

Nickel Ferrite Heterogeneous Base Catalyst for Synthesis of Dihydropyridines

Vijay V. Dabholkar*, Swapnil K. Kurade, Keshav S. Badhe.

Organic Research Laboratory, Department of Chemistry, K. C. College, Churchgate, Mumbai -400 020.

Abstract: The NiFe₂O₄ nanoparticle was found to be an excellent solid base catalyst for the one-pot synthesis of 1,4-DHP via Hantsch reaction of various aromatic aldehyde, ammonium carbonate and a β-dicarbonyl compound at 60°C. This process offers key advantages including short reaction time, high yield, an environmentally friendly synthesis and simple work up process. Nano catalyst easily recovered and recovered catalyst was reused for number of times for compounds synthesis. The yield of product found to be excellent without loss of catalyst activity.

Keywords: Nanoparticle, Hantsch reaction, Heterogeneous solid catalyst, Dihydropyridine, One-pot synthesis.

I. INTRODUCTION

Dihydropyridine (DHP) have attracted increasing interest due to their significant activities[1]. DHP drugs namely, nifedipine, nicardipine and amlodipine are cardiovascular agents for treatment of hypertension. The disease like congestive heart failure cured by DHP calcium antagonist which have been marked as excellent drug[2].

They possess antidiabetic activities[3], neuroprotective[4] and platelet antiaggregation[5]. Additionally, hydrogenation of α,β-unsaturated aldehyde and ketones[6,7], synthesis of alkaloids [8] and asymmetric reductive amination of aldehyde [9] such as asymmetric reaction catalyzed by DHP as a organocatalyst.

MCRs emerged as a means to achieve atom economy and benign synthesis by virtue of their convergent, productivity, easy execution and generation of highly diverse and complex product from easily available starting materials in a single operation[10]. The importance of MCR in the organic synthesis has been attract industrial, academic and researchers, have been focused, especially on the design and development of multicomponent procedures for the generation of libraries of heterocyclic compound[11].

Generally, 1,4-DHP are synthesized by Hantzsch reaction which involves the condensation of aldehyde, β-ketoester and ammonia or ammonium acetate carried out in acetic acid or by refluxing in ethanol for a long time [12]. A number of methods have been reported in literature for this condensation reaction which involve the use of ultrasound irradiation[13,14], ionic liquid[15], metal triflates[16],

molecular iodine[17], microwave[18,19,20,21,22], silica gel/NaHSO₄[23], TMSCl-NaI[24] and cyanuric chloride[25].

In spite of potential utility of these reported methods, most of them suffer from drawbacks such as long reaction time, high temperature, use of strong oxidants, low yield, occurrence several side products and the used of expensive and toxic transition metallic reagents. Therefore, exploring the new catalytic system that could be superior to the existing one with regards toxicity, handling and recyclability. In this report we introduce NiFe₂O₄ nanoparticle, a heterogeneous solid catalyst to overcome these limitation. Nowadays, nanocatalyst emerged as new fertile field in research and innovation for the development of catalyst in nanorange. The catalytic properties of nanoparticles are due to their size and crystal lattice parameters.

Nanosized spinel ferrite particles having structural formula MFe₂O₄ (M= divalent metal ion eg-Mn, Mg, Zn, Ni, Co, Cu etc.) are one of the most attracting a kind of soft magnetic material due to interesting and important properties such as high specific heating, low saturation magnetic moment, low magnetic transition temperature[26,27]. Due to all these properties, these nanoparticle have many technical application such as catalysis[28], nano devices[29] and magnetic pigment[30].

II. RESULT AND DISCUSSION

XRD Analysis

In the effort to develop new methodology for the synthesis of DHPs, we started our study have environmentally benign properties with the base catalyzed Hantzsch condensation by subjecting catalytic amount of NiFe₂O₄ nanoparticle, a heterogeneous base catalysis.

NiFe₂O₄ nanoparticles were synthesized by co-precipitation method[31]. The structural characterization of NiFe₂O₄ nanoparticles were done by X-ray Diffraction using CuKα radiation (λ = 1.54059 Å) at 40 kV and 15 mA shown in Figure 1. The XRD patterns show the formation of single phase inverse cubic spinel nickel ferrite (the XRD peaks were compared to the standard PDF card number 742081 for inverse cubic nickel ferrite)

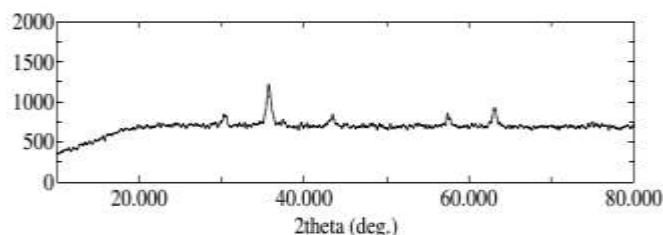


Fig 1. XRD patterns for NiFe₂O₄ nanoparticles sintered at 450°C

Morphological analysis

The morphology of NiFe₂O₄ nanoparticles were studied using SEM shown in Figure 2. Most of the particles are found to be spherical in shape.

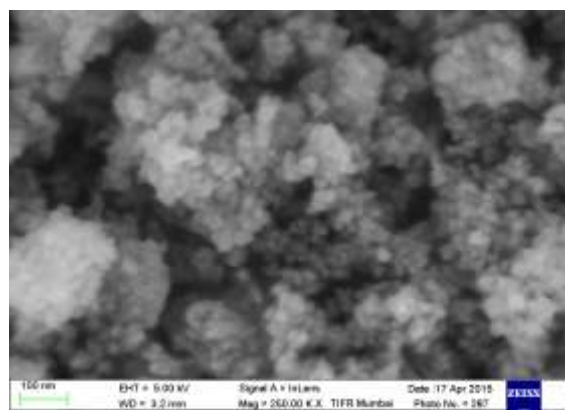
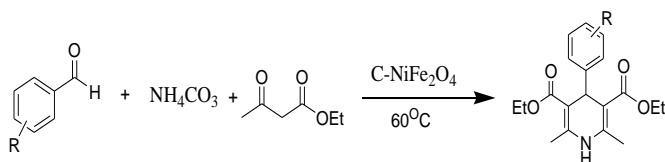


Fig.2. SEM image for NiFe₂O₄ nanoparticles sintered at 450°C

Thus to find out the best reaction conditions and reactivity of different aldehyde in three component reaction Hantzsch condensation reaction by the use of NiFe₂O₄ nanocatalyst as a heterogeneous base catalyst for the synthesis of 1,4-DHP is our objective in the present investigation.

The reaction between benzaldehyde, Ethyl acetoacetate and ammonium carbonate was chosen as a model reaction for optimizing various parameters (Scheme 1). Initially, the reaction was tried in presence of NiFe₂O₄ catalyst in aqueous medium at room temperature. But the reaction could not complete for long time. When the temperature of reaction raised gradually to 60°C, TLC showed reaction starts to change the intermediate formed converted into desired product. Further increased in temperature did not show any significant change in yield of product.



Scheme 1: Synthesis of 1,4-DHP

In search of optimal solvent, the reaction were carried out in different solvents such as water, ethanol, methanol, DMF, DMSO along with small quantity of water in order to dissolved the ammonium carbonate in the reaction mixture. The better results were obtained in polar protic solvent as compared to polar aprotic solvent (Table 1) but the best results was observed when we used ethanol as reaction solvent. We also carried out the reaction in solvent free condition but it showed some traces of product.

Table 1: Synthesis of 1,4-DHP under different solvent systems at 60°C.

Entry	Solvent	Yield of product (%)
1	H ₂ O	45
2	EtOH(2 drop of H ₂ O)	78
3	MeOH(2 drop of H ₂ O)	65
4	DMF(2 drop of H ₂ O)	40
5	DMSO(2 drop of H ₂ O)	48
6	Without solvent	Trace

Reaction conditions: Benzaldehyde (3mmol), Ammonium Carbonate (3mmol), Ethyl acetoacetate (6mmol), Catalyst (0.03g), Temperature (60°C).

Quantity of catalyst to required for the reaction also determined and we observed that yields were affected by catalyst loading (Table 2). We have varied the catalyst concentration from 0.01g to 0.05g we found that best yield was obtained by using 0.03g catalyst. Further increasing the catalyst quantity yield did not show significant change Instead was found to be constant. Recovery and reusability of catalyst are very important factors for practical application of heterogeneous catalytic system.

Table 2: Effect of different quantity of NiFe₂O₄ catalyst on reaction.

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.01	40
2	0.02	62
3	0.03	78
4	0.04	78
5	0.05	78
6	Without catalyst	-

Reaction conditions: Benzaldehyde (3mmol), Ammonium Carbonate (3mmol), Ethyl acetoacetate (6mmol), Ethanol (5ml), (2 drops of H₂O), Temperature (60°C).

The recovered catalyst could be used for number of times without noticeable change in activity (Table 3).

Table 3: Reusability of NiFe₂O₄ catalyst

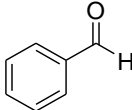
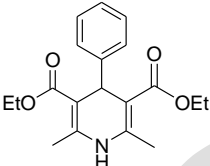
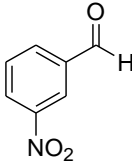
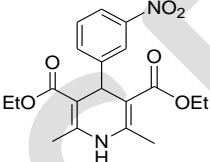
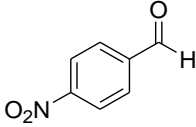
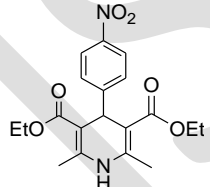
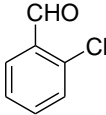
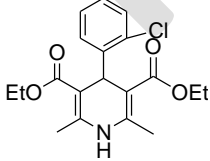
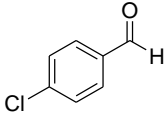
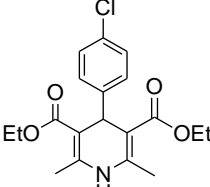
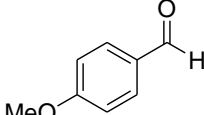
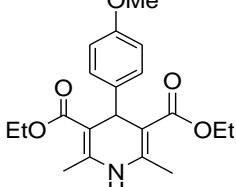
Run	Yield of product (%)
1	78
2	78
3	77
4	76

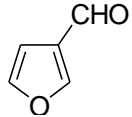
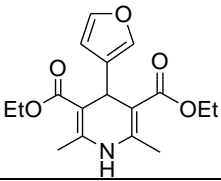
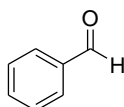
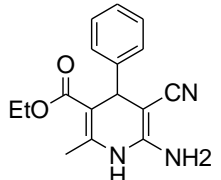
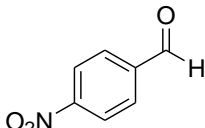
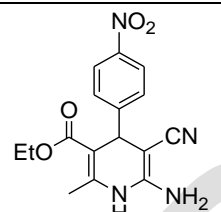
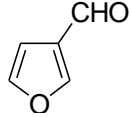
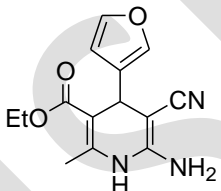
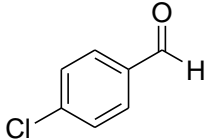
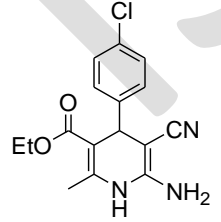
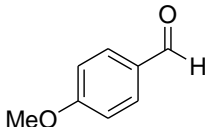
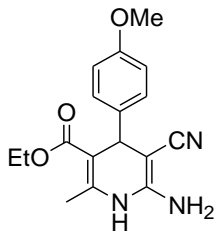
Reaction conditions: Benzaldehyde (3mmol), Ammonium Carbonate (3mmol), Ethyl acetoacetate (6mmol),

Ethanol (5ml), (2 drops of H₂O), Catalyst (0.03g), Temperature (60°C).

Under the similar reaction conditions, we synthesized series of 1,4-DHPs by using different aromatic aldehyde, result summarized in (Table 4.). Aromatic aldehyde carrying electron withdrawing substituent reacted in shorter reaction time and to give excellent yields of corresponding 1,4-DHP compared to aromatic aldehyde carrying electron releasing substituent.

Table 4: Synthesis of series of 1,4-DHPs using NiFe₂O₄ nano-particles at 60°C.

Entry	Substituted benzaldehyde	Product	Yield (%)	Time (min)	Melting Point (°C)	Melting point Reported (°C)
1			78	40	158-160	156-158 ^[32]
2			80	35	162-164	161-163 ^[32]
3			82	30	129-131	128-129 ^[32]
4			77	37	126-127	126-127 ^[32]
5			80	36	145-147	143-145 ^[32]
6			80	45	160-162	160-162 ^[32]

7			84	54	160-162	161-163 ^[32]
8			82	35	188-190	188-190 ^[33]
9			83	30	173-175	175-176 ^[33]
10			81	55	203-204	204-205 ^[33]
11			81	34	198-200	202-204 ^[34]
12			79	45	189-190	188-190 ^[34]

Reaction conditions: Substituted aromatic aldehyde (3mmol), Ammonium Carbonate (3mmol), Ethyl acetoacetate (6mmol), Ethanol (5ml), (2 drops of H₂O), Catalyst (0.03g), Temperature (60°C).

III. EXPERIMENTAL SECTION

3.1. Chemicals and Apparatus

All chemicals are procured from Merck Chemicals Ltd. Mumbai, India. All chemicals were A.R. grade and used without further purification.

Compounds purity was checked by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and Spot visualization on TLC was carried out in an iodine or UV chamber. Melting points of compounds were determined using open capillary tubes on an electro thermal apparatus. FT-IR Spectra were recorded on Bruker Spectrometer in the region of 400-4000 cm^{-1} . ^1H and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $\text{CDCl}_3/\text{DMSO}-d_6$ as solvent and TMS as an internal standard (chemical shifts in δ ppm). Powder X-ray diffraction pattern were recorded with monochromatic Cu K α radiation ($\lambda = 1.54059 \text{ \AA}$) at 40 kV and 15 mA using Shimadzu 7000S diffractometer. The morphological information gathered using scanning electron microscope ZEISS Ultra FESEM.

3.2. General procedure for synthesis of NiFe_2O_4

NiFe_2O_4 nanoparticles were synthesized by co-precipitation method. Starting material for the synthesis of NiFe_2O_4 , were used NaOH, Nickel nitrate and ferric nitrate. De-ionised water were used for preparation of aqueous solution of nickel nitrate and ferric nitrate. NaOH solution was slowly added to aqueous salt solution of nickel nitrate and ferric nitrate until pH of solution reached to 10-11. Once pH of solution reached to 10-11, stirred solution at 80 $^\circ\text{C}$ for an hour. After an hour cooled precipitate to room temperature and was washed with de-ionised water till pH of filtrate become 7. After kept for overnight drying, obtained grinded and calcined at 450 $^\circ\text{C}$ for 3 hrs.

3.3. General procedure for synthesis of 1,4-DHP

In a 50 ml round bottom flask, ethyl acetoacetate (6mmol), ammonium carbonate (3mmol) and benzaldehyde (3mmol) were stirred in presence of NiFe_2O_4 (0.03g) in solvent ethanol along with 2-3 drops of water in order to dissolved ammonium carbonate at 60 $^\circ\text{C}$ for required time. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was heated in order dissolved solid product formed and filtered. Catalyst wash with hot ethanol. Filtrate concentrate and solid product obtain was filtered and recrystallised from hot ethanol. Purity of product checked by using TLC, M.P and characterized by using ^1H -NMR and ^{13}C -NMR.

IV. SPECTRAL DATA

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(Entry. 1):

Yellow colored crystalline solid, **IR (KBr, cm^{-1}):** 3350 (N–H), 3034 (Ar–H), 2953 (CH_3), 1755 (C=O, ester), **^1H -NMR (500 MHz, DMSO- d_6 , δ ppm):** 1.333 (*t*, 6H, 2x CH_3), 2.509 (*s*, 6H, 2x CH_3), 3.990 (*q*, 4H, 2x CH_2), 4.862 (*s*, 1H, CH), 7.086–7.216(*m*, 5H, Ph), 8.794(*s*, 1H, NH). **^{13}C NMR(500MHz,DMSO d_6 , δ ppm):**14.589(CH_3),18.636(CH_3),39.690(CH_2),59.384(CH),102.282–148.595(2xC=C,ArC),167.372(C=O). **MS m/z:** 328 (M+).

2,6-Dimethyl-4-(3-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester(Entry.2):

Yellow colored crystalline solid, **IR (KBr, cm^{-1}):** 3435 (N–H), 3084 (Ar–H), 2985 (CH_3), 1734 (C=O, ester), 1558 (C–NO $_2$), **^1H -NMR (500 MHz, DMSO- d_6 , δ ppm):** 1.135 (*t*, 6H, 2x CH_3), 2.510 (*s*, 6H, 2x CH_3), 3.990 (*q*, 4H, 2x CH_2), 4.848 (*s*, 1H, CH), 7.153–7.227(*m*,4H, Ph),8.848(*s*, 1H,NH). **^{13}C NMR(500MHz,DMSO d_6 , δ ppm):**14.147(CH_3),18.228(CH_3),39.089(CH_2),59.195(CH),101.049–147.393(2xC=C,ArC),166.487(C=O).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(Entry. 5) :

Yellow colored crystalline solid, **IR (KBr, cm^{-1}):** 3334 (N–H), 3084 (Ar–H), 2944 (CH_3), 1746 (C=O, ester), 616 (C–Cl), **^1H -NMR (500 MHz, DMSO- d_6 , δ ppm):** 1.135 (*t*, 6H, 2x CH_3), 2.510 (*s*, 6H, 2x CH_3), 3.990 (*q*, 4H, 2x CH_2), 4.848 (*s*, 1H, CH), 7.153–7.264 (*m*,4H, Ph),8.848(*s*, 1H,NH). **^{13}C NMR(500MHz,DMSO d_6 , δ ppm):**14.115(CH_3),18.162(CH_3),39.626(CH_2),59.005(CH),101.160–147.077(2xC=C, ArC),166.708(C=O).

V. CONCLUSION

A one pot high yielding synthetic protocol has been developed for achieving 1,4-DHP using an environmentally benign and recyclable nanocatalyst NiFe_2O_4 , a heterogeneous base catalyst. This method has advantages of being concise, highly efficient, friendly to environment, low catalyst loading and inexpensive.

ACKNOWLEDGEMENT

Authors are thankful to the Principal and Management of K. C. College, Chuchgate, Mumbai for constant encouragement and providing necessary facilities. Authors are also thankful to, The Director, TIFR Mumbai for spectral data.

REFERENCES

- [1]. Shan,R., Velazquez,C. and Knaus,E.E.(2004) *J. Med. Chem.*,47, 254-261.

- [2]. Vo,D., Matowe,W.C., Ramesh, M., Iqbal, N., Wolowyk,M.W., Howlett,S.E. and Knaus,E.E.(1995) *J. Med. Chem.*, 38, 2851
- [3]. Ogawa, A.K., Willoughby,C.A., Bergeron,R., Ellsworth,K.P., Geissler,W.M., Myer,R.W., Yao,J., Harris,G. and Chapman,K.T.(2003) *Bioorg. Med. Chem. Lett.*,13, 3405-3408.
- [4]. Klusa,V.(1995) Cerebrocrast, neuroprotectant cognition enhancer. *Drugs Future*, 20,135-138.
- [5]. Bretzel,R.G.,Bollen,C.C., Maeser E. and Federlin,K.F.(1993) *Am. J. Kidney Dis.*,21,53-64.
- [6]. Yang,J.W., Fonseca,M.T.H. and List,B.A.(2004) *Angew. Chem. Int. Ed. Engl.*,43, 6660-6662;
- [7]. Martin,N.J.A. and List,B.(2006) *J. Am. Chem. Soc.*,128,13368-13369.
- [8]. Rueping,M., Antonchick,A.P. and Theissmann ,T.A. (2006) *Angew. Chem. Int. Ed. Engl.*,45, 3683-3686.
- [9]. Hoffmann, S., Nicoletti,M. and List,B.(2006) *J. Am. Chem. Soc.*,128,13074-13075.
- [10]. Jin,T.S.,Wang,A.Q.,Cheng,Z.L., Zhang,J.S. and Li,T.S.(2005) *Synth. Commun.*,35,137.
- [11]. Ren,Z.,Cao,W.,Tong,W. and Jin,Z.(2005) *Synth. Commun.*,35,2509.
- [12]. B.Love,B. and Snader, K.M.(1965) *J. Org. Chem.*,30,1914-1916.
- [13]. Guo,S. and Yuan,Y.(2010)*Chin. J. Chem.*,28, 811-817;
- [14]. Ruiz,E., Rodríguez,H., Coro,J., Niebla,V., Rodríguez,A., Martínez-Alvarez,R., Novoa de Armas,H., Suárez,M. and Martín, N.(2012) *Ultrason. Sonochem.*,19, 221-226.
- [15]. Yadav,J.S., Reddy,B.V.S., Basak,A.K. and Narsaiah, A.V. (2003)*Green Chem.*,5, 60-63.
- [16]. Wang,L.M., Sheng,J., Zhang,L., Han,J.W., Fan,Z., Tian,H. and Qian,C.T.(2005) *Tetrahedron*,61, 1539-1543.
- [17]. Ko,S., Sastry, M.N.V., Lin,C. and Yao , C.-F.(2005) *Tetrahedron Lett.*,46, 5771-5774.
- [18]. Anniappan,M., Muralidharan,D. and Perumal,P.T.(2002) *Synth. Commun.*,32, 659-663;
- [19]. Khadikar,B.M.,Gaikar,V.G. and Chitnavis,A.A.(1995) *Tetrahedron Lett.*,36, 8083-8086;
- [20]. Öhberg, L. and Westman, J.(2001) *Synlett*,1296-1298;
- [21]. Agarwal,A. and Chauhan,P.M.S.(2005) *Tetrahedron Lett.*,46,1345-1348;
- [22]. Kuraitheerthakumaran,A.,Pazhamalai,S. and Gopalakrishnan, M.(2011)*Chin. Chem. Lett.*,22, 1199-1202.
- [23]. Chari,M.A. and Syamasundar,K.(2005)*Catal. Commun.*,6, 624-626.
- [24]. Sabitha,G., Reddy,G.S.K.K., Reddy,Ch.S. and Yadav,J.S.(2003) *Tetrahedron Lett.*,44, 4129-4131.
- [25]. Sharma,G.V.M., Reddy,K.L., Lakshmi,P.S. and Krishna,P.R.(2006) *Synthesis*,1, 55-58.
- [26]. Xu,Q., Wei,Y., Liu,Y., Ji, X., Yang,L. and Gu,M.(2009) *Solid State Sci.*,11(2), 472-478.
- [27]. M.B.Tian, *Magnetic Material*. Beijing,Tsinghua (2001)*University Press*.
- [28]. Sloczynski,J., Janas,J., Machej,T., Rynkowski,J. and Stoch,J.(2000) *Appl Catal B.*, 24(1),45-60.
- [29]. Ajayan,P.M. and Redlich, P.(1997) *J. Micro.*,185(2) ,275-282.
- [30]. Wang,X., Yang,G., Zhang,Z.,Yan,L. and Meng,J.(2007) *Dyes Pigm.*,74(2),269-272.
- [31]. Joshi,S., Kumar,M., Chhoker,S., Srivastava,G., Jewariya ,M. and Singh,V.N.(2014) *Journal of Molecular Structure*,1076, 55-62.
- [32]. Nasr-Esfahani,M., Montazerzohori,M. and Raeatikia,R.(2014)*Maejo Int.J.Sci.Technol.*, 8(01) ,32-40.
- [33]. Moshtaghi Zonouz, A.and Moghani,D.(2011) *Synth. Commun.* , 41,2152.
- [34]. Marco-Contelles,J., León,R., de los Ríos,C., Guglietta,A., Terencio,J., López,M.G., García,A.G. and Villarroya M.(2006) *J. Med.Chem.*,49, 7607.