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## RESEARCH ARTICLE

# SIX MEMBERED NITROGEN HETEROCYCLES USING $\text{NiFe}_2\text{O}_4$ NANO CATALYST

Vijay V Dabholkar<sup>1\*</sup>, Swapnil K Kurade<sup>2</sup> and Keshav S Badhe<sup>3</sup>

Department of Chemistry, Kishichand Chellaram College, Churchgate, Mumbai- 400 020

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### ABSTRACT

A simple and efficient procedure for the synthesis of dihydropyrimidione-2(1H)ones using nanoparticulate  $\text{NiFe}_2\text{O}_4$  as recyclable catalyst for one pot three component reaction to afford corresponding product with excellent yield. The reaction was run in thermal condition. The protocol has key features such as catalyst used is in expensive, ecofriendly catalyst preparation and environmentally benign. The catalyst can be run for number of times without loss of its catalytic activity.

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### INTRODUCTION

Dihydropyrimidione-2(1H)-one and related compounds have gained much attention as they exhibit a wide range of pharmacological and biological activities such as anti-hypertensive agents, anticancer drugs, calcium channel blocker and neuropeptide-Ynpy [1,2] moreover, they were found to be antiviral, antitumour, antibacterial and anti-inflammatory properties [3,4]. Thus the development of of facile and environmentally friendly synthetic methods towards dihydropyrimidinones constitutes an active area of investigation in organic synthesis.

Current organic methodologies seriously focus on multicomponent reaction as they possess great ability to produce the complex and highly functionalized organic molecules with simple operation in a single step. On account of these, MCR exhibit higher atom economy and selectivity underlying such reaction, consuming less energy, environmental and time saving [5, 6, 7]

The most simple and straightforward procedure for synthesis of dihydropyrimidione-2(1H)-one reported by biginelli involves the three component condensation of beta-ketoester, aldehyde and urea in refluxing ethanol containing a catalytic amount of HCl [8] albeit in low yields. Therefore, in the view of the pharmacological importance of these compounds, many researcher involves to improve synthetic method by applying several catalytic methods such as  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  [9],  $\text{Cu}(\text{OTf})_3$  [10],  $\text{LnCl}_3$  [11], Baker's yeast [12], heteropoly acids [13],  $\text{Mn}(\text{OAc})_3$  [14],  $\text{Al}(\text{HSO}_4)_3$  [15], P-sulphonic acid

calixarene [16], functionalized SBA-15 [17], natural HEU type Zeolite [18], different lewis acids [19-24], polyphosphate ester [25,26], zirconium (IV) chloride [27]. Many of these existing methods involves stoichiometric amount of catalyst, strong acidic condition, longer reaction times, low yield, cumbersome product isolation and environmental pollution. Therefore, exploring the new catalytic method to overcome these drawbacks is a challenging task to organic chemist.

Therefore improvement with respect to the above have been continuously sought among the catalyst, heterogeneous catalyst are gaining more and more importance, mainly due to their environmentally benignness they have advantages viz. recyclability, selectivity, easy separation, reusability etc. as a part of our interest in this area, we initiated an investigation of to explore the generation of efficient catalytic processes via nanocatalysis [28] as a viable option many scientific studies in nanocatalysis activity with particle size, moreover many other factors such as geometry, composition, surface area to volume ratio play an important role in their catalytic reactivity and selectivity.

Synthesis of Dihydropyrimidione-2(1H)-one using base catalyst nickel ferrite, a kind of soft magnetic materials has many technical applications such as microwave devices [29], sensor [30], magnetic pigment [31] and catalysis [32]. This ferrite has most of the technological importance [33]. As a part of our ongoing research in the field of developing new methodologies for the synthesis of heterocycles, in this paper we present  $\text{NiFe}_2\text{O}_4$  nanoparticulate, a heterogeneous base

\*Corresponding author: **Vijay V Dabholkar**

Department of Chemistry, Kishich and Chellaram College, Churchgate, Mumbai- 400 020

catalyst for scalable synthesis of Dihydropyrimidione-2(1H)-one by three component reaction.

## RESULTS AND DISCUSSION

$NiFe_2O_4$  nanoparticles were synthesized by co-precipitation method [34]. The structural characterization of  $NiFe_2O_4$  nanoparticles were done by X-ray Diffraction using CuK radiation ( $\lambda = 1.54059 \text{ \AA}$ ) at 40 kV and 15 mA shown in Fig 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)

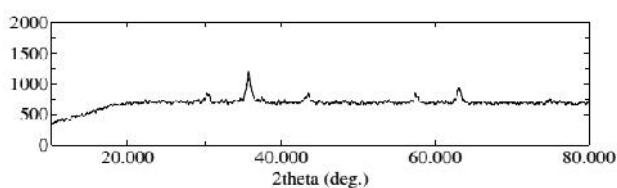


Figure 1 XRD patterns for  $NiFe_2O_4$  nanoparticles sintered at  $500^\circ\text{C}$

### Morphological analysis

The morphology of  $NiFe_2O_4$  nanoparticles were studied using SEM shown in Fig 2. Most of the particles are found to be spherical in shape.

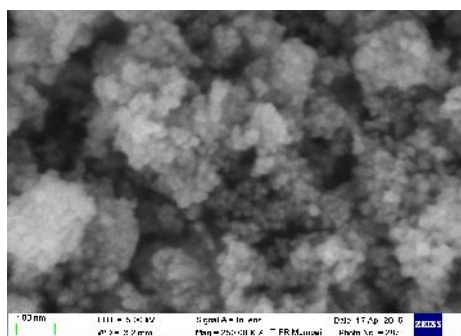
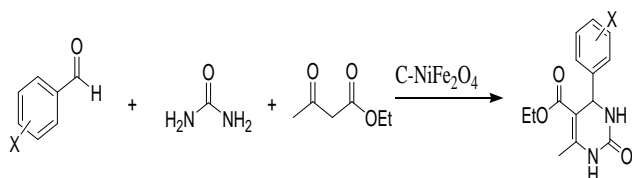


Figure 2 SEM image for  $NiFe_2O_4$  nanoparticles sintered at  $500^\circ\text{C}$

First of all, the model reaction of aromatic aldehyde, ethyl acetoacetate and urea/thiourea was conducted to screen the optimal conditions (Scheme 1). Initially, we carried out the reaction at room temperature in presence of  $NiFe_2O_4$  as catalyst but the reaction could not proceed for long time (2-4 hours). But the temperature of reaction raised to  $70^\circ\text{C}$ , from the T.L.C. we observed that the drastic change in reaction as intermediate formed in the reaction were converted to desired product.



Scheme 1 Synthesis of Dihydropyrimidinones

The efficiency of reaction is affected mainly by the amount of nanoparticulate  $NiFe_2O_4$  catalyst table 1. In absence of catalyst no product was obtained indicating that catalyst is necessary for the reaction. The optimal quantity of  $NiFe_2O_4$  was 0.02g;

beyond this quantity of catalyst there is no much change in yield of product.

Table 1 Effect of different quantity of  $NiFe_2O_4$  catalyst on reaction

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.01	48
2	0.02	89
3	0.03	89
4	0.04	89
5	0.05	89

### Reaction conditions

Benzaldehyde (3mmol), Urea (4mmol), Ethyl acetoacetate(3mmol), no solvent,  $NiFe_2O_4$  catalyst, temperature ( $70^\circ\text{C}$ ). The recovered catalyst could be used for number of times without noticeable change in activity (table2).

Table 2 Reusability of  $NiFe_2O_4$  catalyst

Run	Yield of product (%)
1	89
2	89
3	88
4	87

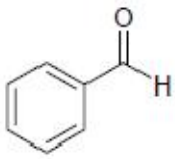
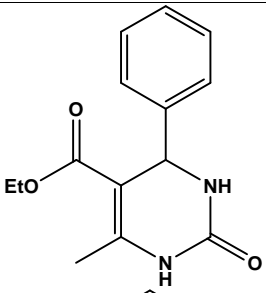
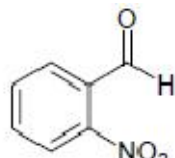
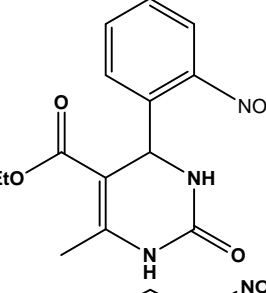
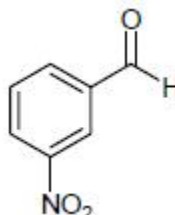
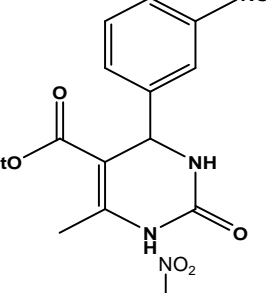
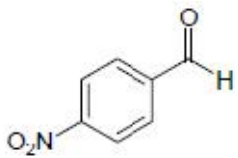
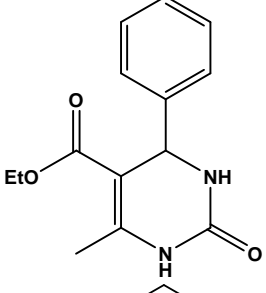
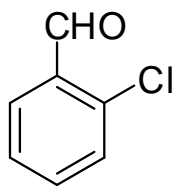
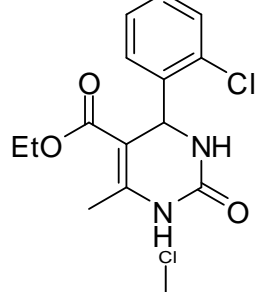
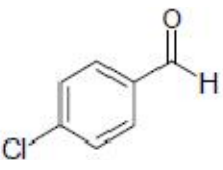
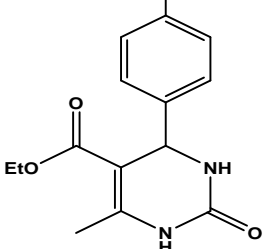
### Reaction conditions

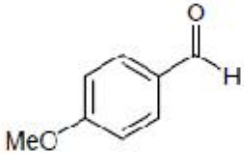
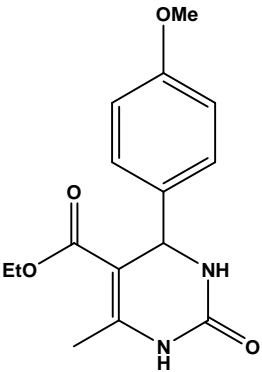
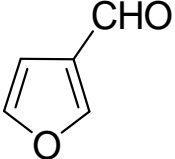
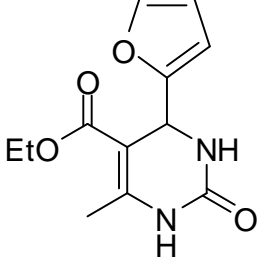
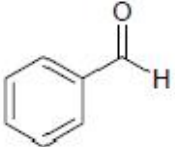
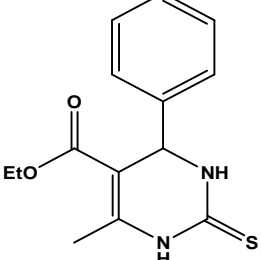
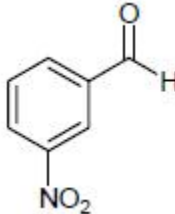
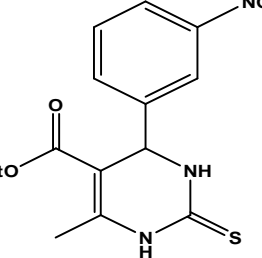
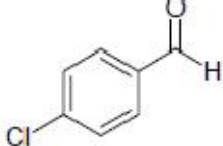
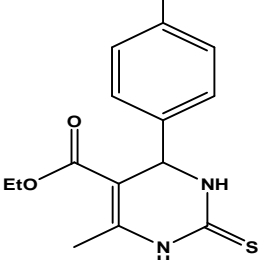
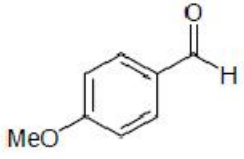
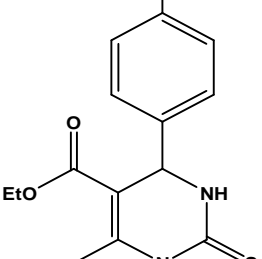
Benzaldehyde (3mmol), Urea (4mmol), Ethyl acetoacetate (3mmol), no solvent,  $NiFe_2O_4$  catalyst (0.02g), temperature ( $70^\circ\text{C}$ ). In order to study the mechanistic pathway we carried out the reaction in three different pathways .theoretically, three routes are available viz. enamine mechanism, iminium mechanism and knoevengel mechanism.

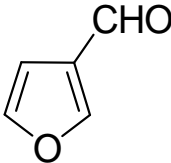
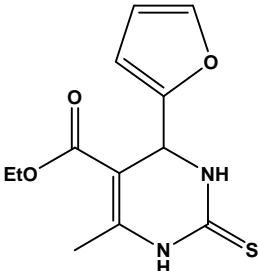
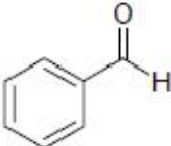
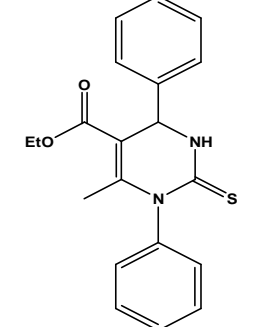
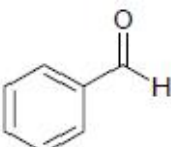
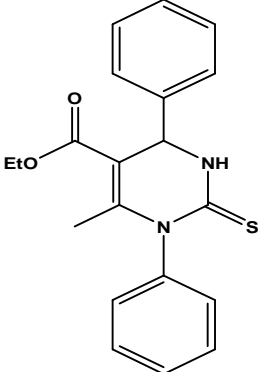
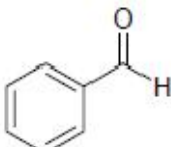
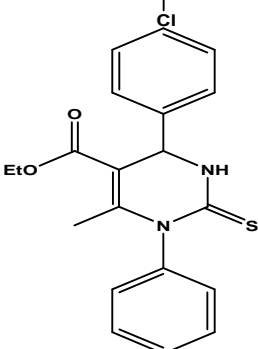
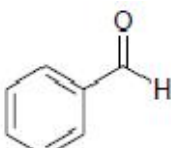
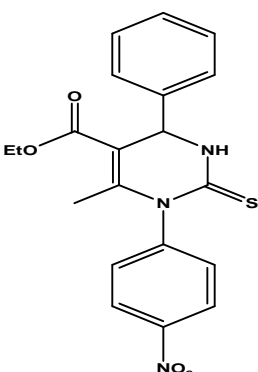
To find out the exact pathways for synthesis of dihydropyrimidinones in presence of  $NiFe_2O_4$  catalyst, we carried out three sets of reactions. For first time, ethyl acetoacetate was treated with urea, enamine product was formed, which was then treated with benzaldehyde in the presence of  $NiFe_2O_4$  catalyst desired product was not formed. Secondly, benzaldehyde was treated with urea yielded iminium ion which was then treated with ethyl acetoacetate in presence of  $NiFe_2O_4$  catalyst to give 3,4-dihydropyrimidinone and finally, ethyl acetoacetate treated with benzaldehyde as a result of which knoevengel condensate was obtained which was further treated with urea in presence of  $NiFe_2O_4$  catalyst, desired product was not formed.

Hence it may be confirmed that, second route using iminium route is the most possible for synthesis of 3, 4-dihydropyrimidinone in presence of  $NiFe_2O_4$  heterogeneous base catalyst. In order to study the scope of this procedure, a series of dihydropyrimidinone/thione were synthesized with above optimized conditions listed in table 3. It is clear from the table 2 that, aromatic aldehyde, carrying either electron withdrawing or electron donating substituent's afford high yield of products and another noticeable feature of this protocols is that of the survival of a variety of functional group such as halides, nitro, methoxy groups.

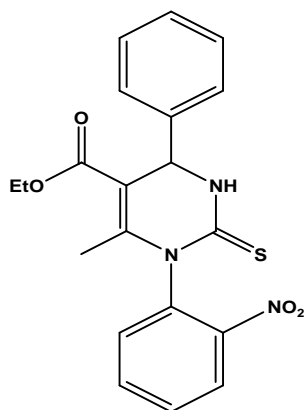
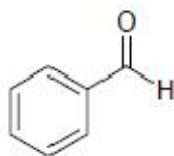
**Table 3** Synthesis of a series of dihydropyrimidinone/thione using NiFe<sub>2</sub>O<sub>4</sub> nano particles at temperature 70°C

Sr No	Substituted benzaldehyde	Product	Yield (%)	Time (min)	Observed M.P.(°C)	Reported M.P.(°C)
1			89	45	204-206	202-204 <sup>[35]</sup>
2			92	35	205-207	206-208 <sup>[35]</sup>
3			90	40	225-227	226-227 <sup>[35]</sup>
4			88	35	210-212	209-210 <sup>[37]</sup>
5			87	40	216-218	217-218 <sup>[37]</sup>
6			89	40	214-216	213-215 <sup>[35]</sup>

7			86	50	201-203	201-203 <sup>[35]</sup>
8			85	60	208-210	209-211 <sup>[36]</sup>
9			90	50	208-209	208-210 <sup>[35]</sup>
10			90	40	204-206	206-207 <sup>[35]</sup>
11			88	45	191-193	192-194 <sup>[37]</sup>
12			85	55	151-153	150-152 <sup>[35]</sup>

13			86	65	160-162	-
14			85	55	205-206	-
15			85	60	198-200	-
16			83	60	202-203	-
17			83	65	212-214	-

18



84

65

208-209

-

Acid sensitive group like furfuraldehyde also reacted very well under same condition without formation of side product and cinnamaldehyde produced high yield of the product under our reaction condition without polymerization or no decomposition. Thiourea and its substituted analogue has been reacted under same condition with similar success to provide the corresponding thioderivatives of 3, 4-dihydropyrimidin-2 (1H)-ones.

#### Experimental section

Melting points of all synthesized compounds were measured on electro thermal apparatus using open capillary tubes and are uncorrected. TLC for purity of compounds were performed on silica gel coated aluminum plate (Merck) as adsorbent and which are analyzed with U.V. light as visualizing agent. 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 TMS as an internal standard and  $CDCl_3/DMSO-d_6$  as solvent (chemical shifts in ppm). Powder X-ray diffraction pattern were collected with monochromatic Cu K 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.

#### General procedure for synthesis of $NiFe_2O_4$

$NiFe_2O_4$  nanoparticles were synthesized by co-precipitation method. Nickel nitrate, ferric nitrate and sodium hydroxide were used as starting materials. Aqueous solutions of ferric nitrate and nickel nitrate were prepared in de-ionized water and NaOH solution was added to it slowly and the solution were stirred continuously using a magnetic stirrer until a pH level of 10–11 was reached. This solution was heated at 80 $^{\circ}C$  for an hour. The precipitate was thoroughly washed with distilled water till pH of filtrate become 7. It was kept overnight for drying. The obtained powder was grounded and kept for calcination at temperatures 500 $^{\circ}C$  for 3 h.

#### General procedure for synthesis of Dihydropyrimidinones Using $NiFe_2O_4$ Catalyst

In a 25ml round bottomed flask, aryl aldehyde (3mmol), urea (4mmol), and  $NiFe_2O_4$  (0.02g) were stirred at 70 $^{\circ}C$  till the reactants were fully consumed (TLC).

To this reaction mixture Ethyl acetoacetate (3mmol) was added and the reaction mixture was stirred at 70 $^{\circ}C$  till the complete consumption of ethyl acetoacetate. After completion of reaction, the precipitate that obtained recrystallized from hot ethanol.

#### 6-Methyl-4-(4-nitro-phenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Sr. No:4)

White Solid, IR (KBr) [ $cm^{-1}$ ]: 3455  $cm^{-1}$  (NH), 1652  $cm^{-1}$  (C=O ester); 1600  $cm^{-1}$  (amide C=O); 1509 & 1347( $NO_2$ ).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ): ppm= 1.103 (t, 3H,  $CH_3$ ), 2.273 (s, 3H, $CH_3$ ), 3.996 (q, 2H,  $CH_2$ ), 5.280 (s, 1H, CH), 7.505-7.890 (m, 4H, ArH), 8.224 (s, 1H, NH), 9.351 (s, 1H, NH).  $^{13}C$  NMR (500 MHz,  $DMSO-d_6$ ): ppm= 14.505( $CH_3$ ), 18.312( $CH_3$ ), 54.225( $CH_2$ ), 59.819(CH), 98.717-152.520(C=C, ArC), 165.512 (C=O).

#### 4-(2-Chloro-phenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Sr. No: 5)

White Solid, IR (KBr) [ $cm^{-1}$ ]: 3220  $cm^{-1}$  (NH), 1689  $cm^{-1}$  (C=O ester); 1635  $cm^{-1}$  (amide C=O); 617 $cm^{-1}$  (-Cl).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ): ppm= 1.00 (t, 3H,  $CH_3$ ), 2.305 (s, 3H,  $CH_3$ ), 3.900 (q, 2H,  $CH_2$ ), 5.636 (s, 1H, CH), 7.271-7.415 (m, 4H, ArH), 7.697(s, 1H, NH), 9.266 (s, 1H, NH).  $^{13}C$  NMR (500 MHz,  $DMSO-d_6$ ): ppm=14.305( $CH_3$ ), 18.098( $CH_3$ ), 51.955( $CH_2$ ), 59.511(CH), 98.362- 151.882 (C=C, ArC), 165.381(C=O).

#### 6-Methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (Sr. No: 9)

White Solid, IR (KBr) [ $cm^{-1}$ ]: 3324  $cm^{-1}$  (NH), 1665  $cm^{-1}$  (C=O ester); 1571  $cm^{-1}$  (amide C=S).  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ): ppm= 1.110 (t, 3H,  $CH_3$ ), 2.510 (s, 3H,  $CH_3$ ), 4.020 (q, 2H,  $CH_2$ ), 5.180 (s, 1H, CH), 7.221-7.369 (m, 5H, ArH), 9.652 (s, 1H, NH), 10.333 (s, 1H, NH).  $^{13}C$  NMR (500MHz,  $DMSO-d_6$ ): ppm= 14.431( $CH_3$ ), 17.593 ( $CH_3$ ), 54.484 ( $CH_2$ ), 60.016(CH), 101.176-145.465(C=C, ArC), 165.570(C=O). MS  $m/e = 276$  (M+)

## CONCLUSION

In this research, we have developed a new procedure for synthesis of Dihydropyrimidinone-2 (1H)-one using

nanoparticulate NiFe<sub>2</sub>O<sub>4</sub>, heterogeneous solid base catalyst at 70<sup>0</sup>C. This methodology underlines the potential of nanocatalysis which offers significant advantages with regard to simplicity in operation, green aspect of avoiding toxic catalyst. The catalyst reusability makes the reaction economically useful.

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