Tetrahedron Letters 50 (2009) 1754–1756

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions

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ARTICLE INFO

Article history:
Received 20 November 2008
Revised 24 January 2009
Accepted 29 January 2009
Available online 1 February 2009

Keywords:
Nanoparticle
Polyhydroquinoline derivative
Hantzsch condensation
Green chemistry

ABSTRACT

Polyhydroquinoline derivatives have been prepared efficiently in a one-pot synthesis via Hantzsch condensation using nanosized Nickel (Ni) as a heterogeneous catalyst. The present method does not involve any hazardous organic solvents or catalysts. The smaller size of Ni (80 ± 0.5 nm) having a higher surface to volume ratio has promising features for the reaction response such as the shortest reaction time, excellent product yields, simple work-up procedure, and purification of products by non-chromatographic methods.

The efficiency of heterogeneous catalysis in organic synthesis can be improved by employing nanosized catalysts because of their extremely small size and large surface to volume ratio. Recently, it has been proved that Ni nanoparticles as catalysts offer great opportunities for a wide range of applications in organic synthesis and chemical manufacturing processes including the chemo selective oxidative coupling of thiols,[1] reduction of aldehydes and ketones,[2–4] hydrogenation of olefins,[5] and supports for hydrogen adsorption.[6] The metal nanoparticles are generally unstable, and the exploration of appropriate support for stabilizing catalytic nanoparticles is a key factor in their successful and wide applications in heterogeneous catalysis. Thus, the remarkable catalytic activity and easy synthesis, operational simplicity, ecofriendliness, and recoverability of the Ni nanoparticle encouraged us to utilize this as a catalyst for the synthesis of polyhydroquinoline derivatives having a 1,4-dihydropyridine moiety.

Recently, much attention has been directed toward the multicomponent synthesis of 1,4-dihydropyridyl compounds because of a variety of biological activities such as Ca^{2+} channel blockers.[7] Moreover, they also have common features of various bioactive compounds such as vasodilators, bronchodilators, antiatherosclerotics, antitumor, heptatoprotective, and antidiabetic agents for the treatment of cardiovascular diseases including hypertension.[8,9] The current studies reveal that 1,4-dihydropyridine exhibits several medicinal applications which include neuroprotectant,[10] platelet antiaggregatory activity,[11] cerebral antischemic activity in the treatment of Alzheimer's disease,[12] and chemo sensitizer acting in tumor therapy.[13] These examples clearly demonstrate the remarkable potential of 1,4-dihydropyridine derivatives as a source of valuable drugs.

Realizing the importance of polyhydroquinoline derivatives in the synthesis of various drug sources, reported in many classical methods such as conventional heating,[14,15] the progress in this field is remarkable for microwave irradiation and ultrasound,[16,17] various catalysts such as trimethylsilyl chloride (TMSCl),[18] ionic liquid,[19,20] silica perchloric acid ($HClO_4$–SiO_2),[21] HY-Zeolite,[22] montmorillonite K-10,[23] cerium(IV) ammonium nitrate,[24] iron(III) trifluoroacetate,[25] heteropoly acid,[26] $Sc(OTf)_3$,[27] and *p*-TSA.[28]

Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, high costs, harsh reaction conditions, and the use of a large quantity of volatile organic solvents. Thus, the possibility of performing multicomponent reactions under solvent free conditions with heterogeneous catalysts like Ni nanoparticles could enhance their efficiency from an economic as well as a green point of view. Therefore, a new efficient method for the preparation of polyhydroquinoline is desired.

The nickel (Ni) nanoparticle has attracted much attention because of its applications as a catalyst and as conducting or magnetic material. The synthesis of Ni nanoparticles by the reduction of nickel chloride with hydrazine in cationic water in an oil microemulsion of water/CTAB (cetyltrimethyl ammonium bromide)/*n*-hexane at 70 °C has been studied. The particle size increased while

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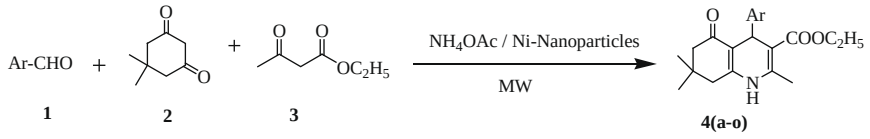
doi:10.1016/j.tetlet.2009.01.140



Scheme 1. Nickel nanoparticle-catalyzed synthesis of polyhydroquinoline derivatives under solvent-free conditions.

Table 1
Ni nanoparticles-catalyzed Hantzsch condensation of polyhydroquinoline derivatives

Products[a]	Ar	Time (min)	Yield[b] (%)	Mp (°C)	
				Found	Lit
4a	2-ClC_6H_4	1.5	94	206–208	208–210[15]
4b	4-OH,3-$CH_3OC_6H_3$	1.5	89	209–211	210–212[15]
4c	3-$NO_2C_6H_4$	1.5	85	174–176	177–178[15]
4d	3-OHC_6H_4	1.5	88	218–220	220–222[17]
4e	4-ClC_6H_4	1	90	245–247	245–246[20]
4f	4-OHC_6H_4	1.5	90	231–233	232–234[20]
4g	4-$NO_2C_6H_4$	1.5	89	244–246	242–244[20]
4h	C_6H_5	1	95	202–204	204–205[21]
4i	4-$CH_3C_6H_4$	1	91	261–263	261–262[21]
4j	4-$OCH_3C_6H_4$	1.5	92	255–257	258–259[21]
4k	$C_6H_5CH{=}CH$	1	90	205–207	206–207[21]
4l	4-BrC_6H_4	1	92	252–253	254–255[21]
4m	2-Furyl	1	96	246–248	248–249[21]
4n	2-Thienyl	1	95	237–239	241–142[21]
4o	4-$N(CH_3)_2C_6H_4$	1	85	230–232	233–234[15]

[a] All products were characterized from their spectroscopic (IR, ^{1}H NMR, and MS) data and compared with authentic samples.
[b] Isolated yields.

increasing nickel chloride concentration or decreasing hydrazine concentration. However, a smaller particle size was obtained at a higher ratio of CTAB to *n*-hexane. The solid product exhibits electronic, paramagnetic, optical and better catalytic properties significantly different from those of bulk material due to its extremely small size and large surface area. In this work, the Ni nanoparticles were prepared[29] by using the reported micro-emulsion method.[30] The reduction reaction could be expressed as

$$2Ni^{2+} + N_2H_4 + 4OH^- \rightarrow 2Ni + N_2 + 4H_2O$$

Multicomponent reactions are special types of synthetically useful organic reactions that give complex products in one-pot and attract the attention of chemists. To the best of our knowledge, there have been no examples of the use of Ni nanoparticles as catalysts for the synthesis of polyhydroquinolines in the past. Here, we would like to report the use of Ni-nanoparticles for the synthesis of polyhydroquinoline derivatives through a four component reaction including aromatic aldehydes **1**, dimedone **2**, and ethyl acetoacetate **3** to give compound **4** in one-pot under microwave irradiation[31] as shown in Scheme 1. It is evident that electron-rich and electron-deficient aldehydes as well as heterocyclic systems such as Thiophene-2-carboxaldehyde and Furan-2-carboxaldehyde reacted smoothly to produce high yields of products. The results with different aromatic aldehydes are summarized in Table 1.

Herein, the series of polyhydroquinoline derivatives was presented by applying the method mentioned above. We found that aromatic aldehydes containing different functional groups at different positions worked well and did not show differences in the yield of products. We have examined the recovery and reuse of the catalyst. The catalysts were recovered by a simple work-up

Table 2
Reutilization of Ni nanoparticles in the synthesis of polyhydroquinoline of benzaldehyde

Run	Fresh	1	2	3	4
Yield (%)	95	95	93	93	94

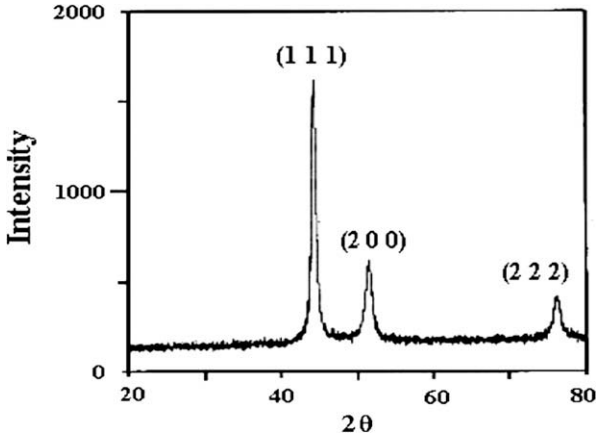


Figure 1. X-ray diffraction spectrum of freshly prepared Ni nanoparticles using CuKα (1.54 Å) radiation; the pattern (1 1 1), (2 0 0), and (2 2 2) revealing the fcc structures.

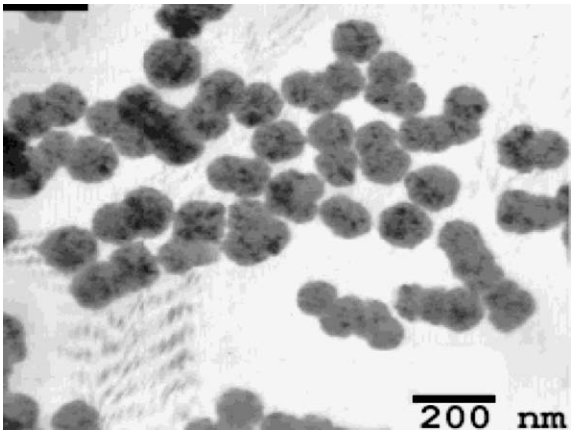


Figure 2. Transmission electron micrograph of synthesized Ni nanoparticles (80 ± 0.5 nm) for transmission electron microscopy. A drop of ethanol containing nanoparticles was placed on an amorphous carbon film (of ca. 3 nm thickness) deposited on a commercial copper grid and dried at room temperature in air.

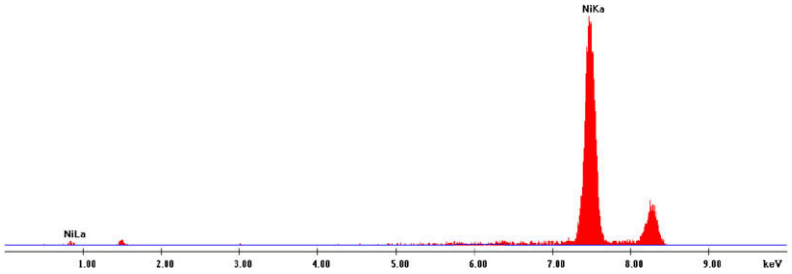


Figure 3. EDAX pattern of Ni nanoparticles.

using the 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 second, third, and fourth uses was almost the same as that in the first run as has been shown in Table 2.

To determine the appropriate concentration of the catalyst Ni nanoparticles, we have investigated the model reaction of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate at different concentrations of Ni nanoparticles such as 2, 4, 6, 8, 10, and 12 mol %. We found the products in 30%, 45%, 60%, 75%, 95%, and 95% yields, respectively. This indicates that 10 mol % of Ni nanoparticles produces the best results with respect to product yield.

Morphology and structural investigations of Ni nanoparticles: XRD: In Figure 1, an X-ray measurement was performed on a Rigaku D/max III.V X-ray diffractometer using Cu-Kα radiation (λ = 0.154 nm). Accordingly, the sample for XRD was obtained by recovering the nickel nanoparticle from the solution using the centrifugation method, and finally the obtained precipitate was dried and washed by ethanol. Three characteristic peaks (2θ = 44.5, 51.8, and 76.4) marked by their indices (111), (200), and (222) corresponding Ni were observed. A single-phase face-centered cubic (FCC) structure[32] and the size were calculated from the full width at the half maxima (FWHM) of the strongest peak (111) by using the Scherer formula. The size of the calculated particles is comparable with the corresponding size from TEM analysis.

TEM: The particle size was determined by a TEM image using JEOL Model JEM-200 EX at 80 kV. The sample for TEM analysis was obtained by diluting the dispersed solution with ethanol and a drop of the diluted solution was placed onto a Formvar-covered copper grid. The solution was evaporated in air at room temperature. For better dispersion, the nanoparticle ethanol-dispersed solution was sonicated for 1 min. Figure 2 shows the TEM image of purified Ni nanoparticles, where a fairly uniform particle size of 80 ± 0.5 nm is evident.

EDAX: Figure 3 shows an energy-dispersive spectrum indicating the chemical composition of freshly prepared Ni after the reactions. Interestingly, total composition of Nickel nanoparticles was found in the resultant sample.

In conclusion, we have demonstrated for the first time that Ni, in the form of nanoparticles, is a potential alternative to the use of noble-metal-based catalysts for Hantzsch condensation. The present microwave irradiation procedure provides an efficient and very simple solvent-free method for the synthesis of polyhydroquinoline via Hantzsch condensation using Ni nanoparticles as a catalyst. This catalyst is expected to contribute to the development of more environment-benign methods and forms part of nanometal chemistry. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent yields, shorter reaction time, and the easy work-up procedure makes this procedure more attractive in synthesizing a variety of these derivatives.

Acknowledgments

We gratefully acknowledge the financial assistance received for this work from the University Grants Commission, New Delhi, and also thank Dr. Ramphal Sharma, Thin Film and Nanotechnology Laboratory, Department of Physics, Aurangabad, for his continuous support.

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