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Original Research Article

One-pot synthesis of 1,4-dihydropyridine derivatives using nano-cerium oxide as an efficient catalyst

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ABSTRACT

Dihydropyridine derivatives have been identified as calcium channel blockers and are predominantly utilized in cosmetics and pharmaceuticals. These compounds are often used as intermediates for producing biologically active products, including drugs, herbicides, insecticides, and fungicides. The applications of pyridines and their benzo derivatives have been described over the past decade along with natural products containing the pyridine ring system. These applications are classified into three categories: biological, chemical and functional. Functional applications based on the physical properties of pyridines and their benzo-derived compounds describe colors, flavors, and ionic liquids. Chemical applications, based on the chemical properties of pyridines and benzo derivatives, describe reagents in analytical chemistry as well as catalysts and reagents in organic synthesis. Biological applications based on the environmental activity of pyridine compounds in pharmaceutical, agrochemical and veterinary products have been presented in this study. In this research study, the synthesis of 1,4-Dihydropyridine derivatives was investigated through a three-component one-pot reaction using nano-cerium oxide catalyst.

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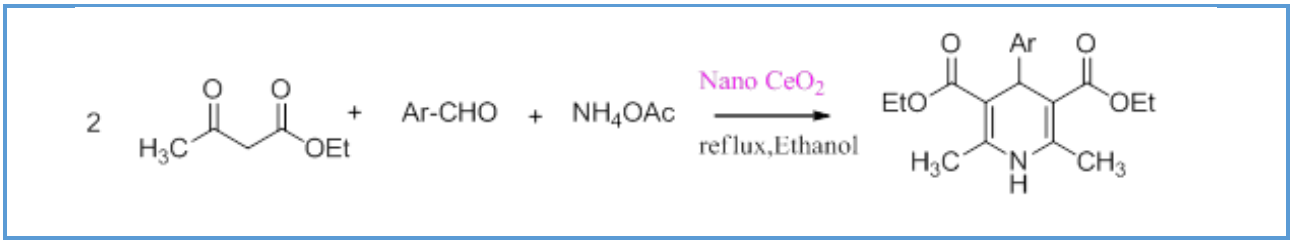
Graphical Abstract



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Introduction

Pyridine was undoubtedly produced using early alchemists by heating animal bones and other organic matter; however, the earliest documented reference is attributed to the Scottish scientist Thomas Anderson. Anderson investigated the oil content obtained through high-temperature heating. Among other substances, he separated a colorless liquid with an unpleasant odor, from which he separated into pure pyridine two years later. He described it as a highly soluble solution in water, readily soluble in concentrated acids and salts upon heating, and only slightly soluble in oils. Today, most pyridine is synthetically produced using various reactions. In fact, 17 tons of pyridine is produced worldwide. Among the largest production sites for pyridine, eleven are located in Europe. Major producers of pyridine include the food, chemical, life sciences, chemical-royal and organic chemical industries. Pyridine production increased significantly in the early 1980 s with an annual production capacity of 190 tons in mainland China. The US-Chinese Joint partnerships are now considered the world leader in pyridine production.

1,4-dihydropyridines are heteroaromatic compounds that are considered by chemists due to their medicinal and biological properties. One of the most important derivatives of 1,4-Dihydropyridines are 1,8-dioxo-decahydroacridines, which have many applications and medicinal properties such as anti-malarial, anti-cancer, anti-tumor and anti-bacterial properties. Multi-component reactions play an important role in synthetic chemistry due to their ability to synthesize small quasi-drug molecules with great structural diversity.

This compound has many uses. It is actually a multifunctional solvent and a building block for other types of organic compounds. Pyridine is widely used as a multifunctional solvent. In solvent spectroscopy (NMR), disposed pyridine is a common solvent. In industrial organic chemistry, it is important both as a basic building block and as a solvent and reagent in organic synthesis. It is a raw material in the synthesis of compounds used as intermediates in the manufacture of insecticides, herbicides, drugs, foodstuffs, dyes, rubber chemicals, explosives and disinfectants. This compound is used as a denaturant for antifreeze mixtures and sometimes as a ligand in coordination chemistry [1, 2]. Pyridine has many uses. It can be used to produce paints and solvents. Pyridine rings are found in many natural products, including vitamins such as niacin and vitamin B6, and coenzymes such as the nicotinamide adenine dinucleotide. Many drugs and pesticides contain pyridine. Examples include antimicrobials, antiviruses, antioxidants, antibacterials, antimalarials, anti-inflammatory drugs, psychedelic antagonists, and disinfectants.

Nitrogen-containing heterocyclic compounds, including pyridine, interact with environmental surfaces (such as soils and sediments) through pH-dependent mechanisms, including partitioning to soil organic matter, cation exchange, and surface complexation. Such adsorption of pyridine to surfaces reduces the rate of degradation by microbes and other organisms and thus reduces toxicity [3–5]. Therefore, synthesis 1,4-Dihydropyridine is of a great importance for organic chemists due to their high pharmacological and biological activities. There are several procedures for the synthesis of 1,4-Dihydropyridine using nanocatalysts [6–9]. As a part of our work on multicomponent reactions (MCRs) and developing new methodologies for the synthesis of various heterocyclic compounds, we are going to introduce nano-CeO_2 as a suitable catalyst for the synthesis of

1,4-Dihydropyridine at ambient conditions (Scheme 1).

Cerium dioxide (CeO_2) catalysts were fabricated using microemulsion and inoculation methods and were detected by X-ray diffraction (XRD) analysis and scanning electron microscopy (SEM). At the same time, the desulfurization activity of the catalysts was investigated. The results revealed that active particles at the nanoscale and high desulfurization effect by microemulsion have a significant advantage compared to the traditional inoculation method [10–12]. Active catalysts still maintain high and stable desulfurization activity over a wide range of temperatures from 450 to 600 °C. Among a number of ready-made catalysts, the desulfurization rate of nano-cerium oxide is the highest, and when the temperature is above 550 °C, it reaches up to 80% [13]. As the particle size decreases, the probability of agglomeration of the particles increases because of the interaction due to van der Waals forces. This reduces the density of nanoparticles and the non-uniformity of the structure. Wet forming methods are used to remove nanoparticle agglomerates and increase density. Ceria (CeO_2) has been well used as a promoter in reducing the emission of pollution from mobile sources. Oxygen storage materials mainly contain ceria, zirconia, and alumina. Ceria is the main component of a three-way catalyst (TWC) that is used for environmental cleaning purposes. Furthermore, catalysis such as the oxidation of hydrocarbons, the removal of total organic carbon from the car exhaust gas conversion has also been provided [14]. Corrosion resistance can be excellent due to a layer of aluminum oxide on the surface. Exposure to air effectively prevents further oxidation. There is an interest in cerium dioxide nanoparticles in a wide range of applications, such as cerium electrolytes, oxygen and solid oxide fuel cells, solar cells, catalyst sensors, including water and gas change reactions, and automotive catalysts have also been used. In all these cases of the use of nanostructures, it is expected that cerium-based compounds improve their properties.

Nanocatalysts are widely used in organic synthesis today [15–32]. In this study, we used a nano- CeO_2 catalyst for the synthesis of 1,4-Dihydropyridine.

Experimental

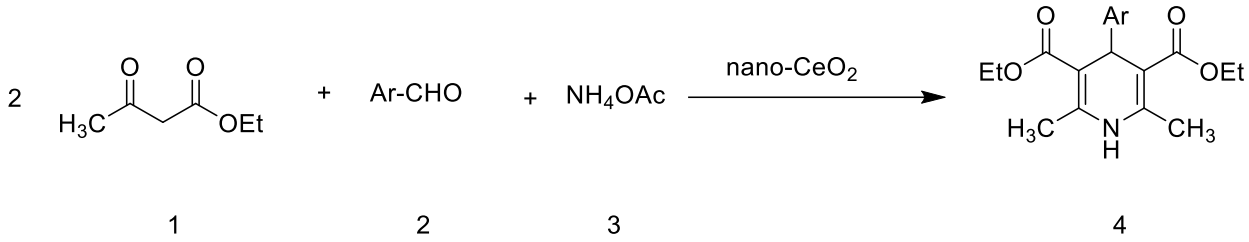
Material and methods

Chemicals were supplied from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. (USA). Melting points were taken as uncorrected using a digital Electrothermal melting point apparatus (model 9100**,** Electrothermal Engineering Ltd., Essex, UK). ^{1}H-NMR spectra were obtained using a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (Internal standard: TMS) and values were expressed in ppm. The IR spectra were recorded using a Thermo Nicolet FT-IR (model Nexus-870**,** Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrometer. Mass spectra were obtained using an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington, USA). The purity of compounds was confirmed by TLC. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

General procedure for the synthesis of Dihydropyridine derivatives

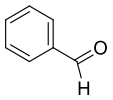
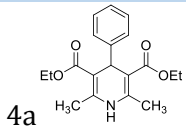
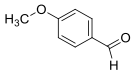
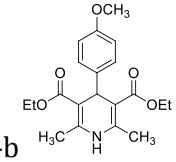
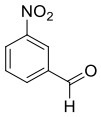
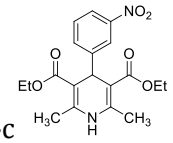
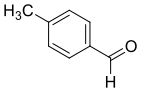
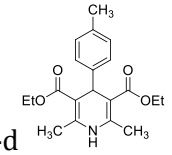
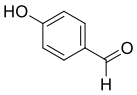
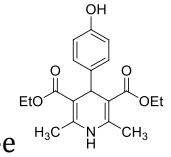
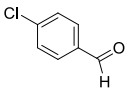
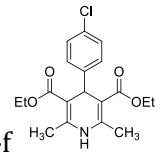
1 mmol aldehyde (0.151 g), 2 mmol ethyl acetoacetate (0.26 mL), 1 mmol ammonium acetate (0.11 mL) in the presence of 0.05 g cerium oxide nano-catalyst were added to a 25 mL flask, and then 5 mL ethanol was added. The mixture was stirred by means of a magnetic

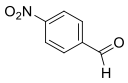
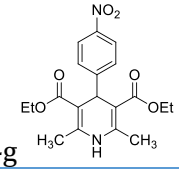
stirrer under reflux conditions. The rate of reaction progress was tracked using TLC in a mixture of ethyl acetate and n-hexane in a ratio of 1: 3. After the reaction was complete, it was filtered, and distilled water was added dropwise to the contents under the filter paper to precipitate. Then, the precipitate recrystallized from Ethanol (Scheme 1, Table 1).



Scheme 1.

Table 1. Synthesis of Dihydropyridine derivatives catalyzed by cerium oxide nano-catalyst

Entry	Aldehyde	Product	Time (h)	Melting Point Reported[33]	Melting Pint Observed	Yield (%)
1		 4a	2	158-160	59-161	94
2		 4b	2	158-159	160-161	92
3		 4c	2	160-162	162-163	95
4		 4d	2	137-139	139-140	92
5		 4e	2	229-232	230-231	93
6		 4f	2	144-146	146-148	96

7		 4g	2	130-133	133-134	97

Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridin-3,5-dicarboxylate (4a)

IR (KBr) (ν_{max}/ cm^{-1}): 3327, 1732 and 1491. ^{1}H NMR (400 MHz): δ 1.23-1.27 (t, 6H), 2.35 (s, 6H), 4.05-4.19 (q, 4H), 5.07 (s, 1H), 5.77 (bs, 1H, -NH), 7.18-7.51 (m, 5H, Ar-H). ^{13}C NMR (100 MHz): δ 14.3, 19.7, 39.7, 60.3, 104.4, 127.9, 128.1, 128.4, 143.8, 147.8, 167.9.

Diethyl-2,6-dimethyl-4-nitrophenyl-1,4-dihydropyridin-3,5-dicarboxylate (4g)

IR (KBr) (ν_{max}/ cm^{-1}): 3331, 1738, 1562, 1495 and 1381. ^{1}H NMR (400 MHz): δ 1.28-1.31 (t, 6H), 2.41 (s, 6H), 4.12-4.25 (q, 4H), 5.22 (s, 1H), 5.86 (bs, 1H, -NH), 7.23-7.78 (m, 4H, Ar-H).

Synthesis of Cerium Oxide (CeO_2) Nanostructures

Cerium oxide nanopowder was prepared by precipitation method using $CeCl_3.7H_2O$ (Merck, purity >99.5%) and NH_3 (Merck, purity >99%). Initially, $CeCl_3.7H_2O$ was dissolved in deionized water, then the mixture was stirred for 30 min and then NH_3 (0.5 mol) was added to the aqueous solution until a jelly form was formed at a pH of about 8.5. The resulting synthetic gel was then washed with boiling distilled water and dried at 80 °C for 24 h. The gel was dried and calcined at 700 °C for 2 h. The SEM, TEM and XRD spectra of the catalyst are given below (Figure 1-3) [34].

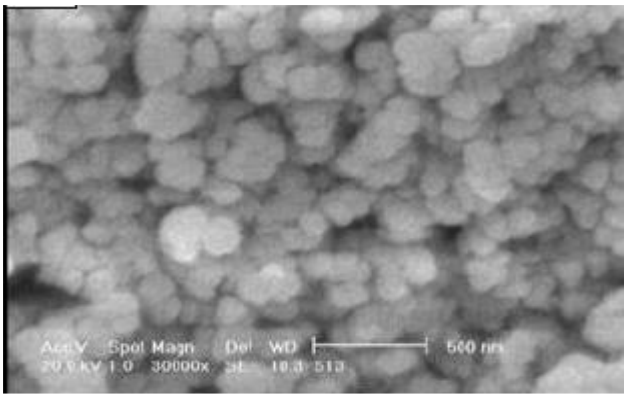


Figure 1. SEM spectra of nano CeO_2

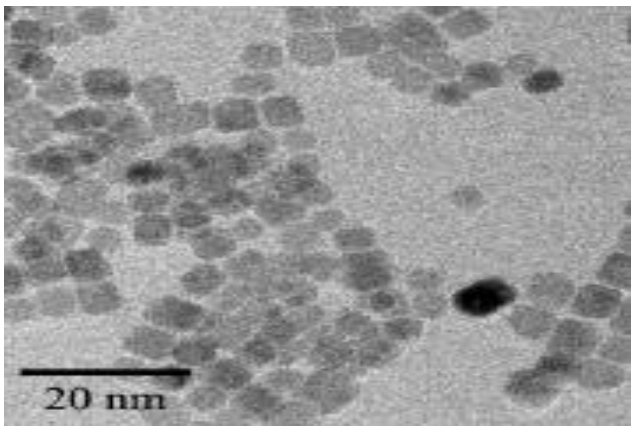


Figure 2. TEM spectra of nano CeO_2

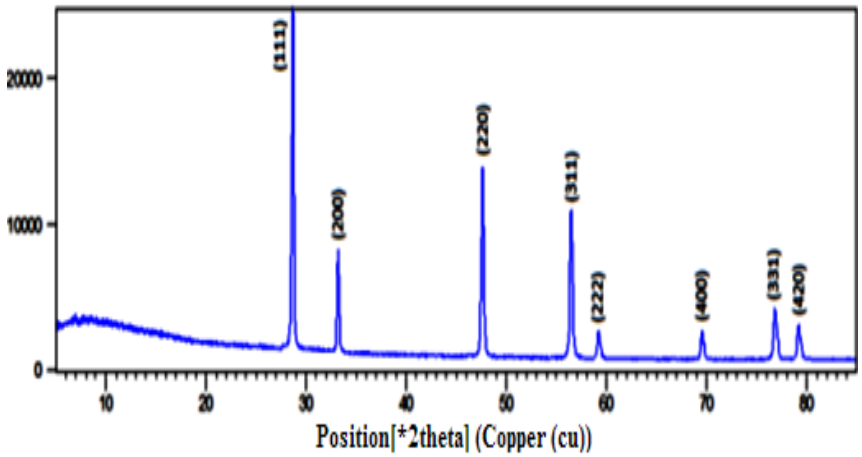


Figure 3. XRD spectra of nano CeO_2

Result and Discussion

To optimize the amount of catalyst, 2 mmol of ethyl acetoacetate, 1 mmol of aldehyde, 1 mmol of ammonium acetate, and various amounts (0.01, 0.02, 0.03, 0.05, and 0.08 g) of cerium oxide nano-catalyst were used. Table 2 represents the test results performed to optimize the amount of catalyst in the presence of different amounts of cerium oxide nano-catalyst. The results presented in the table show that the amount of 0.05 g of cerium oxide nano-catalyst had the best efficiency.

The reaction of preparing 1,4-dihydropyridine using 2 mmol of ethyl acetoacetate and 1 mmol (0.151 g) of aldehyde with 1 mmol of ammonium acetate was performed in the presence of cerium oxide nanocatalyst with different solvents and the results are listed in Table 3. These experiments yielded better results in ethanol solvent.

Table 2. Comparison of amount of catalysts for the synthesis of **4a**

Entry	Amount of catalyst	Yield (%)[a]
1	0.02 g	80
2	0.03 g	89
3	0.05 g	94
4	0.08 g	94

[a] Yields were analyzed by GC

Table 3. Synthesis of **4a** in the presence of different solvents using nano-CeO_2 as a catalyst

Entry	Solvent	Yield (%)[a]
1	THF	68
2	C_2H_5OH	94
3	CH_3CN	85
4	$CHCl_3$	71
5	water	90
6	Solvent-free	92

[a]Yields were analyzed by GC

Reusability of nano CeO_2

In the following, the reusability of nano CeO_2 investigated. At the end of the reaction, the catalyst recovered by a simple filtration, washed with methanol, dried and subjected to a second run of the reaction process. To assure that the catalysts were not dissolved in methanol, they were weighed after filtration and before use and reuse for the next reaction. In Table 4, the comparison of efficiency of nano CeO_2 in synthesis of **4a** after five times is reported. As shown in Table 2 the first reaction using recovered CeO_2 afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields were gradually decreased.

After comparing the results for the synthesis of **4a** with other methods, it is revealed that the nano-magnesium aluminate catalyst performed the reaction faster and with higher efficiency (Table 5).

Table 4. Reuse of the nano CeO_2 for synthesis of **4a**

Entry	Run	Yield(%)[a]
1	First	94
2	Second	92
3	Third	90
4	Fourth	88
5	Fifth	85

Isolated yields

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

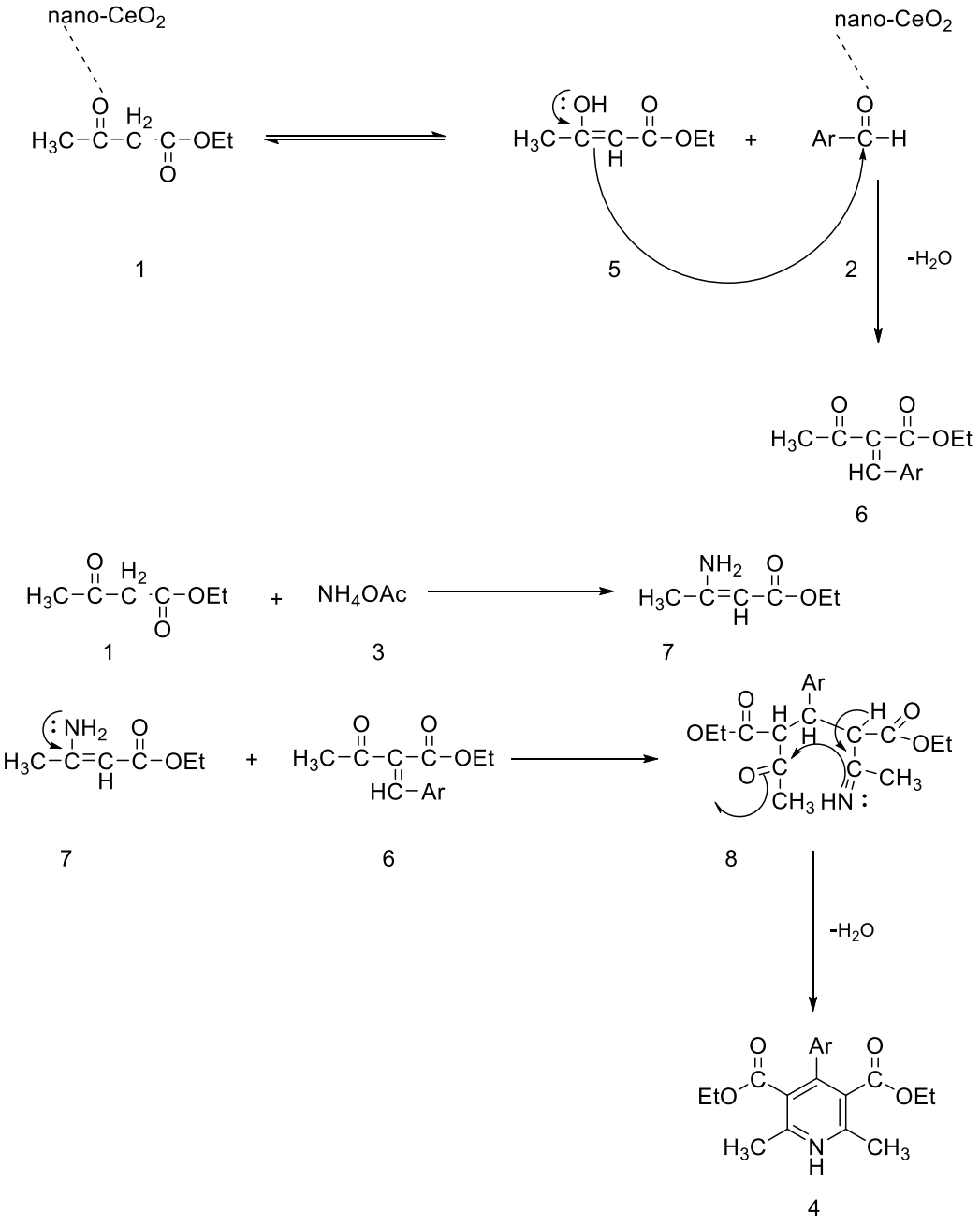
Entry	Catalyst	Yield (%)	Time (h)	Ref.
1	MTSA	88	4	[35]
2	$ZnCl_2$	42	6	[35]
3	$AlCl_3$	64	8	[35]
4	$FeCl_3$	43	6	[35]
5	$BiCl_3$	70	6	[35]
6	$Bi(OTF)_3$	76	6	[35]
7	$BiBr_3$	60	6	[35]
8	nano CeO_2	94	2	Present study

The proposed mechanism for the synthesis of 1,4-dihydropyridine derivatives in the presence of cerium oxide nanocatalyst is as follows: Initially, the first pyridine makes a nucleophilic attack to the catalyst-activated aldehyde. After that, it is dehydrated in the presence of the catalyst by the loss of a water molecule. The second molecule of pyridine then comes into the action under Michael's reaction and turns into the desired product by losing the proton (Scheme 2).

Conclusions

Pyridines are essential material in medicinal chemistry due to their weak basicity, water solubility, hydrogen bond-forming ability, and small molecular size. The pyridine moieties are used in many drugs and pesticides. Today, chemists are trying to develop low-risk, environmentally friendly methods for synthesizing a variety of materials. In this synthesis, an attempt has been made to use a suitable and cost-effective method for the production of the desired material in order to become a general method for synthesis. Pyridine is used in this reaction. Pyridine is

present in the natural structure of many substances. So far, many articles have been reported on their production with different catalysts and without catalysts under different conditions. In this study, we considered another way to synthesize this substance. Pyridine derivatives were produced using 1 mmol of aldehyde, 2 mmol of ethyl acetoacetate and



Scheme 2.

1 mmol of ammonium acetate in the presence of cerium oxide nanocatalyst under reflux conditions. This method has many advantages, including:

- The reaction can be maintained for a very long time, without the need to add solvent or additional heat energy.
- Due to the constant reaction temperature, we can achieve good efficiency of the reaction.
- The catalyst used has good thermal stability and high efficiency.
- The reaction needs a short time and has a high efficiency.
- The advantages of this method are as follows: Since the catalyst used is a solid nano-catalyst, it is therefore a useful method in chemistry. The reaction is multicomponent and ideal, and in this reaction, there is no need to separate the intermediates. The reaction is performed in a short time and with the best efficiency and high selectivity.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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