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FULL PAPER

# Synthesis of indeno [1,2-b] pyridine derivatives in the precense of Nano $CeO_2$/ZnO

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The core of indenopyridine is present in group 4-azafluronone alkaloids, which is shown with its simplest member, Onikinine. Many of the derivatives of indenopyridine have exhibited bonding activities with the Adenosine A2a receptor and inhibited phosphodiesterase in the treatment of neurological disorders and inflammatory diseases. They also act as antagonists to calcium and herbicides. In this way, these compounds are known to be chemical and biological heterocycles. As a result, the convenient synthesis of these molecules has attracted the attention of the organic synthesis community. In this study, we presented the synthesis of indopyridine with the use of nano-$CeO_2$/ZnO as a heterogeneous and recyclable catalyst with high efficiency under reflux conditions.

**KEYWORDS**

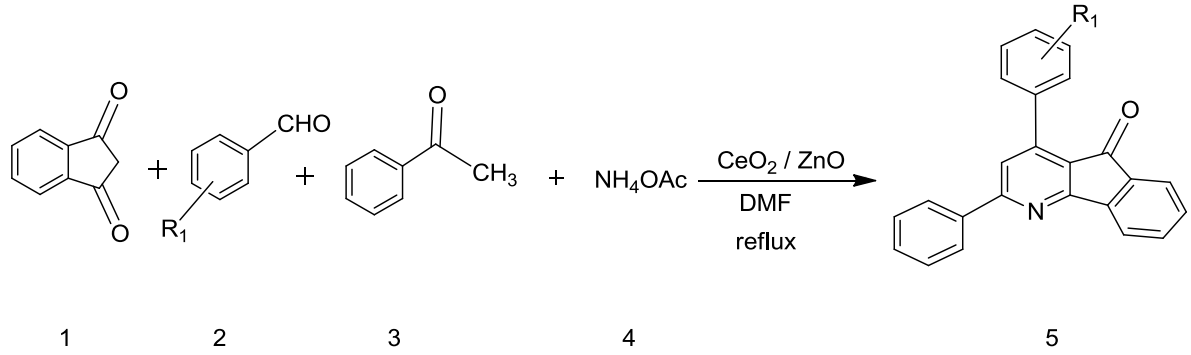
Indenopyridine; synthesis; $CeO_2$-ZnO; catalyst; heterogeneous.

## Introduction

The indenopyridine nucleus is present in the 4-azafluorenone group of alkaloids. 4-Azafluorenones (5H-Indeno [1,2-b]pyridin-5-ones) are naturally occurring alkaloids isolated from the root of the plant Polyalthiadebilis (Pierre) belonging to the family of Annonaceae. As the core structural unit in a wide range of natural products, azafluorenone has recently inspired much research [1]. These substances are effective inhibitors of spermatogenesis in animals and also show antifungal activity. Hydrogenated indenopyridines have potential antidepressant activity. A series of derivatives of 4- (2-amino-3-cyano-5-exo-4H-indeno [1,2-b] pyridine benzene sulfonamide have been synthesized and their anti-cancer activity against breast cancer cell line in vitro has been investigated (MCF7). Thus, these compounds are known as heterocycles of great chemical and biological importance. Considering the importance of heterocyclic compounds, numerous methods have been developed for the synthesis of indeno [1,2b] pyridines[2]. According to available reports, Indeno [1,2-b] pyridine has topoisomerase inhibitory activity and anti-proliferative activity in human colon cancer cells (HCT15), breast (T47D), prostate cancer (DU145), and cervical cancer (HeLa)[3-6]. Despite numerous rational strategies for cancer treatment, chemotherapy using derivatives of indeno [1,2-b] pyridine remains one of the most well-known and common methods to treat cancer. Several compounds-containing the skeleton of indenopyridine have exhibited significant biological activities, including anti-cancer, anti-inflammatory, anti-depression, and coronary vasodilator activities [7].

In our effort to develop new catalytic systems, in this study, we presented a suitable and efficient protocol for the preparation of indeno[1,2-b]pyridinethrough the reaction of aldehydes, 1,3-indandione, ammonium acetate and acetophenone in the

presence of a catalytic amount of Nano-$CeO_2$-ZnO in DMF as a solvent (Scheme1).




**SCHEME 1** Synthesis of indeno [1,2-b] pyridine derivatives

## Experimental

*Material and methods*

Chemicals were supplied from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. All products were characterized by spectra and physical data. Characterizations were carried out using the Melting points (Electrothermal 9100), $^1$H-NMR (Bruker 500 MHz), TEM (HRTEM, TF 20 Tecnai G2 200 kV FEI), Fourier transform infrared (model Nexus-870, Nicolet Instrument), Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel.

*Preparation of catalyst nano-$CeO_2$/ZnO*

Zinc oxide nanostructures were prepared by magnetic stirring method. A mixture of CeCl2 (1.04 g), ZnCl2 (4.09 g) and distilled water (300 mL) was stirred at room temperature. A drop of ammonia ($NH_4OH$) was added to bring the pH of the mixture to 10.15 and stirred 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 [8].

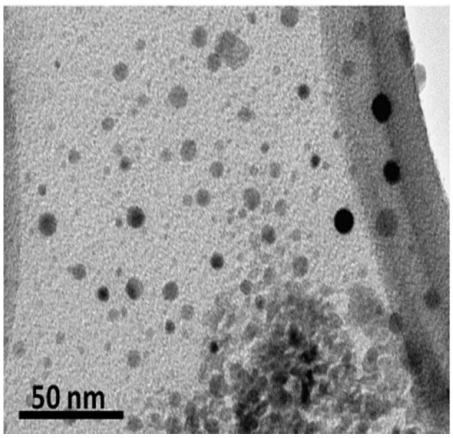



**FIGURE 1** TEM image of nano $CeO_2$/ZnO

*Typical procedure for preparation of indeno [1,2-b] pyridine derivatives*

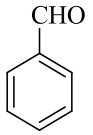
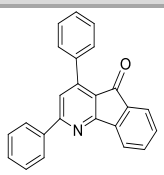
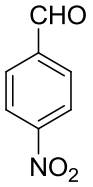
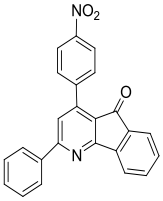
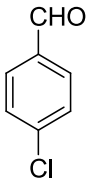
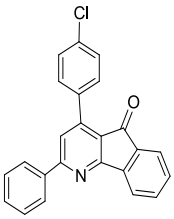
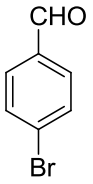
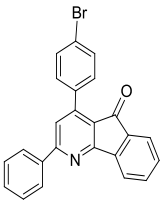
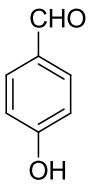
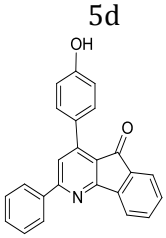
Amixture of 1, 3 Indandione (1 mmol), aldehyde (1 mmol),acetophenone (1 mmol), ammonium acetate (2, 50 mmol) and nano $CeO_2$/ZnO(0.05 g) and 5 mL of DMF were refluxed. After completion of the reaction, the solvent was evaporated. 10 mL of water and 12 mL of ethyl acetate was added to the mixture and the upper phase was poured into the beaker using a separating funnel, and 1 g of sodium sulfate is added to dehydrate the solvent. The mixture was stirred with a magnetic stirrer for 5 minutes and then filtered; the solvent was evaporated and the product was recrystallized in ethanol.

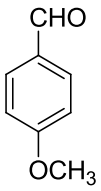
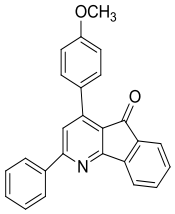
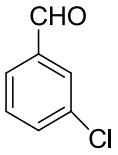
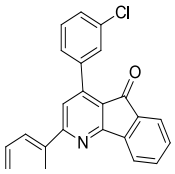
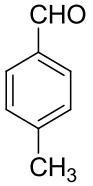
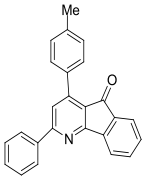
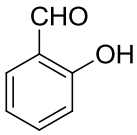
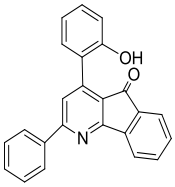
**5f**. IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3074, 1653, 1626. $^1$H NMR (DMSO-d6, 400 MHz, ppm): 8.37–8.25 (m, 2H),8.05–7.98 (m, 1H), 7.95–7.84 (m, 2H),

7.68–7.61 (m, 1H), 7.59–7.50 (m, 3H), 7.39–7.23 (m, 2H), 6.73–6.85 (m, 2H), 3.89 (s, 3H, $OCH_3$). MS (EI, 70 ev): m=z 363.

**5i**. IR (KBr) (vmax, cm−1): 3421, 3063, 2922, 1710, 1602. 1H NMR (DMSO-d6, 400 MHz, ppm): d 9.19 (s, 1H), 8.50–8.36 (m, 2H),7.98–7.98 (m, 1H), 7.81–7.73 (m, 2H), 7.67–7.62 (m, 1H), 7.56–7.51 (m, 3H), 7.38–7.29 (m, 2H), 6.78–6.88 (m, 2H). MS (EI, 70 ev): m=z 349.

**TABLE 1** Preparation of indeno [1,2-b]pyridine derivatives

| Entry | Aldehyde | product | Time (h) | Yield (%) | Experimental Melting Point | Theory Melting Point[9] |
|---|---|---|---|---|---|---|
| 1 |  |  5a | 3 | 94 | 234-236 | 234-235 |
| 2 |  |  5b | 3 | 96 | 237-238 | 236-237 |
| 3 |  |  5c | 3 | 96 | 260-261 | 258-260 |
| 4 |  |  5d | 3 | 95 | 267-269 | 266-268 |
| 5 |  |  5e | 3 | 93 | 225-227 | 224-226 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 |  |  5 | 3 | 96 | 197-198 | 195-197 |
| 7 |  |  5g | 3 | 96 | 258-259 | 258-260 |
| 8 |  |  5h | 3 | 97 | 236-238 | 235-237 |
| 9 |  |  5i | 3 | 92 | 199-200 | 197-199 |

## Results and discussion

Multicomponent reactions have drawn much attention as a tool for the synthesis of useful and widespread compounds, including medications. In this respect, the multi-component method is very interesting due to the fact that the products are formed in a single step, and an increase in their diversity is easily possible by changing the reaction components. Chemoselective synthesis, regioselective synthesis, or stereoselective synthesis high-value chemicals and parallel synthesis to produce a set of small molecules will contribute to the growth of solvent-free multicomponent reactions in the near future. It is evident from the growing number of publications in this field that the possibility of using multi-component technology allows reaction conditions to be always accessible, which is of great importance for organic synthesis. Thus, diversity-oriented synthesis is rapidly becoming one of the patterns in the modern drug discovery process. This has led to the growth of research in the field of chemical analysis and, consequently, rapid aggregation of not only molecular diversity but also molecular complexity. As a result, multicomponent reactions, are experiencing an enormous boom. In recent years, the discovery of catalysis with small organic molecules called organic catalysts has been a significant scientific breakthrough that has many advantages, including less energy required for activation, high stability, a metal-free environment, reduced toxicity, and mild reaction conditions. Organic catalysis strategies have been highly taken into account because of their application in organic synthesis due to their ability to facilitate chemical transformations with a stoichiometric amount of an organic

compound [10]. Multicomponent reactions (MCRs) are highly valuable processes in organic and pharmaceutical chemistry because of their high atomic efficiency and applications in combinatorial chemistry. Heterocycles are important scaffolds and make up the pharmacists of many successful drugs. Recently, poly-aryl pyridine derivatives have attracted much attention since they are present in a wide range of drugs such as antimalarial drugs, vasodilators, anesthetics, anticonvulsants, as well as in agricultural chemicals such as fungicides, pesticides, and herbicides [11].

Due to their characteristics, such as surface-active sites, high stability, and specific surface area, nanocatalysts have attracted much attention. These properties exhibit excellent catalytic performance, such as high and selective activity required in industrial production [12].

The most important achievement of nanotechnology in catalyst science is the unification of the size and distribution of active catalytic pores. This is because if we can have the same distribution of size and properties of active centers, we will not face different reactions. This means that we will not have by-products, and we will not have to spend a lot of money on separation. Moreover, environmental pollution will be reduced without byproducts. Nanocatalysts accelerate the reaction speed compared with catalysts, and the efficiency of the products is higher than other catalysts [13].

*Comparison of catalyst efficiency in the synthesis of indeno [1,2-b] pyridine*

Initially, the reaction between 1,3Indandione, benzaldehyde, acetophenone and ammonium acetate was examined for the synthesis of indeno [1,2-b] pyridine as a model. The results gained from this study were compared with the results of the articles reported in Table 2. As shown in Table 2, the best efficiency is achieved in the shortest time by zinc oxide catalyst.

**TABLE 2** Comparison of catalysts for the synthesis of **5a**

| Entry | Catalyst | Time(h) | Yield(%) |
|---|---|---|---|
| 1 | $SiO_2Cl$ | 3.5 | 85 |
| 2 | $NaHSO_4/SiO_2$ | 4 | 85 |
| 3 | $H_{14}[NaP_5W_{30}O_{110}]$ | 5 | 88 |
| 4 | $RuCl_3$ | 3 | 88 |
| 5 | Nano-$CeO_2$/ZnO | 3 | 94 |

*Optimization of the amount of catalyst in the synthesis of indeno [1,2-b] pyridine*

In order to determine the appropriate amount of catalyst, the synthesis reaction of **5a** was intended as the model reaction, and different values of catalyst were evaluated. The catalyst has a low reaction efficiency in small amounts, and the amount of efficiency is constant and cost-effective by increasing it and less amount with better efficiency was selected (Table 3).

**TABLE 3** Comparison of amount of catalysts for the synthesis of **5a**

| Entry | Amount of catalysts(g) | Yield (%)[a] |
|---|---|---|
| 1 | 0.02g | 66 |
| 2 | 0.03g | 80 |
| 3 | 0.05g | 94 |
| 4 | 0.08g | 94 |
| 5 | 0.1g | 94 |

*Optimization of the temperature in the synthesis of indeno [1,2-b] pyridine*

To reach the appropriate temperature conditions, the model reaction was performed at different temperatures and reflux. As indicated, the highest efficiency was observed in reflux conditions (Table 4).

**TABLE 4** Comparison of various temperature for the synthesis of **5a**

| Entry | Time(h) | Temperature (°C) | Yield(%) |
|---|---|---|---|
| 1 | 3 | 25 | 66 |
| 2 | 3 | 50 | 75 |
| 3 | 3 | reflux | 94 |

*Optimization of the solvent in the synthesis of indeno [1,2-b] pyridine*

For optimizing the solvent, the model reaction was performed in water, ethanol and DMF, acetonitrile and chloroform, where the DMF had the best efficiency under reflux conditions (Table 5).

**TABLE 5** Synthesis of **5a** in the presence of different solvents using nano-ZnO/$CeO_2$ as a catalyst

| Entry | Solvent | Yield (%)[a] |
|---|---|---|
| 1 | THF | 68 |
| 2 | $C_2H_5OH$ | 91 |
| 3 | $CH_3CN$ | 85 |
| 4 | $CHCl_3$ | 71 |
| 5 | water | 91 |
| 6 | DMF | 94 |
| 7 | Solvent-free | 90 |

The catalyst is stable in solvents and the reaction time is 3 hours and no change in efficiencies is achieved with increasing time.

*Reusability of ZnO/$CeO_2$ catalyst*

After completion of the model reaction, 10 mL of ethyl acetate was added to the contents on filter paper containing catalyst. The mixture was stirred using a magnetic stirrer at room temperature for 5 minutes. The reaction mixture was smoothed. Because the catalyst is insoluble in ethyl acetate, it remained on the filter. Then, in order to reuse the catalyst, the substances on the filter were washed several times with acetone. After drying, the reaction with it was repeated to evaluate the potency of the catalyst (Table 6).

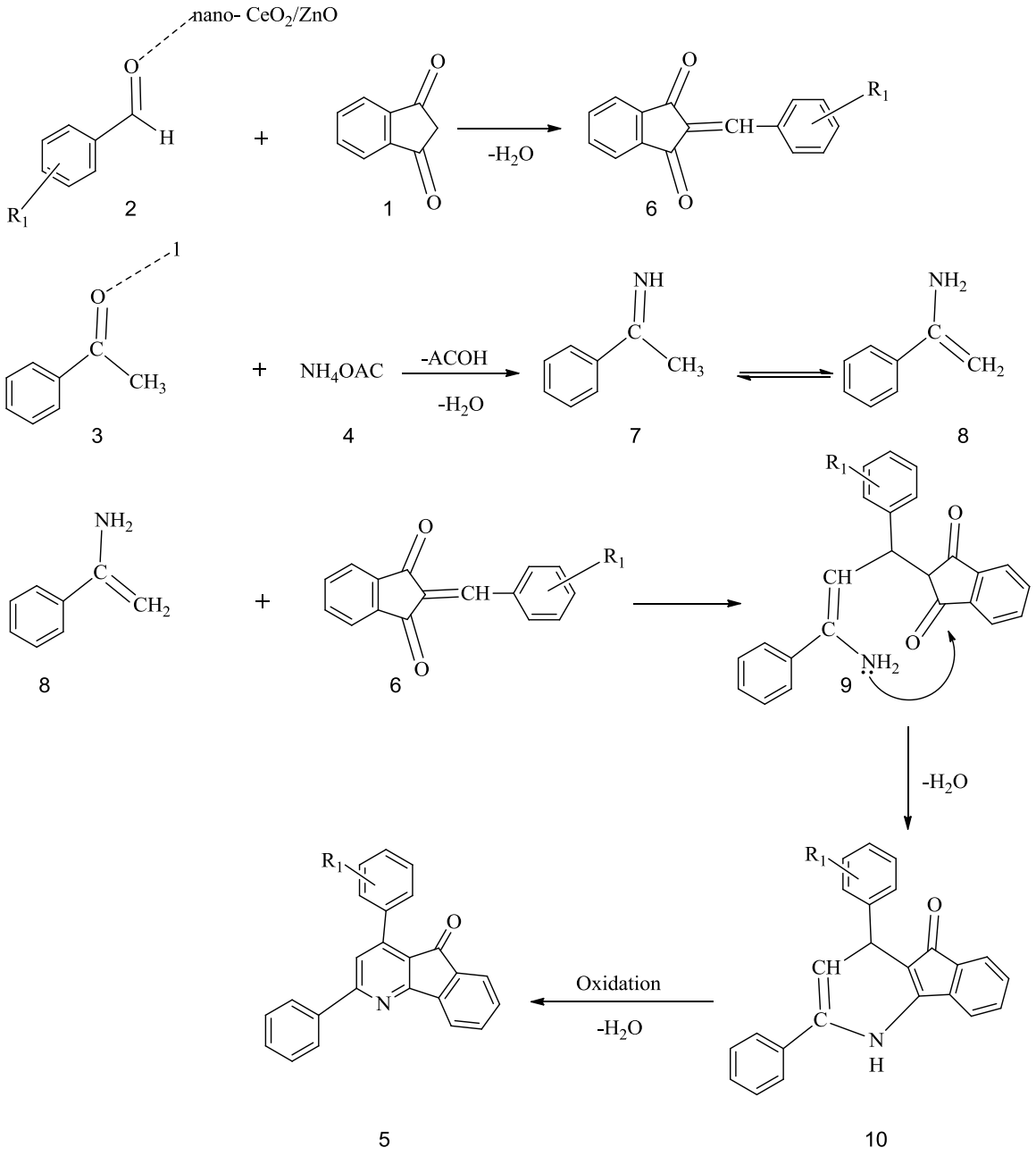
**TABLE 6** Reuse of the nanoZnO/$CeO_2$for the synthesis of **5a**

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

The proposed mechanism for the synthesis of indeno [1,2-b] pyridine derivatives in the presence of nano $CeO_2$/ZnOnanocatalyst is as follows (Scheme 2):

The catalyst acts as Lewis acid and activates the carbonyl group in the aldehyde. Then Indandion 1 and 3 attack it as a nucleophile and after removing the water, intermediate 6 is obtained. Acetophenone also reacts with ammonium acetate and after

tautomerization, intermediate 8 is obtained. Compounds 6 and 8 react and after removing the water and oxidizing, the desired product is obtained.




**SCHEME 2** Mechanism for the synthesis of indeno [1,2-b] pyridine derivatives

## Conclusion

As the core structural unit in a wide range of natural products, many indenopyridine derivatives have recently attracted much research. These substances are effective inhibitors of spermatogenesis in animals and also show antifungal activity. Hydrogenated indenopyridines have potential antidepressant activity. A series of their derivatives have anti-cancer activity. Thus, these compounds are known as heterocycles of great chemical and biological importance. Several compounds-containing the skeleton of indenopyridine exhibited important biological activity, including anti-inflammatory activity and coronary

vasodilator. There are more reports in this respect.

Among the advantages of this method are as follows:

1-Because the catalyst exploited is a solid nanocatalyst, so it is a suitable method in chemistry.

2-Reaction quotient is high.

3-Products are easily purified by crystallization in N-N dimethylformamide (DMF) solvent

4-Separation of products is carried out by smoothing with filter paper, and the percentage of loss of products during the purification process is very minimal.

5-Reaction is a single-stage four-component condensation, so no intermediate isolation is needed, thus saving time, cost, and energy.

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