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Nanocrystalline copper(II) oxide-catalyzed one-pot four-component synthesis of polyhydroquinoline derivativesunder solvent-free conditions

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Abstract

The efficient and environmentally friendly method for the one-pot synthesis of polyhydroquinolines has been developed in the presence of CuO nanoparticles. The multi-component reactions of aldehydes, dimedone, ethyl acetoacetate andammonium acetate were carried out under solvent-free conditions to afford some polyhydroquinoline derivatives. This method provides several advantages including high yields, low reaction times and little catalyst loading.

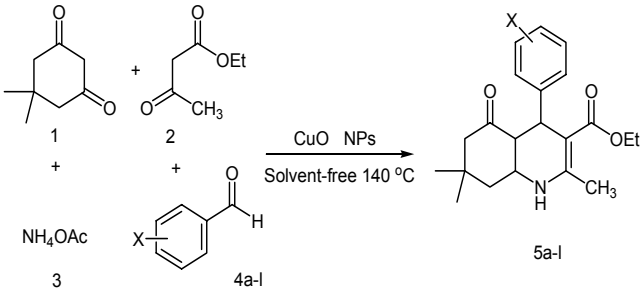
1. Introduction

During the last decades, nanocrystalline metal oxides has interested significant attention as efficient catalysts in many organic reactions due to their high surface-to-volume ratio and coordination parts which provides a larger number of active sites per unit area compared to their heterogeneous counter parts [1,2]. In recent years, CuO nanoparticles (CuO NPs) have extensively considered interests because of the role of copper(II) oxideingas sensors [3], semiconductors [4]and in the preparation of a wide range of organic-inorganicnanostructured composites [5].In addition,copper oxide nanoparticles, in particular, being available, cheap and require only mild reaction conditions to produce high yields of products in short reaction times compared to traditional catalysts and can also be recycled.Nanocrystalline copper(II) oxides have been used as an efficient heterogeneous catalyst in various organic transformations such as: C-

arylation reactions [6], cross-coupling reactions [7], alkyne-azidecycloadditions [8],CO and NOoxidation [9] and synthesis of propargylamines [10].

The research in multi-component reactions (MCRs) is an encouraging and hot topic of organic chemistry because of their advantageous in preparation of small molecule heterocyclic libraries and in drug discovery procedures [11]. Although MCRs are efficient, environmentally friendly, fast, atom economic and time saving style. They supply an effective tool for the preparation of various compounds with pharmaceutical and biological properties [12].

In recent years, great attention has been paid to the synthesis of polyhydroquinolines because of its highly absolute biological and physiological activities [13].Derivatives of these compounds are known to possess important pharmaceutical, antifungal, Antitumor and other bioorganic properties [14,15].In addition, these compounds have found wide usage in drugs including nifedipine, nicardipine and amlodipine [16]. There are several methods reported in literatures for the synthesis of polyhydroquinolines*via*four-component coupling of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of various catalysts including L-proline [17], $HClO_4$-SiO_2 [18], molecular iodine [19], PTSA [20], Ni nanoparticles [21], polymers [22], Baker's yeast [23]. Consequently, synthesis of polyhydroquinoline derivatives with the aim to develop new drug molecules has been an active area of the research. Herein we wish to report a novel, green and mild method to the synthesis of polyhydroquinolines via multi-component coupling of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of CuO nanoparticles (Scheme 1). In the view of recent interest in the use of heterogeneous nanocatalysts we have developed CuO NPs as recyclable, easy to handle, inexpensive, non-volatile, non-explosive, and eco-friendly catalyst which can be used in catalysis many organic transformations.



Scheme1. Synthesis of polyhydroquinolines using CuO nanoparticles under solvent-free conditions.

2 Experimental

2.1 Materials and characterization

Chemicals were purchased from the Sigma-Aldrich and Merck in high purity. All the materials were of commercial reagent grade and were used without further purification. Copper(II) oxidenanoparticles were prepared according to the procedure reported by Jang et al [8]. All melting points are uncorrected and were determined in capillary tubes on Boetius melting point microscope. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker 400 MHz spectrometer with $CDCl_3$ as solvent using tetramethylsilane (TMS) as an internal standard, the chemical shift values are in δ. FT-IR spectrum was recorded on Magna-IR, spectrometer 550 Nicolet in KBr pellets in the range of 400–4000 cm^{-1}. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of products was visualized by SEM (LEO 1455VP).

2.2. Synthesis of CuO nanoparticles

A solution of copper acetate (1.0 g) and acetic acid (1.0 mL) in 250 mL of distilled water was

heated at 100 °C. Then 0.8 g of NaOH was added quickly under vigorous stirring. The reaction mixture being cooled to room temperature and the obtained black powders were separated by centrifugation. The collected precipitate then washed several times with distilled water, ethanol and dried at 100 °C for 10 h.

XRD pattern of the CuO nanoparticles is shown in Figure 1.All reflection peaks can be readily indexed to pure cubic crystal phase of nanocrystallinecopper(II)oxide As shown in Figure 1.

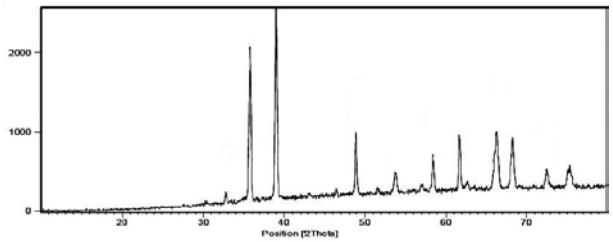


Fig. 1. The XRD pattern of copper(II) oxide nanoparticles.

Also no specific peaks due to any impurities wereobserved. The crystallite size diameter (D) of the CuO nanoparticles has been calculated by Debye–Scherrer equation ($D = K\lambda/\beta\cos\theta$), where β FWHM (full-width at half-maximum or half-width) is in radians and θ is the position of the maximum of diffraction peak, K is the so-called shape factor, which usually takes a value of about 0.9, and k is the X-ray wavelength (1.5406 Å for Cu Kα). Crystallite size of zinc oxide has been found to be 54 nm.

In order to investigate the morphology and particle size of CuO nanoparticles, SEM image of copper (II)oxide nanoparticles was presented in Figure 2. These results show that spherical CuOnanoparticles were obtained with an average diameter of 40–50 nm as confirmed by XRD analysis.

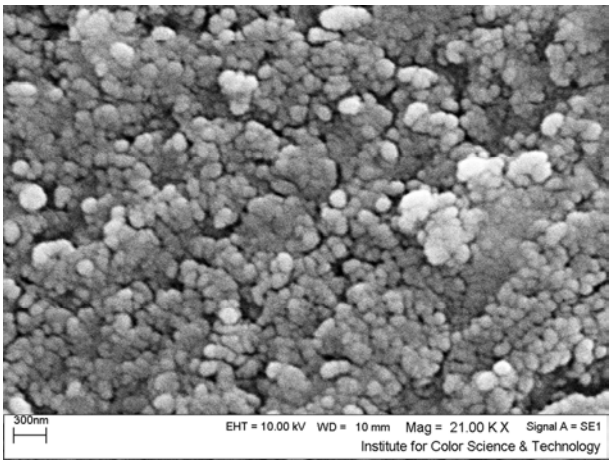


Fig. 2.SEM image of CuO nanoparticles.

2.3. General procedure for the preparation of polyhydroquinolines

A mixture of aldehyde (1 mmol), dimedone (1mmol), ammonium acetate (1.5mmol), ethyl acetoacetate (1 mmol) and CuO nanoparticles (0.02 gr, 0.2mmol, 20 mol%) in a round bottom flask was heated in the oil bath at 140 °C for appropriate times. During the procedure, the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and the reaction mixture was dissolved in chloroform. The catalyst was insoluble in $CHCl_3$ and separated. The solvent was evaporated and the solid obtained recrystallized from ethanol to afford the pure polyhydroquinolines.

All the products were characterized and identified with m.p., ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopy techniques.Spectral data of new compounds are given below:

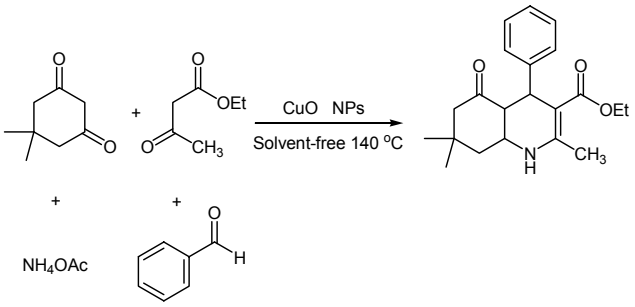
Ethyl-2,7,7-trimethyl-4-(3-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5b):Mp°C: 212–214. ^{1}H NMR(400 MHz, CDCl3): δ:0.94 (s, 3H), 1.06 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 2.17 (m, 6H), 2.34(m, 4H),

4.08 (q,J=7.2 Hz, 2H), 5.10 (s,1H), 6.17 (s, 1H), 6.92 (s, 1H), 6.99-7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 19.3, 21.1, 27.1, 29.4, 32.7, 36.1, 40.9, 50.8, 59.8, 106.1, 112.1, 126.6, 127.1, 127.8, 128.6, 135.3, 143.5, 144.2, 148.7, 167.5, 195.7; IR (KBr) *v*: 3294, 3081, 2962, 1695, 1612, 1528,1487, 1383, 1283, 752 cm^{-1}.

Ethyl-2,7,7-trimethyl-4-(4-thiomethylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5h): Mp^{o}C: 241–243. ^{1}H NMR (400 MHz, CDCl3): δ: 0.92 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.13-2.16 (m, 6H), 2.24-2.27 (m, 4H), 2.82 (s, 3H), 4.12 (q, J=7.1 Hz, 2H), 5.11 (s, 1H), 6.16 (s, 1H), 7.08-7.10 (d, 2H), 7.19-7.21 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 19.2, 27.3, 29.4, 32.5, 36.3, 40.8, 44.1, 50.8, 59.8, 106.1, 126.6, 127.3, 128.5, 136.9, 145.2, 145.1, 149.2, 167.1, 195.4; IR (KBr) *v*: 3311, 3076, 2968, 1691, 1614, 1526, 1485, 1379, 1286, 748 cm^{-1}.Ethyl-2,7,7-trimethyl-4-(4-formylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i):Mp^{o}C: 196–197. ^{1}H NMR (400 MHz, CDCl3): δ: 0.81 (s, 3H), 0.98 (t, J=7.1 Hz, 3H), 1.93-2.24 (m, 6H), 2.42-2.48 (m, 4H), 3.93 (q, J=7.1 Hz, 2H), 4.82 (s, 1H), 6.11 (s, 1H), 7.13-7.15 (d, 2H), 7.22-7.24 (d, 2H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.3, 19.1, 27.0, 29.5, 32.5, 35.7, 40.6, 50.8, 59.7, 106.0, 111.7, 113.2, 128.9, 139.8, 143.8, 149.6, 157.7, 167.5, 187.3, 195.7; IR (KBr) *v*: 3291, 3078, 2961, 2873, 1692, 1616, 1523, 1481, 1391, 1282, 754 cm^{-1}.

3. Results and discussion

In early studies, to optimize the reaction conditions, reaction of benzaldehyde, dimedone, ethyl acetate and ammonium acetate was chosen as the model reaction for the one-pot synthesis of corresponding polyhydroquinoline derivatives (Scheme 2).



Scheme2. The model reaction for the synthesis of polyhydroquinolines in the presence of CuO NPs.

The reaction conditions were optimized on the basis of the solvent, catalyst and varying temperatures for the synthesis of polyhydroquinolines.Our initial studies were carried out by using several catalysts including SiO_2, Al_2O_3,$TiO_2$and CuOin various reaction conditions. The best results were obtained when the reactions were carried out in the presence of CuO NPs under solvent-free conditions at 140 ^{o}C (Table 1).

Table 1. Optimization of the model reaction by using various catalysts andsolvents.[a]

Entry	Catalyst	solvent	Time (min)	Yields (%)[b]
1	SiO_2	EtOH	100	30
2	Al_2O_3	EtOH	120	35
3	TiO_2	EtOH	140	25
4	CuO	EtOH	80	50
5	CuO	DMF	140	35
6	CuO	Toluene	300	15
8	CuO	Solvent-free	50	70
9	CuO NPs	Solvent-free	30	90

[a]Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.5 mmol).

[b] Isolated yields.

In continuation of our research the model reaction was carried out by using various

amounts of CuO nanoparticles. The optimum amounts of CuO NPs wereobtained 20 mol%. Increasing of this amount did not show any changes in yield and time of the reaction.

The influence of solvent was studied when the model reaction was performed by using CuO in various solvents and under solvent-free conditions (Table 1, Entries 4-8) andthe best results were obtained under solvent-free conditions (Table 1, Entry 8). As a result of these experiments, we used copper(II) oxide nanoparticles as the excellent catalyst in the synthesis of polyhydroquinolines. The significant results of Table 1 are related tothe reactivity of catalytic nanoparticles which is largely determined by the energy of surface atoms that can be easily gauges with the number of neighboring atoms by the bonding modes and accompanying energies of small molecules to be transformed on the nanoparticles surfaces.

In order to establish the optimum ratio of reactants the model reaction was carried out several times in the presence of copper oxide nanoparticles. The bestresults were obtained when benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate were employed as substrates in a 1:1:1:1.5 ratio. To study the scope of this process, we next utilized a variety of aldehydes to investigate four-component reactions under the optimal conditions (Scheme 2, Table 2). The resulting of Table 2 shows aryl aldehydes with electron-withdrawing group such as NO_2, Cl and Br on *para* position reacted with very smoothly, which resulted to produce polyhydroquinolinesin shorter reaction times and higher yields. In addition the reaction of sterically hindered aldehydes was performed slowly in compared to unhindered aldehydes.

Table 2. One-pot synthesis of polyhydroquinolinescatalyzed by copper oxide (II) nanoparticles.[a]

Product	X	Time (min)	Yield[b]	M.p (°C)
5a	H	30	90	201-203[21]
5b	3-Me	40	80	212-214
5c	4-Me	35	85	262-263[21]
5d	4-OMe	38	85	254-256[21]
5e	4-Cl	20	95	245-246[21]
5f	4-Br	25	92	251-252[21]
5g	4-NO_2	22	95	245-247[21]
5h	4-SMe	25	88	241-243
5i	4-CHO	25	90	196-197
5j	4-F	25	88	184-185[18]
5k	3-NO_2	30	85	173-175[21]
5l	4-OH	35	80	232-233[21]

[a]All reactions were carried out under solvent-free conditions

[b] Isolated yields.

Catalyst recovery

After completion of the reaction, the reaction mixture was dissolved in chloroform and then the catalyst was separated by simple filtration. The copper oxide nanoparticles was washed three to four times with chloroform and methanol and dried at 100°C for 5 h. The separated catalyst was used several times with a slightly decreased activity as shown in Figure 3.

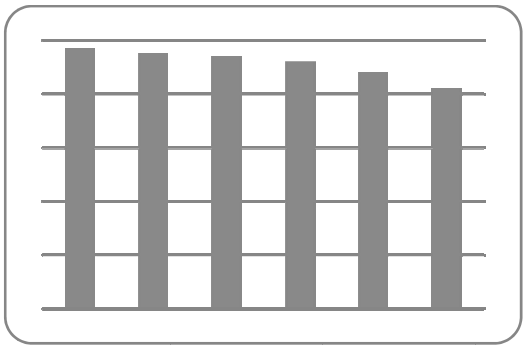


Figure 3. Recoverability of CuO nanoparticles.

4. Conclusion

In conclusions an efficient, mild and green method for the synthesis of polyhydroquinolineshas been developed using CuO nanoparticles under solvent-free conditions. The products were obtained in excellent yields and the reaction times were significant low. The present approach demonstrates a simple and significantly method in the presence of novel nano-scale materials.

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