



NICKEL FERRITE CATALYSED SYNTHESIS OF HEXAHYDROQUINOLINE DERIVATIVES IN AQUEOUS MEDIA

Karthik K. Krishnan*, Vijay V. Dabholkar, Amresh Baitha, Sandeep Gulve

*Organic Research Laboratory,
Department of Chemistry,
Guru Nanak College, G.T.B Nagar, Mumbai - 400037, INDIA
email: karthik.krishnan1986@yahoo.com

ABSTRACT

A general and convenient practical approach for the synthesis of hydroquinoline derivatives has been achieved via one-pot four-component Hantzsch condensation of aromatic aldehydes, dimedone, malononitrile and ammonium acetate in the presence of a catalytic amount of Nickel Ferrite (NiFe_2O_4), in water under reflux. Simple work-up, mild reaction conditions, inexpensive non-toxic catalyst and excellent yields are the advantages of this method.

KEYWORDS: Hexahydroquinoline, Nickel Ferrite, Magnetic nanoparticles

INTRODUCTION

Nowadays, aqueous mediated reactions have captured a considerable attention in organic synthesis due to both economic and environmental safety reasons. Water can be an ideal solvent for organic reaction due to its abundance, economical nature, high polarity and existence of strong hydrogen bonding also supplemented by convenient work up and purification carried out by simple filtration or extraction.^{1,2} Large surface tension, high specific heat capacity and cohesive energy, salting in or salting out effect, variation of pH etc. are some of the unique properties of water that can significantly impact the reactions performed in this media. In particular, reactions with negative activation volume are reported to occur faster in water than in organic solvents.^{3,4} Breslow, in 1980 rediscovered the use of water as a solvent in organic reaction which proved that hydrophobic effects strongly increase the rate of organic reaction.⁵ In last decade, water has been extensively used as an environmentally benign solvent for many chemical transformation including multicomponent reactions. Most MCRs require activation by a catalyst and are operated in organic solvents, but it was found that several MCRs, such as the Passerini, Biginelli, Hantzsch and Ugi reaction, could efficiently proceed in aqueous medium under catalyst or catalyst free condition.⁶⁻⁹ Till date numerous chemists have reported multicomponent reactions in aqueous medium.

Nano catalysis has quickly gained momentum in the recent past as they are ideal in terms of the surface area they provide for the reaction. However they encounter the problem of tedious work-up, separation of the catalyst and its reusability. Conventional techniques such as filtration and decantation are not efficient because of the very small size of the catalyst particles. This limitation hampers the economics and sustainability of nano catalysts. To overcome the separation problems of the nano catalysts, magnetically active nano particles have recently emerged as viable alternatives to conventional materials for catalyst supports.^{10,11}

Pure or doped nickel ferrite nano particles are common and frequently used in several catalytic processes. High reactivity of NiFe₂O₄ surfaces is well-known; NiFe₂O₄ has been used as a catalyst in a typical industrial process such as the water-gas shift (WGS) reaction.¹² Similarly, NiFe₂O₄ has also been examined as a catalyst in photo catalytic water oxidation using [Ru(bpy)₃]²⁺ as a photosensitizer and S₂O₈⁻² as a sacrificial oxidant.¹³

Over the last few years the Hantzsch reaction¹⁴, and its products 1,4-dihydropyridines (DHP) have attracted immense attention of synthetic chemists due to their therapeutic and pharmacological properties such as vasodilator, antitumor, bronchodilator, geroprotective, antimalarial, anti-inflammatory, antiasthmatic and antibacterial.^{15,16} 1, 4-DHP nucleus containing drugs nimodipine, lacidipine possess improved calcium channel antagonist activity^{17,18} and the cardiovascular agents such as nifedipine, nicardipine, and amlodipine are effective against treatment of hypertension.¹⁹

Due to its biological importance, several methods have been reported for synthesis of polyhydroquinolines. The classical method involves three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or refluxing alcohol.²⁰⁻²⁵

However, these methods suffer from drawbacks of a long reaction time, usage of an excess of organic solvent, and lower yields. Several alternate and more efficient methods have been developed for the synthesis of polyhydroquinoline derivatives by ionic liquids,^{26,27} TMSCl - NaI,²⁸ metal triflates,²⁹ I₂,³⁰ ceric ammonium nitrate,³¹ polymers,^{32,33} organo-catalyst,³⁴ solvent free conditions and microwave irradiation,³⁵ and under grinding.³⁶ The grinding method was the best synthetic route reported for synthesis of polyhydroquinolines. Use of all the other methods were limited in terms of high temperatures, expensive metal precursors, catalysts that are harmful to environment, and longer reaction. In search of a better method for synthesis of polyhydroquinoline derivatives Nickel ferrite nano particles were examined as a viable green catalyst.

RESULTS AND DISCUSSION

NiFe₂O₄ nanoparticles were synthesized by sol-gel (citrate gel technique)³⁷ and the synthesised NiFe₂O₄ nanoparticles were characterized using Powder XRD and SEM.

X-Ray Diffraction

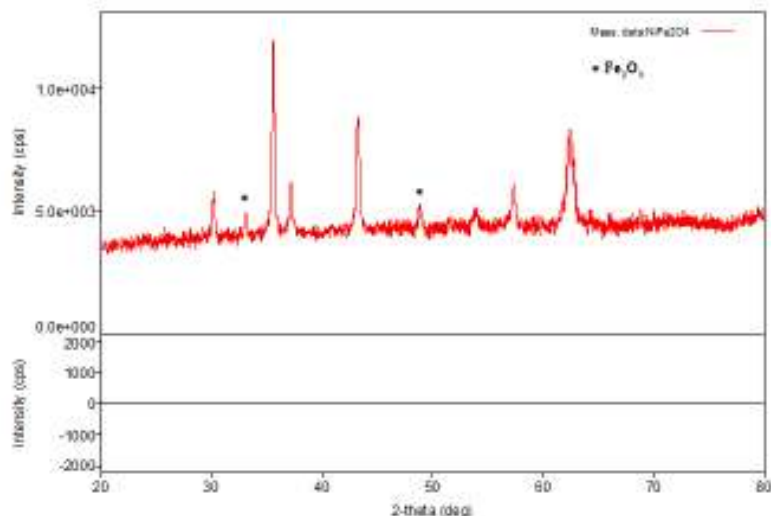


Fig. 1 X-ray diffraction patterns of NiFe₂O₄ nanoparticles prepared by sol–gel, calcined at 600°C

The sharp peaks appearing in the X-Ray diffractograms shows fully crystalline phase of nickel ferrite (NiFe₂O₄) with well pronounced cubic spinel crystal structure. The main peak is centered at $2\theta = 35.6^\circ$ and corresponds to the crystal plane with Miller indices (3,1,1) which is characteristic of NiFe₂O₄ cubic spinel. However, the sample showed some extra peaks (**Fig. 1**). These peaks were indexed according to standard JCPDS Card No. 87-1166 and corresponded to the presence of hematite phase (α -Fe₂O₃).

The average crystallite sizes of particles were calculated for NiFe₂O₄ sample using the high intensity peak at $2\theta = 35.6^\circ$ with the help of the Debye-Scherrer equation.³⁸ The average crystallite size and the lattice strain was calculated as 31.14nm and 0.0038 respectively.

SEM

Scanning electron microscopy (SEM) was used to study the morphology of the synthesized NiFe₂O₄ samples. **Fig 2** shows SEM images of NiFe₂O₄ MNP calcined at 600°C.

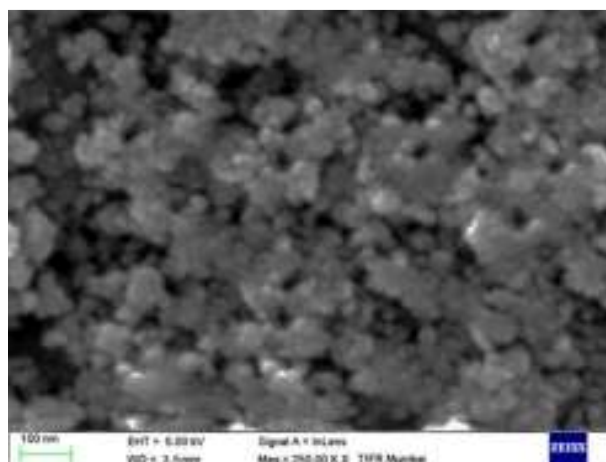
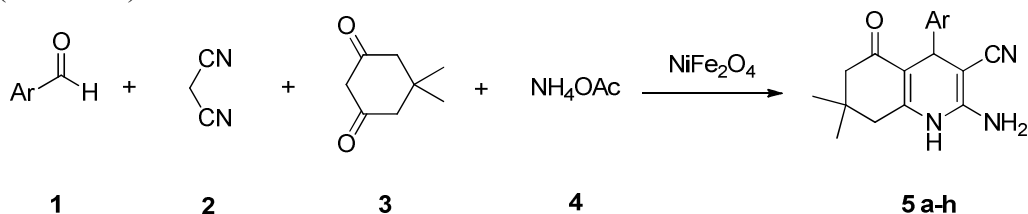


Fig. 2 SEM image for NiFe₂O₄ nanoparticles prepared by sol–gel, calcined at 600°C

The SEM image shows that the FNPs consists of almost uniform particles size and reveals that the particles are more or less spherical in shape. The particles size is in a good agreement with the results obtained from X-ray analysis.

The synthesised NiFe_2O_4 NP was used as a heterogeneous base catalyst for one pot tandem enamionone intermediate synthesis of substituted hexahydroquinoline (**5**) by four component reaction between aryl aldehydes (**1**), malononitrile (**2**), dimedone (**3**) and ammonium acetate (**4**) (**Scheme 1**).



Scheme 1 Four component synthesis of substituted hexahydroquinolines

Initially, we engaged dimedone, ammonium acetate, benzaldehyde and malononitrile as model substrates for the optimization of reaction conditions.

Solvent Screening

The reaction was examined under various solvent and solvent mixtures (**Table 1**). Water as solvent (Table 1, Entry 1) resulted in excellent yield (89%) of desired product compared to other solvents.

Entry	Solvent (10ml)	Time (min)	Yield of product (%)
1	H ₂ O	45	89
2	EtOH	60	82
3	MeOH	60	80
4	EtOH : H ₂ O (1:1)	60	82
5	MeOH : H ₂ O (1:1)	40	75
6	Acetic Acid	120	58
7	DMF	180	66
8	DMSO	180	60
9	Toluene	180	15
10	DCM	180	16

Table 1 Optimization of solvent for one-pot tandem synthesis of hexahydroquinolines.

Catalyst Quantity

To study the effect of catalyst and its quantity, the model reaction was carried out without any catalytic assistance in aqueous media varying the temperature criteria from room temperature to reflux condition. However the reaction failed to proceed even after prolonged stirring at RT to Reflux. Moreover the same reaction was employed by varying the quantity of catalyst from 5 to 30 mol% under reflux condition (**Table 2**). The desired product

hexahydroquinoline was obtained in excellent yield (89%) at 20 mol% of NiFe₂O₄ (and the time of reaction completed in 60mins (Table 2, Entry 7).

Entry	Catalyst quantity (mol %)	Condition	Time (min)	Yield of product (%)
1	Without catalyst	RT	180	No reaction
2	Without catalyst	60 °C	180	No reaction
3	Without catalyst	Reflux	180	No reaction
4	5	Reflux	80	48
5	10	Reflux	60	78
6	15	Reflux	60	80
7	20	Reflux	60	89
8	25	Reflux	60	89
9	30	Reflux	60	89

Table 2 Optimization of catalyst quantity for one-pot tandem synthesis of hexahydroquinolines.

Reusability of the catalyst

After completion of the reaction, the catalyst was separated using a magnet. It was reused after washing with ethanol and acetone. It was observed that the activity of the catalyst did not show any significant decrease even after using them in four successive reactions (Fig. 3).

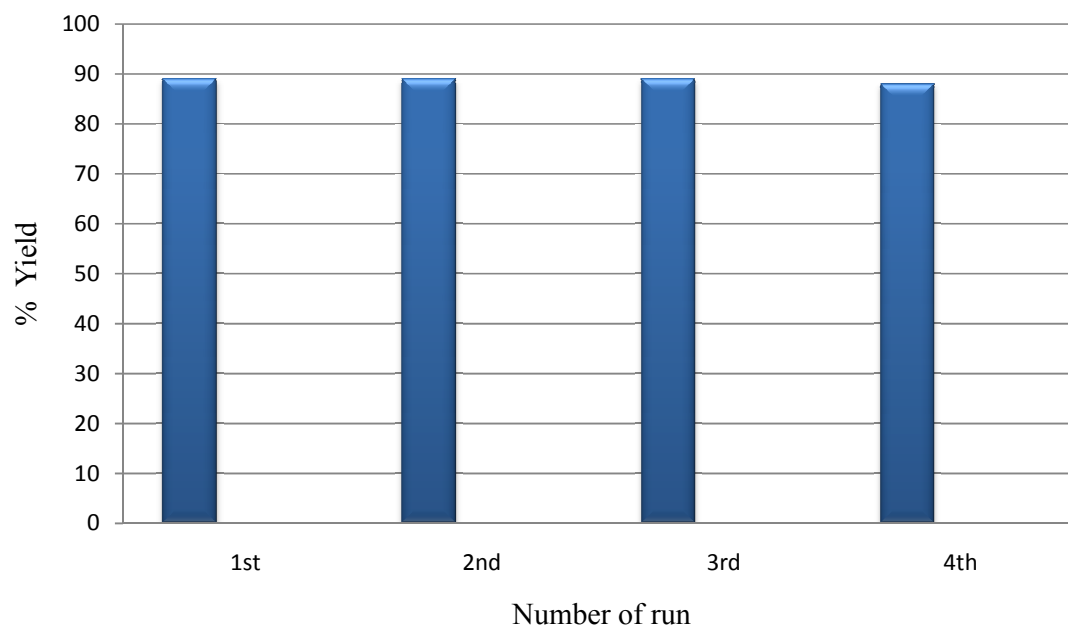


Fig. 3. Reusability of NiFe₂O₄ catalyst in model reaction

With the standard optimized parameter, the scope of this reaction which was investigated by synthesizing a library of hexahydroquinoline derivatives using 20 mol% of Nickel Ferrite nanoparticles at reflux condition using water as a reaction medium (Table 4.3). The optimized

tandem methodology gave good to excellent yields of the product using a wide spectrum of aromatic aldehydes.

Sr. No.	Ar	Product	Yield (%)	Time (min)	Melting Point (°C)	
					Found	Reported
1	C ₆ H ₅ -	5a	89	60	282-284	280–281 ³⁵
2	4-ClC ₆ H ₄ -	5b	93	60	286-288	290–291 ³⁹
3	2,4-Cl ₂ C ₆ H ₃ -	5c	91	50	>300	-
4	3-NO ₂ C ₆ H ₄ -	5d	91	55	282-284	282-283 ³⁵
5	4-NO ₂ C ₆ H ₄ -	5e	87	80	290-292	-
6	4-MeOC ₆ H ₄ -	5f	85	45	287–289	289-293 ³⁵
7	4-MeC ₆ H ₄ -	5g	81	80	290-293	294–295 ³⁵
8	2,4-(MeO) ₂ C ₆ H ₃ -	5h	80	45	280-283	-

Reaction condition: Dimedone (3 mmol), ammonium acetate (3.3 mmol), aryl aldehyde (3 mmol), malononitrile (3.3mmol) and NiFe₂O₄ NP (20 mol%) as a catalyst in 10 ml water.

Table 3 Synthesis of hexahydroquinoline derivatives from tandem reaction with different aryl aldehydes.

EXPERIMENTAL SECTION

All chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets pre-coated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. The products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones. Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ¹H-NMR and ¹³C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d₆ as solvent and TMS as internal standard.

General procedure for the synthesis of NiFe₂O₄ nanoparticles

Stoichiometric amounts of Ni (NO₃)₂.6H₂O and Fe(NO₃)₃.9H₂O were dissolved in 200 ml of deionised water in 1:2 molar ratio. They were stirred for 1 h to get a homogenous solution.

Citric Acid solution was prepared in deionised water and was added to the solution of metals and this solution was stirred for further 15 mins. The ratio of citric acid (chelating agent) to the metal contents was maintained at 1:1. A small amount of NH₃ was added drop wise to the solution to adjust the pH value at 7.0. The solution was heated, stirred continuously to transform into a highly viscous gel. Continuous heating of this gel, led to the formation of dark brown magnetic nanopowders of NiFe₂O₄ through a self-propagating combustion process. This powder was ground with mortar and pestle and calcined at 600°C for 6h.

General procedure for the synthesis of hexahydroquinolines 5a – 5h

In a 50 ml round bottom flask dimedone (3 mmol), ammonium acetate (3.3 mmol) and NiFe₂O₄ in water (10 ml) were added. Then the reaction mixture was stirred at 100°C till completion of the reaction as indicated by TLC. Afterward, malononitrile (3 mmol), and aryl aldehyde (3 mmol) were charged, and the mixture was refluxed for the time reported in **Table 3**. After completion of reaction [monitored by TLC, ethyl acetate: n-hexane (3:7)], the catalyst was separated using a magnet and the reaction mixture was stirred at RT. The obtained solid was filtered off and recrystallized from ethanol to afford pure product.

2-Amino-4-(4-chloro phenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8 - hexahydroquinoline (5b)

Yellow solid; **m. p.** (°C) : 290-291; **IR** (KBr, cm⁻¹): 3355(NH₂), 3199, 2967, 2185(CN), 1657(C=O), 1602 (C=C), 1487, 1368; **¹H NMR** (500 MHz, DMSO, δ ppm) : 0.91 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.20 (dd, 2H, CH₂), 2.41 (dd, 2H, CH₂), 4.42 (s, 1H, CH), 5.93 (s, 2H, NH₂), 7.23 (d, 2H, Ar-H), 7.29 (d, 2H, Ar-H), 9.02 (bs, 1H, NH); **¹³C NMR** (500 MHz, DMSO, δ ppm) : 27.13, 29.22, 32.50, 38.05, 50.47, 57.88, 109.07, 121.68, 125.08, 128.51, 146.33, 151.56, 152.19, 158.13, 194.41

CONCLUSIONS

1. The reported method provides an efficient and diversity oriented four component route for the tandem synthesis of a series of hexahydroquinoline derivatives in aqueous media using Nickel Ferrite nanoparticles as an magnetically separable eco-friendly catalyst.
2. Experimental simplicity, excellent yields, shorter reaction time, simple work up procedure, purification of products by non-chromatographic method and high atom economy are the notable features of this protocol.

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