Review Paper:

Synthesis of 1, 4-Dihydropyridines using Different Nanocatalyst Systems

Phasage Deepak Babasaheb[1], Sharma Sanjay K.[1] and Srivastava Sonia Chahar[2]*
1. Green Chemistry and Sustainability Research Group, Department of Chemistry, JECRC University, Jaipur, INDIA
2. Department of Chemistry, S.S. Jain Subodh PG College, Jaipur, INDIA
*soniachahar@gmail.com

Abstract
1, 4-dihydropyridine (1, 4-DHP) is an important class of heterocyclic scaffold which possesses a wide variety of applications in biological and pharmacological field. In this review, we discuss the synthesis of 1, 4-dihydropyridine by using various nanocatalytic systems since 2010. Nanocatalyst provided efficient and green approach for the synthesis of 1, 4-DHP.

Keywords: Green synthesis, Hantzsch condensation, 1,4-Dihydropyridine (1,4-DHP), Metal oxide Nanocatalyst.

Introduction
1, 4-dihydropyridine scaffolds represent heterocyclic unit of remarkable biological and pharmacological efficiency[53]. More than a hundred years ago, the reaction to produce 1,4-dihydropyridine was reported by Hantzsch[26]. These are important precursors due to their pharmacological and biological activities such as antihypertensive[33], anti-anginal and as calcium channel blockers[8,10,11,22,51] for the treatment of cardiovascular diseases.[9,46] A number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure.1, 4-DHP also acts as NADH mimics for the reduction of carbonyl compounds and their derivatives. Apart from these, 1,4-DHP also possesses many more pharmacological activities such as anti-bacterial, anti-cancer, anti-microbial, anti-tubercular, antioxidant, antiulcer, CFTR, antimalerial and HIV-I protease inhibitory and many more.[25,41,49,57]

1, 4-hihydropyridine is generally synthesized by condensation of aldehydes, β-ketoester and ammonia or ammonium acetate. The number of attempt have been under taken to improve this Hantzsch reaction using different alternate process in the literature. These includes reaction in microwave[1,28,42] using ionic liquids[27] and reaction at higher temperature[12,44,47] reactions using TMSI[48], I_2[29], $Yb(OTf)_3$[58], CAN[30], Silica gel/$NaHSO_4$[16] and $Sc(OTf)_3$[18]. However, these reactions have certain disadvantages like longer reaction time, use of expensive catalyst, higher temperature and tedious isolation process.

Synthetic applications and their medicinal importance encourage researcher to develop new and green synthetic approach to overcome the disadvantages associated to Hantzsch condensation. In this context, various nanocatalytic systems have been developed to synthesize pharmacologically important 1,4-dihydropyridine motifs.

In this review, we have covered the research papers published since 2010 which have used nano material as heterogeneous catalyst for the synthesis of 1,4-dihydropyridine. The focus of the review is mainly on exploring the application of various nanomaterials that have been used for the synthesis of 1,4-dihydropyridine via multi-component one-pot pathways. The nano catalytic systems are highly advantageous over conventional methods. Due to enormous activity and selectivity of nanocatalyst, the reaction completed with high yield and lower reaction time. In this review, we briefly summarized the various mono and multimetallic nanocatalytic systems.

Mono Metal / Metal Oxide Nanocatalyst
Iron (Fe) based nanocatalyst: Iron based nanocatalyst is most important class of catalyst for the synthesis of 1, 4-DHP. Due to the insolubility and paramagnetic nature, this catalyst can be easily separated and recycled. Iron oxides including maghemite (Fe_2O_3) and magnetite (Fe_3O_4) are widely used for preparation of nanomaterials due to their inherent biocompatibility.

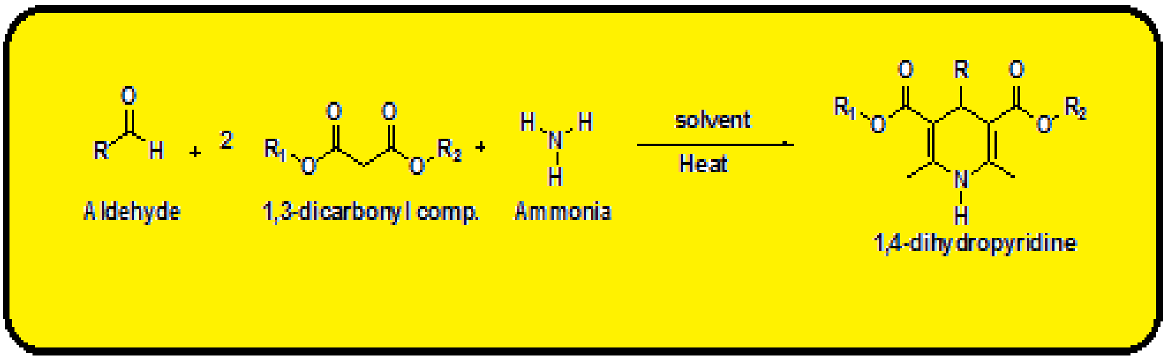


Figure 1: Conventional one-pot multi component strategy for 1, 4-dihydropyridine synthesis.

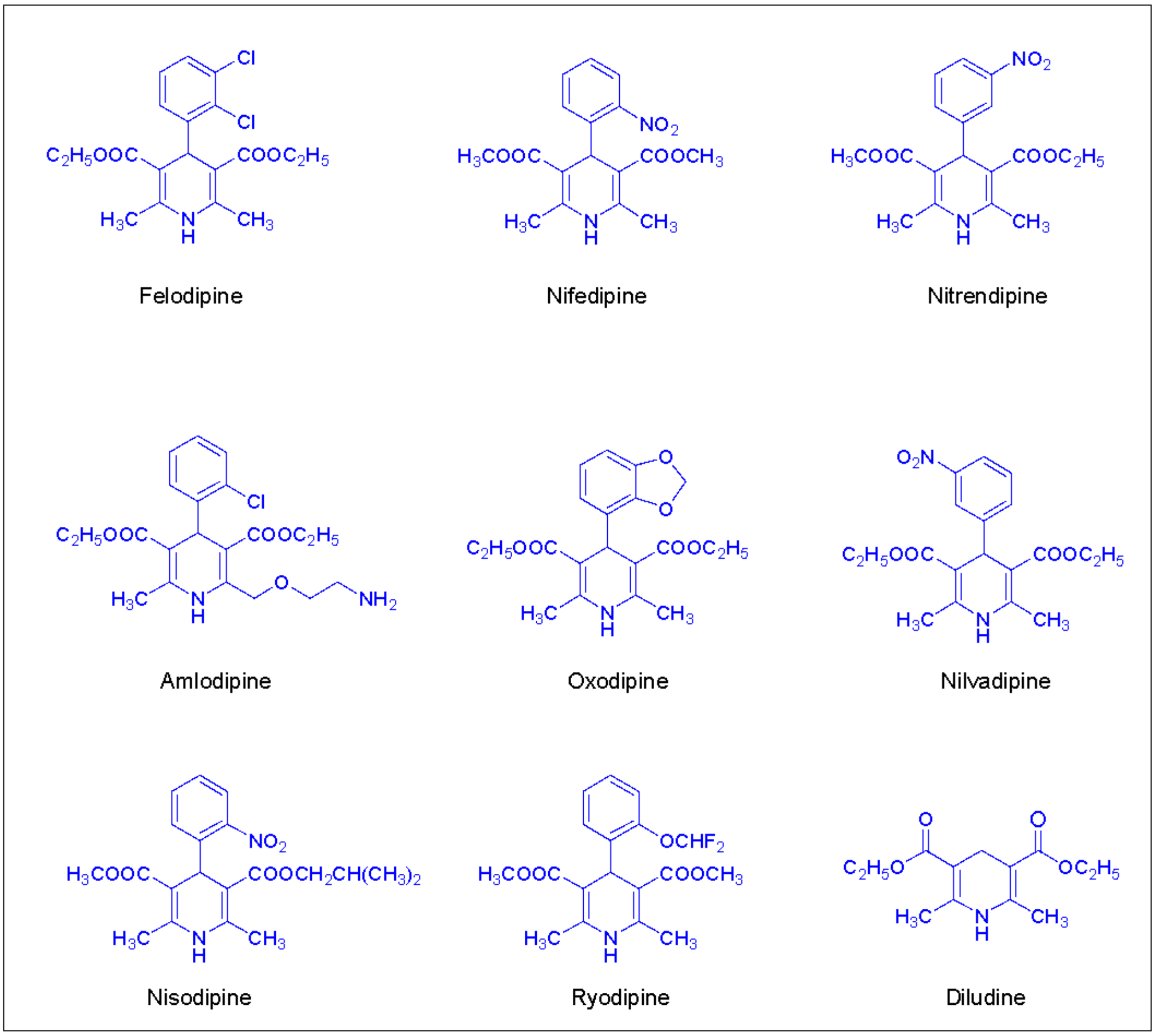
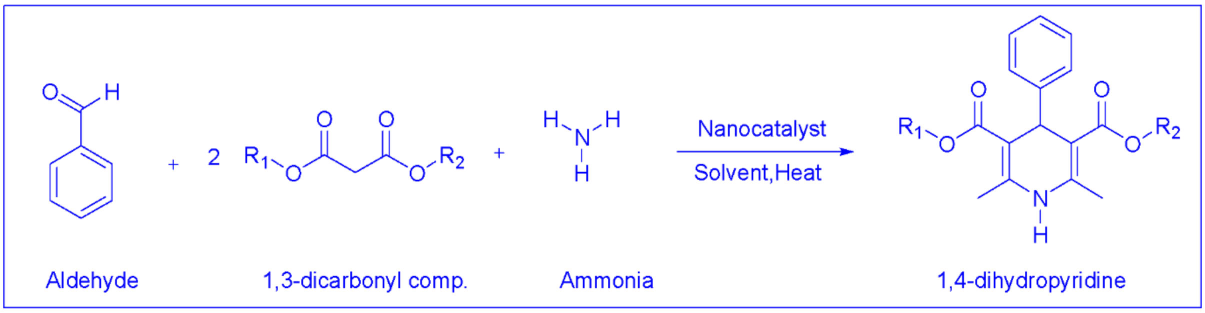


Figure 2: Commercial drugs containing 1,4-dihydropyridine as core moiety



Scheme 1: Synthesis of 1,4-dihydropyridine using Fe-based nanocatalyst

Yang et al[60] reported as efficient one-pot three component reaction of aromatic amines, α, β-unsaturated aldehydes and β-keto ester using magnetic nanocrystalline Fe_3O_4 as catalyst for synthesis of 1,4-dihydropyridine under mild conditions. Similarly, Shafiee et al[50] used perchloric acid adsorbed on magnetic Fe_3O_4 nano-particles coated with silica (Fe_3O_4@SiO_2-$HClO_4$) as a recyclable nanocatalyst for the preparation of 1, 4-dihydropyridine derivatives. They one pot reaction of cinnamaldehyde, aromatic amines and methyl/Ethyl acetoacetate under solvent free condition to achieve high yield of desired 1, 4-DHP.

Dam et al[17] reported green approach for synthesis of 1,4-dihydropyridine derivatives via one pot condensation of dimedone or 4-hydroxycumarine, aldehydes and ammonium acetate using Fe_3O_4@SiO_2 nanoparticles as a heterogeneous catalyst in water as green solvent at reflux condition to achieved desired 1,4-DHP's with high yield. Similarly, Esfahani et al[21] prepared 1,4-dihydropyridine by using magnetic Fe_3O_4 nanoparticles under solvent free condition. Reaction with 1, 3-cyclohexanedione derivatives, ammonium acetate and β-keto ester and nanocatalyst at 60°C yielded 84-96% desired product.

Maleki et al[34] developed magnetite/chitosan as a magnetically recyclable heterogeneous nanocatalyst for one pot four component synthesis of 1,4-dihydropyridine. The condensation of various aromatic aldehydes, dimedone or 1, 3- cyclohexandione, methyl/ethyl acetoacetate and ammonium acetate under ethanol as solvent at room temperature in 30-140 min. yielded 88-95% of desired 1,4-dihydropyridine derivatives.

Bamnori et al[5] synthesized 1, 4-dihydopyridine by using $SnCl_4$-functionalized nano-Fe_3O_4 encapsulated with silica particles. The condensation of aldehydes, 1,3-dicarbonyl compound and ammonium acetate under ultrasonic irradiation produced excellent yield of 1,4-dihydropyridines.

Ghanbari et al[23] used Wells-Dawson heteropolyacid based magnetic inorganic-organic nanohybride materials ($Fe_3O_4@SiO_2@ADMPT/H_6P_2W_{18}O_{62}$) as potent Lewis acid catalyst for synthesis of 1,4-dihydropyridine from reaction of various aromatic aldehydes with ethyl acetoacetate and ammonium acetate with excellent yield. The nanohybrid catalyst was prepared by chemical anchoring of wells-Dawson heteropolyacid $H_6P_2W_{18}O_{62}$ onto the surface of functionalized Fe_3O_4 nanoparticles with 2,4-bis(3,5-dimethylpyrazol)-triazine (ADMPT) linker.

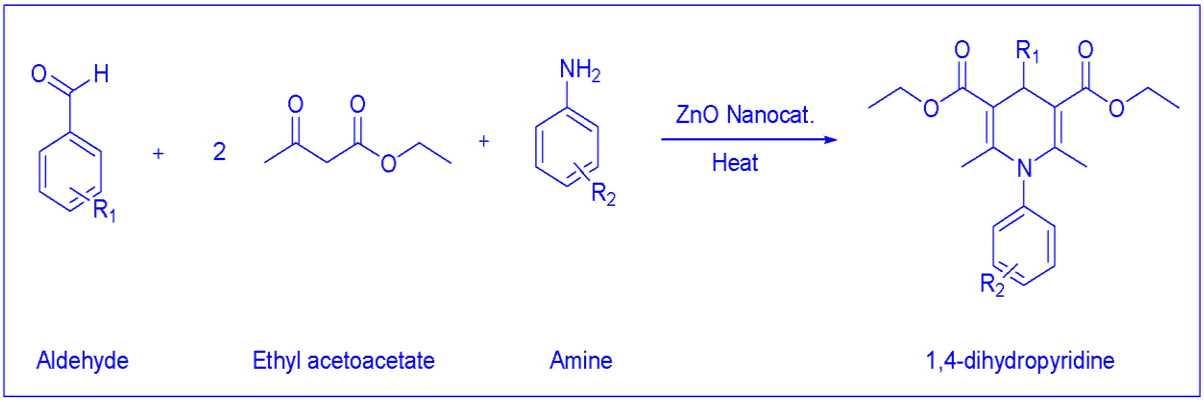
Maleki et al[35] prepared 1,4-dihydropyridine by reaction of benzaldehyde, β-keto ester and ammonium acetate and magnetic guanidinylated chitosan nanocomposite catalyst in ethanol as solvent under reflux condition for 15 min. to produce desired product in high yield. Pourien et al[43] reported novel biocompatible core/shell $Fe_3O_4@GA@$ Isinglass catalyst for ultrasonic synthesis of 1,4-dihydropyridine derivatives. Reaction was with aldehydes, ethyl acetoacetate, dimedone and ammonium acetate in ethanol under ultrasonic irradiation for 30-70 minutes to yield 61-92% of desired 1,4-dihydropyridine.

Hajizadeh et al[24] prepared halloysite nanotubes modified by Fe_3O_4 nanoparticles used for the green synthesis of 1,4-dihydropyridine. Halloysite is an natural eco-friendly nanotube with aluminosilicate structure. The condensation reaction with aldehydes, 1,3-dicarbonyl compound and ammonium acetate in ethanol under reflux condition yielded 88-96% of desired 1,4-dihydropyridine within 20-30 minutes.

Similarly, Taheri-Ledari et al[55] studied catalytic effect between ultrasound waves and pyrimidines-2,4-diamine functionalized magnetic nanoparticles (Fe_3O_4/SiO_2-PDA) and applied for synthesis of 1,4-dihydropyridine. Reaction of aldehydes, 1,3-dicarbonyl compound and ammonium acetate in ethanol under ultrasound wave at room temperature for 10-20 minutes yielded 68-91% of 1,4-dihydropyridine derivatives.

Table 1
Synthesis of 1,4-Dihydropyridine using Fe-based nanoparticles.

Catalyst	Solvent	Temp.(°C)	Time (min.)	Yield (%)
Nanocrystalline Fe_3O_4[60]	Ethanol	RT	6-8 h	62-80
$Fe_3O_4@SiO_2$-$HClO_4$[50]				
$Fe_3O_4@SiO_2$ Nanoparticle[17]	Water	Reflux	10-30	82-95
Fe_3O_4 nano[21]	Neat	80	05-50	72– 94
Fe_3O_4@chitosan[34]	Ethanol	RT	40 -80	88-95
$Fe_3O_4@SiO_2$-$SnCl_4$[5]	Ethanol	Reflux	12-25	89-96
$Fe_3O_4@SiO_2@ADMPT/H_6P_2W_{18}O_{62}$[23]	Ethanol	70	20-40	85-93
Fe_3O_4 guanidinylated chitosan[35]	Ethanol	Reflux	15	84-89
Core /shell Fe_3O_4@GA@Isinglass[43]	Ethanol	Ultrasound	35-70	61-92
Hal-Fe_3O_4[24]	Ethanol	Reflux	20-30	88-96
Fe_3O_4/SiO_2-PDA[55]	Ethanol	Ultrawave RT	10	68-90



Scheme 2: Synthesis of 1,4-Dihydrpyridine using Zinc based nanocatalyst

Zinc (Zn) based nanocatalyst: Zinc oxide nanoparticles are widely used as catalyst in various organic transformations due to its unique features such as environment friendliness and inexpensiveness. Dehghanizadeh et al[19] used zinc oxide nanoparticles as heterogeneous nanocatalyst for the synthesis of 1, 4-dihydropyridine. The condensation reaction is performed using substituted aldehydes, dimedone, ammonium acetate and ethyl acetoacetate at 110°C for 10-30 minutes under solvent free condition to obtained excellent yield of 1,4-dihydropyridine. The simple process of recycling of catalyst, excellent yield, simple work up process free of any side product are some of the advantages of this method.

In alternate method, Reen et al[45] prepared N-substituted derivatives of 1,4-dihydropyridines using one pot three component reaction of aldehydes, β-dicarbolyl compounds and substituted aromatic amines with 15 mole % of ZnO nanoparticles at moderate temperature under solvent free condition. The easy recoverability and reusability of catalyst, solvent free condition, short reaction time and easy isolation procedure are some of the merits of this method.

Alinezhad et al[3] reported a simple, efficient and convenient one step method for synthesis of 1,4-dihydropyridine using Cu-doped ZnO nanocrystalline powder as a heterogeneous catalyst. The reaction of aldehydes, ethyl acetoacetate and ammonium acetate in aqueous media under reflux condition using 10 mole % of Cu-doped ZnO nanocrystalline powder as catalyst resulted in excellent yield in 0.5 to 2 hrs. Properties of zinc oxide can be modified by doping with some other metals.

As chemical and physical properties of copper are similar to that of zinc oxide therefore copper act as important doping metal. Copper also has ability to alter the luminescence and microstructure of zinc oxide crystal.

Naik et al[40] reported synthesis of 1,4-dihydropyridine by using zinc oxide nanoparticles under microwave irradiation in ethanol as solvent. A series of 1,4-dihydropyridine have been prepared by three component reaction of β-dicarbonyl compound, aromatic aldehydes and ammonium acetate using crystalline Nano-ZnO catalyst in ethanol under microwave irradiation. The reported methodology offers several advantages such as simple procedure, greener condition, excellent yield and short reaction time.

Abaszadeh et al[2] report ultrasonic irradiated synthesis of 1,4-dihydropyridine by using multicomponent reaction of cyclic eneminoketones, malanonitrile and aromatic aldehydes in the presence of zinc oxide nanocatalyst in ethanol at 80°C. High reaction conversion, short reaction time and easy isolation process are some of the advantages of this method.

Other metal nanocatalyst: Bajaj et al[4] reported CuO nanoflakes for the synthesis of 1,4-dihydropyridine under microwave irradiation condition. The condensation of aromatic aldehydes, ethyl acetoacetate and ammonium acetate using copper oxide nanoflakes in ethanol:water mixture at 70°C under microwave condition produced 1,4-dihydropyridine derivatives in good yield. The nanoflakes assisted methodology offers several advantages such as simple synthetic method, mild reaction condition, easy isolation method and economic recycle of catalyst.

Recently, Cahyana et al[13] introduced copper iodide nanoparticles for synthesis of 1,4-dihydropyridine. The condensation of aldehydes, ethyl acetoacetate and ammonium acetate in ethanol using 10 mol. % of CuI nanocatalyst at moderate temperature for 120 minutes yielded 85% of desired 1,4-dihydrfopyridine derivatives.

Kiasat et al[31] used ϒ-Alumina nanoparticles for the synthesis of one pot synthesis of 1,4-dihydropyridine derivatives via multicomponent Hantzsch reaction at 90°C under solvent free condition. Reaction of aromatic aldehydes, ethyl acetoacetate and ammonium acetate produced 1,4-DHP within 5 to 35 minutes up to 95% yield. ϒ-Al_2O_3 has wide range of industrial applications as catalyst due to more stability, large pore volume, high activeness and strong adsorption.

Safari et al[53] introduced nickel nanoparticles catalysed synthesis of C_5-unsubstituted 1,4-dihydropyridine via unsymmetrical Hantzsch reaction under solvent free condition. Nickel nanoparticles act as a mild Lewis acid that catalyse condensation of ethyl acetoacetate, aromatic aldehydes, acetophenone derivatives and ammonium acetate to yield 85-97% of desired product within 1 to 1.5 h under solvent free condition at room temperature.

Table 2
Synthesis of 1,4-dihydropyridine using zinc based nanoparticles.

Catalyst	Solvent	Temp.(°C)	Time (min.)	Yield (%)
ZnO Nanoparticles[19]	Neat	110	10-30	72-94
ZnO Nanoparticles[45]	Neat	80	80-120	82-92
Cu doped ZnO nanoparticles[3]	Water	100	30-120	90-98
ZnO Nanoparticles[40]	Ethanol	MW	25-55	88-93
ZnO nanoparticles[2]	Ethanol	80 (ultrasound)	30-120	90-98

Tajbaksh et al[56] synthesised 1,4-dihydropyridine using TiO_2 nanocatalyst. The condensation of aldehydes, ethyl acetoacetate, ammonium acetate and titanium dioxide nanoparticles (10 mol. %) stirred in ethanol at 80°C for 1.75 to 4 hrs produced 50-95 % yield of desired 1,4-DHP derivatives.

Safari et al[53] reported highly efficient cobalt nanoparticles for synthesis of C_5-unsubstitiuted 1,4-dihydropyridine by condensation of dimedone, acetophenone, aromatic aldehydes and ammonium acetate. Cobalt nanocatalysts are magnetically separable and easily recycled. This methodology offered several advantages such as easy synthesis, high reaction conversion, simple operation process, eco-friendly and recovery of catalyst.

Mixed Metal / Metal Oxide Nanocatalyst

Kasi et al[32] prepared copper ferrite as reusable heterogeneous catalyst for synthesis of 1,4-dihydropyridine. The one pot condensation reaction of substituted aromatic aldehydes, ethyl acetoacetate and ammonium acetate in ethanol at room temperature in presence of nanocrystalline copper ferrite powder as catalyst achieved excellent yield (85-98% within 4-10h) of 1,4-dihydropyridine. This method had more advantages over convential method such as mild reaction condition, easy isolation process, excellent yield and easy recovery of catalyst.

Naik et al[39] used Lewis acid-based nano $ZnFe_3O_4$ as heterogeneous catalyst for synthesis of 1, 4-dihydropyridine by reacting with substituted aldehydes, ethyl acetoacetate and ammonium acetate under water as solvent at room temperature to produce 90-96% of yield within 30 minutes. The catalyst is magnetic in nature, inexpensive, highly effective and recyclable and reusable even after 5 times without loss of catalytic activity.

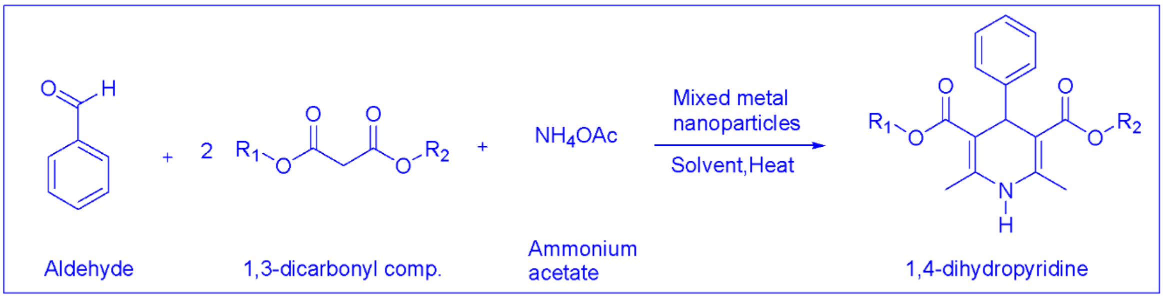
Maleki et al[36] used silica coated magnetic $NiFe_2O_4$ nanoparticles supported on $H_{14}(NaP_5W_{30}O_{110})$ for one pot synthesis of 1,4-dihydropyridine. The reaction of aldehydes, 1,3-dicarbonyl compound, methyl ethyl acetoacetate and ammonium acetate under solvent free condition at 120°C for 10 minutes yielded 65-92% of desired product. Preyssler heteropolyacid $H_{14}(NaP_5W_{30}O_{110})$ is excellent support material used for catalyst support because of its remarkable properties such as high thermal and hydrolytic stability, low surface area, acidic protons and high solubility in polar solvents.

Mirjalili et al[37] prepared $TiCl_2$/nano-ϒ-Al_2O_3 as a novel green heterogeneous solid catalyst by immobilization of $TiCl_2$ on the surface of nano-ϒ Al_2O_3. The activity of catalyst is confirmed by synthesis of 1,4-dihydropyridine of three component coupling reaction of aldehydes, 1,3-dicarbonyl compound and ammonium acetate under solvent free condition with excellent yield in short reaction time.

Maleki et al[38] reported new protocol to prepare dihydropyridine using biopolymer based magnetic nanocomposite ϒ-Fe_2O_3@Cu@Cellulose as catalyst. Various derivatives of 1,4-dihydropyridine were prepared by condensation of substituted aldehydes, ethyl acetoacetate and ammonium acetate under solvent free condition at room temperature as 80-92% yield. The role of copper nanoparticles was more important along with ϒ-Fe_2O_3. Their synergistic effect appeared when both of these (Fe_2O_3 @Cu) were coated on biopolymer. This method has several advantages such as easy operation, clean and green process, simple and easy isolation, re-usability and high yield.

Table 3
Synthesis of 1, 4-dihydropyridine using mono metal/metal oxide nanoparticles.

Catalyst	Solvent	Temp.(°C)	Time (min.)	Yield (%)
CuO Nanoflakes[4]	EtOH:water	70 (microwave)	80-120	65-93
CuI Nanoparticles[13]	Ethanol	RT	120	85
ϒ-Al_2O_3 nanoparticles[31]	Neat	90	5-35	80-95
Ni Nanoparticles[53]	Neat	RT	1-1.5 h	85-97
TiO_2 Nanoparticles[56]	Ethanol	80	1.75-4h	50-95
Co Nanoparticles[53]	Neat	RT	1-6 h	75-98



Scheme 3: Synthesis of 1, 4-dihydropyridine using mixed metal/metal oxide nanocatalyst.

Table 4
Synthesis of 1,4-Dihydropyridine using $NiFe_2O_4$ magnetic nanoparticles

Catalyst	Solvent	Temp.(°C)	Time (min.)	Yield (%)
Copper ferrite Nanoparticles[32]	Ethanol	RT	4-10 h	85-98
$ZnFe_2O_4$ Nanoparticles[39]	Water	RT	30	90-96
$NiFe_2O_4$@SiO_2-$H_{14}NaP_5W_{30}O_{110}$[36]	Neat	120	10	65-92
$TiCl_2$/nano-ϒ-Al_2O_3[37]	Neat	90	1.3-5 h	50-95
ϒ-Fe_2O_3@Cu@Cellulose[38]	Neat	RT	Rxn.completion	80-92
NiO/ZrO_2 Nanoparticles[7]	Ethanol	RT	20-45	89-98
ZnO@SnO_2 nanoparticles[54]	Neat	80	10-20	96
Fe-C-O-Mo alloy nanorods[59]	Ethanol	Reflux	150	92
$NiFe_2O_4$ nanoparticles[14]	Ethanol	RT	1-4 h	83

Bhaskaruni et al[7] reported Nickel oxide loaded on Zirconia (NiO/ZrO_2) as a nano catalyst for synthesis of 1,4-dihydropyridine. The Lewis acid nature of catalyst proved an excellent choice for the one pot four components fusion reaction with 2,3,4-methoxy benzaldehyde, ethyl acetoacetate, cyclohexane and ammonium acetate in ethanol as solvent at room temperature to yield 89-98% within 20-45 minutes.

Sapkal et al[54] reported synthesis of 1,4-dihydropyridine via one-pot three component condensation of ethyl acetoacetate, substituted aldehydes and ammonium acetate in the presence of ZnO@SnO_2 nanoparticles under solvent free condition at 80°C to obtain 96% desired product within 10-20 minutes.

Wu et al[59] prepared magnetic Fe-C-O-Mo alloy nano rods from chemical decomposition of a screw for synthesis of dihydropyridine and dihydropyrimidone derivatives. The reaction of aldehydes, acetoacetic ester and ammonium acetate under reflux condition in presence of ethanol as solvent in presence of Fe-C-O-Mo nanorods produced 92% yield of desired product in 150 minutes. The catalyst represents very high re-usability and stability even after 8 reaction cycles.

Cahyana et al[14] synthesized 1,4-dihydropyridine with cinnamaldehyde using $NiFe_2O_4$ magnetic nanoparticles as catalyst under ethanol as solvent with two drops of water at room temperature for 1 to 4 hrs to achieve excellent yield up to 83%. This catalyst has spinel structure in which Fe^{3+} occupies tetrahydral site while Ni^{2+} and Fe^{3+} both occupy octahedral site.[15,20]

Conclusion

In this review, we summarized different synthetic approaches of 1,4-dihydropyridine synthesis by using various mono and mixed metal nanocatalyst. Nanocatalyst method replaced conventional reaction condition requirements such as strong acidic condition, high temperature, longer reaction time and tedious product isolation process. Nano approach now becomes more popular trend for 1,4-dihydropyridine synthesis being green, highly selective and eco-friendly. Review provides synthetic approach towards benzimidazole and would be more beneficial for designing of superior catalyst systems in future.

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