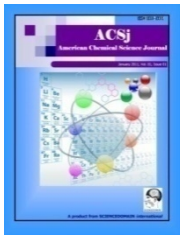

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$Fe_{0.2}Al_{1.8}Zn_1O_4$ Composite: An Efficient Catalyst for the Synthesis of 1, 4-Dihydropyridine Derivatives

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Authors' contributions

This work was carried out in collaboration between all authors. Author VMJ performed the said work. Author RPP designed the study and wrote the protocol. Authors SUT and SSK managed the analyses of the study and wrote the draft of manuscript. Authors SKV and AMZ managed the statistical analysis and provide the catalyst. Authors SBS and KLA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

A simple and rapid protocol has been developed for the synthesis of 1, 4-dihydropyridine derivatives in short reaction time to afford the products in excellent yield. Operational simplicity, clean reaction, high yield, simple work up are the significant advantages of the present protocol.

Keywords: $Fe_{0.2}Al_{1.8}Zn_1O_4$, Aldehyde; 1, 4-Dihydropyridines; EAA.

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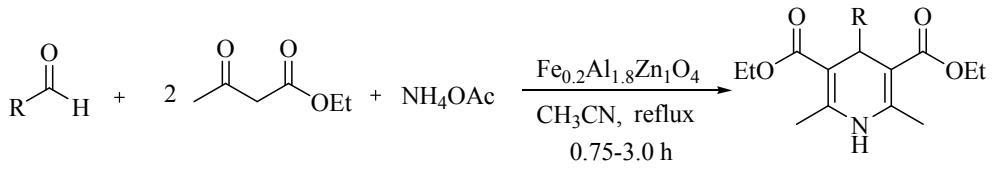
1. INTRODUCTION

1, 4-Dihydropyridine derivatives are the biologically active potent heterocyclic compounds possessing pharmacological and medicinal properties. Dihydropyridine (DHP) skeleton is an integral part of many commercial drugs used in the treatment of hypertension such as amlodipine, nicardipine, nifedipine etc. [1]. 1, 4-Dihydropyridine derivatives are documented in literature for anti-inflammatory [2], antiulcer [3], anticonvulsant [4], antitubercular [5], antimicrobial etc. activities [6]. These also act as potential antagonists [7] as well as antidyslipidemic and antioxidant agents [8]. 1, 4-Dihydropyridine and their derivatives are therapeutically significant compounds due to their ability to bind to calcium channels and thus decreasing the flow of transmembrane calcium current [9]. Thus vast biological activities of these compounds have attracted the attention of synthetic organic chemists to synthesize such molecules.

The first classical method for the synthesis of 1,4-DHPs carried out by Hantzsch and Liebigs involves the one pot condensation of aldehydes with 1,3-dicarbonyl compounds and ammonia either in acetic acid or in an refluxing alcohol for a prolong time. Due to certain disadvantages associated with this method; different protocols were developed in due course by the scientific community from academia as well as industry for the synthesis of these heterocyclic compounds which comprise the use of heterogeneous catalysts such as silica sulfonic acid [10], alumina [11], alumina sulfuric acid [12], HY-Zeolite [13] etc. Other Lewis acid catalysts including $Mg(ClO_4)_2$ [14], phenylboronic acid [15], molecular iodine [16] are also reported for their catalytic efficiencies in the synthesis of these heterocyclic compounds. Furthermore the use of ionic liquid [17], ultrasound [18] or microwave [19] irradiation is also reported. However, research is mainly focused on the modification by optimization of the Hantzsch reaction to minimize reaction time, maximize reaction conversion and offer high purity 1, 4-DHPs.

Heterogeneous catalysts are always superior to homogeneous ones in many aspects. Currently the study of multicomponent reactions by heterogeneous catalysts has become an active part of ongoing research due to several advantages associated with the heterogeneous catalysts over homogeneous counterparts such as easy separation, recycling ability, minimization of metal traces in products after isolation etc.

As a part of our research in the development of new methods for the synthesis of heterocyclic compounds [20]; in present work we wish to report the synthesis of 1, 4-dihydropyridine derivatives by the condensation reaction between aldehyde, ethylacetoacetate and ammonium acetate using the composite $Fe_{0.2}Al_{1.8}Zn_1O_4$ as an efficient catalyst in acetonitrile under reflux condition (Scheme 1).



Scheme 1 Synthesis of 1,4-dihydropyridines catalyzed by $Fe_{0.2}Al_{1.8}Zn_1O_4$ nanocomposite catalyst

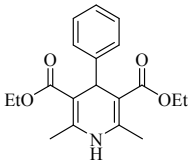
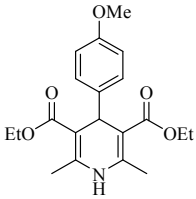
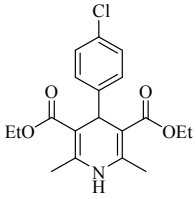
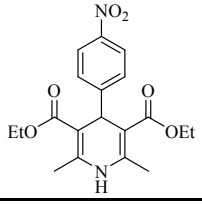
2. EXPERIMENTAL DETAILS

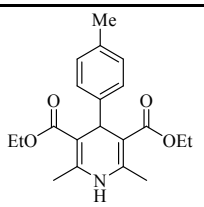
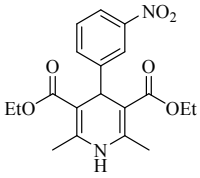
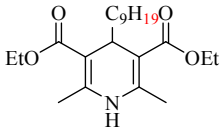
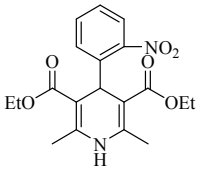
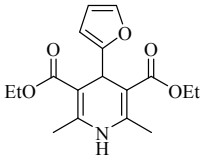
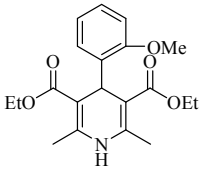
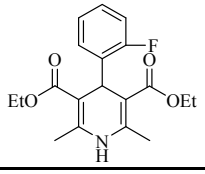
The chemicals used were SD fine made and were used without further purification. Melting points of the synthesized compounds were recorded in capillaries open at one end and were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian spectrophotometer using $CDCl_3$ solvent and TMS as the reference. IR spectra of the samples were recorded on Perkin FTIR spectrometer using KBr discs. The catalyst was synthesized by reported literature sol-gel method [21-23].

2.1 General Procedure for Synthesis of 1, 4-dihydropyridine Derivatives

A mixture of aldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1.5 mmol) and the composite $Fe_{0.2}Al_{1.8}Zn_1O_4$ catalyst (10 mol %) in acetonitrile (2 mL) was refluxed for appropriate reaction time as specified in Table 1. The progress of reaction was monitored by Thin Layer Chromatography (25% EA: Hexane). After completion of reaction as indicated by TLC; the reaction mass was diluted with acetonitrile and filtered off to separate the catalyst. The residue being recovered catalyst; on subsequent washings with acetonitrile twice followed by drying it at 100 ^{o}C can be recovered and reused. The filtrate was concentrated on rotary evaporator and purified by crystallization from ethanol to obtain the pure product.

Table 1. Synthesis of 1, 4-dihydropyridines using composite- $Fe_{0.2}Al_{1.8}Zn_1O_4$ catalyst

Entry	R	Product	Time (hr)	Yield (%)[@]	Melting point (ºC)
1	Ph		0.75	98	156
2	4-$MeOC_6H_4$		1.5	95	159
3	4-ClC_6H_4		1.0	91	141-143
4	4-NO_2 C_6H_4		1.5	89	127

5	4-MeC_6H_4		0.75	89	160-61
6	3-NO_2 C_6H_4		1.75	80	163
7	n-C_9H_{19}		4.25	78	----
8	2-NO_2 C_6H_4		3.5	77	119
9	2-Furyl		2.0	89	163-65
10	2-$MeOC_6H_4$		2.5	87	148-149
11	2-FC_6H_4		3.0	92	151

[@]Reactions were carried on aldehyde (1mmol), EAA (2 mmol) and NH_4OAc (1.5 mmol) using $Fe_{0.2}Al_{1.8}Zn_1O_4$ (10 mol %) in 2 drops HCl and CH_3CN

All aldehydes reacted smoothly to afford the corresponding 1, 4-dihydropyridines in excellent yield (Table 1). The spectral data of representative compounds is mentioned below:

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-phenylpyridine-3, 5-dicarboxylate (Entry 1, Table 1): Yield: 98%; Colorless solid; m.p.156 ^{o}C ; IR (KBr) : 500, 620, 1050, 1100, 1180, 1200, 1500, 1667, 1690, 2350, 2867, 3440 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J =7.2Hz, 6H), 2.35 (s, 6H), 4.09 (q, 4H), 4.97 (s, 1H), 5.7(brs, 1H), 7.08 - 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.28, 19.23, 39.59, 59.56, 103.92, 126.06, 127.89, 144.10, 147.61, 167.54.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-(4-methoxy-phenyl) pyridine-3, 5-dicarboxylate (Entry 2, Table 1): Yield: 92%; Colorless solid; m.p.194 °C; IR(KBr) : 500, 700, 1000, 1050, 1200, 1250, 1300, 1500, 1700, 2400, 3300 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (t, J =7.1Hz, 6H), 2.38 (s, 6H), 3.94 (s, 3H), 4.05 (q, J = 7.1Hz, 4H), 4.87 (s, 1H), 5.92 (s, 1H), 6.88 (d, J = 8.7Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.68, 19.55, 39.13, 55.30, 59.85, 104.53, 113.62, 129.19, 140.79, 144.17, 158.30, 167.98.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-(2-nitro-phenyl) pyridine-3, 5-dicarboxylate (Entry 8, Table 1): Yield: 75%; colorless solid; m.p.172-173 °C; IR (KBr): 757, 858, 1020, 1103, 1190, 1217, 1284, 1309, 1352, 1434, 1492, 1529, 1618, 1649, 1689, 3020, 3442 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.34 (s, 6H), 3.79 (s, 6H), 5.73 (s, 1H), 5.87 (s, 1H), 7.21 - 7.30 (m, 1H), 7.41 - 7.54 (m, 2H), 7.66 - 7.70 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 19.0, 34.29, 52.84, 103.0, 125.65, 126.88, 130.88, 132.70, 142.10, 145.42, 147.54, 167.62.

3. RESULTS AND DISCUSSION

Different aldehydes were used with ethyl acetoacetate, ammonium acetate and $Fe_{0.2}Al_{1.8}Zn_1O_4$ in acetonitrile to illustrate generality of the condensation reaction. The results are summarized in Table 1. The present protocol affords products in good yields. Products were obtained in short reaction time. This method tolerates a variety of functional groups such as methyl, methoxy, hydroxyl, halides etc under the reaction conditions. Importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving moderate to excellent yields of desired products. The substituent on the aromatic ring of aldehyde did not show much difference in the yield of products.

After completion of reaction, the catalyst was recovered by diluting the reaction mass with hot ethanol followed by filtration and the recovered catalyst was reused for few more cycles (Table 2). During washing with the solvent, it is clearly evident that there was no leaching of catalyst and was confirmed by performing the reaction with the residue as the recovered catalyst. The catalyst reusability study was carried out using the model reaction of benzaldehyde (1 mmol), EAA (2 mmol) and NH_4OAc (1.5 mmol) using $Fe_{0.2}Al_{1.8}Zn_1O_4$ (10 mol %) in 2 drops HCl for the synthesis of diethyl 1, 4-dihydro-2, 6-dimethyl-4-phenylpyridine-3, 5-dicarboxylate (Entry 1, Table 1) whose results are summarized in Table 2. Reusability of the catalyst was studied for three successive recycles which afforded good yield of products indicating that the catalyst can be reused without appreciable loss of catalytic acivity.

Table 2. Recycle study of the $Fe_{0.2}Al_{1.8}Zn_1O_4$ composite catalyst

Run	Fresh	I	II	III
Yield (%)	98	96	95	94

From our investigations, we observed that the catalyst shows excellent to good reactivity with promising yields even for the next three cycles in the same reaction. Since, there was no observable loss in the percentage yield; there is no leaching of the catalyst. Table 3 shows the comparative study of the effect of $Fe_{0.2}Al_{1.8}Zn_1O_4$ composite with some literature protocols on the synthesis of 1,4-dihydropyridines. From literature the use of alcoholic solvent or solvent free conditions was useful for the synthesis of Hantzsch's dihydropyridines. But with our catalyst; acetonitrile suited well.

Table 3. Comparative study of effect of $Fe_{0.2}Al_{1.8}Zn_1O_4$ composite on the synthesis of 1, 4-dihydropyridines

Entry	Catalyst	Conditions	Yield (%)	Reference
1	Sulfonic acid on silica gel (0.2 g/mmol)	hexane or neat, 60ºC, 4.5-7 h	85-95	[10]
2	Alumina-H_2SO_4 (0.2 g/3mmol)	MeOH, 70ºC, 2-5 h	82-95	[12]
3	HY-zeolite (10 mg/mmol)	EtOH, reflux, 2.5-3.5 h	70-90	[13]
4	I_2 (30 mol %),	EtOH, r.t., 2.5-5 h	80-95	[16]
5	$Fe_{0.2}Al_{1.8}Zn_1O_4$ (10 mol %)	ACN, 2-drops HCl, reflux, 0.75-4.25 h	77-98	[Present method]

4. CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of 1, 4-dihydropyridines by using the composite $Fe_{0.2}Al_{1.8}Zn_1O_4$ as a solid catalyst, which has many advantages such as ease of preparation, easy handling, reusability and insolubility in most organic solvents. The present protocol affords the 1, 4-dihydropyridines in moderate to excellent yield within short reaction time. We believe this catalyst as a valuable addition to the synthesis of heterocyclic compounds such as 1, 4-dihydropyridine derivatives.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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