

Nickel Nanoparticles: An Ecofriendly and Reusable Catalyst for the Synthesis of 3,4-Dihydropyrimidine-2(1*H*)-ones via Biginelli Reaction

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Nickel nanoparticles (Ni NPs) appeared to exhibit the catalytic activity in one-pot cyclocondensation reaction for the preparation of 3,4-dihydropyrimidine-2(1*H*)-ones via Biginelli reaction from aromatic/heteroaromatic/aliphatic aldehydes, urea/thiourea and ethyl acetoacetate under microwave irradiation has been described. The UV absorbance spectra showed metallic Ni characteristics and appreciate with the particle size determined by Transmission electron microscopy (TEM). After reaction course the Ni NPs can be re-covered and reused without any apparent loss of activity.

Key Words: Nickel, Nanoparticles, Biginelli reaction, Aldehydes, UV-visible

Introduction

Recently, metal nanoparticles in the form of nanocatalyst have emerged as viable alternative to conventional materials in various field of chemistry and attracted marvelous interest of chemists. Metal nanoparticles are known to be promising material for the rising heterogeneous catalysts in a variety of organic transformations.¹ Nanoparticles have the potential for improving the efficiency, selectivity, and yield of catalytic processes. In particular, the Ni NPs has ability to disperse into the solution and provide higher surface to volume ratio while participating in the reaction. Higher selectivity of Ni NPs towards reaction proceeds through less waste and fewer impurities, which could lead to safer technique and reduced environmental impact. Now, Ni NPs as catalysts have been investigated in a number of organic reactions² including the α -alkylation of methyl ketones,^{2a} chemo selective oxidative coupling of thiols,^{2b} supports for hydrogen adsorption,^{2c} reduction of aldehydes and ketones,^{2d-f} hydrogenation of olefins,^{2g} Wittig-type olefination for the stilbenes synthesis from alcohol,^{2h} hydrogenation and transfer hydrogenation reaction,²ⁱ Hantzsch condensation^{2j} and hydrothermal Heck reaction.^{2k} Thus, the significant catalytic property with operational simplicity, high reactivity, environmental friendliness, reduce reaction times and reusability of Ni NPs confident us to employ as catalyst for Biginelli reaction.

At the present time, multi-component reaction have attracted considerable attention in organic synthesis as they can produce target products in a single operation without isolating the intermediates and thus reducing the reaction times and energy input.³ The compounds bearing dihydropyrimidinones moiety are common in variety of biologically important natural products and potent drugs including anti-viral,⁴ anti-inflammatory,⁵ analgesic,⁶ anti-mitotic,⁷ anti-cancer,⁸ and anti-hypertensive agents.⁹ Dihydropyrimidinones are also screened as neuropeptide antagonists, agent in treating anxiety and recently as anti-oxidant agents.¹⁰ Therefore, realizing the importance of 3,4-dihydropyrimidin-2-(1*H*)-ones in the synthesis of various drug sources many synthetic methods have been developed. These methods involve the use of catalysts like, mont-KSF,¹¹ InBr₃,¹² EPZ-10,¹³

CuCl-LiCl,¹⁴ ZrOCl₂·8H₂O,¹⁵ silica triflate,¹⁶ ionic liquid,¹⁷ MgCl₂,¹⁸ ZnClO₄·6H₂O,¹⁹ HClO₄-SiO₂,²⁰ Al₂O₃/MeSO₃H,²¹ cellulose sulphuric acid,²² yttria-zirconia²³ and use of microwave technique.²⁴

Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction time, comparatively low yields, harsh reaction conditions, use of large quantity of organic solvents, and use of column chromatographic purification technique. Therefore, to overcome the drawbacks mentioned above a new efficient method using microwave irradiation for the preparation of dihydropyrimidinones is desired. Thus, the possibility of performing Biginelli reaction under microwave irradiation (solvent-free condition) with heterogeneous catalyst like Ni NPs could enhance their efficiency from an economic as well as green point of view. Microwaves irradiation represents an alternative way of power input into chemical reactions and processes. Reaction times are significantly reduced as compared to conventionally (thermally) heated systems while maintaining acceptable yields and selectivities.

The synthesis of Ni NPs by the reduction of NiCl₂ with hydrazine using cetyltrimethyl ammonium bromide (CTAB) in water/*n*-hexane at 70 °C has been achieved. In this hydrazine not only acts as a reducing agent (for Ni²⁺ → Ni) but also provide an inert atmosphere by releasing N₂ gas that forbid the formation of nickel oxide. The particle size was controlled by maintaining the p^H, concentration of hydrazine and CTAB. Ni NPs presumably with its zero valence state shows the catalytic activity for the one-pot three-component cyclocondensation in Biginelli reaction. Generally metal nanoparticles are unstable; to acquire the stability the metal nanoparticles are expected to show the enhanced catalytic effect in organic chemistry.

Experimental

General experimental. Chemicals were purchased from Merck, Aldrich and Rankem chemical companies and were used without further purification. All yields refer to isolated products. The purity determination of the substrates and reaction

monitoring were accompanied by thin layer chromatography (TLC), and visualized under ultra-violet (UV) light. Melting points were determined in open capillaries and are uncorrected. All compounds are well known and were identified by comparison with those of the authentic samples.

Structural analysis and characterization of catalyst was performed using XRD, TEM, EDAX and UV-vis spectrophotometer analysis. From these analytical techniques we got an idea about the size, composition and the catalytic behavior of Ni NPs.

TEM: TEM image was obtained by using JEOL JEM-200 EX model at 80 kV. The sample was subjected by evaporating a drop of ethanol solution containing well dispersed Ni NPs and placed onto a Formvar-covered copper grid. The particle size was determined as shown in Figure 1.

EDAX: From Figure 2 EDAX analysis indicated that, within the detection limits, nickel was the only element present in these particles. Absence of oxygen proved that nickel is present in zero valence state.

UV-vis spectra: In the Figure 3 UV-vis absorbance spectra showed that, the characteristic broad band appeared at ~364 nm having absorbance of 1.03 for the solution of 8 mol % in ethanol. The less absorbance is due to the free and smaller particle size.

Experimental procedure for the Biginelli reaction. A mixture of aromatic/heteroaromatic/aliphatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea/thiourea (1 mmol) and Ni NPs (8 mol %) which was taken in Borosil beaker. The reaction mixture was homogenized with the help of glass rod and irradiated in microwave oven (360 W) by interval of 10 s. The progress of reaction was checked on TLC. After completion, the reaction mixture cooled at room temperature. Then, it was extracted with ethyl acetate; the organic layer was dried over sodium sulphate and concentrated in a vacuum to afford the crud products. The crud products were purified by crystallization in ethanol. The Ni NPs were recovered by centrifuging the aqueous layer and reutilized four times for the same reaction.

Spectral data of representative compounds.

(4a): $^1\text{H NMR}$ (DMSO- d_6) δ 9.20 (s, 1H, NH), 7.76 (s, 1H, NH), 7.28 (s, 5H, Ar), 5.16 (d, 1H, $J = 3.6$ Hz, CH), 3.45 (q, 2H, $J = 7.08$ Hz, OCH $_2$), 2.25 (s, 3H, CH $_3$), 1.09 (t, 3H, $J = 7.06$ Hz, CH $_3$); Mass m/z 259 (M-1H).

(4f): $^1\text{H NMR}$ (DMSO- d_6) δ 9.26 (s, 1H, NH), 7.79 (s, 1H, NH), 7.60 (dd, 1H, $J = 1.8, 3.0$ Hz, Ar), 6.34 (d, 1H, $J = 3.3$ Hz, Ar), 5.23 (d, 1H, $J = 3.3$ Hz, CH), 4.05 (q, 2H, $J = 7.04$ Hz, OCH $_2$), 2.43 (s, 3H, CH $_3$); 1.09 (t, 3H, $J = 7.03$ Hz, CH $_3$); Mass m/z 249 (M-1H).

(4n): $^1\text{H NMR}$ (DMSO- d_6) δ 9.04 (s, 1H, NH), 7.57 (s, 1H, NH), 4.65 (t, 1H, CH), 4.05 (m, 2H, OCH $_2$), 2.16 (s, 3H, CH $_3$), 1.40-1.15 (m, 6H, -(CH $_2$) $_3$), 1.05 (t, 3H, CH $_3$), 0.94 (t, 3H, CH $_3$); Mass m/z 239 (M-1H).

Results and Discussion

In continuation of our efforts to investigate new protocols²⁵ recently, we have prepared and used Ni NPs for Hantzsch condensation.^{2j} Encouraged by these results we would like to disclose here our ongoing investigation on the development of facile and efficient method for the synthesis of dihydropyri-

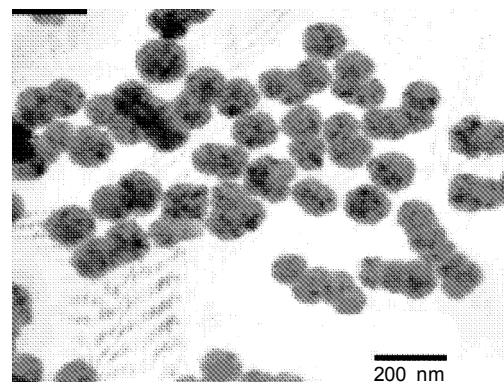


Figure 1. Transmittance electron micrograph of Ni NP.

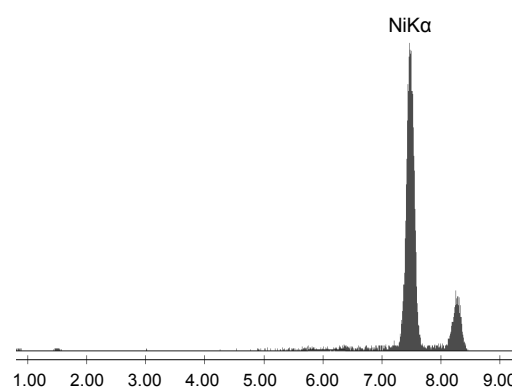


Figure 2. EDAX pattern of Ni NPs.

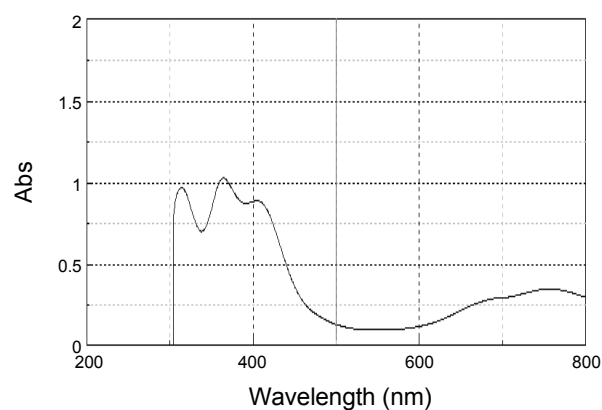
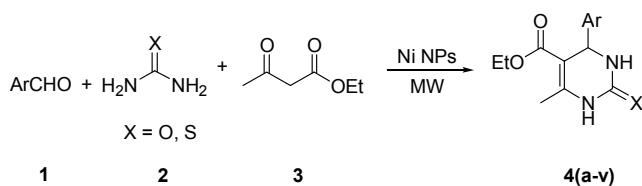


Figure 3. UV-vis spectrum of 8 mol % Ni NPs in ethanol.

midinones. At the outset of this study, no example of Ni NPs catalyst has been reported for Biginelli reaction.

Initially, experiments were performed to examine the catalytic activity of Ni NPs with benzaldehyde **1**, urea **2** and ethyl acetoacetate **3** as representative substrates under microwave irradiation at 360 W as shown in Scheme 1.

We turned our attention toward screening of appropriate concentration of Ni NPs as 2, 4, 6, 8 and 10 mol %. In the first stage we have carried out the reaction in absence of Ni NPs, we found the insignificant yield of product. Afterward we have selected 2 mol % Ni NPs to catalyze the model reaction and found that the dihydropyridinone **4a** was obtained in 56% yield



Scheme 1

Table 1. Screening of catalyst (Ni NPs) concentration for the synthesis of dihydropyrimidinone of benzaldehyde with urea

Entry	Mol %	Time (min)	Yield (%) ^a
1	0	7	25
2	2	3	56
3	4	3	68
4	6	3	80
5	8	3	98
6	10	3	98

^aIsolated yields.**Table 2.** Synthesis of dihydropyrimidinone derivatives catalyzed by Ni NPs

Products ^a	Ar	X	Time (min)	Yield (%)	M. P. ^{Ref} (°C)
4a	C ₆ H ₅	O	3	98	203 - 205 ²⁴
4b	4-ClC ₆ H ₄	O	3	95	214 - 216 ²⁴
4c	2-ClC ₆ H ₄	O	3	90	221 - 223 ¹²
4d	4-NO ₂ C ₆ H ₄	O	5	92	210 - 212 ²⁴
4e	3-NO ₂ C ₆ H ₄	O	4	94	230 - 232 ²⁴
4f	2-Furyl	O	3	95	207 - 209 ¹⁷
4g	4-OCH ₃ C ₆ H ₄	O	4	95	200 - 202 ²⁴
4h	4-OHC ₆ H ₄	O	4	93	231 - 233 ¹²
4i	C ₆ H ₄ CH=CH	O	5	90	230 - 232 ¹⁴
4j	3-FC ₆ H ₄	O	4	94	206 - 208 ²⁴
4k	3-OH,4-OMeC ₆ H ₃	O	5	87	185 - 187 ²⁴
4l	4-Pyridyl	O	3	95	188 - 190 ¹⁵
4m	2-Thienyl	O	3	96	208 - 210 ²⁴
4n	n-C ₄ H ₉	O	7	80	155 - 157 ¹⁷
4o	C ₂ H ₅	O	7	81	172 - 174 ²⁰
4p	C ₆ H ₅	S	5	95	210 - 212 ¹⁵
4q	4-OCH ₃ C ₆ H ₄	S	5	92	195 - 197 ²⁴
4r	4-ClC ₆ H ₄	S	5	89	196 - 198 ²⁰
4s	4-OHC ₆ H ₄	S	7	89	202 - 204 ²¹
4t	3-OHC ₆ H ₄	S	7	88	179 - 181 ²⁴
4u	3-NO ₂ C ₆ H ₄	S	7	87	205 - 207 ²⁴
4v	n-C ₄ H ₉	S	7	80	136 - 138 ²⁴

^aAll products were characterized from their melting points and spectroscopic (¹H NMR and MS) data and compared with authentic samples.**Table 3.** Reutilization of Ni NPs for the synthesis of dihydropyrimidinone of benzaldehyde with urea

Run	Fresh	1	2	3
Yield (%)	98	98	96	96

within 3 min. Furthermore, by loading 4 and 6 mol % Ni NPs to catalyze the model reaction successively we found the dihydropyrimidinone **4a** in 68% and 80% yields respectively. Moreover, when the reaction was subjected with 8 and 10 mol % Ni NPs amazingly it has been found the dihydropyrimidinone **4a** was obtained in excellent yields 98% within 3 min. This indicates that 8 mol % of Ni NPs produce the best results with respect to product yield as shown in Table 1.

With optimized condition in hand, we have explored the scope and generality of our methodology. Herein, the series of dihydropyrimidinone derivatives were prepared by employing the 8 mol % Ni NPs. We found that aromatic as well as heteroaromatic aldehydes containing different functional groups at different position worked well and did not shown the difference in the yield of products but by using aliphatic aldehydes for the preparation of dihydropyrimidinone derivatives we found comparatively less yields as shown in Table 2.

In the last stage of our experiment we have examined the recovery and reusability of the catalyst. The Ni NPs offer an additional advantage of being separable by simple work-up procedure using centrifugation method and reused during four consecutive runs without any apparent loss of activity for the same reaction. It is noteworthy that the yield of the product in the first, second and third uses were almost the same as that in the fresh run as has been shown in Table 3.

Conclusion

In conclusion, the use of Ni NPs as an effective catalyst has been demonstrated for the clean and rapid cyclocondensation of aromatic/heteroaromatic/aliphatic aldehydes, urea/thiourea and ethyl acetoacetate under microwave irradiation. The mild reaction condition, low catalyst loading, excellent functional group tolerance, high to product yields and simple work-up procedure demonstrate the attractive feature of this protocol. The approach of recovery and reusability of the catalyst is significant toward environmentally benign procedure.

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