

Short Communication

Efficient clay supported Ni⁰ nanoparticles as heterogeneous catalyst for solvent-free synthesis of Hantzsch polyhydroquinoline

Lakshi Saikia, Dipanka Dutta, Dipak Kumar Dutta*

Materials Science Division, CSIR-North East Institute of Science and Technology, Jorhat, 785 006, Assam, India

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ABSTRACT

A green and efficient multicomponent one-pot synthesis of Hantzsch polyhydroquinoline was achieved by the condensation of aldehydes, dimedone, ethylacetoacetate and ammonium acetate at room temperature using environmentally benign modified Montmorillonite supported Ni⁰-nanoparticles as catalyst. The well dispersed Ni⁰-nanoparticles having a high surface to volume ratio have promising features for the reaction such as easy removal of the catalyst, solvent-free, shorter reaction time, high product yields (about 95%) and easy work up procedure. There is no significant effect of electron withdrawing or donating nature of substituent on aldehydes in the formation of polyhydroquinoline derivatives.

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1. Introduction

4-Substituted 1,4-dihydropyridine (DHP) nucleus comprises a large family of medicinally important compounds such as Ca²⁺ channel blockers and some of the representative compounds of this class possess acaricidal, insecticidal, bactericidal and herbicidal activities [1]. 1,4-Dihydropyridine possesses a variety of biological activities, such as, vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agent [2–5]. Photocatalytic oxidation of these compounds to pyridine derivatives constitutes the principal metabolic pathway in biological systems [6]. Therefore, oxidative aromatization of DHPs has been a subject of great interest of organic and medicinal chemists.

Realizing the importance of polyhydroquinoline derivatives, several synthesis methods have been reported, like conventional heating [7], refluxing in acetic acid [8] and microwave irradiation [9] and ultrasound [10]. Different other approaches for the syntheses of polyhydroquinoline derivatives using various catalysts, such as TMSCl [11], ionic liquids [12,13], L-proline [14], polymers [15], Yb(OTf)₃ [16], Sc(OTf)₃ [17], HClO₄-SiO₂ [18], ceric ammonium nitrate [19], heteropoly acid [20], p-TSA [21], HY-zeolite [22] and Mont. K10 [23] have also been reported and some of the methods are associated with several shortcomings such as long reaction times, expensive reagents, harsh reaction conditions, low-product yields and the use of large quantity of volatile organic solvents.

In recent years, heterogeneous catalysts are gaining more importance due to environmental and economic factors. The efficiency can

be improved by using nanosized catalysts because of their small size and large surface to volume ratio. It has been observed that Ni⁰-nanoparticles as catalysts offer great attention for a wide range of applications in organic transformations such as chemo-selective oxidative coupling of thiols [24], reduction of aldehydes and ketones [25–27], hydrogenation of olefins [28] and support for hydrogen adsorption [29]. Recently, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity and environmentally benign processes. The multi-component reactions are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds. The possibility of performing multi-component reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view.

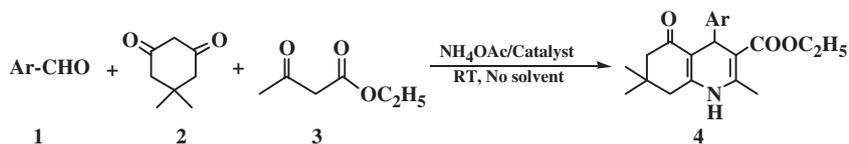
Herein, we would like to report Hantzsch polyhydroquinoline derivative synthesis catalyzed by modified Montmorillonite supported Ni⁰-nanoparticles under solvent-free conditions, using aromatic aldehyde, dimedone, ethylacetoacetate and ammonium acetate. This method not only preserves the simplicity, but also consistently gives the corresponding products in good to excellent yields. The modified clay support has paved the way for better dispersion of the Ni⁰-nanoparticles which results in higher catalytic activity.

2. Experimental

2.1. Materials and method

Naturally occurring Montmorillonite contains impurities like silica sand, iron oxide, etc. and were purified by dispersion cum sedimentation technique [30] to collect the <2 μm fraction. The reagents were

* Corresponding author. Tel.: +91 376 2370 081; fax: +91 376 2370 011.
 E-mail address: dipakkr Dutta@yahoo.com (D.K. Dutta).



Scheme 1. Modified Montmorillonite supported Ni⁰-nanoparticle catalyzed synthesis of polyhydroquinone under solvent-free condition.

purchased from Acros Organic, Aldrich, Spectrochem and Merck and used as received from the supplier without further purification.

2.2. Preparation of clay supported Ni⁰-nanoparticles

The preparation of modified Montmorillonite and supported Ni⁰-nanoparticles was carried out as reported earlier [31]. In a synthetic methodology, a known amount of acid treated clay was taken in a 100 ml beaker to which 10 ml (0.05 mM) aqueous solution of Ni (CH₃COO)₂ was added under vigorous stirring condition. The stirring was continued for 5–6 h followed by evaporation to dryness in rotary evaporator. The dry composite thus obtained was dispersed in 50 ml ethylene glycol in a double necked round bottom flask and refluxed for 6 h under nitrogen atmosphere to form an in situ solid product of Ni⁰-nanoparticles. The materials were recovered, washed with methanol until it was free from ethylene glycol and dried at about 40 °C for 12 h. The Ni loading in the supported catalysts was determined by AAS analysis and found to be 4.85 wt.%.

2.3. Characterization

The modified clay support and supported Ni⁰-nanoparticles were characterized by using PXRD, surface area analyzer and transmission electron microscopy (TEM) studies [32]. The powder XRD was recorded in Rigaku Ultima IV machine with Cu K α radiation ($\lambda = 1.5409 \text{ \AA}$). The textural properties measured by using Autosorb-1 (Quantachome, USA) and transmission electron microscopy (TEM) image were recorded on a JEOL JEM-2011 electron microscope.

2.4. Synthesis of Hantzsch polyhydroquinoline derivatives

To a mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), and ammonium acetate (1.5 mmol) in a 10 ml round bottom flask, modified Mont. supported Ni⁰-nanoparticle catalyst (25 mg) was added [Scheme 1]. The mixture was homogenized and stirred at room temperature for 20–25 min, the progress of the reaction was monitored by thin layered chromatography. After completion, 10 ml dichloromethane was added to the reaction mixture; the

catalyst was removed by filtration and washed with dichloromethane and acetone. Then, the liquid portion was extracted with ethyl acetate and water to remove any unreacted ammonium acetate; the organic layer was dried over sodium sulfate and concentrated in vacuum to afford the crude products. The pure product was obtained by recrystallization from ethanol.

3. Results and discussion

The XRD patterns of modified Montmorillonite (AT-Mont.) along with parent clay are shown in Fig. 1. The significant structural modification of Montmorillonite was reflected in their relative intensity and location of basal spacing (d_{001}). The parent Montmorillonite clay exhibited an intense basal peak at $2\theta = 7.06^\circ$, corresponding to basal spacing of 12.5 Å. When the clay is activated with mineral acid under controlled conditions for different time periods, the intensity due to basal spacing (d_{001}) decreases. From the XRD [Fig. 2], the characteristic peaks at $2\theta = 44^\circ$, 51.8° and 76° marked by their indices (111), (200) and (222) indicate the formation of Ni⁰ in the nanoparticles. The TEM study [Fig. 3] also reveals the formation of well dispersed Ni⁰-nanoparticles of size less than 10 nm on modified Montmorillonite.

The supported Ni⁰-nanoparticles were investigated as a catalyst in the synthesis of polyhydroquinoline derivatives i.e. condensation of benzaldehyde, dimedone, ethylacetoacetate, and ammonium acetate in the presence of catalytic amount of Ni⁰-nanoparticles under solvent-free conditions at room temperature, which afforded product 4a in 95% yield [Table 1]. Such reaction occurs with a wide range of aromatic aldehydes carrying either electron-donating or electron withdrawing substituents in the ortho, meta, and para positions [Table 1]. The products were established by comparing their melting points and the spectral data for selected compounds. A possible explanation for the better yield in solvent-free conditions is that the eutectic mixture having uniform distribution of the reactants brings the reacting species in close proximity to react than in solvent.

To investigate the effects of solvent, the condensation reaction of benzaldehyde, dimedone, ethylacetoacetate, and ammonium acetate in various organic solvents at room temperature using 4.85 wt.% Ni⁰-nanoparticles as the catalyst was carried out. About 75% of the expected

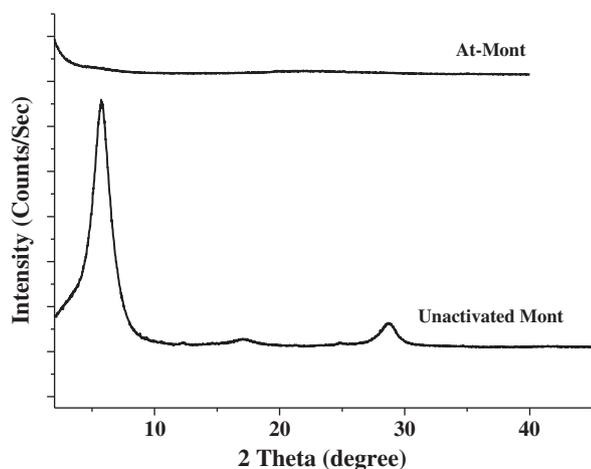


Fig. 1. Powder XRD pattern of unactivated and acid treated Montmorillonite (At-Mont.).

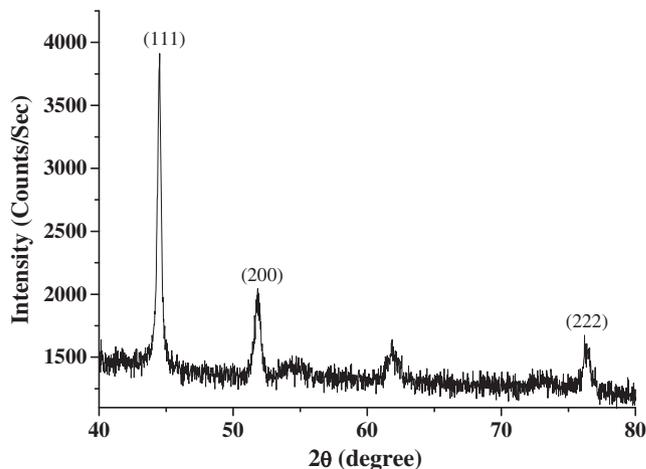


Fig. 2. Powder XRD pattern of Ni⁰-nanoparticles supported on modified Montmorillonite.

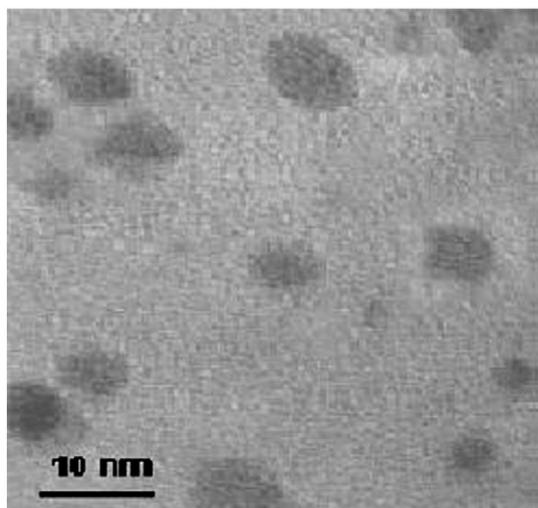


Fig. 3. Representative TEM image of Ni⁰-nanoparticles on modified Montmorillonite.

product 4a was obtained when the solvent was ethanol. Obviously, the polar solvents such as ethanol and acetonitrile [Table 2] were much better than non polar solvents. It was observed that in the presence of solvent the reaction takes more time to give high yields of product under similar ratio of the reactants. This may be due to the competitive adsorption of the solvent with the substrate molecule on the catalyst surface; hence reaction under solvent-free condition gives better yields in less time. The model reaction was carried out without any catalyst, but the product formation was in poor yield. Therefore, the catalyst plays an important role in the success of the reaction in terms of rate and yields of Hantzsch polyhydroquinoline derivatives. The reaction was also investigated with acid activated Mont. alone as catalyst and only a negligible amount of product formation was observed. Therefore, it is evident that supported Ni⁰-nanoparticles are the active sites.

Table 1
Modified Montmorillonite supported Ni⁰-nanoparticle catalyzed Hantzsch condensation.

Sr. no.	Ar	Time (min)	Yield %
4a	C ₆ H ₅	15	95
4b	2-Cl.C ₆ H ₄	15	91
4c	4-Cl.C ₆ H ₄	15	88
4d	2-NO ₂ .C ₆ H ₄	20	87
4e	3-NO ₂ .C ₆ H ₄	15	85
4f	4-NO ₂ .C ₆ H ₄	20	89
4g	2-OH.C ₆ H ₄	25	82
4h	4-OH.C ₆ H ₄	25	87
4i	4-OMe.C ₆ H ₄	20	92
4j	4-NMe ₂ .C ₆ H ₄	25	86
4k	2,4-Cl.C ₆ H ₃	10	91

Reaction condition: aromatic aldehydes (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), ammonium acetate (1.5 mmol) and catalyst – 25 mg, room temperature.

Table 2
Effect of solvent on Hantzsch polyhydroquinoline synthesis.

Solvent	Reaction time (h)	Yield (%)
C ₂ H ₅ OH	4	75
CH ₃ CN	4	66
Ph-CH ₃	4	40
CH ₂ Cl ₂	4	37
No solvent	15 min	95

Reaction condition: benzaldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), ammonium acetate (1.5 mmol) and catalyst – 25 mg, room temperature.

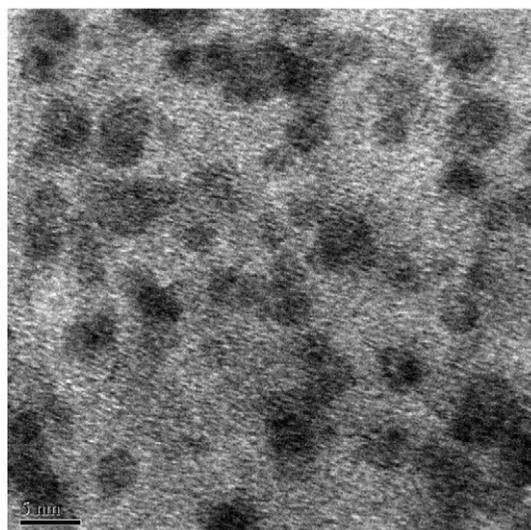


Fig. 4. TEM of Ni⁰-nanoparticles recovered after run no. 1 of the Hantzsch condensation.

The reusability of supported Ni⁰-nanoparticles was tested under similar reaction condition. The catalyst was separated by filtration, washed, dried and reused for Hantzsch condensation for a fresh reaction mixture up to run no. 4. The results in Fig. 5 showed that there is a decrease in product yield in subsequent reuse i.e. 95% in run no. 1 decreased to 81% in run no. 4. The stability of the used catalyst recovered after run no. 1 was investigated by HRTEM [Fig. 4] and there is no significant change in size or shape of the Ni⁰-nanoparticles. The nanoparticles were well dispersed on the support and sized in the range of 3–10 nm. The effect of nickel loading of 1.0, 3.0 and 4.85 wt.% of the catalyst, on the condensation reaction of benzaldehyde, dimedone, ethylacetoacetate, and ammonium acetate was investigated and the corresponding yields of 41.3%, 69% and 95% were found. This clearly indicates that 4.85 wt.% of Ni nanoparticles showed the best efficacy.

A comparison of the efficiency of catalytic activity of the modified Montmorillonite supported Ni⁰-nanoparticles with several previous methods is presented in Table 3. The results show that the present method is better compared to some of the earlier reports in terms of yield and reaction time.

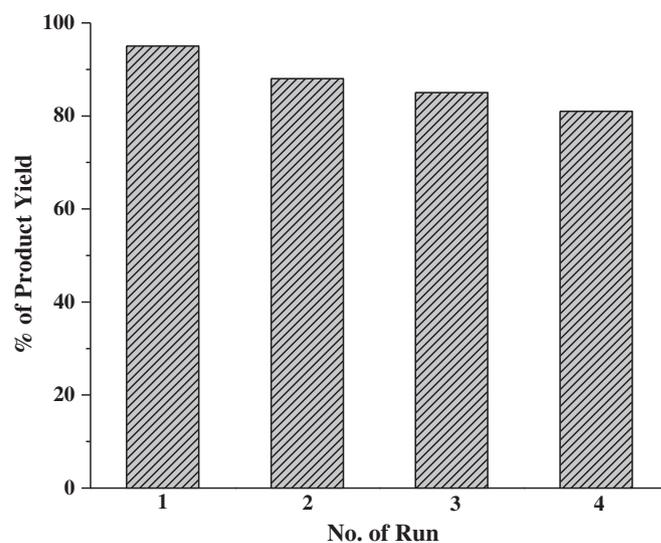


Fig. 5. Reusability of supported Ni⁰-nanoparticles catalyst for the reaction of benzaldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), ammonium acetate (1.5 mmol) and catalyst – 25 mg.

Table 3

Comparison of catalytic activity of modified Montmorillonite supported Ni⁰-nanoparticles with several known catalysts.

Entry	Condition	Yield (%)	Ref.
1	Yb(OTf) ₃ , EtOH, rt, 5 h	90	[16]
2	Sc(OTf) ₃ , EtOH, rt, 4 h	93	[17]
3	CAN, EtOH, rt, 1 h	92	[19]
4	p-TSA, EtOH, rt, 2 h	93	[21]
5	HY-Zeolite, CH ₃ CN, rt, 2 h	93	[22]
6	Modified Mont. supported Ni ⁰ -nanoparticles, solvent-free, 0.25 h	95	This work

4. Conclusion

In conclusion, we have reported that four-component Hantzsch condensation reaction can effectively be performed with modified Montmorillonite supported Ni⁰ nanoparticle catalyst without using any organic solvent. The yield of Hantzsch polyhydroquinoline derivatives obtained was up to 95% at room temperature. So, the present procedure provides an efficient and very simple method for the synthesis of polyhydroquinoline derivatives. The advantage of this method is its facile conditions and the product can be isolated very easily with excellent purity and that too without the use of column chromatography and the catalyst is recyclable. The simplicity of the present process makes it an interesting alternative to other approaches. The catalyst is expected to contribute to the development of environmentally benign methods and forms a part of the nanomaterial chemistry.

5. ¹H NMR of few representative compounds

Compound 4a: ¹H NMR (300 MHz, CDCl₃) 0.96 (s, 3H), 1.07 (s, 3H), 1.18 (t, 3H), 2.15–2.36 (m, 4H), 2.38 (s, 3H), 4.06 (q, 2H), 5.07 (s, 1H), 5.8 (s, 1H), 7.06–7.34 (m, 5H);

Compound 4e: ¹H NMR (300 MHz, CDCl₃) 0.94 (s, 3H), 1.08 (s, 3H), 1.21 (t, 3H), 2.11–2.26 (m, 3H), 2.30–2.38 (m, 4H), 3.67 (q, 2H), 5.15 (s, 1H), 6.88 (s, 1H), 7.34 (t, 1H);

Compound 4i: ¹H NMR (300 MHz, CDCl₃) 0.96 (s, 3H), 1.07 (s, 3H), 1.21 (t, 3H), 2.13–2.28 (m, 3H), 2.34–2.38 (m, 4H), 3.75 (s, 3H), 4.07 (q, 2H), 5.03 (s, 1H), 5.82 (s, 1H), 6.72–6.76 (m, 2H), 7.21–7.24 (m, 2H);

Compound 4j: ¹H NMR (300 MHz, CDCl₃) 0.97 (s, 3H), 1.08 (s, 3H), 1.23 (t, 3H), 2.10–2.26 (m, 3H), 2.30–2.37 (m, 4H), 2.87 (s, 6H), 4.08 (q, 2H), 4.96 (s, 1H), 5.88 (s, 1H), 6.62 (d, J = 8.2 Hz, 2H), 7.16 (d, 2H).

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