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Graphical Abstract

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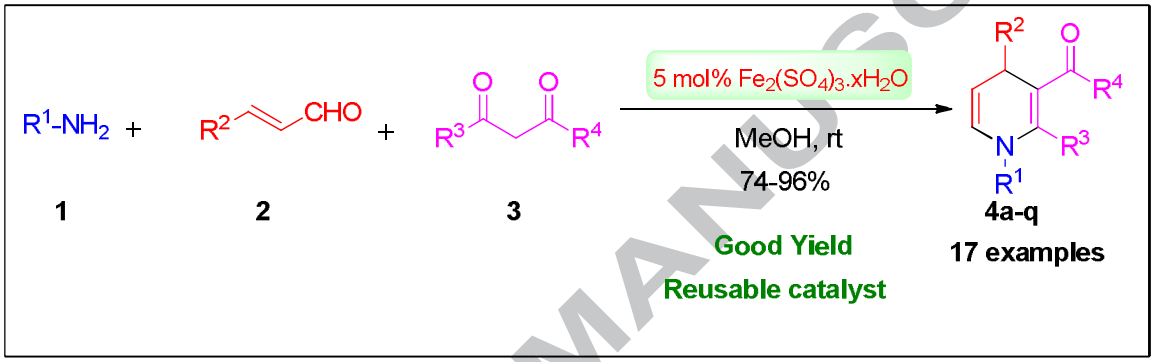

Hydrated ferric sulfate catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridines using three-component reaction

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Keywords: 5,6-unsubstituted 1,4-dihydropyridines, *α,β*-unsaturated aldehydes, amines, 1,3-diketones, hydrated ferric sulfate [$Fe_2(SO_4)_3.xH_2O$]

Abstract

A wide variety of 5,6-unsubstituted 1,4-dihydropyridines derivatives (**4a–q**) were synthesized through a one-pot three-component reaction from *α,β*-unsaturated aldehydes, amines and 1,3-diketones at room temperature using hydrated ferric sulfate as a Lewis acid catalyst. The key features of the present protocol are mild and simple reaction procedure, good to excellent yields, and use of inexpensive, recyclable and environmentally benign catalyst.

The design and efficient synthesis of bioactive compounds is one of the main objectives of organic and medicinal chemistry.[1] One of the most useful ways to achieve this goal is to articulate a synthetic strategy that allows the formation of several bonds in a single pot. Among the various synthetic approaches, multicomponent reactions[2] (MCRs) have emerged as a powerful tool in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds due to lesser number of reaction and purification steps, high selectivity and atom economy, simplicity and good yields.[3] Thus, development of new multicomponent reactions and improving the known MCRs are an area of considerable current interest in contemporary organic synthesis. 1,4-Dihydropyridines, important class of nitrogen heterocycles, are found in numerous synthetic pharmaceutical agents.[4] Various 1,4-dihydropyridine-based drug molecules such as amlodipine, clevidipine, felodipine, nicardipine, etc. are already

marketed to reduce systemic vascular resistance and arterial pressure.[5] In addition, they exhibit a diverse range of biological properties such as calcium channel blockers,[6a] HIV protease inhibition,[6b] inhibition of topoisomerase I,[6c] MDR reversal,[6d] neuroprotection,[6e] radioprotection,[6f] cocaine dependent regulator,[6g] and TGFβ signal inhibitors.[6h] They are also useful synthetic precursors specially in the preparation of libraries of alkaloid-like compounds and variety of nitrogen-containing heterocycles such as piperidines or pyridines.[7] The synthesis of these heterocycles has long been an area of immense interest resulting in the development of efficient synthetic approaches for 1,4-dihydropyridines. Among them, the direct condensation of *α,β*-unsaturated aldehydes with amines and 1,3-carbonyl compounds in presence of suitable catalyst for the synthesis of 5,6-unsubstituted 1,4-dihydropyridines is well documented in literature. Over the last few years, several reagents have been explored as catalysts to access these compounds, such as sulfated mixed metal oxides,[8a] perchloric acid adsorbed on magnetic Fe_3O_4 nanoparticles coated with silica,[8b] Brønsted acid–thiourea co-catalyst,[8c] $InCl_3$,[8d] iodine,[8e] nano CuO,[8f] L-Proline,[8g] chiral binol-derived phosphoric acid derivatives,[8h] $Mg(ClO_4)_2$,[8i] $Sc(OTf)_3$[8j] and cerium ammonium nitrate (CAN).[8k] Other synthetic methods developed for the construction of 5,6-unsubstituted 1,4-dihydropyridines are as follows: $PdCl_2$ catalyzed 1,4-conjugated addition of enamines and cinnamaldehyde,[9a] Michael addition of *β*-enaminocarbonyl compounds with *α,β*-unsaturated aldehyde,[9b] three-component reaction using amines, and *α,β*-unsaturated aldehyde and dimethyl acetylenedicarboxylate (DMAD)[9b] or enaminones[9c] and microwave assisted [4+2] cycloadditions of 1-azadienes with allenic esters.[9d,e] Some of these methods are associated with certain limitations such as use of excess[8a,9c] and expensive catalyst,[8a-d,8h,8j,9a] low yields,[8i-j,9b-c] requirement of multistep sequences[9b] and harsh reaction conditions.[8d,9e-f] Consequently, there is still a need to find out greener reusable catalyst, which provides better yields at room temperature. Recently, ferric sulfate [$Fe_2(SO_4)_3.xH_2O$] has received considerable attention as a mild, inexpensive, and reusable catalyst for various organic transformations, such as tetrahydropyranylation of alcohols,[10a] preparation of acylals from aldehydes,[10b] 2,3-unsaturated glycosides via Ferrier rearrangement,[10c] and per- O-acetylation of sugars,[10d] synthesis of tetrahydroquinoline,[10e] tetrahydropyrido[2,3-c]-coumarin derivatives,[10f] 1H-pyrazole-4-carbodithioate[10g] and 3-[(alkyl/arylthio)(aryl)methyl]-1H-indole derivatives.[10h] The unique solubility of the catalyst in acetonitrile/methanol and insolubility in DCM enables us

to use it as both homogenous and heterogeneous catalyst. Moreover, it can also be easily recovered at the end of reaction by adding DCM. Due to its wide applicability as a catalyst, we presume that it would be an efficient catalyst for the one-pot three-component reaction for the synthesis of the 5,6-unsubstituted 1,4-dihydropyridines derivatives. In this letter, we would like to disclose our successful results for the one-pot synthesis of 5,6-unsubstituted 1,4-dihydropyridines from *α,β*-unsaturated aldehydes, amines and acyclic 1,3-carbonyl compounds as shown in Scheme 1.

(**Scheme 1**)

For the present study, the mixture of cinnamaldehyde (1 mmol), benzylamine (1 mmol) and methyl acetoacetate (1 mmol) was stirred in presence of 5 mol % of $Fe_2(SO_4)_3.xH_2O$ in methanol (3 mL) for 2 h at room temperature. The product 5,6-unsubstituted 1,4-dihydropyridines (**4a**) was isolated in 92% yield after chromatographic purification (entry 1, Table 1) and it was characterized from ^{1}H NMR, ^{13}C NMR and mass spectra. The same set of reactions were also carried out using 10 and 15 mol% of $Fe_2(SO_4)_3.xH_2O$ in methanol under identical reaction condition and it provided the desired product **4a** (entry 2 and 3, Table 1) in 89%, and 82% yields, respectively.

(**Table 1**)

From these observations, it is clear that the yield of the product **4a** reduces slowly with increasing the amount of catalyst from 5% to 15%. To find out a suitable solvent system, the similar reactions were conducted in ethanol, *iso*-propanol, *n*-BuOH, DCM, acetonitrile, 1,4-dioxane, THF, DMF and DMSO under identical reaction conditions (entries 4–12, Table 1). The best yield was obtained in methanol using 5 mol% catalyst with the shortest reaction time, which are summarized in Table 1. It was also observed that no desired product was obtained in absence of catalyst even after 12 h of stirring at room temperature and only the starting substrates were recovered (entry 13, Table 1). After optimizing the reaction condition, various amines such as 4-methylbenzylamine, methoxybenzylamine and *α*-methylbenzylamine were examined with cinnamaldehyde and methyl acetoacetate under identical reaction conditions and the desired products **4b-d** were isolated in good yields (entries 2-4, Table 2). Similarly, a wide variety of aliphatic amines such as *n*-butylamine, *sec*-butylamine, *n*-heptylamine, 1-hexadecylamine and

cyclohexylamine were also scrutinized with cinnamaldehyde and methyl acetoacetate under similar reaction conditions and the desired 5,6-unsubstituted 1,4-dihydropyridines (**4e-i)** were obtained in excellent yields (entries 5-9, Table 2). Likewise, numerous *β*-keto esters such as ethyl acetoacetate, *tert*-butyl acetoacetate and ethyl butyrylacetate on reaction with cinnamaldehyde and benzyl amine provided desired 5,6-unsubstituted 1,4-dihydropyridines (**4j-4l)** in good to excellent yields under identical reaction condition (entries 10-12, Table 2). Furthermore, various acyclic 1,3-diketones such as acetylacetone, benzoylacetone and dibenzoylmethane on reaction with benzylamine, cinnamaldehyde afforded the desired dihydropyridines (**4m-4o**) in good yields (entries 13–15, Table 2). When the similar reactions were examined with cyclic 1,3-diketone such as 1,3-cyclohexanedione and dimedone, cinnamaldehyde and benzylamine, it gave complicated reaction mixture and no desired products were isolated. It is worthwhile to mention that *β*-keto esters react faster as compared to acyclic 1,3-diketones in the present reaction.

(**Table 2**)

To expand the scope of the present protocol, reactions were carried out with other *α,β*-unsaturated aldehyde such as crotonaldehyde with benzylamine and methyl acetoacetate/ethyl acetoacetate under similar reaction conditions and the desired dihydropyridines (**4p-4q**) were obtained in good yields (entries 16 and 17, Table 2). Unfortunately, the reaction with aromatic amine such as aniline gave inseparable complex reaction mixture under identical reaction condition.

All the products **4a–q** was characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra, and mass spectra. On the basis of the reported literature,[8a,8c,8g, 8l-m] a plausible mechanism for the formation of substituted 5,6-unsubstituted 1,4-dihydropyridines **4** is depicted in Scheme 2. There are two possible mechanistic pathways. In ***Pathway A***, we believe that a condensation reaction between *α,β*-unsaturated aldehydes (**1**) and amine (**2)** gives *α,β*-unsaturated imine intermediate **A** in the presence of catalyst $Fe_2(SO_4)_3.xH_2O$. Then the enolize form of *β*-keto ester or 1,3-diketone reacts with *α,β*-unsaturated imine intermediate **A** to provide intermediate **B,** which undergoes cyclization followed by dehydration to give the desired 5,6-unsubstituted 1,4-dihydropyridine (**4**) (Scheme 2). In ***Pathway B****,* there is also another possibility that activated *β*-keto ester or 1,3-

diketone (**3)** reacts with amine **2** to form *β*-enaminones **D** as an intermediate in the initial step. The second step involves Michael addition of an *α,β*-unsaturated aldehyde (**1)** to the *β*-enaminone **D** to form intermediate **E**, which undergoes intramolecular cyclization to form hydroxytetrahydropyridine **F**. Finally, the desired 5,6-unsubstituted 1,4-dihydropyridine **4** is obtained after dehydration as shown in Scheme 2.

(**Scheme 2**)

Finally, the structure of one of the representative compounds such as **4a** was confirmed unambiguously by single crystal X-ray diffraction analysis (see the Supplementary data) (Fig. 1). A racemic mixture was obtained and that the structure of **4a** in Fig. 1 represents only one enantiomer (S configuration) present in the Unit Cell. Otherwise there is no congruence between a racemic mixture (both enantiomers in equal amounts) obtained in Scheme 2 and the single crystal X-ray structure of a single enantiomer.

(**Figure 1**)

The efficient recovery of the catalyst at the end of the reaction is highly desirable. The reusability test of the catalyst was performed as follows: a mixture of cinnamaldehyde (10 mmol), benzylamine (10 mmol), methyl acetoacetate (10 mmol) and $Fe_2(SO_4)_3.xH_2O$ (0.5 mmol, 0.205 g) was taken in 30 mL of methanol and it was stirred for 2 h at room temperature. After completion of the reaction, methanol was removed in a rotatory evaporator and the crude residue was dissolved in 25 mL of dichloromethane. On adding dichloromethane, the catalyst separated out and it was filtered off through a Büchner funnel, washed with another 5 mL of DCM and dried. The recovered catalyst was used for a similar set of reactions for three more consecutive cycles. Each reaction with recovered catalyst was carried out for 2 h using the same reaction procedure. The yields and the number of experiments conducted are shown in the bar diagram in Figure 2. The required product **4a** was isolated in 86% yield after concentrating dichloromethane followed by purification through a silica gel column chromatography. The yield of the reaction decreased relatively in the fourth cycle which may be due to weight loss of the catalyst during handling in each cycle.

(**Figure 2**)

The efficiency and generality of the present protocol can be realized at a glance by comparing our results with those of some reported procedures as shown in Table 3. The results have been compared with respect to the mole percent of the catalyst used, reaction time and yields. It can be easily visualized that the reactions are considerably faster and give better product yields on using only 5 mol % of $Fe_2(SO_4)_3.xH_2O$ as compared to other catalyst as shown in Table 3.

(**Table 3**)

In short, we have achieved the synthesis of 5,6-unsubstituted 1,4-dihydropyridines derivatives using *α,β*-unsaturated aldehydes, amines and 1,3-diketone in the presence of catalytic amount of $Fe_2(SO_4)_3.xH_2O$ in methanol. The reaction is compatible with variety of aliphatic amine and 1,3-diketone compounds. In comparison to other Lewis acids catalyst, $Fe_2(SO_4)_3.xH_2O$ has been found to be effective, mild, and less expensive. Moreover, due to its recyclability, the present method may open up a simple, mild and less expensive pathway for the synthesis of 5,6-unsubstituted 1,4-dihydropyridines in good yields. The application of synthesized dihydropyridines as dienophile in *aza*-Diels-Alder reaction is going on in our laboratory, and the results will be reported in due course.

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Supporting Information

Supplementary data (X-ray crystallographic data (CIF files) of **4a** spectral data of all compounds and copies of ^1H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:

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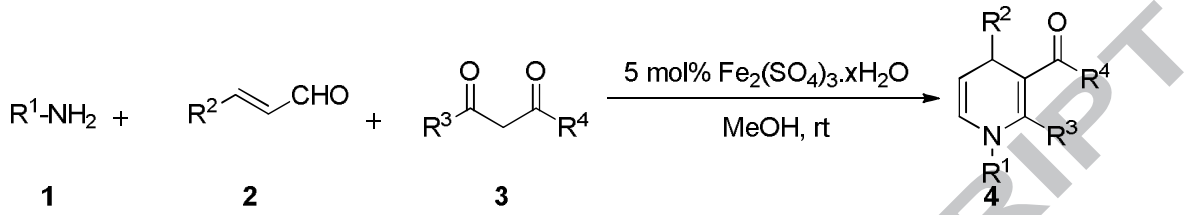
11. *General Procedure for the preparation of 5,6-unsubstituted 1,4-dihydropyridines*: The catalyst hydrated ferric sulfate (0.021g, 0.05 mmol) was added to a stirred mixture of *α,β*-unsaturated aldehyde (**1**, 1 mmol) amine (**2**, 1 mmol) and 1,3-diketone (**3**, 1 mmol) in 3 mL of methanol and it was kept for stirring at room temperature. After completion of the reaction as monitored by TLC, methanol was removed in a rotary evaporator and the crude residue was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with water followed by brine solution and finally it was dried over anhydrous sodium sulfate. The organic extract was concentrated in a rotary evaporator and the crude residue was purified through a silica gel (60-120 mesh) column chromatography. The desired products (**4a-4q**) were eluted with a mixture of hexane/ethyl acetate (9:1).

Spectroscopic data of the 5,6-unsubstituted 1,4-dihydropyridine derivatives: *Methyl 1-benzyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (**4a**)*: Brown Solid, mp 74-75 °C; R_f (10% ethyl acetate/hexane) 0.36; IR (KBr) 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.32 (m, 2 H), 7.31-7.27 (m, 5 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.19-7.14 (m, 1 H), 5.96 (d, *J* = 7.6 Hz, 1 H), 5.0 (dd, *J* = 5.6, 7.2 Hz, 1 H), 4.68-4.55 (m, 3 H), 3.53 (s, 3 H, OMe), 2.42 (s, 3 H, Me) ppm.^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.40, 149.13, 148.61, 131.04, 129.56, 128.86 (2 C), 128.29 (2 C), 127.47, 127.34 (2 C), 126.19(2 C), 126.03, 108.01, 100.02, 53.67, 50.64, 40.06, 16.01 ppm. HRMS (ESI) calcd for $C_{21}H_{21}NO_2$ ($M + H^+$) 320.1651, found 320.1652. *Ethyl 1-benzyl-2,4-dimethyl-1,4-dihydropyridine-3-carboxylate (**4q**):* Gummy liquid; R_f (10% ethyl acetate/hexane) 46; IR (KBr) 1677 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.21 (m, 3 H), 7.15 (d, *J* = 7.6 Hz, 2 H), 6.54 (d, *J* = 9.2 Hz, 1 H), 4.98 (dd, *J* = 5.2, 9.2 Hz, 1 H), 4.77 (d, *J* = 16.8 Hz, 1 H), 4.30 (d, *J* = 17.2 Hz, 1 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 3.90 (quin, *J* = 6.4 Hz, 1 H), 2.37 (s, 3 H, Me), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.05 (d, *J* = 6.4 Hz, 3 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.87, 155.28, 137.77, 129.09 (2C), 127.65, 126.37 (2 C), 124.12, 112.24, 98.58, 59.25, 55.71, 53.25, 19.69, 16.74, 14.82, ppm. HRMS (ESI) calcd for $C_{17}H_{21}NO_2$ ($M + H^+$) 272.1651, found 272.1651.



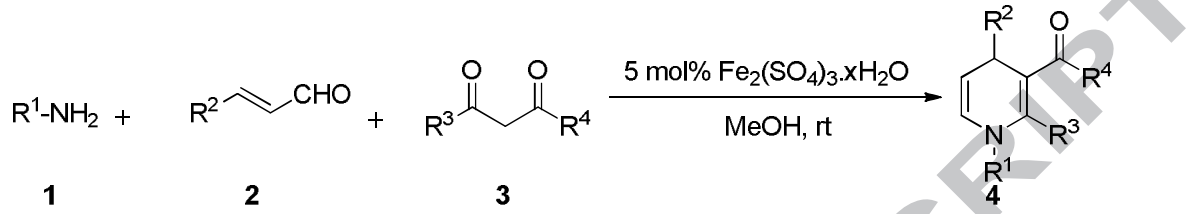
Scheme 1. One-pot synthesis of 5,6-unsubstituted 1,4-dihydropyridine derivatives

Table 1. Effect of solvent and catalyst loading on the synthesis of 5,6-unsubstituted 1,4 dihydropyridine (**4a**)[a]

Entry	Catalyst (mol%)	Solvent	Time	Yield[b]%
1	5	MeOH	2	92
2	10	MeOH	2	89
3	15	MeOH	2	82
4	5	EtOH	2	87
5	5	Isopropanol	3	68
6	5	*n*-BuOH	3	61
7	5	DCM	6	56
8	5	CH_3CN	6	41
9	5	1,4-Dioxane	6	28
10	5	THF	6	trace
11	5	DMF	6	42
12	5	DMSO	6	45
13	None	MeOH	12	-

[a] All the reactions were performed with benzylamine (1.0 mmol), cinnamaldehyde (1.0 mmol), and methyl acetoacetate (1.0 mmol) in the presence of $Fe_2(SO_4)_3.xH_2O$ as catalyst in 3 mL of indicated solvent at room temperature. [b]Isolated yields.

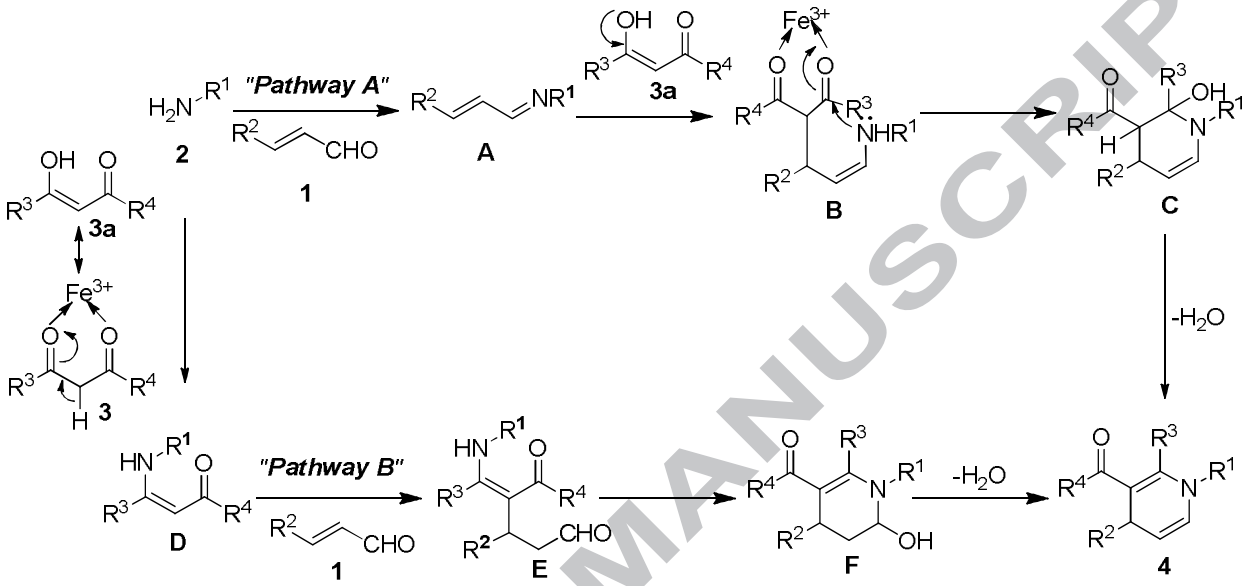
Table 2. Scope and yields of various 5,6-unsubstituted 1,4-dihydropyridines[a]



1 **2** **3** **4**

Entry	R^1	R^2	R^3	R^4	Product (**4**)	Time (h)	Yield[b] (%)
1	$PhCH_2$	Ph	Me	OMe	**4a**	2	92
2	4-Me-$PhCH_2$	Ph	Me	OMe	**4b**	2	94
3	4-MeO-$PhCH_2$	Ph	Me	OMe	**4c**	2	89
4	$PhCH(CH_3)$	Ph	Me	OMe	**4d**	2	84
5	Butyl	Ph	Me	OMe	**4e**	1	94
6	2-Butyl	Ph	Me	OMe	**4f**	1	96
7	Heptyl	Ph	Me	OMe	**4g**	1	94
8	$Me(CH_2)_{15}$	Ph	Me	OMe	**4h**	2	92
9	Cyclohexyl	Ph	Me	OMe	**4i**	2	87
10	$PhCH_2$	Ph	Me	OEt	**4j**	2	91
11	$PhCH_2$	Ph	Me	O*t*Bu	**4k**	2	82
12	$PhCH_2$	Ph	Et	OEt	**4l**	2	88
13	$PhCH_2$	Ph	Me	Me	**4m**	3	78
14	$PhCH_2$	Ph	Me	Ph	**4n**	3	74
15	$PhCH_2$	Ph	Ph	Ph	**4o**	3	85
16	$PhCH_2$	Me	Me	OMe	**4p**	2	78
17	$PhCH_2$	Me	Me	OEt	**4q**	2	84

[a]The reactions were carried out with amines (1.0 mmol), α,β-unsaturated aldehydes (1.0 mmol), and 1,3-carbonyl compound (1.0 mmol) in the presence of 5 mol % of $Fe_2(SO_4)_3.xH_2O$ in 3 mL of MeOH at room temperature. [b]Isolated yields.



Scheme 2. Plausible mechanism for the formation of 5,6-unsubstituted 1,4-dihydropyridines (**4**)

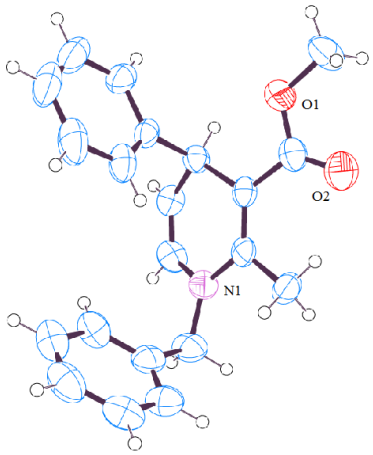


Figure 1. Single crystal X-ray structure of compound **4a** (CCDC 997063).

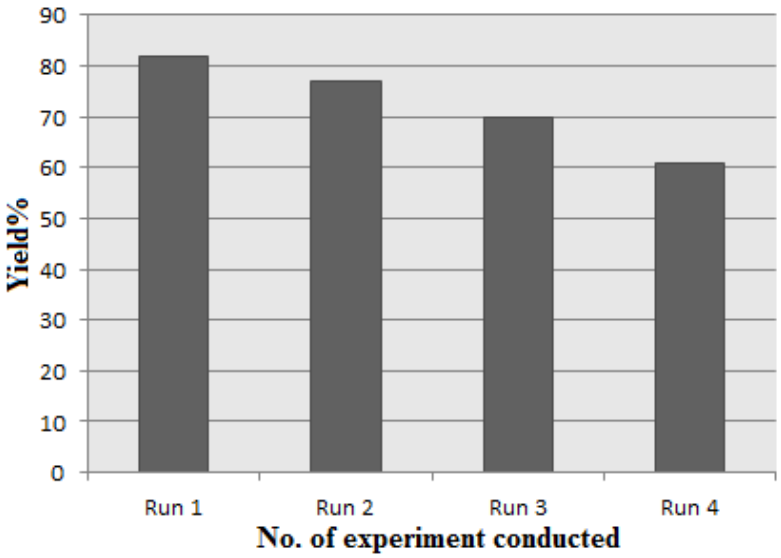


Figure 2. Reusability of the catalyst in methanol.

Table 3. Comparison of our result with other results using different catalysts[a]

Entry	Catalyst	Amount	Time	Yield[b,c,]%
1	$SO_4^{2-}/Ce_{0.07}Zr_{0.93}O_2$	20 mol%	1.5	84[8a]
2	Thiourea-Ammonium Salts	10 mol%	12	80[8c]
3	Binol-derived phosphoric acid	10 mol%	--	54[8h]
4	$Sc(OTf)_3$	5 mol%	16	75[8j]
5	$Fe_2(SO_4)_3.xH_2O$	5 mol%	2	91[d]

[a]All reactions were carried out with cinnamaldehyde, benzylamine and ethyl acetoacetate (1:1:1 ratio) at room temperatures. [b]Isolated Yields [c] Reported method with other catalysts. [d]The present protocol.