

Silica (NPs) supported Fe (III) as a reusable heterogeneous catalyst for the one-pot synthesis of 1, 4-dihydropyridines under mild conditions

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Abstract. A cheap and recyclable silica (NPs) supported Fe (III) was prepared as heterogeneous catalyst for the synthesis of various substituted 1,4-dihydropyridines via condensation of aldehydes with ethyl acetoacetate and ammonium acetate in ethanol. The products were separated from the catalyst simply by filtration and the catalyst could be recycled and reused for several times without noticeable decrease in the catalytic activity.

Keywords. Heterogeneous catalyst; 1,4-dihydropyridine; multi-component; nano silica; Hantzsch reaction.

1. Introduction

Current literature reveals that 1,4-dihydropyridines exhibit interesting pharmacological and biological properties. Thus, they have been used as calcium channel modulators for the treatment of cardiovascular disorders.¹ The 1,4-DHPs may lead to other beneficial effects such as regression of left ventricular pressure and vascular hypertrophy, renal protection and antiatherogenic activity.^{2–4} Furthermore, the DHP skeleton is common in many bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and hepatoprotective agents.^{5,6} They also function as neuroprotectants, as antiplatelet treatment of aggregators and are important in Alzheimer's disease as antiischaemic agents.⁷ Among 1,4-DHPs, there are also examples of drug-resistance modifiers,⁸ antioxidants⁹ and a drug for the treatment of urinary urge incontinence. In order to model and understand these biological properties and to develop new chemotherapeutic agents based upon the 1,4-DHP motif, considerable effort has been devoted to establish efficient and rapid methods for their synthesis (figure 1).¹⁰

Recently, a number of modified methods have been developed.^{11,12} Some procedures comprise the use of microwaves,¹³ ionic liquids,¹⁴ high temperatures at reflux,¹⁵ TMSCl–NaI,¹⁶ InCl₃,¹⁷ I₂,¹⁸ NaHSO₄/SiO₂,¹⁹ HClO₄/SiO₂,²⁰ CAN,²¹ Na- and Cs-Norit carbons,²² tetrabutylammonium hydrogen sulfate,²³ fermenting Baker's yeast,²⁴ organocatalysts²⁵ and metal triflates.²⁶ However, some of these methods suffer from the drawback of green chemistry such as prolonged reaction

times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions have been under permanent attention. The best known procedure for the preparation of symmetrical 1,4-DHPs is the classical Hantzsch synthesis: a multicomponent condensation involving two molecules of β -ketoesters, one molecule of aldehyde and one molecule of ammonia.²⁷ The demand for environmentally benign procedure with heterogeneous and reusable catalyst promoted us to develop a safe alternate method for the synthesis of 1,4-dihydropyridines in the presence of silica (NPs) supported Fe (III) (scheme 1).

2. Experimental

The products were isolated and characterized by physical and spectral data. ¹H NMR and ¹³C NMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Melting points were determined on Electro thermal 9200, and are not corrected. Silica (NPs) supported Fe (III) was obtained according to the method reported in the literature. Microscopic morphology of products was visualized by SEM (LEO 1455VP).

2.1 Preparation of silica (NPs) supported Fe (III)

In a 100 ml flask, nano silica gel (25 g) and FeCl₃.6H₂O (2 g) (8% of the weight of SiO₂ NPs) were vigorously

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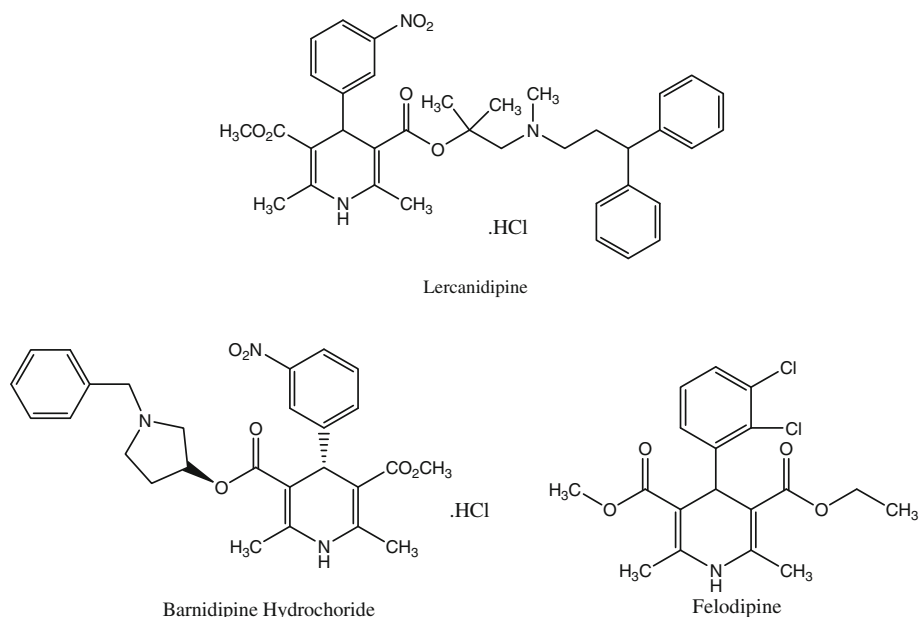
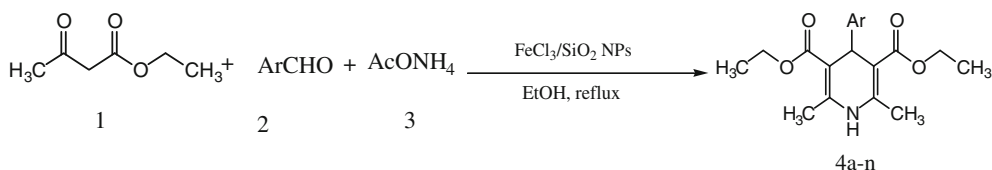


Figure 1. The pharmaceutical compounds with DHP skeleton.



Scheme 1. Synthesis of 1,4-dihydropyridines on silica (NPs) supported Fe (III) under reflux conditions.

stirred under solvent-free conditions at room temperature for 24 h to achieve a homogeneous adsorption. The obtained powder was yellow and heated for 1 h at 100°C to activate the catalyst.

2.2 Preparation of 1,4-dihydropyridine derivatives

A mixture of aldehyde 1 (1 mmol), ethyl acetoacetate 2 (2 mmol), ammonium acetate 3 (2 mmol) and silica (NPs) supported Fe (III) (0.6 mol%) was heated at

reflux in ethanol (3 mL). The reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was filtered and the heterogeneous catalyst was recovered. The filtrate was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over Na_2SO_4 . After evaporation of the solvent, the crude yellow products were purified by crystallization from ethanol to afford 1,4-dihydropyridines.

2.3 Reusability of catalyst

The recovered catalyst from the experiment was washed by acetone (3×5 mL). Then, it was dried in an oven at 100°C and used in the synthesis of 1,4-dihydropyridines. Then the catalyst was recycled for five times.

2.4 Selected spectral data

2.4a Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f): ^1H NMR (400 MHz, CDCl_3): $\delta = 1.23$ (t, 6H, $2\text{CH}_3\text{CH}_2$), 2.31 (s, 6H,

Table 1. Reaction of *p*-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate in diverse catalytic conditions.

Entry	Catalyst (mol%)	Time (min)	Yield, ^a %
1	none	180	0
2	FeCl_3 (10)	150	41
3	SiO_2 NPs (10)	130	27
4	$\text{FeCl}_3/\text{SiO}_2$ (10)	100	75
5	$\text{FeCl}_3/\text{SiO}_2$ NPs (0.8)	20	93
6	$\text{FeCl}_3/\text{SiO}_2$ NPs (0.6)	20	94
8	$\text{FeCl}_3/\text{SiO}_2$ NPs (0.5)	20	90

^aIsolated yield

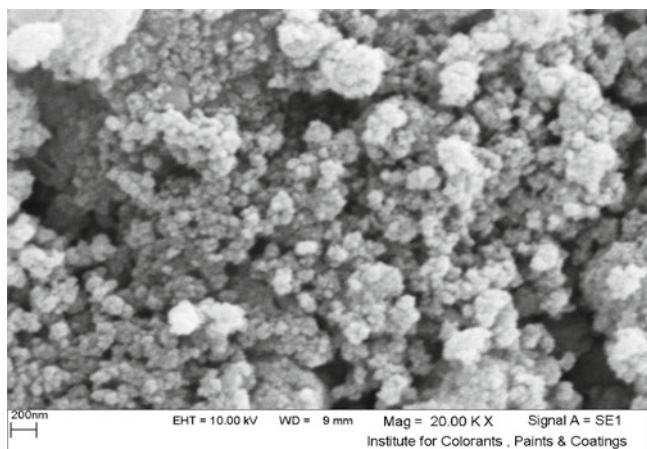
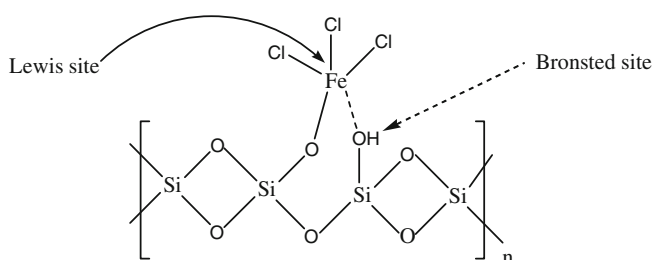


Figure 2. SEM image of the FeCl₃/SiO₂ NPs.



Scheme 2. Bronsted acidity arising from inductive effect of Lewis acid center coordinated to nanosilica support.

2CH₃), 4.09 (q, 4H, 2CH₃CH₂), 4.94 (s, 1H, CH), 5.82 (s, 1H, NH), 7.16 (d, 2H, 2CH_{arom.}), 7.33 (d, 2H, 2CH_{arom.}). ¹³C NMR (100 MHz, CDCl₃): δ = 14.2,

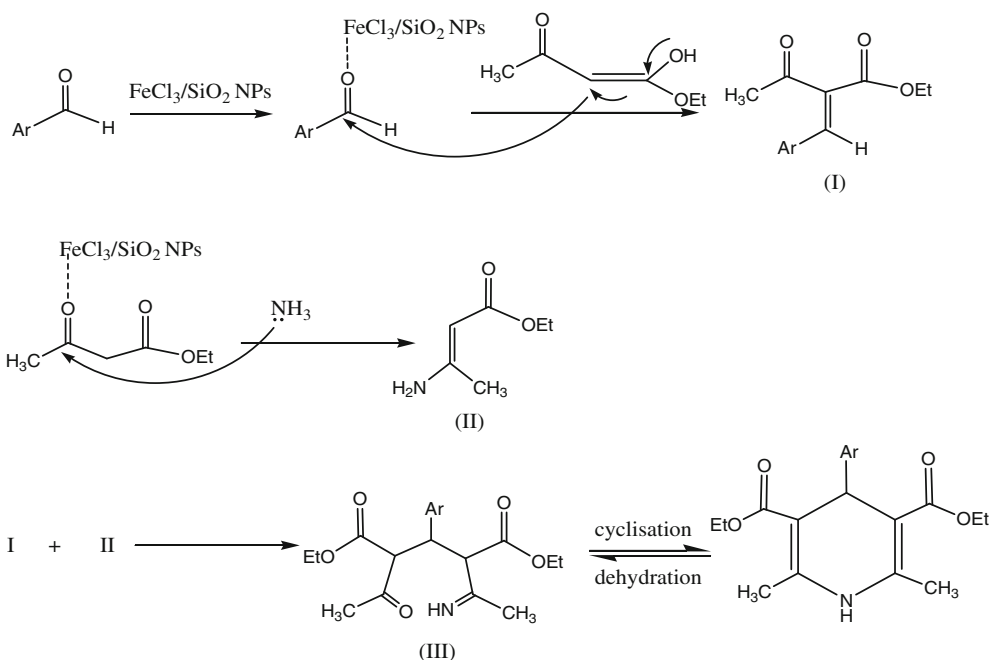
19.4, 39.3, 59.8, 103.4, 119.8, 129.8, 130.8, 144.3, 146.9, 167.5. FT-IR (KBr): 3355, 1696, 1651, 1487, 1213, 1092, 783 cm⁻¹.

2.4b *Diethyl 4-(4-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b)*: ¹H NMR (400 MHz, CDCl₃): δ = 1.23 (t, 6H, 2CH₃CH₂), 2.36 (s, 6H, 2CH₃), 4.09 (q, 4H, 2CH₃CH₂), 5.09 (s, 1H, CH), 5.72 (s, 1H, NH), 7.26 (d, 2H, 2CH_{arom.}), 8.09 (d, 2H, 2CH_{arom.}). ¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 19.4, 39.3, 59.8, 103.4, 119.8, 130.0, 130.8, 144.3, 146.9, 167.5. FT-IR (KBr): 3343, 1706, 1646, 1486, 1212, 1115, 786 cm⁻¹.

2.4c *Diethyl 4-(2-thienyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4m)*: ¹H NMR (400 MHz, CDCl₃): δ = 1.24 (t, 6H, 2CH₃CH₂), 2.31 (s, 6H, 2CH₃), 4.09 (q, 4H, 2CH₃CH₂), 4.99 (s, 1H, CH), 5.88 (s, 1H, NH), 7.12 (d, 1H, 1CH_{arom.}), 7.20 (d, 1H, 1CH_{arom.}), 7.29 (d, 1H, 1CH_{arom.}). ¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 19.3, 39.6, 59.7, 103.8, 126.1, 127.8, 144.3, 147.8, 167.8. FT-IR (KBr): 3358, 1686, 1641, 1487, 1215, 1082, 773 cm⁻¹.

3. Results and discussions

We report here a simple and convenient method for the synthesis of 1,4-dihydropyridines by condensation of aldehydes with ethyl acetoacetate and ammonium



Scheme 3. The proposed mechanism of the synthesis of 1,4-dihydropyridines in the presence of silica (NPs) supported Fe (III).

Table 2. Preparation of 1,4-dihydropyridines in the presence of silica (NPs) supported Fe (III) in different solvents.

Entry	Solvent	Time (min)	Yield, ^a %
1	CH ₃ CN	70	37
2	Toluene	90	31
3	H ₂ O	90	49
4	EtOH	20	94
5	EtOH/H ₂ O	60	73
6	Solvent-free	75	29

^aIsolated yield**Table 3.** The catalyst reusability for the synthesis of 1,4-dihydropyridines.

Entry	Cycle	Yield, ^a %
1	Fresh	94
2	1	94
3	2	94
4	3	93
5	4	93
6	5	93

^aIsolated yield

acetate in ethanol at reflux conditions in the presence of silica (NPs) supported Fe (III). Silica (NPs) supported Fe (III) is an inexpensive heterogeneous reagent, which can be prepared easily by treating ferric chloride with silica nanoparticle. Ease and safety in handling, rate enhancement, high yields and easy work up procedures for reuse are the properties which made us to use this interesting reagent as a catalyst. To the best of

our knowledge there are no reports on the applicability of silica (NPs) supported Fe (III) for the synthesis of 1,4-dihydropyridines in the literature.

In the preliminary experiments, the catalytic behaviours of five types of catalyst were compared in the reaction of *p*-nitrobenzaldehyde, ethyl acetoacetate and ammonium acetate at reflux conditions (table 1).

In the absence of catalyst, the reaction did not progress at all. Notably, silica (NPs) supported Fe (III) shows an activity higher than those reported in heterogeneous, we believe that nano silica surface chemistry plays an important role in this reaction.

To obtain a visual image of the supported catalyst, scanning electron microscopy (SEM) was carried out. By SEM image some information about the morphology of the catalyst particles was obtained as presented in figure 2. The SEM image shows particles with diameters in the range of nanometers to micrometers. As indicated in figure 2, the gray particles is nano silica which are supported by FeCl₃ white particles.

Silica (NPs) supported Fe (III) can act as Bronsted and Lewis acid catalysts,²⁸ as illustrated in scheme 2.

The effect of catalyst and its abilities to act as a Brønsted or Lewis acid (empty π orbital of Fe in silica (NPs) supported Fe (III)) is suggested in scheme 3. In this mechanism, we propose that an acid–base interaction between silica (NPs) supported Fe (III) and lone pair of oxygen polarizes C=O bond of aldehyde. Then Knoevenagel product (I) and ester enamine (II) were prepared by this interaction. Condensation of these two fragments gives intermediate (III) which subsequently cyclizes to the 1,4-dihydropyridine.²⁹

Table 4. Silica (NPs) supported Fe (III) catalysed synthesis of 1,4-dihydropyridines **4a–n**.

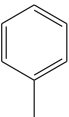
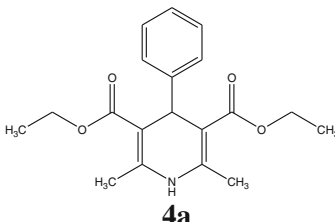
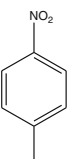
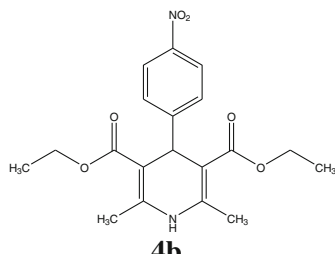
Entry	Ar	Time (min)	Product	Yield, ^a %	Mp (°C)	
					Measured	Reported
1		30		91	157–159	158–160 ³⁰
2		20		94	128–130	129–131 ³⁰

Table 4. (continued)

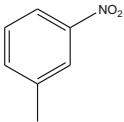
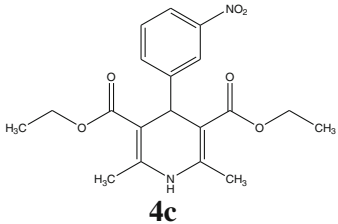
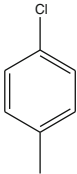
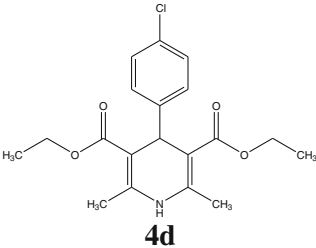
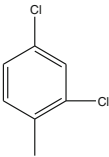
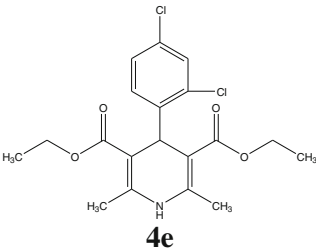
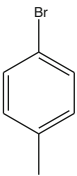
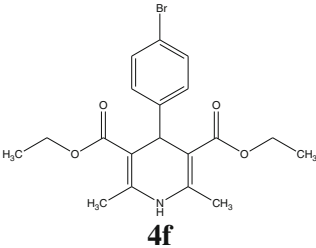
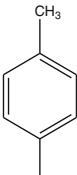
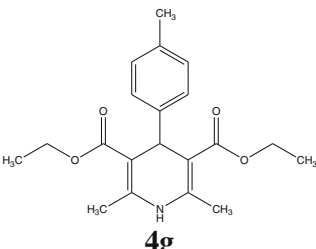
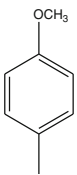
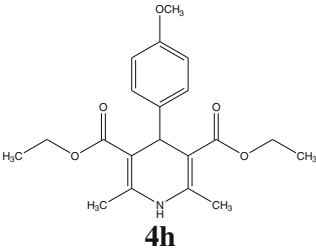
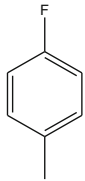
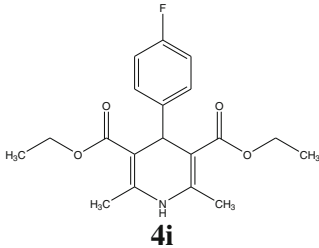
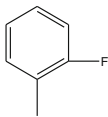
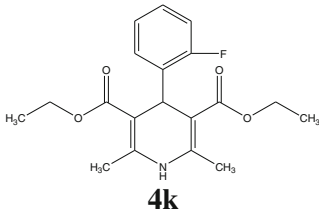
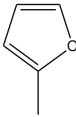
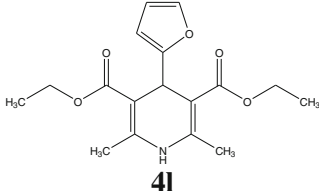
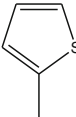
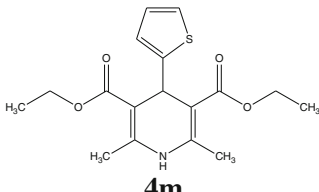
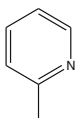
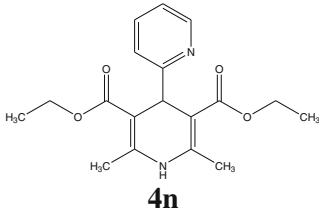
Entry	Ar	Time (min)	Product	Yield, % ^a	Mp (°C)	
					Measured	Reported
3		25	 4c	89	161–163	162–164 ³⁰
4		20	 4d	93	145–147	147–148 ³⁰
5		28	 4e	93	153–155	–
6		32	 4f	87	161–162	162–164 ²⁹
7		40	 4g	87	133–135	135–137 ³¹
8		40	 4h	85	160–162	161–163 ³⁰

Table 4. (continued)

Entry	Ar	Time (min)	Product	Yield, ^a %	Mp (°C)	
					Measured	Reported
9		35		89	156–158	150–152 ³²
10		25		86	147–149	–
11		27		91	160–162	160–161 ³¹
12		33		91	170–172	171–173 ³¹
13		26		90	166–168	–

^aIsolated yield

Expectedly, the catalytic system should be influenced by various reaction parameters, such as amount of the employed catalyst and solvent system. To establish the optimal reaction conditions, a set of experiments varying the amount of silica (NPs) supported Fe (III), and effect of solvent were taken into account.

We have screened effect of different solvents with varying polarity and protic nature. It was observed that ethanol proved to be the best choice for this reaction over any organic solvents such as acetonitrile and

toluene. Also, it was observed that the good results were not obtained in solvent-free conditions. The results are presented in (table 2).

First, we optimized the amount of silica (NPs) supported Fe (III) as catalyst in the model reaction. The optimum amount of silica (NPs) supported Fe (III) was chosen to be 0.6 mol%. The same reaction was carried out five times consequently to check the reusability of catalyst and it was found that, all the five times, it gave almost the same yield of product without significant decrease in activity (table 3).

The study was then extended to preparation of various 1,4-dihydropyridines using silica (NPs) supported Fe (III) in high yields. Reactions were carried out in ethanol at reflux conditions. The results are listed in table 4.

4. Conclusion

In conclusion, it was demonstrated that a novel readily available, economic silica (NPs) supported Fe (III) has been prepared. This catalyst could behave as recyclable and heterogeneous solid acid for the synthesis of various substituted 1,4-dihydropyridines. The condensation of aldehydes with ethyl acetoacetate and ammonium acetate in ethanol afforded 1,4-dihydropyridines, offering the practical convenience in the product separation from the catalytic system. The merit of this methodology is that it is simple, fast, mild and efficient.

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