Heterogeneous bimetallic $ZnFe_2O_4$ nanopowder catalyzed synthesis of Hantzsch 1,4-dihydropyridines in water

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Heterogeneous bimetallic $ZnFe_2O_4$ nanopowder catalyzed synthesis of Hantzsch 1,4-dihydropyridines in water.

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ABSTRACT

The mixed metal oxide $ZnFe_2O_4$ nanopowder, a dual Lewis acid–base combined catalyst is found to efficiently catalyse a multicomponent synthesis of 1,4-dihydropyridines from aldehydes, ethyl acetoacetate and ammonium acetate in water. This procedure offers several advantages including high yields, short reaction times, a simple work-up procedure, and a benign eco-footprint. This method takes advantage of the fact that water, a green solvent is used in combination with $ZnFe_2O_4$nanoparticles as catalyst which can be easily recovered magnetically and reused for further runs.

1. Introduction

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Therefore, researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis.[1]

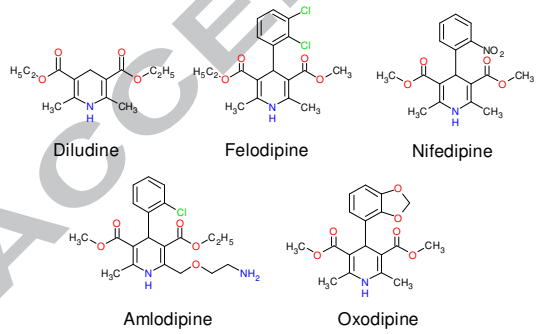
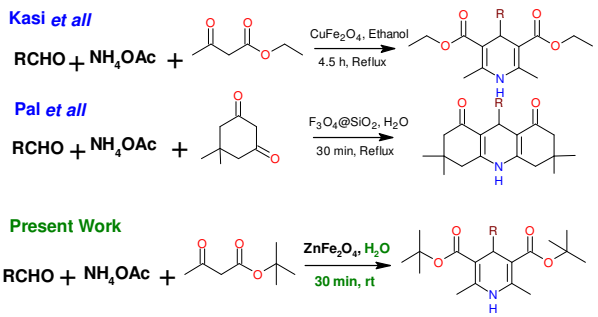


Figure 1. Drugs containing 1,4-DHP moieties.

For several decades, five- and six-membered heterocyclic compounds containing nitrogen, sulphur and oxygen have been very significant in the field of medicinal chemistry. As they display considerable pharmacological activity, these bioactive heterocyclic compounds, and approaches to their synthesis, have been important topics of interest to medicinal chemists. Thus, ever since the first report of the Hantzsch synthesis of 1,4-dihydropyridines (DHP), a number of strategies have been developed for their synthesis[2] because of the wide range of their biological and pharmacological actions, such as for their calcium channel blocking and antitumor, anti-inflammatory, and analgesic activities.[3] Specifically, 1,4-DHP compounds play important roles in medicinal chemistry, for example in nifedipine, amlodipine, diludine, felodipine, and oxodipine (Fig-1), which are the best selling drugs used in the treatment of cardiovascular diseases.[4]



Scheme 1. Magnetic nanopowder catalysed synthesis of 1,4-dihydropyridine.

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Generally, 1,4-DHPs are synthesized by the Hantszch method, which involves cyclocondensation of aryl or alkyl aldehyde, a *β*-dicarbonyl compound and ammonia in the presence of mineral acids at room temperature or reflux condition for a long time.

On the other hand, much effort has been expended to develop more efficient methods for the synthesis of 1,4-DHPs, such as using microwave irradiation,[5] solar thermal energy,[6] ultrasound irradiation,[7] solid support,[8] metal triflates as catalyst,[9] reactions in ionic liquid,[10] $InCl_3$,[11] I_2,[12] $SiO_2/NaHSO_4$,[13] $SiO_2/HClO_4$,[14] CAN,[15] ZnO[16] and Grignard reagents.[17] It is noteworthy that all these protocols have employed thermal reaction conditions, disposal of toxic solvents and catalysts often poses a problem. For these reasons, effort has been made to replace conventional catalysts with eco-friendly and green process catalysts.

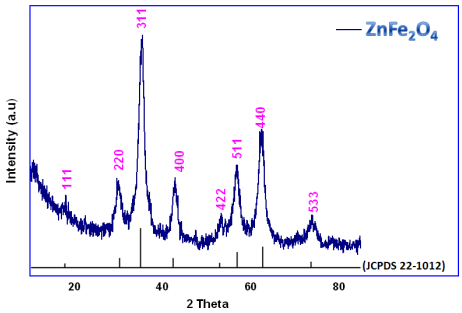


Figure 2. Powder XRD of obtained $ZnFe_2O_4$ nano catalyst by microwave method

One of the most attractive synthetic strategies favoured by organic chemists is the use of heterogeneous catalysts in increasing the efficiency of a wide range of organic syntheses. Heterogeneous catalysis is being used in the fine chemicals industry because of the need and demand for more environment-friendly production technology. This trend is assisted by the availability of catalytic materials and modern techniques of creating and investigating specific active sites on catalyst surfaces.[19] In particular, mixed metal oxides nanoparticles have emerged as an efficient catalyst in modern synthetic organic chemistry.[20] These nanoparticles exhibit both the Lewis acid and the Lewis base character at their surface.[20]

Table 1: Synthesis of 1,4-dihydropyridines.

Entry	R	R^1	Time (min)	Yield(%)[a,b]
1a	C_6H_5	*t*-Bu	30	90
1b	4-MeO-C_6H_5	*t*-Bu	30	96
1c	4-Cl-C_6H_5	*t*-Bu	30	95
1d	4-F-C_6H_5	*t*-Bu	30	95
1e	C_6H_5	Et	30	94
1f	4-MeO-C_6H_5	Et	30	93
1g	4-OH-C_6H_5	Et	30	90
1h	4-F-C_6H_5	Et	30	95
1i	2-Pyridyl	Et	30	92
1j	2-Furyl	Et	30	92
1k	C_6H_5	Me	30	95
1l	4-MeO-C_6H_5	Me	30	95
1m	4-OH-C_6H_5	Me	30	90
1n	4-F-C_6H_5	Me	30	87
1o	2-Pyridyl	Me	30	90
1p	2-Furyl	Me	30	90

[a]All the products were characterized by ^{1}H NMR,^{13}C NMR and mass spectroscopy studies and compared with the literature mps.
[b]Yields of isolated products.

Magnetic nanoparticles have received considerable attention in recent years owing to their interesting biological applications such as drug delivery,[21a] magnetic resonance imaging,[21b] bioseparation,[21cd] biomolecular sensors[21e] and magneto-thermal therapy.[21fg] Despite their wide use in biological systems, much less attention has been focused on the catalytic behavior of magnetic nanoparticles in organic transformations.[22]

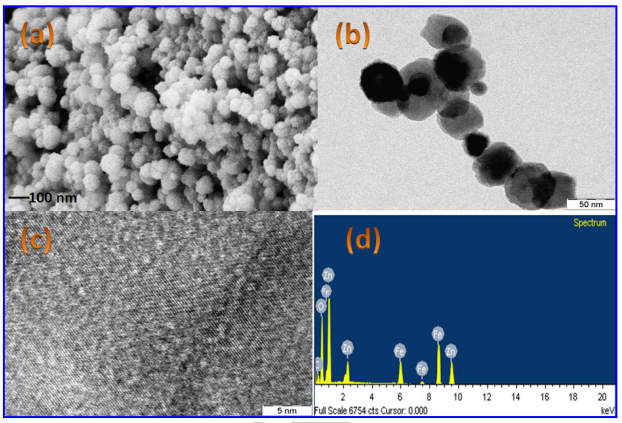
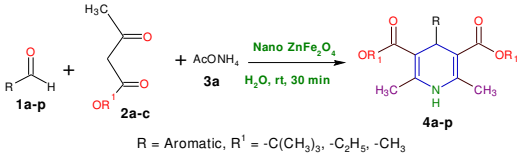


Figure 3. (a) SEM images of $ZnFe_2O_4$ nano catalyst; (b) TEM images of noanocrystals (c) HRTEM of $ZnFe_2O_4$ nano catalyst (d) EDX analysis spectrum of obtained $ZnFe_2O_4$ nano catalyst.

Recently, Pal and co-workers exploited the high surface area and reactive morphology of the Fe_3O_4@SiO_2 nanoparticles for 1,4-DHPs synthesis at refluxed temperature in water (Scheme 1).[23a] Kasi and co-workers also used catalytic amounts of magnetic $CuFe_2O_4$ nanoparticles for 1,4-DHPs synthesis at refluxed temperature in ethanol (Scheme 1).[23b] Although these results are promising, there is still room for further development of an environment friendly, less expensive and easily separable, reusable catalytic system for 1,4-DHPs synthesis.

$ZnFe_2O_4$ nanoparticles are inexpensive, effective, safe, recyclable, and require only mild reaction conditions to produce high yields of products in shorter duration than that is possible with traditional catalysts.[20] Therefore, in continuation of our efforts on nanomaterials,[24] we herein present a green and efficient method for the synthesis of 1,4-DHPs using $ZnFe_2O_4$ nanoparticles as a catalyst at room temperature (Scheme 1).



Scheme 2. Synthesis of 1,4-dihydropyridine (ESI†).

In literature, there are several methods known for the synthesis of spinel zinc ferrite. The $ZnFe_2O_4$ used in this work was synthesized according to a modified method (ESI†).[24b] The prepared crystalline $ZnFe_2O_4$-NPs was characterized by FTIR, powder X-ray diffraction (XRD), scanning electron microscopy (SEM), highresolution transmission electron microscopic (HRTEM) analysis, EDX with elemental analysis and solid state UV spectroscopy (for the preparation and other characterization see ESI†).

Nanocrystalline structure of the prepared $ZnFe_2O_4$-Nps was determined by powder X-ray diffraction (XRD) as shown in Fig 2. All the observed reflections could be assigned to cubic spinel lattice indicating their single phase structure with no traces of other impurity phases (e.g. Fe_2O_3, ZnO etc.). The peaks could be indexed as (220), (311), (400), (422), (511), (440) and (533), which are characteristics of single-phase cubic spinel structure

(JCPDS card no. 22-1012).[25] The morphology and structure of the product were investigated by scanning electron microscopy as shown in Fig. 3a. It is clear from the image in Figure 3a that, the spherically shaped $ZnFe_2O_4$ nanoparticles have diameter within the range of ~160-200 nm. High-resolution transmission electron microscopy (HRTEM) at an accelerating voltage of 200 kV was employed to know the morphology and size of prepared $ZnFe_2O_4$ nanoparticles (Fig. 3b) and the individual particles appear to be single-crystalline, as shown by lattice imaging in Fig. 3c. Elemental analyses of the as-synthesized $ZnFe_2O_4$ nanoparticles were performed at EDX equipped onto SEM. Quantitative EDX showed that Fe, Zn and O were the main elemental components (Fig. 3d).[26]

To examine the versatility of the $ZnFe_2O_4$-NPs, the preparation of 1,4-DHPs was tested using a modified Hantzsch procedure. Treatment of one equivalent of benzaldehyde **1a** and ammonium acetate **3a** with 2 equiv of tert-butyl acetoacetate (tbob) **2a** in the presence of 40mg of $ZnFe_2O_4$ in water afforded the corresponding 1,4-DHP **4a** (Scheme 2,Table 1, entry 1) in 90% yield at room temperature.[27] Under similar conditions, various substituted aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents were converted into the expected 1,4-DHPs in good to excellent yields, and the results are summarized in Table 1. To the best of our knowledge, this is the first report of the preparation of 1,4-DHPs catalysed by nano crystalline $ZnFe_2O_4$ in water at room temparature.

The products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy and also by comparison with authentic samples. The advantages of the present protocols are the shorter reaction times at room temperature, mild reaction conditions and due to the high reactivity of the catalyst the products are obtained in high yields. From a mechanistic point of view, the first step of this reaction can be visualized as the $ZnFe_2O_4$-catalyzed formation of Knoevenagel product 5. A second key intermediate is ester enamine 6, produced by condensation of the second equivalent of the β-ketoester with ammonia. Condensation of these two fragments gives intermediate 7, which subsequently cyclizes to the 1,4-dihydropyridine 4 (Scheme S1, ESI†).

Next, we decided to find the optimal amount of catalyst ($ZnFe_2O_4$) to reach complete conversion of 1,4-DHPs at room temperature. Initially, 10 mg of $ZnFe_2O_4$ was used as a catalyst and it was found to give 60% yield of corresponding 1,4-DHP (**4a**) (Table S1, entry 1, ESI†). On increasing the catalyst loading from 10 to 40 mg, the yield of product was found to increase, however on further increasing the catalyst loading no effective increase in the yield was observed (Table S1). On the optimized amount of catalyst, we found that 40 mg of $ZnFe_2O_4$ could effectively catalyze the reaction for the synthesis of the desired product. After determining the optimized conditions, we also studied the effect of different solvent such as, EtOH, CH_3N, H_2O and they were found to be efficient (Table S1). Water was chosen as the solvent for further study because of its non-toxicity, low cost and wide availability as compared with organic solvents. Although Fe_3O_4@SiO_2 and $CuFe_2O_4$ catalysed reaction produced the product **4a** in less yield within 30 min under similar reaction conditions (Table S1, entry 4 and entry 5).

From the green chemistry point of view, efficient recovery and reuse of the catalyst are highly desirable, thus the recovery and reusability of $ZnFe_2O_4$-NPs were investigated. After completion of the reaction, nanoparticles were separated by using an external magnet. The obtained $ZnFe_2O_4$-NPs powder was washed thoroughly with deionized water, ethanol and acetone to remove the organic impurities. It was then dried at 70 ^{0}C for 15 min and used for the next catalytic cycle. The recovered catalyst was directly used in Hantzsch synthesis of 1.4-DHPs and it was observed that, the catalyst can be reused for five times and product obtained (Fig. S6, ESI†) in good yields. It should be pointed out that no extra care needs to be taken in order to store or handle the catalyst since it is not air or moisture sensitive.

In conclusion, we have developed an efficient, rapid, high-yielding, and eco-friendly methodology for the Hantzsch synthesis of 1,4-DHPs with $ZnFe_2O_4$-NPs as the catalyst. The advantage of $ZnFe_2O_4$-NPs catalyst over Lewis acids lies in its stability, moisture-insensitivity, and low cost. Further efforts will be devoted to extend the scope of the $ZnFe_2O_4$-NPs catalyst in other kinds of transformations. We believe that the present improved modification is a convenient and efficient alternative to the existing methods for the multicomponent synthesis of 1,4-DHPs.

Acknowledgements

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27. A mixture of benzaldehyde **1a** (5 mmol), tert-butyl acetoacetate **2a** (10 mmol), and ammonium acetate **3a** (10 mmol) and $ZnFe_2O_4$ (40 mg) was dissolved in 30 mL of water. The resultant mixture was stirred for 30 min at room temperature. After completion of the reaction (when the starting materials were completely disappeared as per thin layer chromatography projection), the reaction mixture was ultrasonicated by ethyl acetate (15 ml) for 10 min. The separated organic phase was concentrated to get the crude product which was purified by silica gel column chromatography (ethyl acetate/hexanes) to afford the title compounds (**4a**–**p**) (Scheme 2, Table 1). The solid catalyst was collected from water layer by centrifugation. The recovered catalyst was washed several times with water, ethanol and finally by acetone to remove organic impurities, dried at 60 ^{0}C for 20 min and used for another run (for the preparation and other characterization see ESI†).

Graphical Abstract

Heterogeneous bimetallic $ZnFe_2O_4$ nanopowder catalyzed synthesis of Hantzsch 1,4-dihydropyridines in water.

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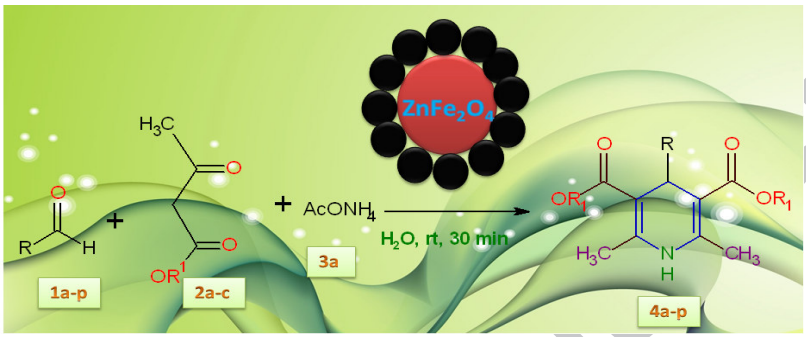
T. R. Ravikumar Naik[a,] ∗ and S. A. Shivashakar[a]



Highlights

- CEM-Microwave assisted synthesis of $ZnFe_2O_4$ nano-catalyst.
- A simple procedure for the conversion of 1,4-Dihydropyridines using $ZnFe_2O_4$ in aqueous medium is described.
- Magnetically recovered heterogeneous catalyst.
- The reaction exhibits generally good yields, mild conditions and broad substrate tolerance.