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ORIGINAL PAPER

An efficient $FeCl_3/SiO_2$ NPs as a reusable heterogeneous catalyzed five-component reactions of tetrahydropyridines under mild conditions

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Abstract A convenient, simple, and multicomponent coupling strategy has been developed for the synthesis of highly functionalized tetrahydropyridines using $FeCl_3/SiO_2$ NPs as catalyst. This method demonstrated five-component coupling reactions of 1,3-dicarbonyl compounds, aromatic aldehydes and amines without an inert atmosphere. Atom economy, good yields, environmentally benign, and mild reaction conditions are some of the important features of this protocol. Notably, this catalyst could be recycled and reused for several times without noticeably decreasing the catalytic activity.

Keywords Tetrahydropyridines · Five-component · Nano silica · Reusable catalyst · One pot

Introduction

Multicomponent reactions (MCRs) have been proved as viable methods to access complex structures in a single synthetic operation from simple building blocks. Specificities of MCRs are high selectivity and atom-economy as well as procedural simplicity due to the formation of carbon–carbon and carbon–heteroatom bonds in one pot [1, 2]. Typically, purification of products resulting from MCRs is also simple since all the organic reagents are consumed and converted into the target product [3–5]. MCRs are also useful methods in medicinal chemistry and allow fast, automated, and high throughput generation of organic compounds [6, 7]. Tetrahydropyridines and their derivatives have received attention owing to their pharmacological activities such as anti-hypertensive [8], anti-bacterial [9], anti-convulsant, and anti-inflammatory [10]. Later, Tripathi and coworkers [11] reported that some of the substituted tetrahydropyridines display antimalarial activity, too. Synthesis of highly substituted tetrahydropyridines [12] has been developed using several approaches such as tandem cyclopropane ring-opening/Conia-ene cyclization [13], imino Diels–Alder reactions [14], aza-Prins-cyclizations [15] intramolecular Michael addition [16] and intramolecular Mannich reaction onto iminium ions [17].

Recently, the syntheses of functionalized tetrahydropyridines have been reported using MCRs in the presence of L-proline/TFA [11], bromodimethylsulfonium bromide (BDMS) [18], tetrabutylammonium tribromide (TBATB) [19], $InCl_3$ [20], $ZrOCl_2{\cdot}8H_2O$ [21], and CAN [22] as a catalyst. Some of these methods violate principles of green chemistry in several instances such as prolonged reaction time, low yield, toxicity, and non-recoverability as well as non-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 has received growing attention in recent years. The demand for environmentally benign procedures with heterogeneous and reusable catalyst made us develop a safe alternate method for the synthesis of tetrahydropyridines in the presence of nanosilica-supported ferric chloride ($FeCl_3/SiO_2$ NPs) (Scheme 1).

Experimental

The products were isolated and characterized by physical and spectral data. ^1H NMR and ^{13}CNMR spectra were recorded on Bruker Avance-400 MHz spectrometers in the

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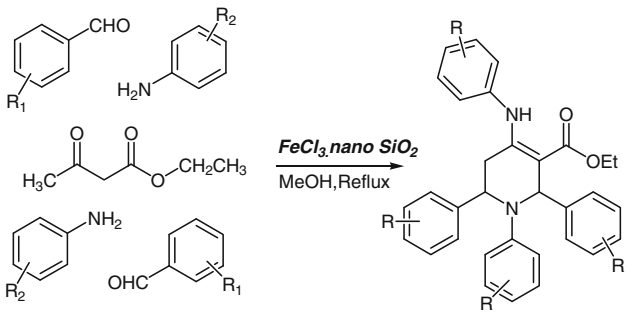


Scheme 1 $FeCl_3$.nano SiO_2 prompted synthesis of tetrahydropyridines under reflux conditions

Table 1 Optimization of reaction conditions for the synthesis of functionalized tetrahydropyridine 1g

Entry	Solvent/ condition	Catalyst (mol%)	Time	Yield[A] (%)
1	MeCN/reflux	$FeCl_3{\cdot}SiO_2$ (10 %)	12	62
2	CH_2Cl_2/reflux	$FeCl_3{\cdot}SiO_2$ (10 %)	12	48
3	H_2O/reflux	$FeCl_3{\cdot}SiO_2$ (10 %)	12	26
4	EtOH/reflux	$FeCl_3{\cdot}SiO_2$ (10 %)	12	67
5	MeOH/reflux	$FeCl_3{\cdot}SiO_2$ (10 %)	12	77
6	MeOH/rt	$FeCl_3{\cdot}SiO_2$ (10 %)	12	51
7	MeOH/reflux	$HClO_4{\cdot}SiO_2$ (15 %)	8	70
8	MeOH/reflux	I_2(15 %)	10	73
9	MeOH/reflux	$InCl_3$(20 %)	9	68
10	MeOH/reflux	$FeCl_3{\cdot}SiO_2$ NPs (1 %)	5	88
11	**MeOH/reflux**	**$FeCl_3{\cdot}SiO_2$ NPs (0·8 %)**	**5**	**91**
12	MeOH/reflux	$FeCl_3{\cdot}SiO_2$ NPs (0.6 %)	7	84
13	MeOH/reflux	None	14	Trace

Bold entry indicates the best result

[A] Isolated yield

presence of tetramethylsilane as internal standard. The IR spectra were recorded on FT-IR Magna 550 apparatus using KBr plates. The elemental analyses (C, H, N) obtained from a Carlo ERBA Model EA 1108 analyzer were carried out on Perkin-Elmer 240c analyzer. Melting points were determined on Electro thermal 9200. Ferric chloride-supported nano silica was obtained according to the method reported in the literature. Microscopic morphology of products was visualized by SEM (LEO 1455VP).

Preparation of nano silica-supported ferric chloride

In a 100-mL flask, nano silica gel (25 g) and $FeCl_3{\cdot}6H_2O$ (2 g) (8 % of the weight of SiO_2 NPs) were vigorously stirred under solvent-free conditions at room temperature for 24 h to achieve a homogeneous adsorption. After that, a yellow powder was obtained which was later heated for 1 h at 100 °C to activate the catalyst.

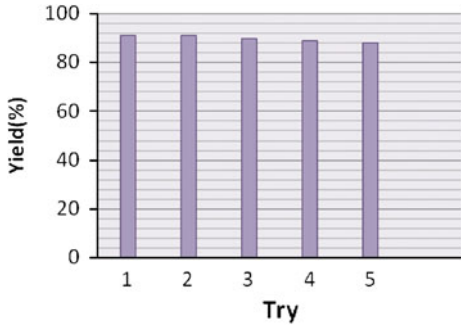


Fig. 1 The catalyst reusability for the synthesis of tetrahydropyridines

Preparation of tetrahydropyridines derivatives

A solution of amine (2 mmol), ethyl acetoacetate (1 mmol), $FeCl_3/SiO_2$ NPs (0.8 mol%) and methanol (3 mL) was being stirred under reflux for 40 min. Then, aldehyde (2 mmol) was added and vigorous stirring continued until the solid precipitation was observed. After being cooled to room temperature, the solid was filtered off and washed with hot methanol. The residue was dissolved in chloroform and then filtered until heterogeneous catalyst was recovered. The filtrate solution was evaporated to afford pure tetrahydropyridines.

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 piperidine. Furthermore, it was recycled for six times.

Selected spectral data

Ethyl 2,6-bis(4-mythylphenyl)-1-(phenyl)-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1b)

Pale yellow solid, mp = 229–231 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.45 (t, 3H, CH_3CH_2), 2.32 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.78 (dd, 1H, H-5), 2.86 (dd, 1H, H-5), 4.33–4.39 (m, 2H, CH_3CH_2), 5.13 (s, 1H, H-6), 6.17 (m, 2H, ArH), 6.41 (s, 1H, H-2), 6.45 (m, 2H, ArH), 6.59 (m, 2H, ArH), 7.01 (m, 2H, ArH), 7.25 (m, 2H, ArH) 7.30–7.31 (m, 6H, ArH), 7.21 (m, 2H, ArH), 10.26 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$)δ ppm = 15.1, 21.3, 21.5, 33.6, 55.0, 57.7, 59.8, 98.2, 112.6, 116.1, 125.5, 125.7, 126.2, 126.6, 128.5, 128.7, 128.8, 129.1, 136.2, 136.7, 138.3, 139.7, 141.4, 147.6, 156.4, 168.0; FT-IR (KBr): 3,437, 2,983, 1,860, 1,647, 1,596, 1,511, 1,443, 1,366, 1,334, 1,249, 1,170, 1,067, 1,029 cm^{-1}; Anal. Calcd for $C_{34}H_{34}N_2O_2$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.13; H, 7.96; N, 5.41.

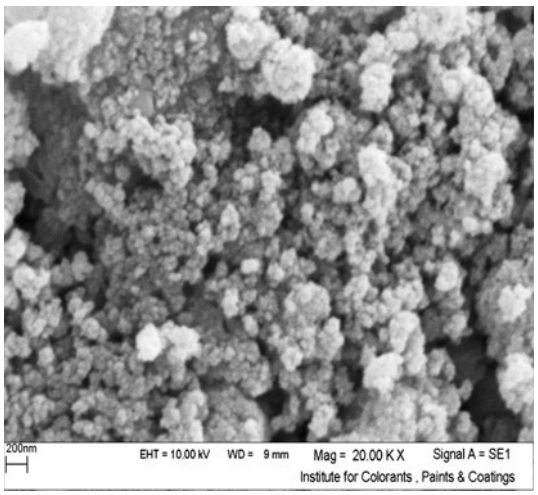


Fig. 2 SEM image of the $FeCl_3/SiO_2$ NPs

Table 2 Synthesis of functionalized tetrahydropyridines (FT)

Entry	R1	R2	FT	Time (h)	Yield[a] (%)
1	4-Cl	H	1a	6	83
2	4-Me	H	1b	8	85
3	4-NO_2	H	1c	7	86
4	3-NO_2	H	1d	6	84
5	4-Br	H	1e	8	85
6	H	4-OMe	1f	5	87
7	H	4-Br	1g	5	91
8	H	4-Me	1h	7	86
9	H	3-Me	1i	9	74
10	4-NO_2	4-OMe	1j	6	87
11	4-Cl	4-Cl	1k	8	82
12	4-Br	3-OMe	1l	9	78
13	2,4-Cl_2	4-Br	1m	12	71
14	4-$N(Me)_2$	2-Me	1n	11	68
15	3-Cl	4-NO_2	1o	8	82

[a] Isolated yield

Ethyl 2,6-bis(4-nitrophenyl)-1-(phenyl)-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1c)

Pale yellow solid; mp = 248–250 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 1.27 (t, 3H, CH_3CH_2), 2.45 (dd, 1H, H-5), 2.49 (dd, 1H, H-5), 4.27–4.34 (m, 2H, CH_3CH_2), 5.01 (s, 1H, H-6), 6.16 (s, 1H, H-2), 6.51 (m, 2H, ArH), 6.73 (m, 2H, ArH), 6.96 (m, 2H, ArH), 7.10 (m, 2H, ArH), 7.21 (m, 2H, ArH), 7.29 (m, 2H, ArH), 7.38 (m, 2H, ArH), 7.81 (m, 2H, ArH), 8.16 (m, 2H, ArH),10.41 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.9, 35.4, 60.1, 60.9, 62.3, 96.6, 118.4, 120.7, 123.5, 124.0, 125.2, 127.1, 128.0, 129.4, 129.8, 136.3, 147.0, 147.2, 149.9, 150.3, 154.2, 156.4, 167.1; FT-IR (KBr): 3,442, 2,981, 1,651, 1,599, 1,506, 1,437, 1,380, 1,346, 1,237, 1,168, 1,121, 1,066, 1,051 cm^{-1}; Anal. Calcd for: $C_{32}H_{28}N_4O_6$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.81; H, 4.84; N, 10.01.

Ethyl 2,6-bis(4-nitrophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1j)

Light yellow solid; mp = 197–199 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.44 (t, 3H, CH_3CH_2), 2.76 (m, 2H, H-5), 3.67 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.37–4.49 (m, 2H, CH_3CH_2,) 5.13 (m, 1H, H-6), 6.33–6.40 (m, 5H, ArH and H-2), 6.69 (m, 4H, ArH), 7.29 (m, 2H, ArH), 7.47 (m, 2H, ArH), 8.15 (m, 4H, ArH), 10.20 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 34.1, 49.6, 55.3, 56.7, 57.9, 96.3, 114.2, 114.9, 123.7, 124.1, 127.6, 127.7, 131.3, 137.2, 140.1, 146.7, 147.4, 149.9, 152.0, 152.2, 155.8, 158.1, 167.9; FT-IR (KBr): 3,211, 2,890, 2,323, 1,670, 1,602, 1,521, 1,469, 1,333, 1,238, 1,184, 1,088 cm^{-1}. Anal. Calcd for: $C_{34}H_{34}N_4O_8$: C, 67.31; H, 5.60; N, 9.22. Found: C, 66.93; H, 5.47; N, 9.29.

Results and discussion

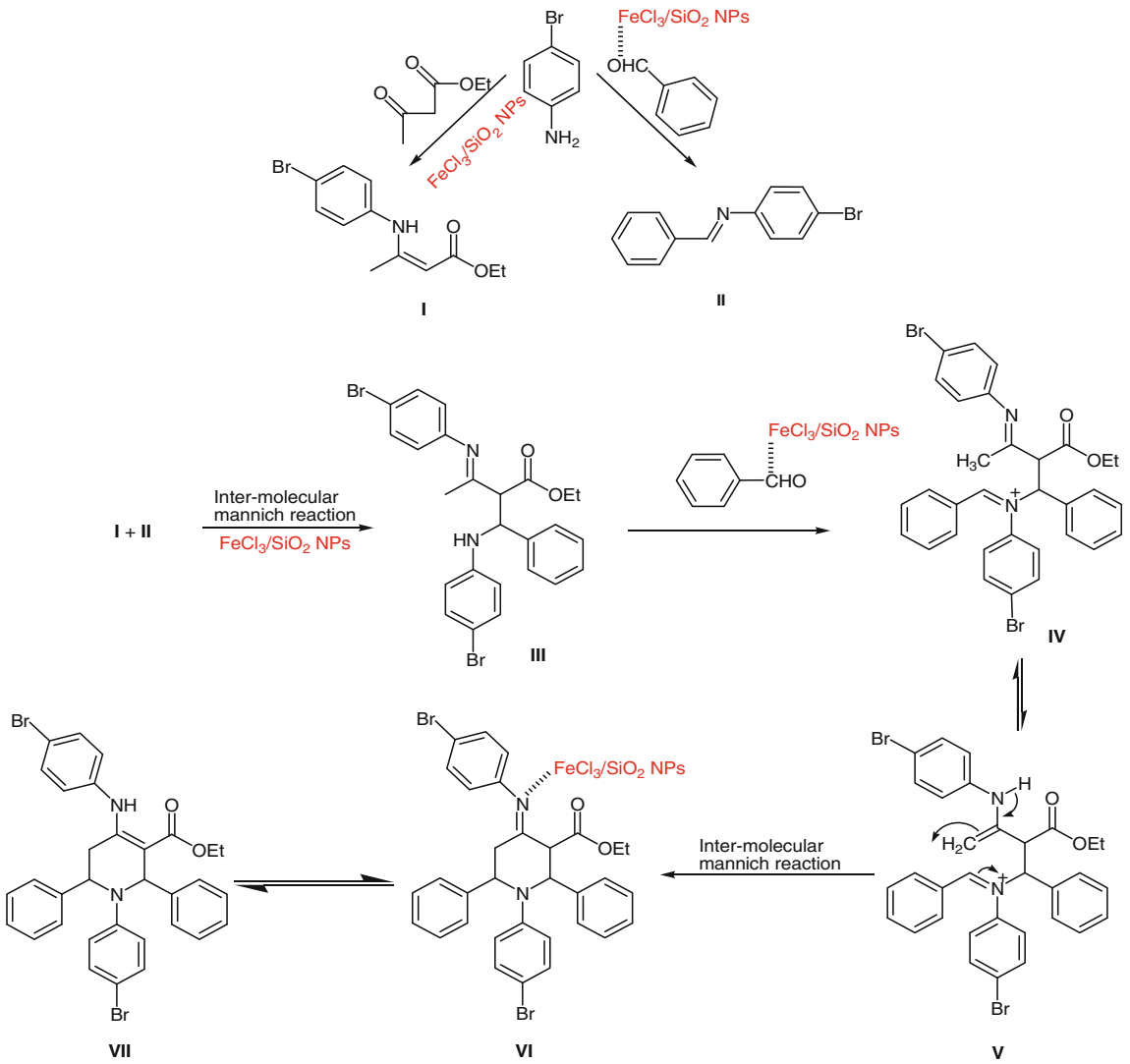
In our initial experiments, the standard reaction conditions were established based on the reactions of benzaldehyde (2 mmol) with ethylacetoacetate (1 mmol) and 4-bromoaniline (2 mmol) in different solvents and catalysts (Table 1). This reaction was carried out using the aprotic (Table 1, entries 1, 2) and protic solvents (Table 1, entries 3–5). The best result was obtained in methanol (Table 1, entry 5).

Next, we studied the model reaction in methanol at different temperatures (Table 1, entries 5, 6). The maximum yield was obtained at reflux conditions (Table 1, entry 5) as the reaction rate increased by raising temperature.

The model reaction in methanol at reflux was also studied using many types of catalysts (Table 1, entries 6–12). In the absence of catalyst, the reaction did not progress at all (Table 1, entry 13). Notably, $FeCl_3/SiO_2$ NPs shows activity levels higher than those reported for heterogeneous catalysts. Hence, we believe that nano silica surface chemistry plays an important role in this reaction.

The best results were obtained with 0.8 mol% of $FeCl_3/SiO_2$ NPs (Table 1, entry 11).

The same reaction was carried out many times in order to check reusability of the catalyst. Interestingly, the same amount of yield was obtained each time without any significant decrease in activity (Fig. 1).



Scheme 2 A proposed mechanism for the synthesis of tetrahydropyridines in the presence of silica (NPs) supported Fe (III)

Scanning electron microscopy (SEM) was carried out to obtain a visual image of the supported catalyst. By SEM images, some information about the morphology of the catalyst particles was collected as presented in Fig. 2. The SEM image shows particles with diameters in the range of nanometers to micrometers (Fig. 2).

After that, the study was extended to the application of $FeCl_3/SiO_2$ NPs in synthesis of substituted tetrahydropyridines using various aldehydes and amine with ethyl acetoacetate. The best result was obtained in the model reaction at reflux and in the presence of $FeCl_3/SiO_2$ NPs 0.8 mol%. The results are listed in Table 2.

A proposed mechanism for this multi-component reaction is outlined in Scheme 2. $FeCl_3/SiO_2$ NPs can serve as a Lewis acidic catalyst for the reaction of 4-bromoaniline and ethyl acetoacetate or benzaldehyde to give the β-enaminone or imine. Then, the enamine **I** and imine **II** provided intermolecular Mannich reaction in the presence of $FeCl_3/SiO_2$ NPs to produce intermediate **III**. The intermediate **III** reacted with aldehyde to produce **IV** by the elimination of a water molecule. The intermediate **IV** underwent tautomerization to produce intermediate **V**. Furthermore, **V** underwent intra-molecular cyclization to obtain functionalized tetrahydropyridine derivatives (**VI**).

Conclusion

To sum up, it was reported that $FeCl_3/SiO_2$ NPs is a highly efficient catalyst for the synthesis of functionalized tetrahydropyridines-scaffolds by means of a five-component condensation of amine, aldehyde, and ethyl acetoacetate in one pot. This method is applicable to a wide range of

substrates, including aromatic aldehydes and amines. In addition, it also provides the corresponding tetrahydropyridines in good to excellent yields. The present methodology offers advantages such as reduced reaction times, high yields, operational simplicity, reduced toxicity of $FeCl_3/SiO_2$ NPs along with catalyst recoverability and recyclability.

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