

Original Article: Preparation of Polyhydroquinolines Using Nano Cerium (IV) Oxide/Zinc Oxide as a Catalyst



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ABSTRACT

Polyhydroquinolines derivatives are important compounds that perform a range of biological functions such as vasodilation, anti-atherosclerosis, liver protection, and anti-diabetic. Several drugs such as nifedipine, nicardipine, and Lacidipine feature a polyhydroxyquinoline scaffold. The common synthesis method of polyhydroquinolines is a one-step condensation reaction of Dimedone, aldehydes with ethyl acetate and ammonia in the presence of various catalysts such as MCM-41, molecular iodine, bread yeast, etc. Herein, we report cerium oxide/zinc oxide nanoparticle as an effective and economical catalyst for the four-component, one-pot reaction to synthesize polyhydroquinolines.

Introduction

Quinolines compounds perform a wide range of functions and play a major part in various pharmaceutical, veterinary medicines, fertilizers, and insecticides [1]. They are also used as optical clarifiers, anti-corrosion, anti-oxidants, and are important

intermediates in organic synthesis [2]. Quinolines are the important class of heterocyclic compounds with a range of medicinal properties. In recent years, the preparation of polyhydroquinolines (1,4-dihydropyridines) has been attempted by many chemists due to their biological and physiological importance [3]. Some quinoline

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derivatives further show antifungal, anti-tumor, anti-arthritis, vasodilator, and anti-diabetic properties [4,5]. Polyhydroquinolines are of great significance in the fields of organic chemistry and pharmaceutical medicine, since they show valuable properties. [6,7]. The therapeutic success of these compounds is attributed to their ability to bind to calcium channels, and thus reduce the passage of calcium flow affecting the calcium balance of cardiovascular tissues, ultimately dilating them, and reducing the blood pressure [8]. Recent studies indicate that 1,4-dihydropyridines can further display antibacterial, anti-tuberculosis, and anti-inflammatory properties, and are also effective in reducing the symptoms of Alzheimer's disease [9-11]. Drugs including nicardipine (Figure 1), lacidipine (Figure 2), nimodipine (Figure 3), and amLodipine (Figure 4) which are used as vascular agents in the treatment of hypertension are feature 1,4-dihydropyridine scaffold.

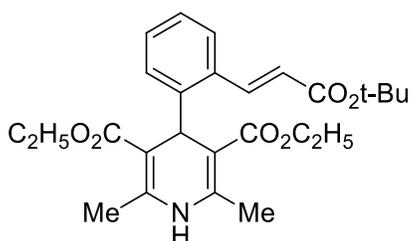


Figure 1. Nicardipine

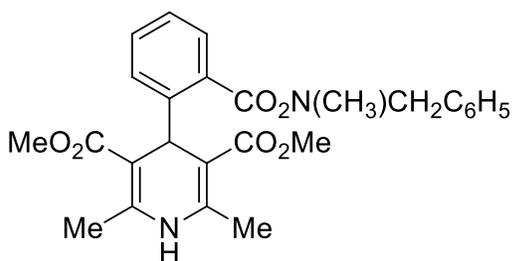


Figure 2. Lacidipine

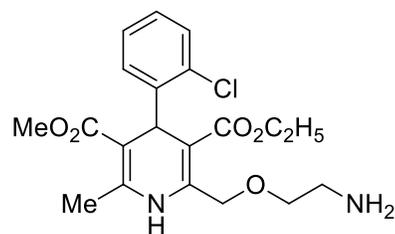


Figure 3. Nimodipine

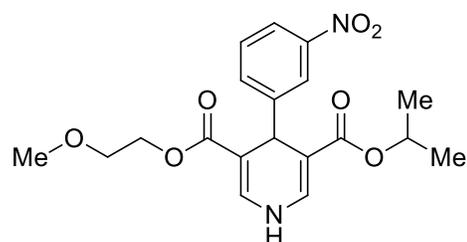


Figure 4. Amlodipine

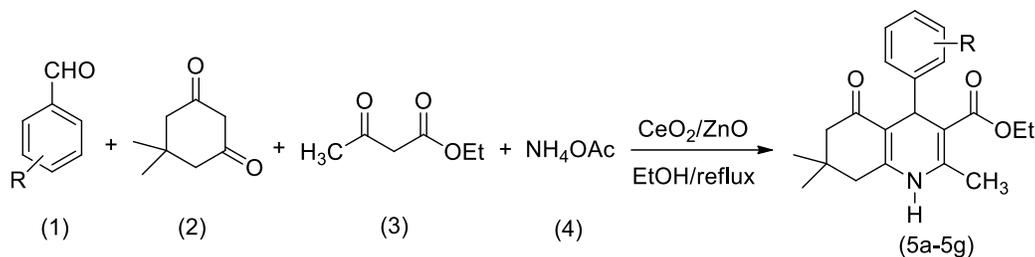
Nanoparticles are utilized in the medical and pharmaceutical industries. Nanoparticles have the ability to bind to nanometer-sized drugs and be specifically absorbed by cancer cells. In this way, healthy cells are not exposed to the drug, and the adverse side effects of the drug are reduced. Other applications of nanoparticles are the production of self-cleaning, or fast-cleaning pavement, and concrete. In addition, they are used in the production of waterproof glass and are economical. We used nano particle on CeO_2/ZnO as a catalyst for the synthesis of Polyhydroquinolines.

Polyhydroquinolines and their derivatives are very crucial heterocyclic compounds function in biological processes and have attracted a lot of attention due to their abundant biological and medicinal activities. Due to the valuable properties of polyhydroquinolines and their derivatives, methods for preparing these important heterocycles have been developed, some of which have already been mentioned.

As a part of our ongoing interest in the nano-cerium (IV) oxide/zinc oxide catalyzed

reactions to carry out various organic transformations, we further explored their catalytic activity towards the synthesis of polyhydroquinolines via a four-component

reaction of an aromatic aldehyde, ethyl acetoacetate, ammonium acetate, and dimedone in the presence of nano $\text{CeO}_2\text{-ZnO}$ (Scheme 1).



Scheme 1. Synthesis of polyhydroquinoline using nano $\text{CeO}_2\text{/ZnO}$

Optimization of reaction conditions

In order to increase the efficiency of the conditions for preparing polyhydroquinoline derivatives, the reaction of trachemibenzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate was selected as the model reaction. To obtain the best results, three important parameters of

catalyst value, solvent, and temperature were investigated for this reaction.

Choice of solvent

The reaction was performed in different solvents. Obviously, the highest yield was observed while using ethanol as a solvent. The results are indicated in Table 1.

Table 1. Synthesis of **5a** in the presence of different solvents using nano- $\text{CeO}_2\text{/ZnO}$ as a catalyst

Entry	Solvent	Yield (%) ^a
1	THF	68
2	$\text{C}_2\text{H}_5\text{OH}$	95
3	CH_3CN	85
4	CHCl_3	71
5	Water	90
6	Solvent-free	92

^aYields were analyzed by GC

Reusability of nano $\text{CeO}_2\text{/ZnO}$

10 mL of ethyl acetate was added to the catalyst separated from the reaction mixture by filtration. The mixture was stirred at room temperature for 5 minutes using a magnetic stirrer. The reaction mixture was filtered, and the catalyst remained on filter paper due to its insolubility in ethyl acetate solvent. Then, to reuse the catalyst, the filter material was washed several times with acetone. After drying, the reaction was repeated to check the potency of the catalyst (Table 2).

Effect of temperature change on model reaction

In this study, various amounts of catalyst were tested at different temperatures to obtain the maximum efficiency. As indicated, the highest efficiency was observed in reflux conditions (Table 3).

Comparison of nano $\text{CeO}_2\text{/ZnO}$ performance with a number of different catalysts in the synthesis of polyhydroquinoline derivatives

By comparing the reaction results with other methods, we found that the nano $\text{CeO}_2\text{/ZnO}$

performed the reaction in a shorter time and with a higher efficiency (Table 4).

To optimize the amount of catalyst, various amounts (0.01, 0.02, 0.03, 0.05, and 0.08 g) of nano CeO₂/ZnO were used. Table 5 represents the test results performed to optimize the amount of catalyst in the presence of different amounts of nano CeO₂/ZnO. The results presented in the table reveal that the amount of 0.05 g of cerium oxide/aluminum oxide nano-catalyst had the best efficiency.

Investigation of the reaction mechanism

The reaction between aromatic aldehyde (1), dimedone (2), ethyl acetoacetate (3), and ammonium acetate (4) is proposed in the presence of the NanoCeO₂/ZnO catalyst in Scheme 2. The catalyst acts as a Lewis acid and attracts electrons of the carbonyl group and activates the carbonyl aldehyde group, which eventually attacks the tautomerized dimedone and produces intermediate 7. Ethyl acetoacetate is coupled with ammonium acetate and reacts with the intermediate 7, following which the water is removed, and the desired product is obtained (Scheme 2) [20].

Table 2. Reuse of the nano CeO₂/ZnO for synthesis of (5a)

Entry	Run	Yield (%) ^a
1	First	95
2	Second	92
3	Third	90
4	Fourth	88
5	Fifth	85

^aIsolated yields

Table 3. Comparison of various temperatures for the synthesis of 5a

Entry	Time(h)	Temperature (°C)	Yield (%) ^a
1	3	25	66
2	3	50	75
3	3	reflux	95

^aIsolated yields

Table 4. Comparison of various catalysts for the synthesis of 5a

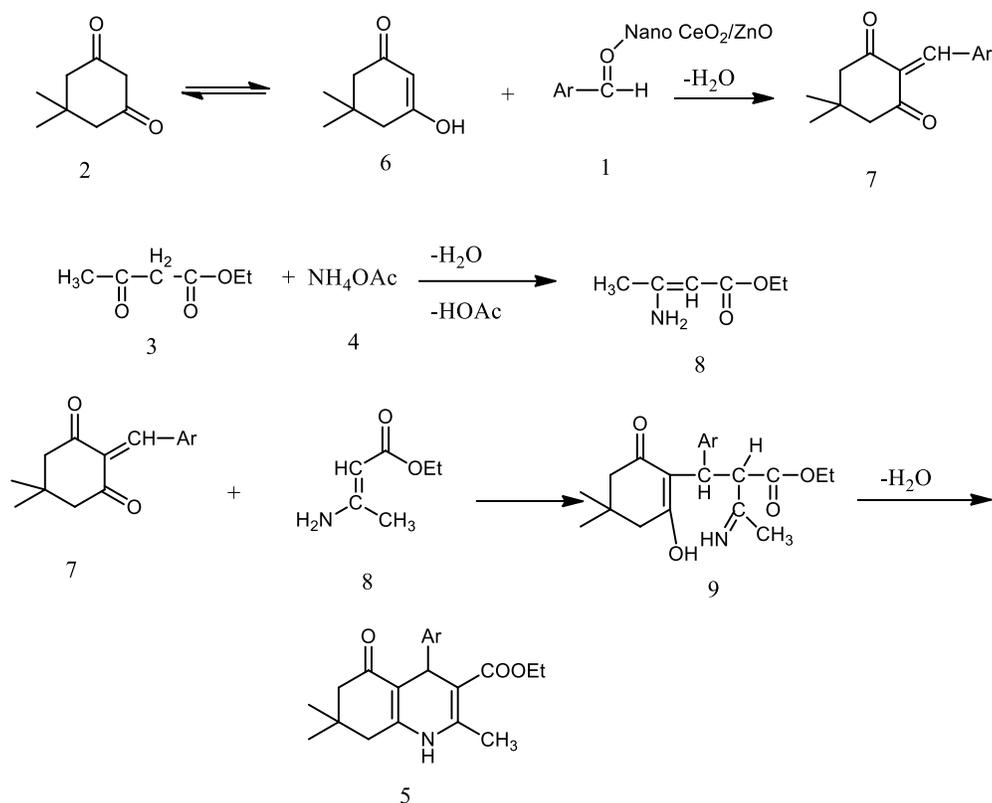
Entry	Catalyst	Yield (%) ^a	Time (h)	Ref.
1	SSA	73	6	[16]
2	CAN	56	4	[17]
3	NH ₄ Cl	85	2	[18]
4	CeCl ₃ .7H ₂ O	60	4	[19]
7	Nano-CeO ₂	91	2	The present study
8	Nano CeO ₂ /ZnO	95	2	The present study

^aIsolated yields

Table 5. Comparison of the amount of catalysts for the synthesis of 5a

Entry	Solvent	Yield (%) ^a
1	0.02g	80
2	0.03g	89
3	0.05g	95
4	0.08g	95

^aYields were analyzed by GC



Scheme 2. The proposed mechanism for polyhydroquinoline using nano CeO₂/ZnO

Experimental

General

Solvents and chemicals in this research project were purchased from the Merck Company and were used without the need for further purification. The structure of the obtained products has been compared and confirmed with the spectra and physical data from literature.

In this paper, various materials and devices were used that have the following specifications: Electrothermal Bransted-9200 was used to measure melting points. The IR spectra were recorded on an IR Tensor-FT using the KBr tablet. ¹HNMR spectra were recorded in ⁶d-DMSO solvent using TMS as an internal standard on a DRX AvanceBruker-400 MHz spectrometer.

Typical experimental procedure for the synthesis of Hantzschpolyhydroquinoline derivatives

A mixture of aldehyde (1 mmol), dimedon (1 mmol), ethyl acetate (1 mmol), ammonium acetate (2 mmol), and catalyst (0.05 g) in ethanol (5 mL) was refluxed for the indicated time (Table 6). After completing the reaction, as indicated by TLC (in a mixture of ethyl acetate and n-hexane in 3:1 ratio), the reaction solvent was evaporated, and then dried ethyl acetate was added and the catalyst was separated by filtration. The residue solvent was removed under reduced pressure. The pure product was obtained by recrystallization from ethanol. Melting points and IR spectra, ¹HNMR of the obtained crystals were taken and compared with the references.

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate (5a): ¹H NMRδ(ppm): 0.93 (s,3H),

1.05 (s,3H), 1.36 (t, 3H, J=6.9), 2.4-2.39 (m,7H), 3.98 (q,2H,J=6.9), 5.04 (s, 1H), 5.89 (s,1H), and 7.23-7.49 (5H,m).

Ethyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-p-tolylquinoline-3-

carboxylate (5b): 0.95 (s,3H), 1.07 (s,3H), 1.29 (t, 3H, J=7.2), 2.13-2.37 (m,7H), 2.38(s,3H), 4.03 (q,2H,J=7.2), 4.67 (s, 1H), 5.53 (S, 1H, NH), and 7.05-7.49 (4H,m).

Table 6. nanoCeO₂-ZnO catalyzed the synthesis of polyhydroquinolines

Entry	Ar	Product	Time (h)	Mp (°C)		Yield (%) ^a
				Observed	Reported	
1	Ph	5a	2	205	204-206[11]	95
2	4-Me-Ph	5b	2.5	264	261-262[12]	91
3	4-MeO-Ph	5c	2.5	243	243-245[11]	92
4	4-Cl-Ph	5d	2	233	230-232[11]	96
5	3-NO ₂ -Ph	5e	2	179	177-178[13]	96
6	4-OH-Ph	5f	2.5	239	237-238[11]	90
7	4-NO ₂ -Ph	5g	2	242	240-242[14]	97

Synthesis of nanocerium (IV) oxide-zinc oxide (CeO₂-ZnO)

Preparation of CeO₂-ZnO nanostructures was carried out by magnetic stirring by stirring CeCl₂ (1.04 g), ZnCl₂ (4.09 g), and distilled water (300 mL) continuously at room temperature for 30 minutes in a balloon. By adding a drop of ammonia (NH₄OH) to bring pH to 10.15 and stir at 80 °C for 6 hours. The resulting white precipitate was washed and dried several times at room temperature with water and ethanol and calcined at 400 °C for 5 hours [15].

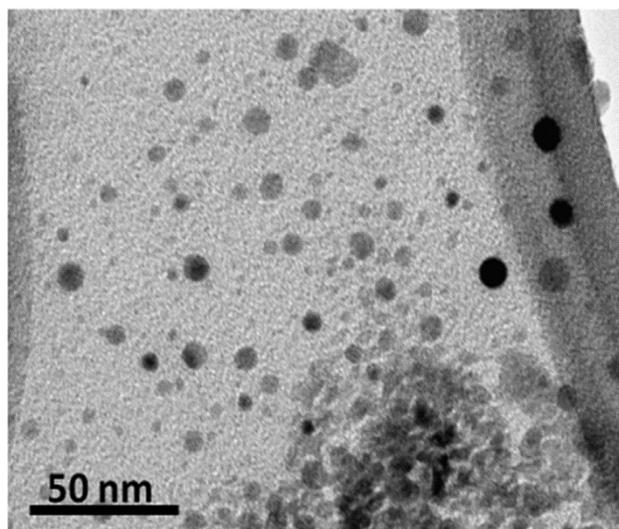


Figure 5. TEM Spectra of nano CeO₂-ZnO

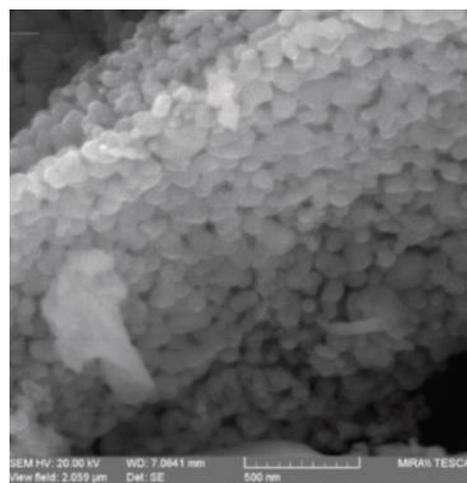


Figure 6. SEM Spectra of nano CeO₂-ZnO

Conclusion

To sum up, we have found a simple, convenient, straightforward, and practical procedure for the synthesis of polyhydroquinolines derivatives in the presence of nano cerium (IV) oxide/zinc oxide as an efficient catalyst. All starting materials are readily available from commercial sources. The advantages of this reaction include easy separation steps, preparation of products with high efficiency, short reaction time, use of recyclable, and environmentally friendly catalysts. The procedure is very simple and can be used as an alternative to the existing procedures

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