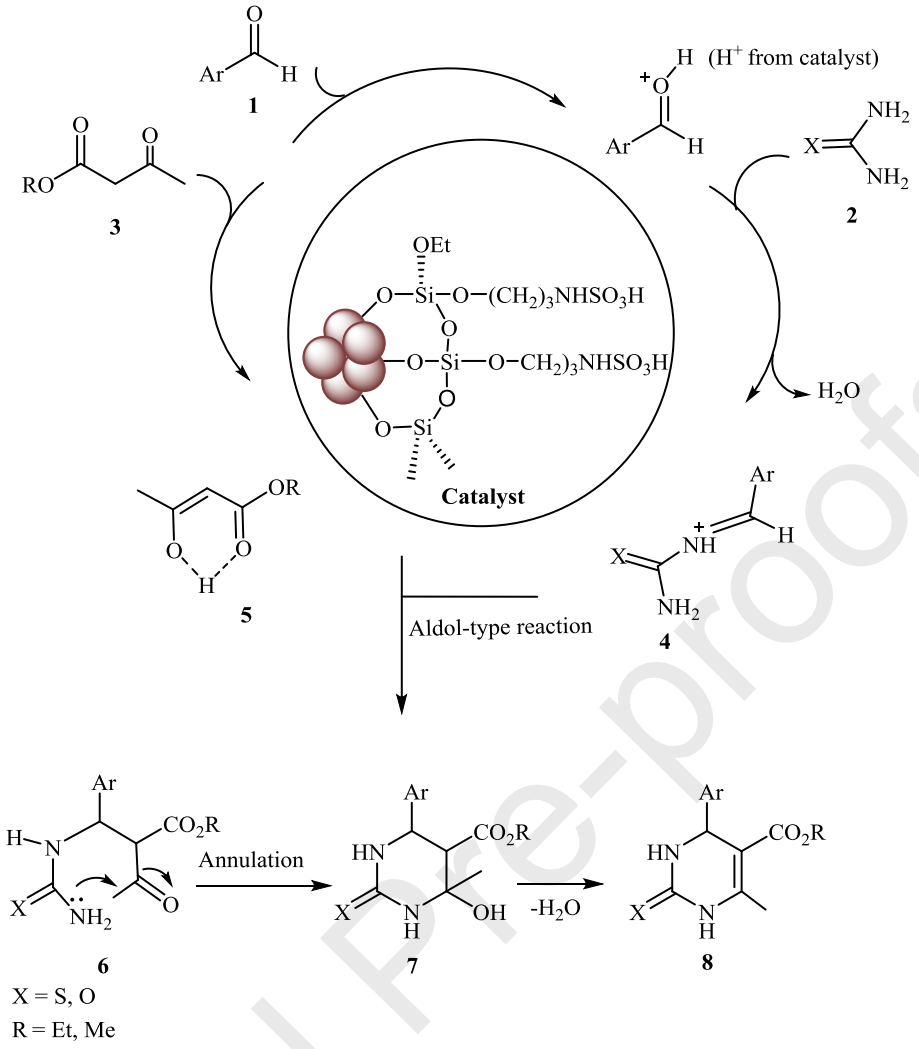
Entry	Aryl aldehyde	X	R	Time (min)	Yield (%)[b]	M.p [Ref]
1	C_6H_5-CHO	O	Et	30	97	201-203 [61]
2	4-ClC_6H_4-CHO	O	Et	27	96	211-213 [62]
3	4-$NO_2C_6H_4$-CHO	O	Et	25	95	207-209 [61]
4	4-MeC_6H_4-CHO	O	Et	40	94	170-171 [61]
5	4-MeOC_6H_4-CHO	O	Et	45	96	200-202 [63]
6	2-Furyl-CHO	O	Et	55	95	204-206 [61]
7	2-Thienyl-CHO	O	Et	60	95	207-208 [61]
8	4-MeOC_6H_4-CHO	S	Et	70	98	150-152 [63]
9	C_6H_5-CHO	S	Et	40	95	202-204 [63]
10	4-MeC_6H_5-CHO	S	Et	45	96	202-204 [63]
11	C_6H_5-CHO	O	Me	25	97	210-212 [61]
12	4-FC_6H_4-CHO	O	Me	20	96	190-192 [63]
13	4-$NO_2C_6H_4$-CHO	S	Et	35	95	193-195 [63]
14	4-ClC_6H_4-CHO	S	Et	30	96	192-193 [63]
15	3-MeOC_6H_4-CHO	O	Et	55	97	150-152 [62]

[a]Reaction conditions: Aryl aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), catalyst: 0.05 g (0.05 g, containing 0.07 mmol SO_3H), solvent-free, 80 °C.

[b]Isolated products**.**

Table 4. Comparison of methods for the synthesis of 3,4-dihydropyrimidone compounds

Entry	Product	Conditions	Time/ min	Yield (%)[Ref]
1		Fe_3O_4@SBA-15/ Solvent-free/85 °C	360	85 [64]
2		PTA@MIL-101/Solvent-free/100 °C	60	90 [65]
3		Cu@PMO-IL/Solvent-free/70 °C	50	92 [66]
4		PTA@ZIF-9(NH_2)/Solvent-free/110 °C/	30	85 [27]
5		GO-PO_3H_2/ Solvent-free/ 80 °C	20	92 [67]
6		BNPs@$SiO_2(CH_2)_3NHSO_3H$/ Solvent-free/80 °C	30	97



Scheme 3. Proposed mechanism for the synthesis of 3,4-dihydropyrimidones

For practical purposes, the ability to easily recycle the catalyst is highly valuable. The recyclability of the BNPs@$SiO_2(CH_2)_3NHSO_3H$ has great importance for both the economic and the synthetic aspects. To check this issue, the recyclability of the catalyst was tested for the preparation of DHPMs. Therefore, the reusability of the catalyst was investigated by isolation of the BNPs@$SiO_2(CH_2)_3NHSO_3H$ from the reaction mixture with simple filtration, washing with ethanol and drying in a vacuum oven at 80 °C for 10 h and reuse it in subsequent runes. The recovered catalyst can be reused at least five times with a small loss in catalyst activity (Fig. 9).

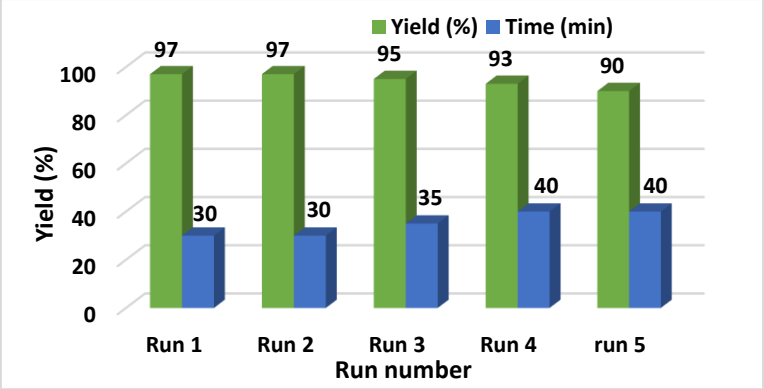


Fig. 9. The reusability of the BNPs@$SiO_2(CH_2)_3NHSO_3H$ in the reaction of benzaldehyde, ethyl acetoacetate, and urea

Since the prepared catalyst showed excellent catalytic activity for the Biginelli reaction, we decided to employ it for the preparation of 1,4-dihydropyridines. For this regard, to achieve the best reaction conditions, BNPs@$SiO_2(CH_2)_3NHSO_3H$ was added to a solution of aromatic aldehyde, 1,3-dicarbonyl compounds and ammonium acetate in EtOH at 70 °C as a model reaction (Table 5). First, the reaction was studied in the presence of different quantities of the catalyst (0.02, 0.04, 0.06 and 0.08 g). The best results were obtained in the yield and reaction time in the presence of 0.06 g (0.08 mmol SO_3H) of BNPs@$SiO_2(CH_2)_3NHSO_3H$ (Table 5, entry 7). Lower temperatures increased the reaction time and reduced yield of product (Table 5, entries 5-6). Furthermore, increasing the amount of catalyst to 0.8 g did not lead to significant increase in the yield of product (Table 5, entry 8).

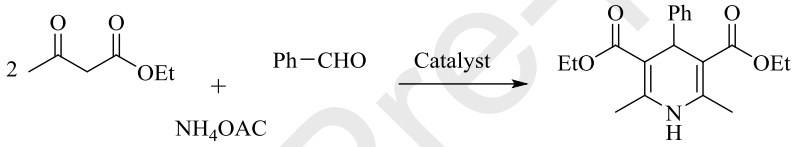
Then, we focused on solvent influence and studied several solvents including CH_3CN, H_2O, DMF, CH_2Cl_2 and EtOH under optimum reaction conditions (Table 6). As can be seen, the nature of solvent has a considerable effect on the reaction rate and the yield of product and EtOH works better (Table 6, entry 5) and other solvents are less effective.

Table 5. Effect of increasing amount of BNPs@$SiO_2(CH_2)_3NHSO_3H$ and temperature on the preparation of 1,4-dihydropyridine[a]

Entry	BNPs@$SiO_2(CH_2)_3NHSO_3H$ (g)	Temp (°C)	Time (min)	Yield (%)[b]
1	-	25	60	-
2	-	70	60	Trace
3	0.02	70	60	50
4	0.04	70	40	75
5	0.06	25	60	60
6	0.06	50	45	80
7	0.06	70	30	97
8	0.08	70	30	98

[a]Reaction conditions: Benzaldehyde (1 mmol), 1,3-dicarbonyl compounds (2 mmol), NH_4OAc (1 mmol), EtOH (7 mL).
[b]Yields refer to pure isolated products**.**

Table 6. Effect of various solvents on the synthesis of 1,4-dihydropyridine derivatives[a]



Entry	Solvent	Yield (%)[a]
1	CH_3CN	85
2	H_2O	50
3	CH_2Cl_2	55
4	DMF	85
5	EtOH	97

[a]Reaction conditions: Benzaldehyde (1 mmol), ethylacetoacetate (2 mmol) NH_4OAc (1 mmol), catalyst (06 g) (0.06 g, containing 0.08 mmol SO_3H), solvent (7 mL).
[a]Isolated yields.

In order to scrutiny the activity of BNPs@$SiO_2(CH_2)_3NHSO_3H$ as a catalyst, a range of aromatic aldehydes were treated with different 1,3-dicarbonyl compounds and ammonium acetate in the presence of BNPs@$SiO_2(CH_2)_3NHSO_3H$ and the desired 1,4-dihydropyridines were formed in excellent yields (90-97 %) (Table 7). The position and nature of the substituent on the aromatic ring had a negligible effect on the yields of the final products. But in general, aldehydes with electron-withdrawing groups have shorter reaction times (Table 7, entries 4,8 and 10). In addition, under optimized reaction conditions, heterocycle aldehydes reacted perfectly and generated desired products with high yields (Table 7, entries 5-7 and 12-13). Furthermore, cyclohexyl aldehyde (as an aliphatic aldehyde) works well in this procedure and produces the desired product in excellent yield (Table 7, entry 14)

We investigated the performance of the introduced catalyst by some of the previously selected protocols and the results are collected in Table 8. It should be noted that, according to Table, the BNPs@$SiO_2(CH_2)_3NHSO_3H$ is a more efficient catalyst with respect to times and yields than these reported catalysts.

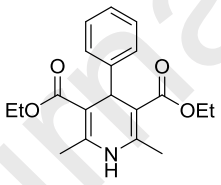
Table 7. Direct synthesis of various 1,4-dihydropyridines with different 1,3-dicarbonyl compounds[a]

Entry	Aldehyde	1,3-dicarbonyl compounds	Time (min)	Yield (%)[b]	M.p [Ref]
1	C_6H_5-CHO	Ethylacetoacetate	30	97	159-161 [68]
2	4-$MeOC_6H_4$-CHO	Ethylacetoacetate	45	93	159-160 [68]
3	4-MeC_6H_4-CHO	Ethylacetoacetate	30	95	131-133 [69]
4	4-ClC_6H_4-CHO	Ethylacetoacetate	25	92	146-148 [68]
5	2-Furyl-CHO	Ethylacetoacetate	30	91	160-162 [68]
6	2-Thienyl-CHO	Ethylacetoacetate	25	95	154-156 [70]
7	3-Pyridyl-CHO	Ethylacetoacetate	35	92	191-192 [71]
8	3-$NO_2C_6H_4$-CHO	Ethylacetoacetate	20	97	163-165 [68]
9	C_6H_5-CHO	Dimedone and Ethylacetoacetate	35	97	203-204 [72]
10	3-$NO_2C_6H_4$-CHO	Dimedone and Ethylacetoacetate	25	90	176-178 [73]
11	4-BrC_6H_4-CHO	Dimedone and Ethylacetoacetate	35	95	263-265 [73]
12	2-Furyl-CHO	Dimedone and Ethylacetoacetate	40	92	246-248 [72]
13	2-Thienyl-CHO	Dimedone and Ethylacetoacetate	30	95	239-241 [72]
14	C_6H_{11}-CHO	Dimedone and Ethylacetoacetate	50	90	222-224 [73]

[a] Reaction conditions: Aldehyde (1 mmol), 1,3-dicarbonyl compound (2 mmol), NH_4OAc (1 mmol), EtOH (7 mL), 70 °C.

[b] Isolated yields.

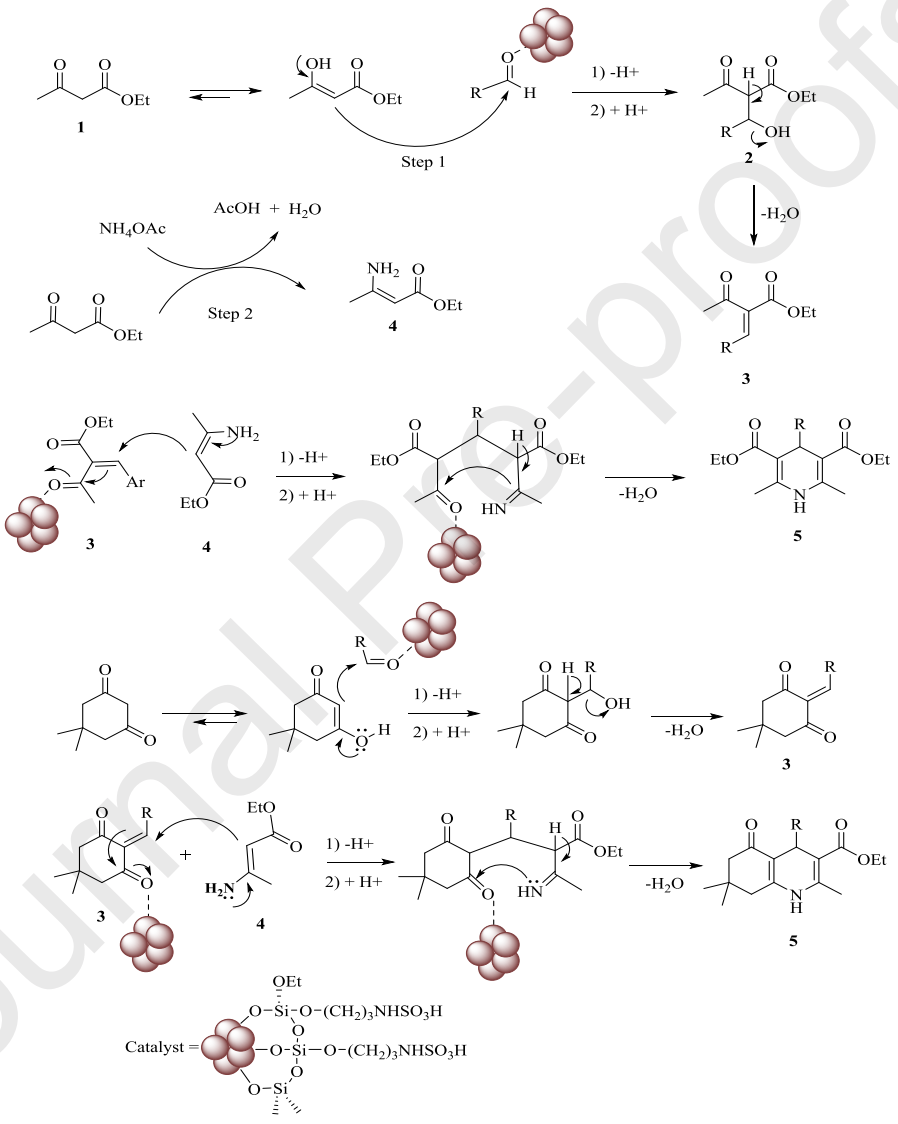
Table 8. Comparison of different catalytic systems for the synthesis of 1,4-DHPs

Entry	Product	Coditions	Time (min)	Yield (%)
1		PEG_{1000}-DAIL/ Toluene/80 °C	40	91 [74]
2		PPh_3/EtOH/Reflux	300	72 [75]
3		Fe_3O_4 NPs/Solvent-free/r.t:	390	73 [76]
4		Fe_2O_3@HAP@Melamine/Solvent-ftee/80 °C	15	94 [77]
5		ZnO NPs/Solvent free/80 °C	120	82 [78]
6		Nicotinic acid/ Solvent free/80 °C	5	95 [9]
7		BNPs@$SiO_2(CH_2)_3NHSO_3H$	30	97

The suggested mechanism for the synthesis of 1,4-DHPs is shown in Scheme 4. First, BNPs@$SiO_2(CH_2)_3NHSO_3H$, which is a Bronsted acidic catalyst, activates aldehyde. Then, synthesis of 1,4-DHP proceeds through the formation of a Knoevenagel condensation product as a key intermediate (**3**). A second key intermediate (**4**) is an ester enamine, which is formed by condensation of the second equivalent of the 1,3-dicarbonyl compound with ammonia. Further condensation between these two key fragments, gives the 1,4-DHP derivatives.

In another survey, reusability and durability of BNPs@$SiO_2(CH_2)_3NHSO_3H$ was checked. For this regard, model reaction was studied in the presence of catalyst. After completion of the

reaction, the catalyst was isolated by filtration, washed by EtOH and dried to use for the subsequent run. It is noteworthy that, catalytic activity of BNPs@$SiO_2(CH_2)_3NHSO_3H$ was maintained within 5 successive recycle runs (Fig. 10). To confirm the catalyst recyclability, the recovered catalyst by EDX and IR techniques was investigated. It should be noted that FT- IR of recovered catalyst after 5th run is similar to the fresh catalyst and EDX pattern of the reused catalyst represents the presence of the all elements in the structure of the catalyst, which affirms the BNPs@$SiO_2(CH_2)_3NHSO_3H$ is recyclable (Fig. 11).



Scheme 4. A possible mechanism for the synthesis of 1,4-DHPs in the presence of BNPs@$SiO_2(CH_2)_3NHSO_3H$

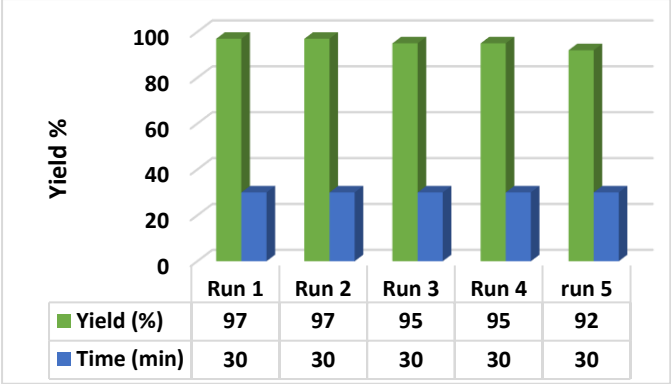


Fig. 10. The reusability of the catalyst for the reaction of benzaldehyde, ethyl acetoacetate, and ammonium acetate

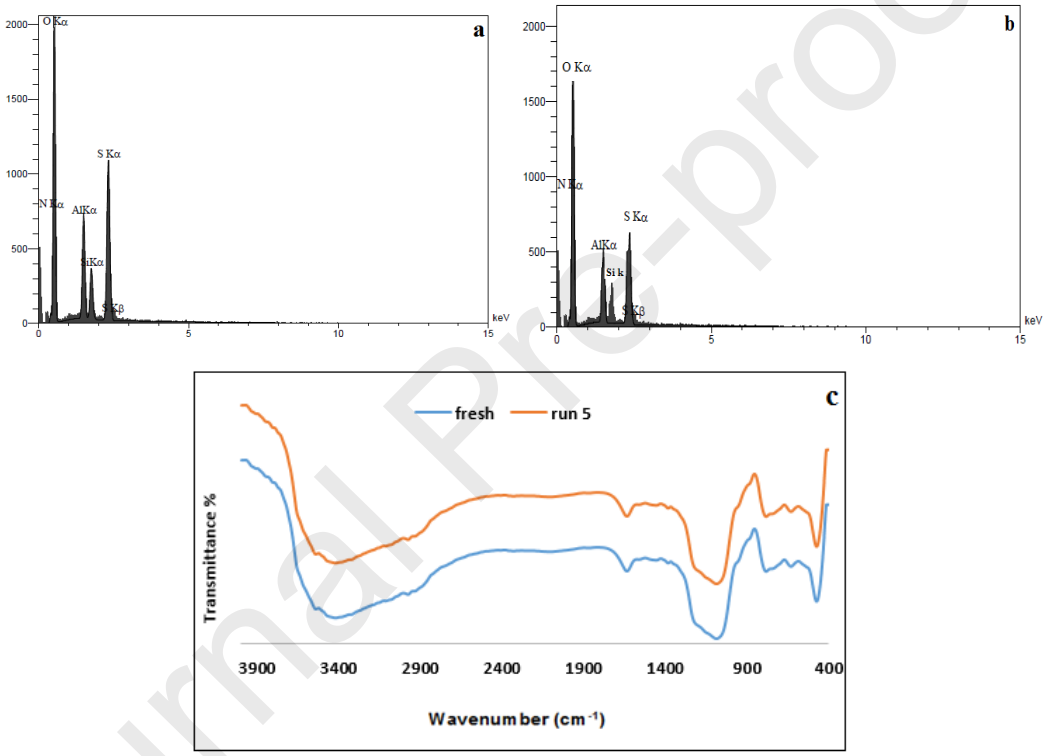


Fig. 11. a) EDX pattern of fresh catalyst b) EDX pattern of recovered catalyst after 5th run c) comparison of FT-IR fresh catalyst and FT-IR 5th run

In another study to confirm the non-leaching of acidic groups to the reaction medium, we performed a hot filtration test. For this purpose, the model reaction for Biginelli synthesis was performed in the presence of the catalyst and after half a reaction time (15 min) (70% yield), the catalyst was removed by simple filtration and residue transferred to another quartz tube and the reaction was stirred in the absence of the catalyst. After several hours, the reaction yield did not change significantly (72% yield as screened by TLC). This test is a good reason for the stability of the catalyst and the leaching of acid groups from the catalyst surface is not seen.

4. Conclusion

In conclusion, this research displays one-pot multicomponent syntheses of 3,4-dihydropyrimidones and 1,4-dihydropyridines catalyzed by efficient and recyclable BNPs@$SiO_2(CH_2)_3NHSO_3H$ in mild reaction condition. Catalytic results showed that boehmite can be a stable, active and effective solid-phase support for the heterogenization of homogeneous catalysts. This solid catalyst demonstrates high acidic strength which leads to greater catalyst efficiency. It is noteworthy that, several unique advantages for the synthesis of DHPM and DHP derivatives are short times, excellent yields, use of mild conditions, easy catalyst separation, simple workup and catalyst recovery up to at least five times with small drop in activity. According to the results, BNPs@$SiO_2(CH_2)_3NHSO_3H$ is superior to many of the reported catalysts in the scientific literature for the preparation of 3,4-DHPMs and 1,4-DHPs.

Acknowledgments

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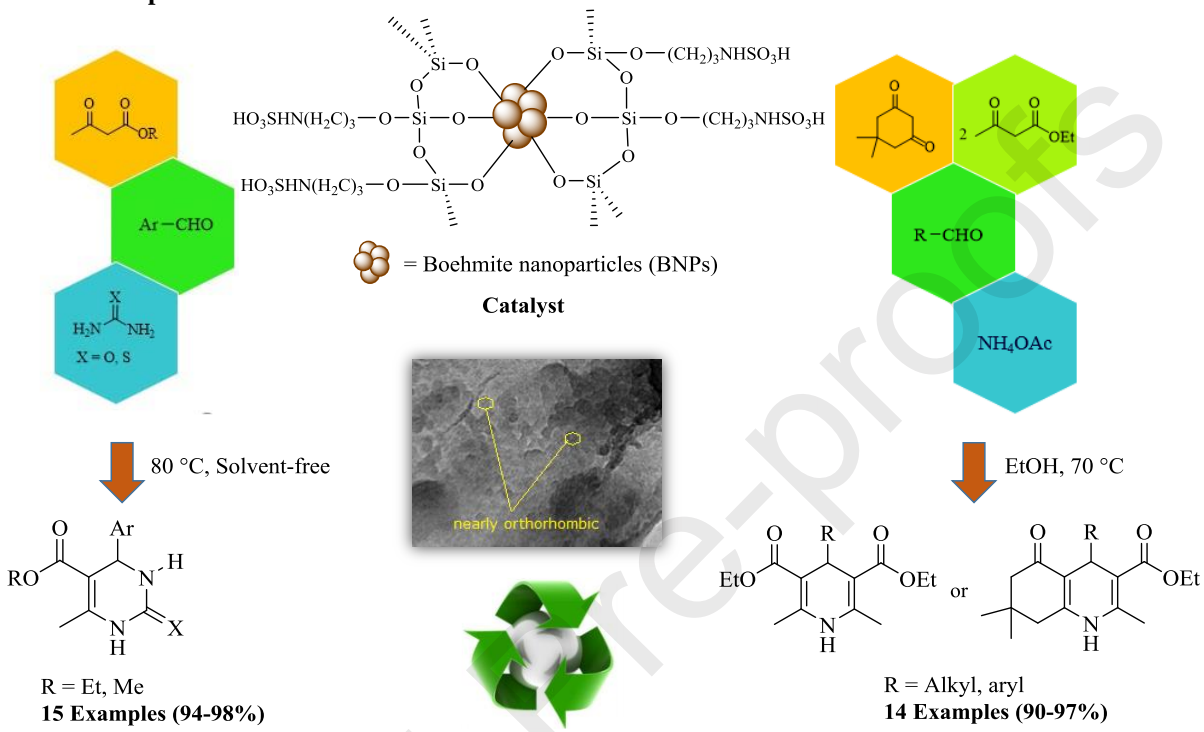
Graphical Abstract



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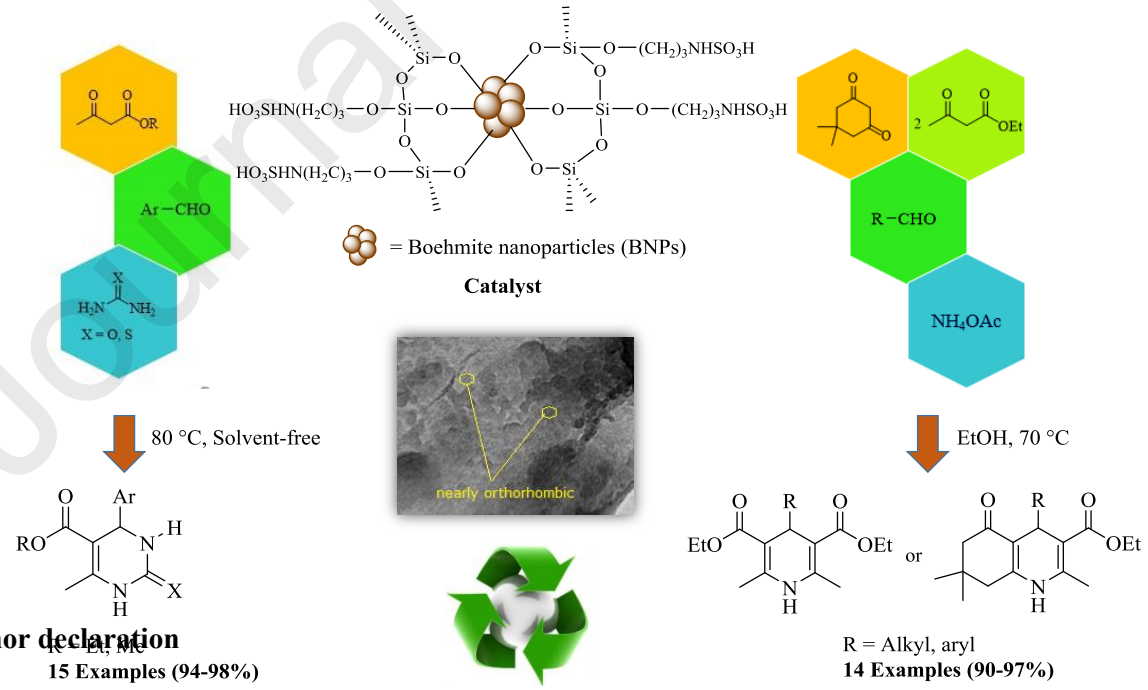
Graphical Abstract

Boehmite nanoparticles functionalized with silylpropyl sulfamic acid (BNPs@$SiO_2(CH_2)_3NHSO_3H$) as a metal free and environmentally friendly catalyst has been found to be effective for the one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and the preparation of 1,4-dihydropyridines derivatives. Some features of this protocol are low cost and available materials, short reaction times, convenient catalyst separation, and no need for a neutral atmosphere.



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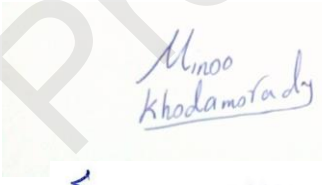

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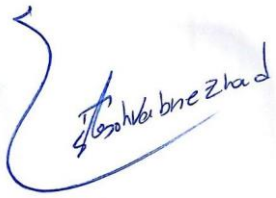

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