

Research Article

Catalytic Synthesis of 3-Methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione Derivatives Using Cerium Oxide Nanoparticles as Heterogeneous Catalyst in Green Conditions

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We have developed a new methodology for the synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione derivatives in excellent yields. A new green chemistry protocol with the reusability of the nanoparticle as catalyst has been developed for the synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione derivatives via one-pot reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, arylaldehydes, and 2-hydroxynaphthalene-1,4-dione in water as green solvent and using cerium oxide nanoparticles (CONPs) as heterogeneous catalyst. The present methodology affords several advantages such as simple procedure, excellent yields, and short reaction time. The catalyst is inexpensive, stable, easily recycled, and reused for several cycles with consistent activity.

1. Introduction

Pyrazolo[3,4-*b*]quinoline derivatives are used as pharmaceutical agents [1], as inhibitors of oncogenic Ras [2], and as a dopant in the multiplayer OLED fabrication [3]. In the past several decades, three general strategies for the synthesis of pyrazolo[3,4-*b*]quinolines have been developed: (1) by the Friedlander condensation reaction of 2-aminobenzophenones and pyrazolin-5-ones [4]. Availability of 2-aminobenzophenones limits the range of applicability of this reaction; (2) by cyclization of 4-arylidene-pyrazolin-5-ones with anilines [5] or 5-*N*-arylpyrazoles with aromatic aldehydes [6]. The method is complicated and has a lower yield; (3) by a three-component one-pot reaction of aromatic aldehydes, 5-amino-3-methyl-1-phenylpyrazole, and dimedone under thermal [7] or microwave condition [8]. Nanoparticles have emerged as sustainable alternatives to conventional materials and as robust, high-surface-area heterogeneous catalyst supports. The presence of a catalyst

is mainly required by both modern organic syntheses and in fine chemical industries. Thus, the chemical nature and the existing form of the catalyst are of vital importance for the reaction. Recently, a great deal of attention has been focused on satisfying the requirements of environmentally benign and sustainable developments [8]. Consequently, there is a great demand for the discovery and development of novel catalysts with higher catalytic activities, lower prices, good recyclability, and less pollution to the environment in their catalytic systems. Cerium oxide has been extensively used in catalytic converters for automobile exhaust systems as an ultraviolet absorber and as an electrolyte for fuel cells [9–12]. Cerium-oxide based materials are famous for their redox properties, because of conversion between Ce³⁺ and Ce⁴⁺ valence states under oxidation and reduction conditions. Cerium oxide-based catalysts are widely used as effective oxidation systems due to their unique properties such as redox, oxygen release, and storage abilities. The remarkable catalytic chemistry involved with nanoceria is mainly due to

high mobility of surface oxygen vacancies [13]. This oxygen vacancy can alter electronic and valence arrangement, which fix the oxidation state. These vacancies are the reason for the altered redox chemistry of nanocerium. Oxygen vacancies are present on the surface, as Ce^{4+} atoms surround Ce^{3+} atoms [14]. Heterogeneous catalysis is a topic of great industrial importance in chemical engineering and, consequently, it plays a significant role in theoretical undergraduate courses. A heterogeneous catalytic reaction involves adsorption of reactants from a fluid phase onto a solid surface, surface reaction of adsorbed species, and desorption of products into the fluid phase. Clearly, the presence of a catalyst provides an alternative sequence of elementary steps to accomplish the desired chemical reaction from that in its absence.

2. Experimental Section

1H NMR were recorded on a Buckner AC-300F 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard with 1H resonant frequency of 300 MHz. The IR spectra were recorded on a Shimadzu model impact 400D FT-IR spectrophotometer using KBr pellets. The melting points of the products were determined by open capillaries and were uncorrected. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was affected with short-wavelength UV light (254 nm).

2.1. Catalyst Preparation. Cerium oxide nanoparticles (CONPs) used in the experiment were produced according to the reported procedure [15] with slight modification. The CeO_2 nanoparticles were synthesized by a precipitation procedure starting from a cerium (IV) nitrate $(NH_4)_2Ce(NO_3)_6$, Merck, solution with ammonia (25%, Merck) as the precipitant in the absence of any capping agent. First, 250 mL of 1.0 mol/L ammonia water in a decanter vessel was added dropwise into 50 mL of a 0.1 mol/L cerium (IV) nitrate solution, while the mixture was stirred vigorously at room temperature. Deionized and doubly distilled water was used to prepare the solutions. White $Ce(OH)_4$ particles were formed immediately. A long period of aging was needed for dehydration and further dissolution recrystallization. Finally, a light yellow CeO_2 powder was obtained. After centrifugation at 4000 r/min and washing with water and ethanol several times the product was obtained. The as-prepared samples were then dehydrated at 80–120°C for about 4–6 h. The CeO_2 nanoparticles were calcined in an oven at temperatures between 200 and 900°C for 2–4 h and then stored for further use.

2.2. Typical Procedure for Preparation of 3-Methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-dione Derivatives (4a-g). A mixture of 3-methyl-1-phenyl-1H-pyrazol-5-amine **1** (1 mmol), arylaldehydes **2** (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol), and cerium oxide nanoparticles (CONPs) catalyst (10 mol %) is stirred under reflux conditions and water as green solvent (10 mL) for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the catalyst is filtered and washed with 20 mL of water

TABLE 1: Synthesis of 3-methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-diones in appropriate times, under reflux conditions and using water as green solvent using cerium oxide nanoparticles (CONPs) catalyst.

Entry	Product	Time (h)	^a Yield (%)
1	4a	4	94.5
2	4b	4.5	88
3	4c	5	66
4	4d	6.5	89.5
5	4e	5	93
6	4f	4.5	90.5
7	4g	4.5	93

^aIsolated yield.

and/or dichloromethane. The filtrate is concentrated on a rotary evaporator. The reaction mixture is extracted with diethyl ether (10 mL). The combined organic layers are dried over anhydrous $MgSO_4$, and the solvent is evaporated to afford 3-methyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-diones, which was purified by recrystallizing from ethanol.

2.3. Spectral Data of Selected Compounds

4-(4-fluorophenyl)-3-methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-dione (4f). IR (KBr, cm^{-1}): 3398, 3023, 2935, 1675, 1509, 1485, 1366, 1307, 1275, 1119, 1073, 860, 755, 683, 518. 1H -NMR ($CDCl_3$) δ /ppm: 3.40 (2H, m), 4.86 (1H, m), 6.36 (2H, d, $J = 7.9$ Hz), 7.08 (2H, d, $J = 8.26$ Hz), 7.19 (3H, m), 7.34 (2H, d, $J = 9$ Hz), 7.39 (2H, m), 7.49 (1H, m), 7.84 (2H, d, $J = 7.95$ Hz); ^{13}C -NMR ($CDCl_3$) δ /ppm: 200.1, 146.5, 145.8, 140.5, 136.6, 133.1, 132.4, 131.2, 129.8, 129.5, 129.2, 128.9, 128.7, 128.3, 126.8, 120.6, 115.2, 114.6, 114.1, 72.5, 54.3. Calcd. mass fractions of elements, w/%, for $C_{27}H_{16}FN_3O_2$ ($Mr = 433.12$): C 74.82, N 9.69, H 3.72. Found: C 74.77, N 9.56, H 3.60. HRMS (EI) Calcd. for $C_{27}H_{16}FN_3O_2$ $[M]^+$, 433.1000, Found 433.1005.

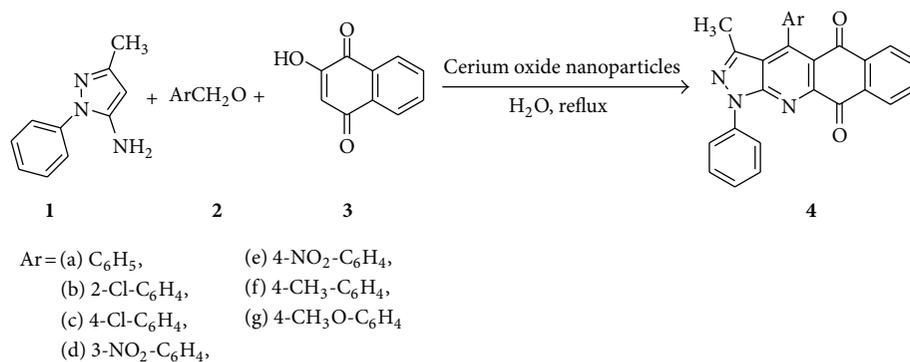
3. Results and Discussion

We report a highly efficient procedure for the preparation of 3-methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-diones using cerium oxide nanoparticles (CONPs) as an efficient heterogeneous catalyst in water (Scheme 1).

The size of the particles has been computed from the width of first peak using Debye Scherrer formula:

$$D = K \frac{\lambda}{\beta \cos \theta} \quad (1)$$

where K is constant, λ is the wavelength of X-rays, β is the full width at half maximum, and θ is the Bragg angle. The average crystallite size of cerium oxide nanoparticles (CONPs) is about 10 nm. All the particles display the uniform cubic morphology with the average particle size of about 70 nm which is in good agreement with the results deduced from the XRD and are shown in Figure 1. The BET specific



SCHEME 1: Synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones using water as solvent and cerium oxide nanoparticles (CONPs) catalyst under reflux conditions.

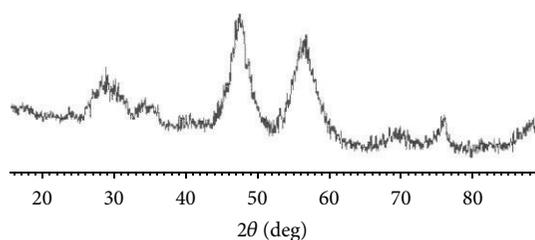


FIGURE 1: XRD pattern for the synthesized cerium oxide nanoparticles (CONPs).

surface area of cerium oxide nanoparticles (CONPs) was $92 \text{ m}^2 \text{ g}^{-1}$.

There were small particles with an average diameter of 5 nm as determined from the TEM images. Particles with eight faces forming an octahedron shape are also present. These octahedra are larger particles ranging from 15 to 100 nm in diameter and are shown in Figure 2.

The results indicate that the product consists of octahedral crystallites with smooth surfaces in the size range of 200–300 nm. In particular, cerium oxide nanoparticles (CONPs), which consist of a cerium core surrounded by an oxygen lattice. The morphologies of the typical sample were examined by scanning electron microscopy (SEM) and are shown in Figure 3.

Based on the optimized reaction conditions, a range of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones (**4**) was synthesized by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**) with arylaldehydes (**2**) and 2-hydroxynaphthalene-1,4-dione (**3**) in H₂O. The reaction proceeded at reflux temperature within 4 h in excellent yields after the addition of the cerium oxide nanoparticles (CONPs) catalyst (the results are summarized in Table 1).

To find the optimal solvent for this reaction, the synthesis of product **4a** was carried out at reflux temperature using CHCl₃, CCl₄, DMSO, THF, C₂H₅OH, H₂O, CH₂Cl₂, C₆H₆, and CH₃CN as solvents, respectively. It is shown in Table 2 that the reactions with H₂O as a solvent resulted in higher yield than other solvents and that H₂O was chosen as the solvent of this reaction.

To optimize the reaction temperature, a range of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,

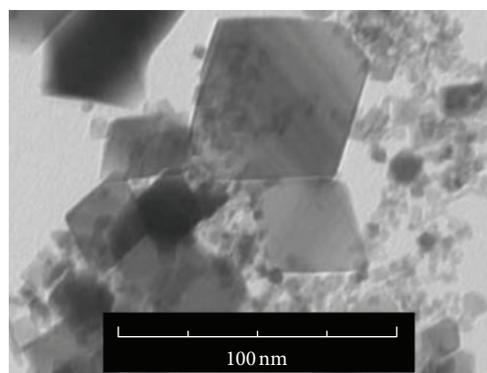


FIGURE 2: TEM image of synthesized cerium oxide nanoparticles (CONPs).

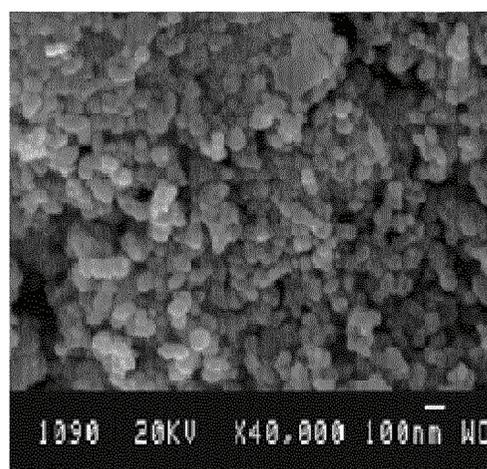


FIGURE 3: SEM images of synthesized cerium oxide nanoparticles (CONPs).

10-diones (**4**) was synthesized by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**) with arylaldehydes (**2**) and 2-hydroxynaphthalene-1,4-dione (**3**) in H₂O. The reaction was carried out in the presence of cerium oxide nanoparticles (CONPs) and the temperature varied from room temperature

TABLE 2: Solvent optimization for the synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**) under reflux conditions and using cerium oxide nanoparticles (CONPs) catalyst.

Entry	Solvent	Time (h)	^a Yield (%)
1	CHCl ₃	7.5	48
2	CCl ₄	9	45
3	DMSO	8	51.5
4	THF	7	56
5	C ₂ H ₅ OH	6	67
6	H ₂ O	4	94.5
7	CH ₂ Cl ₂	8.5	46
8	C ₆ H ₆	8	41
9	CH ₃ CN	4	75

^aIsolated yield.

TABLE 3: Temperature optimization for the synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**), in the presence of water as green solvent and using cerium oxide nanoparticles (CONPs) catalyst.

Entry	Temp (°C)	Time (h)	^a Yield (%)
1	Room (25)	12	40
2	35	9	55
3	45	8.5	64
4	65	7	73.5
5	85	6	80
6	Reflux	4	94.5

^aIsolated yield.

TABLE 4: The synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**) in the presence of reused cerium oxide nanoparticles (CONPs) under reflux conditions.

Entry	^a Yield (%)
1	94.4
2	92
3	88
4	87.5

^aIsolated yield.

(25°C) to 100°C. As shown in Table 3, the reaction at reflux temperature proceeded in highest yield. The best result was obtained by carrying out the reaction using cerium oxide nanoparticles (CONPs) catalyst at reflux temperature (Table 3). Generally the yields are lower when the reactions are carried out at temperatures lower than reflux temperature. We believe that increasing the temperature to accelerate the reaction is apparently favorable. The reaction study (Table 3) showed clearly a different time for completion of reaction. This product can be obtained with maximum of yield at 4 h in the presence of cerium oxide nanoparticles (CONPs) as an efficient heterogeneous catalyst. These results indicate that the reaction temperature plays an important role in the completion of reaction. The results indicate that there is an increase in yield with increase in reaction temperature in the

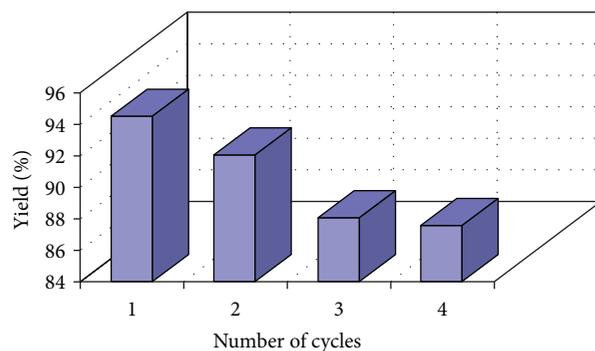


FIGURE 4: Recyclability of cerium oxide nanoparticles (CONPs) catalyst.

presence of cerium oxide nanoparticles (CONPs) catalyst. Prolonged reaction time has no effect upon the yields. Cerium oxide nanoparticles (CONPs) exhibit excellent properties as catalysts [16, 17], high temperature ceramics [18], and for the use in fuel cells. The synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**) was obtained in the presence of cerium oxide nanoparticles (CONPs) which recovered for several times. In each case, the recycled catalyst gave 100% conversion. The high surface area-to-volume ratio of cerium oxide nanoparticles (CONPs) is mainly responsible for their high catalytic activity. In this study, cerium oxide nanoparticles (CONPs) as an interesting catalyst provide a novel method for the synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**). This catalyst shows good selectivity and suitable reusable capacity which is easily separated from the reaction mixture. Cerium oxide nanoparticles (CONPs) as an efficient catalyst in the synthesis of 3-methyl-1,4-diphenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-dione (**4a**) have advantages such as selectivity, recyclability, and good yield of product because of their large specific surface area-to-volume ratio.

3.1. Recycling of Cerium Oxide Nanoparticles Catalyst. One of the advantages of the cerium oxide nanoparticles (CONPs) as the catalyst is its ability to function as a recyclable reaction medium. We were able to separate cerium oxide nanoparticles (CONPs) from the reaction medium easily by filtering the reaction mixture, washing the residue with dichloromethane and or water, and drying it under vacuum. The recovered cerium oxide nanoparticles (CONPs) can be used again for subsequent reactions [19]. In a set of experiments, we investigated the recyclability of the catalyst (Table 4). The durability of cerium oxide nanoparticles (CONPs) catalyst system was examined by condensation consecutively in four cycles (Figure 4).

4. Conclusion

In this method cerium oxide nanoparticles (CONPs) as a heterogeneous catalyst have been developed for the synthesis of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]qui-

noline-5,10-dione derivatives. We have developed a new methodology for the synthesis of 3-methyl-1-phenyl-1H-benzo[g]pyrazolo[3,4-b]quinoline-5,10-dione derivatives in excellent yields. The present methodology affords several advantages such as simple procedure and good yields. The catalyst is inexpensive, stable, easily recycled, and reused for several cycles with consistent activity. This methodology underlines the potential of using new inexpensive and efficient catalyst which offers significant improvements with regard to yield of the products, simplicity in operation, and green aspects of avoiding toxic catalyst. The simple experimental procedure, simple and highly efficient practical method, mild reaction conditions, inexpensive catalyst, and stable, easily recycled, and excellent yields are the advantages of the present method. The catalyst recyclability system makes the reaction economically useful.

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