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Original Research Article

# Nano $CeO_2$ as a new green and recyclable catalyst for the synthesis of 2-aryl Benzoxazole

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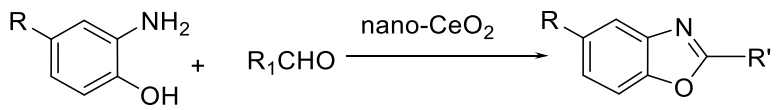
**ABSTRACT**

2-Aryl benzoxazole derivatives have been reported to have a wide range of biological and pharmacological activities. Some of these derivatives have anticoagulant, antispasmodic, diuretic, anti-cancer and anti-anaphylactin properties. In this research, a simple method for the synthesis of high-efficiency 2-aryl benzoxazole through the reaction of aminophenols and aldehyde derivatives under solvent-free conditions in the presence of a catalytic amount of nano-$CeO_2$ is presented. The results revealed that this synthetic reaction is very simple and benzoxazole derivatives produced with good yields compared to other studies. Mild conditions, high speed and short reaction time, simplicity of product separation process, high efficiency and purity of synthesized derivatives are the advantages of the proposed method. As shown in Table 5, the highest efficiency (95%) in a short time (15 min) was obtained in this study, which is very important compared to other previous methods presented.



## Graphical Abstract

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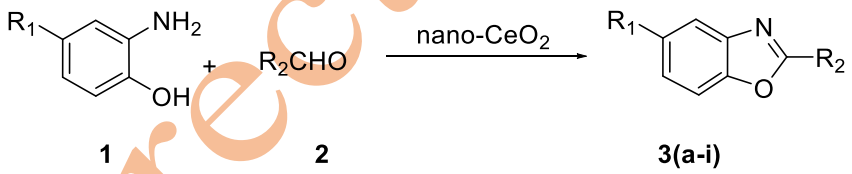
## Introduction

Benz-fused azoles are an important group of organic molecules and are important heterocyclic scaffolds common in biologically active and pharmaceutically active compounds [1]. Benzoxazoles are present in a variety of natural products and are very important in the discovery of drugs [2]. Benzoxazoles are utilized as HIV protease inhibitors [3], partial 5-HT3 receptor agonists [4], HT uptake inhibitors [5], thrombin inhibitors [6], COX inhibitors [7], virus antagonists, and siotmagalu yansanibe virus protease inhibitors [8].

2-Aryl benzoxazoles are important biaryl drugs and have various biological activities including antitumor and antimicrobial properties [9]. For instance, recently 2-aryl benzoxazole JI9561, isolated from Streptomyces extract and acts as a cytotoxic metabolite [10]. 2-Aryl benzoxazoles are also used in industry as vulcanization accelerators, antioxidants and as narcotics in light emitting organic electroluminescence apparatus [11, 12]. Several methods have been developed for the synthesis of 2-aryl benzoxazoles. The most common method for the synthesis of 2-aryl benzoxazoles is the reaction between a carboxylic acid or benzoyl chloride or aldehyde and aminophenol [13–16].

However, most of these methods involve the use of harsh conditions, expensive reagents, long reaction times, and difficult purification methods. As a result, there is a need to devise new methods for the synthesis of these compounds under more appropriate conditions. In our effort to develop new catalytic systems, in this study, we presented a suitable and efficient protocol for the preparation of 2-aryl benzoxazoles through the reaction of aldehydes and aminophenols in the presence of a catalytic amount of nano-$CeO_2$ in solvent-free conditions (Scheme 1). In this research, nano-$CeO_2$ catalyst has been used for the synthesis of benzoxazole compounds and also compared to other articles, the reaction has been done in a shorter time and higher efficiency.




**Scheme 1.** Synthesis of 2-arylbenzoxazole derivatives

In recent years, nanoparticles due to the amazing properties that have shown themselves in various industries such as textile, defense and security industries, medical fields, separation and filtration industries, chemical industries, paint and coating industries, oil industries and industries aerospace, the automotive industry has received a lot of attention. Nanoparticles are materials that have at least one dimension at the nano scale. As the nanoparticle size decreases, the effective surface-to-particle volume ratio increases, the surface effects become stronger, and the catalytic properties increase. nano-$CeO_2$ has very important applications in industry, including them as a catalyst to convert harmful exhaust gases from car exhaust and convert them into less harmful gases. Another important application is in the field of production and storage of hydrogen. The main reason for these applications is the presence of oxygen vacancies on the surface of the series

that act as active sites in the reactions [17]. In this paper, we investigate the application of nano-$CeO_2$ as a catalyst in the synthesis of benzoxazole derivatives.

## Experimental

*Materials and methods*

All products were characterized by mp, IR, 1HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. $^1H$ and $^{13}C$NMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 and 125 MHZ, respectively, with $CDCl_3$ as a solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

*Preparation of Nano-$CeO_2$*

Nano-oxide powder was prepared 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, the mixture was then stirred for 30 min, after which $NH_3$ (0.5 mol) was added to aqueous solution until a gel form was formed at a pH of about 8.5.The resulting synthetic gel was then washed with distilled water and dried at 80 °C for 24 hours. The gel was dried and calcinated at 700 °C for two hours. The scanning electron microscope (SEM, SU-70, Hitachi) and transmission electron microscope (TEM, TF 20 Tecnai G2 200 kV FEI) images of the catalyst are demonstrated in Figure 1 and 2 [18].

The XRD pattern of the samples were carried out to identify crystalline phases and to estimate the crystalline sizes. Figure 3 demonstrates the XRD morphology of $CeO_2$ nanoparticles calcined at 1000 °C for 3 h. The exhibited picks correspond to the (111), (200), (220), (311), (222), (400), (331) and (420) of a cubic fluorite structure of $CeO_2$ identified using the standard data [18].

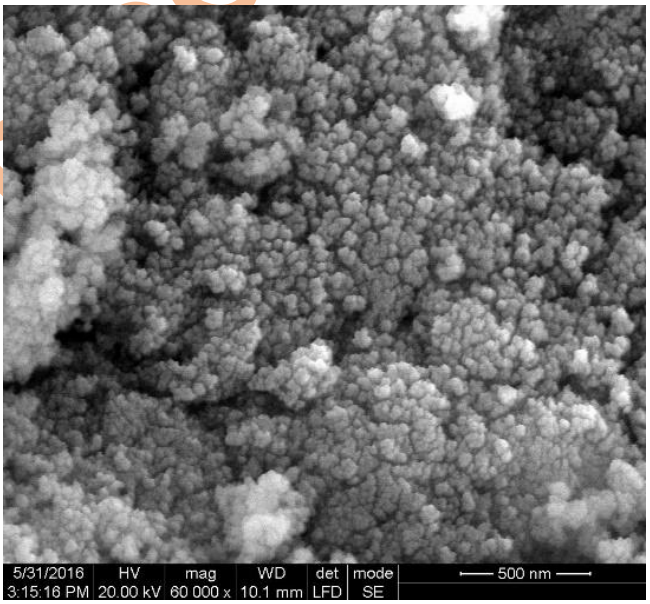



**Figure 1.** SEM spectra of nano $CeO_2$

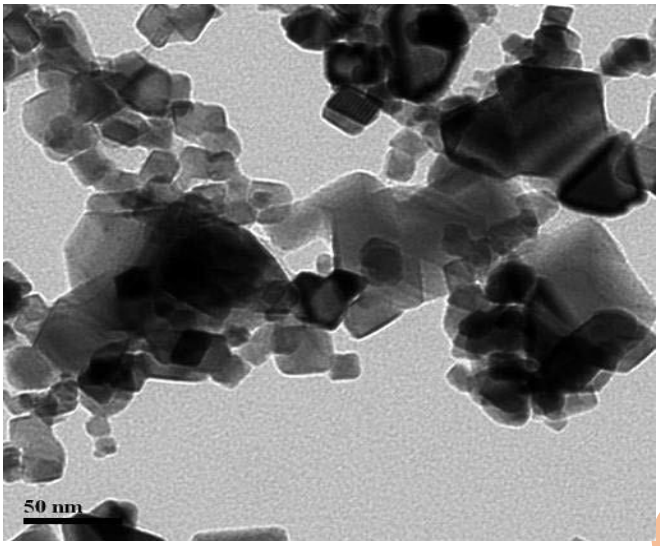



**Figure 2.** TEM spectra of nano $CeO_2$

*Typical procedure for preparation of 2-arylbenzoxazole derivatives*

A mixture of o-aminophenol (1 mmol), aldehydes (1 mmol) and Nano-$CeO_2$ (0.05 g) was heated at 90 °C for the indicated time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloromethane (3×10 mL) then, the reaction mixture was chromatographed over PTLC using petroleum ether-ethyl acetate (4:1) to afford the pure product.

***2-nphenyl benzoxazol (3a):*** mp 103 °C (lit [19]. mp 102 °C), IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3062, 1625, 1563, 1462, 1451, 1333, 1242, and 1042. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 8.2–8.4 (m, 2H), 7.3–7.9 (m, 7H).

***2-(p-tolyl) benzoxazol (3b):*** mp 113–115 °C (lit [19]. mp 113–114 °C), IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3057, 1632, 1546, 1457, 1242 and 1054, $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 8.07–8.41 (m, 2H), 7.09–7.63 (m, 6H), 2.47 (s, 3H).

## Results and Discussion

To optimize the amount of catalyst, the effect of solvent and temperature, reaction of o-aminophenol (1 mmol) with aldehydes (1 mmol) in the presence of a catalytic amount nano-$CeO_2$ was selected as the model reaction. After optimizing the reaction conditions, different aldehydes, both with electron donating and electron withdrawing groups were investigated for the present protocol. It can be clearly seen from data that, all reactions proceeded were performed well and also produced the corresponding products in good yields and in very short reaction times (Table 1).

In other words, we accomplished effects of varied solvents on the synthesis of **3a**. This reaction was performed in presence of different solvents. For instance, water, chloroform, Ethanol, dichloromethane and solvent-free were used. It is evident from data that, the best yields were achieved in Solvent-free condition (Table 2).

To optimize the amount of catalyst, various amounts (0.01, 0.02, 0.03, 0.05, and 0.08 g) of cerium oxide nano-catalyst were used. The results presented in the Table 3 revealed that 0.05 g of cerium oxide nano-catalyst had the best efficiency (Table 3).

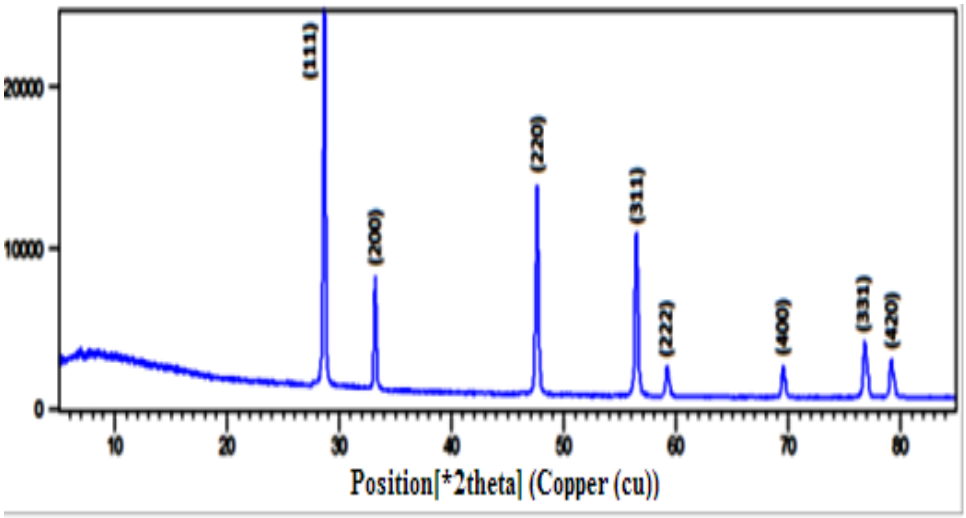



**Figure 3.** XRD spectra of nano $CeO_2$

**Table 1**. Synthesis of 2-arylbenzoxazoles catalyzed by nano-$ZrO_2$

| Entry | R1 | R2 | Product | Time (min) | Yield(%)[a] |
|---|---|---|---|---|---|
| 1 | H | H | 3a | 15 | 95 |
| 2 | H | $CH_3$ | 3b | 15 | 90 |
| 3 | H | Cl | 3c | 15 | 97 |
| 4 | $CH_3$ | H | 3d | 15 | 98 |
| 5 | $CH_3$ | $CH_3$ | 3e | 15 | 92 |
| 6 | $CH_3$ | Cl | 3f | 15 | 97 |
| 7 | Cl | H | 3g | 15 | 92 |
| 8 | Cl | $CH_3$ | 3h | 15 | 93 |
| 9 | Cl | Cl | 3i | 15 | 97 |

[a]Yields of isolated products

**Table 2.** Synthesis of **3a** in the presence of different solvents using nano $CeO_2$ as a catalyst

| Entry | Solvent | Yield(%)[a] |
|---|---|---|
| 1 | DMF | 92 |
| 2 | $C_2H_5OH$ | 87 |
| 3 | $CH_3CN$ | 85 |
| 4 | $CHCl_3$ | 71 |
| 5 | Solvent-free | 95 |
| 6 | water | 91 |

[a]Yields of isolated products

**Table 3.** Comparison of amount of catalysts for the synthesis of **3a**

| Entry | Solvent | Yield (%)[a] |
|---|---|---|
| 1 | 0.02 g | 80 |
| 2 | 0.03 g | 89 |
| 3 | 0.05 g | 95 |
| 4 | 0.08 g | 95 |

[a]Yields of isolated products

After the reaction, 10 mL of ethyl acetate was added to the compounds on filter paper containing catalyst. The mixture was stirred at room temperature for 5 min 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, in order 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 4). As seen in the Table 4, the reaction can be performed up to five times with good efficiency by the recycled catalyst.

**Table 4.** Reuse of the nano $ZrO_2$ for synthesis of **3a**

| Entry | Run | Yield (%)[a] |
|---|---|---|
| 1 | First | 95 |
| 2 | Second | 91 |
| 3 | Third | 90 |
| 4 | Fourth | 88 |
| 5 | Fifth | 85 |

[a]Yields of isolated products

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

| Entry | Catalyst | Yield (%) | Time(h) | Reference |
|---|---|---|---|---|
| 1 | $AuCl_3$ | 66 | 6 | [20] |
| 2 | AuCl | 76 | 6 | [20] |
| 3 | $NaAuCl_4{\cdot}2H_2O$ | 88 | 6 | [20] |
| 4 | Activated carbon | 78 | 4 | [21] |
| 5 | Nano-$MnO_2$ | 78 | 16 min | [22] |
| 6 | $TiO_2/ZrO_2$ | 91 | 15 min | [23] |
| 8 | Nano-$CeO_2$ | 95 | 15min | Present study |

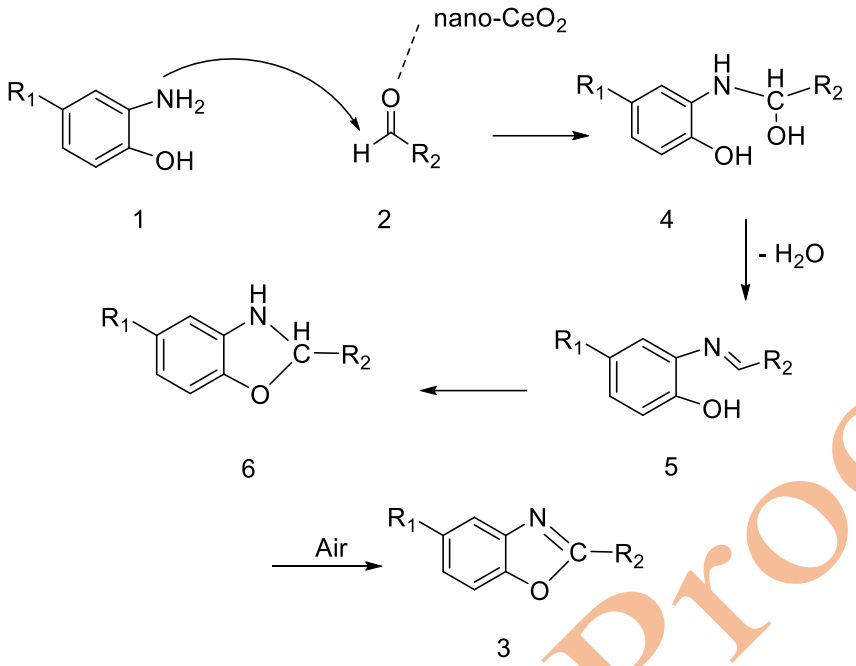
By comparing the reaction results with other methods, we find that the nano-$CeO_2$ catalyst performs the reaction in shorter time and with higher efficiency (Table 5).

The following mechanism is proposed for the synthesis of 2-aryl benzoxazole derivatives in the presence of nano-$CeO_2$ (Scheme 2).

First, the o-amino phenol attacks the catalyst-activated aldehyde, and eventually loses water, resulting in an intermediate 5. The hydroxy group then attacks the double bond and after oxidation, the desired product is obtained.

## Conclusions

In this research study, we developed a novel, simple and efficient method for the synthesis of 2-aryl benzoxazole derivatives by using nano-$CeO_2$ as a catalyst with high efficiency and short time reaction. Nano-$CeO_2$ catalysts are recyclable, heterogeneous, environmentally benign solid catalysts possessing desirable properties such as high thermal and hydrothermal stability. The target nano $CeO_2$ is prerequisite in green chemistry. There are some remarkable properties which are playing noticeable roles, such as: mildness of the conversion, simple experimental part, and also ability of compatible with various functional groups, impressive and efficient yields, short reaction times, and the easy workup procedure. Finally, these features make target procedure more attractive to synthesize a variety of these derivatives. As shown in Table 5, the highest efficiency (95%) in a short




**Scheme 2.** Mechanism of the synthesis of 2-arylbenzoxazole derivatives

time (15 min) was obtained in this study, which is very important compared to other previous methods presented. As shown in Table 3, the best efficiency (95%) was obtained in the solvent-free condition.

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## Disclosure Statement

No potential conflict of interest was reported by the authors.

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