CeO\textsubscript{2}/CuO@N-GQDs@NH\textsubscript{2} nanocomposite as a reusable and efficient catalyst for the synthesis of piperidines

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**ABSTRACT**
An efficient pseudo six-component synthesis of bis-spiropiperidines is presented by one-pot condensation of formaldehyde, aromatic amine and dimedone or N,N-dimethyl-barbituric acid using CeO\textsubscript{2}/CuO@N-GQDs@NH\textsubscript{2} nanocomposite at room temperature. The catalyst has been characterized by SEM, FT-IR, XRD, EDS, TGA, BET, VSM and XPS. Atom economy, reusable catalyst, low catalyst loading, applicability to a wide range of substrates and high yields of products are some of the notable features of this method.

**INTRODUCTION**

Piperidines indicate antibacterial [1], antihistaminic [2], anticonvulsants [3], anti-AIDS [4], anticancer [5] inhibitor [6] and anti-virus activities [7]. Piperidines have been regarded as notable targets of organic synthesis. Therefore, searching for effective ways for the preparation of piperidines is a notable challenge. A number of methods have been improved for the synthesis of piperidines in the presence of catalysts such as iron(III) chloride [8], tartaric acid [9], ZrCl\textsubscript{4} [10], CH\textsubscript{3}COOH [11,12] silica supported tungstic acid (STA) [13], iron(III) trifluoroacetate [14], cerium supported on chitosan [15], Dy (III)/chitosan [16], and silica-supported copper [17]. Some of the reported methods endure drawbacks such as long reaction times, use of toxic and non-reusable catalyst and undesirable reaction conditions. Hence, to avoid these disadvantages, the finding of an effective procedure for the preparation of piperidines is still favored.

Metal oxides indicate a broad class of materials that have been researched extensively owing to their unique attributes and potential usages in various fields [18]. N-GQDs have gained intensive regard owing to the significant features containing stabilizing the antibodies [19], biological [20], drug delivery [21], photocatalysts [22], surfactants [23], bioelectronics [24], electrocatalytic [25], Li-ion battery [26], solar cells [27], photoluminescence [28,29], bioimaging properties [30], and catalytic activity [31]. Potential applications of N-graphene quantum dots were newly reviewed on the basis of theoretical and experimental studies [32-35]. Herein, we reported the use of CeO\textsubscript{2}/CuO@N-GQDs@NH\textsubscript{2} nanocomposite as an efficient catalyst for the preparation of bis-spiropiperidines by one-pot condensation of formaldehyde, aromatic amine and dimedone or N,N-dimethyl-barbituric acid at room temperature (Scheme 1).
EXPERIMENTAL SECTION
Preparation of CeO2/CuO nanoparticles:
(Ce(SO4)2.4H2O) and CuCl2.2H2O with 1:1 molar ratio were dissolved in deionized water. Afterward, an appropriate amount of aqueous sodium hydroxide solution (0.70 M) was added to the above solution until the pH value reached 10. Then, transparent solution was placed in autoclave at 120 °C for 6 h. The obtained precipitate was washed twice with methanol and dried at 60 °C for 5 h. Finally, the product was calcined at 500 °C for 2 h.

Preparation of CeO2/CuO@N-GQDs nanocomposite:
1 g citric acid was dissolved into 20 mL deionized water, and stirred to form a clear solution. After that, 0.3 mL ethylenediamine was added to the above solution and mixed to obtain a clear solution. Then, 0.1 g CeO2/CuO nanoparticles was added to the mixture. The mixture was stirred at room temperature within 5 minutes. Then, the solution was transferred into a 50 mL Teflon lined stainless autoclave. The sealed autoclave was heated to 180 °C for 9 h in an electric oven. Finally, as-prepared nanostructured CeO2/CuO@N-GQDs was obtained, washed several times with deionized water and ethanol, and then dried in an oven until constant weight was achieved.

Preparation of CeO2/CuO@N-GQDs@NH2 nanocomposite: 1 g of CeO2/CuO@N-GQDs nanocomposite was added to the solution of 3-aminopropytriethoxysilane (2 mmol, 0.44 g) in dry toluene (20 mL) and refluxed for 24 h. After completing the reaction, the aminated CeO2/CuO@N-GQDs were separated by a centrifuge, washed with double-distilled water and anhydrous ethanol, and dried at 80 °C for 8 h to give the surface bound amino group CeO2/CuO@N-GQDs@NH2.

General procedure for the preparation of bis-spiropiperidines:
A mixture of formaldehyde (3 mmol), dimedone or N,N-dimethyl-barbituric (2 mmol) aniline derivatives (1 mmol) and CeO2/CuO@N-GQDs@NH2 nanocomposites (4 mg) in ethanol (10 mL) was stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, the catalyst was insoluble in ethyl acetate and it could therefore be recycled by a simple filtration. Water was added, and the precipitate was collected by filtration and washed with water. The crude product was recrystallized or washed with ethanol to give the pure product.

15-(4-Chloro phenyl)-3,3,11,11-tetramethyl-15-azadispiro [5.1.5.3]hexadecane-1,5,9,13-tetrone (4a): White solid, mp 216–218 °C. IR (KBr, ν max /cm⁻¹): 2963, 2925, 2864, 2832, 2796, 1727, 1736, 1705, 1694, 1595, 1496, 1342, 1248, 824, 674, 515. 1H NMR (400 MHz, CDCl3); δ 1.04 (s, 12H, CH3), 2.52 (s, 2H, CH2), 2.64 (d, J = 12.0 Hz, 4H, NH2, CH2).
COCH₃), 2.85 (d, J = 12.0 Hz, 4H, COCH₃), 3.44 (s, 4H, NCH₂), 7.05 (d, J = 8.4 Hz, 2H, Ar–H), 7.26 (d, J = 8.4 Hz, 2H, Ar–H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 28.5, 28.6, 30.8, 32.3, 51.3, 54.9, 65.6, 120.2, 126.4, 129.1, 150.3, 205.9 ppm. Anal. Calcd for C₂₅H₃₀ClNO₄: C, 67.63; H, 6.81; N, 3.15. Found: C, 67.72; H, 6.85; N, 3.24.

15-(4-Bromo phenyl)-3,3,11,11-tetramethyl-15-azadispiro [5.1.5.3]hexadecane-1,5,9,13-tetrone (4b): Yellow solid, mp 200–202 ºC. IR (KBr, ν max /cm⁻¹): 2965, 2938, 1726, 1705, 1693, 1493, 1245, 1223, 1146, 1075, 824, 662, 510. ¹H NMR (400 MHz, CDCl₃) δ 1.05 (s, 6H, CH₃), 1.06 (s, 6H, CH₃), 2.53 (s, 2H, CH₂), 2.68 (d, J = 13.6 Hz, 4H, COCH₂), 2.85 (d, J = 13.6 Hz, 4H, COCH₂), 3.46 (s, 4H, NCH₂), 7.02 (d, J = 7.2 Hz, 2H, Ar–H), 7.34 (d, J = 7.2 Hz, 2H, Ar–H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 28.4, 28.5, 30.6, 32.3, 51.4, 54.7, 65.5, 120.6, 127.3, 128.3, 151.6, 205.7 ppm. Anal. Calcd for C₂₅H₂₉BrNO₄: C, 66.15; H, 6.78; N, 6.24. Found: C, 66.2, H, 6.12; N, 6.27.

15-(4-Nitro phenyl)-3,3,11,11-tetramethyl-15-azadispiro [5.1.5.3]hexadecane-1,5,9,13-tetrone (4f): White solid, mp 198–200 ºC; IR (KBr, ν max /cm⁻¹): 2950, 2932, 1721, 1706, 1535, 1447, 1256, 1223, 990, 765, 668. ¹H NMR (400 MHz, CDCl₃) δ 1.04 (12H, s, CH₃), 2.05 (2H, s, CH₂), 2.44 (2H, s, CH₂), 2.69 (4H, d, J = 13.8 Hz, COCH₂), 2.87 (4H, d, J = 13.8 Hz, COCH₂), 3.52 (4H, s, NCH₂), 7.28 (2H, d, J = 8.0 Hz, ArH), 7.49 (2H, d, J = 8.0 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 20.7, 28.5, 28.6, 30.9, 32.3, 51.3, 54.8, 65.5, 118.7, 119.8, 124.6, 130.5, 132.9, 150.7, 205.9 ppm. Anal. Calcd for C₂₅H₂₉NO₄: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.79; H, 7.94; N, 3.25.

RESULTS AND DISCUSSION

We prepared CeO₂/CuO nanoparticles by easy techniques. A hydrothermal way was used for the preparation of N-GQDs [36]. Aminofunctionalized graphene quantum dots were prepared using 3-aminopropyltriethoxysilane. XRD pattern of CeO₂/CuO, and CeO₂/CuO@N-GQDs@NH₂ nanocomposite showed the formation of uniform morphology of the nanocatalyst, the SEM images prepared using 3-aminopropyltriethoxysilane. The XRD pattern confirms the presence of both CuO (JCPDS No.89-2529) and CeO₂ (JCPDS No 34-0394).

In order to consider the particle size and morphology of the nanocatalyst, the SEM images of CeO₂/CuO and CeO₂/CuO@N-GQDs@NH₂ nanocomposite were provided; Fig. 2. The SEM images of the CeO₂/CuO@N-GQDs@NH₂ nanocomposite showed the formation of uniform particles, and the energy-dispersive X-ray spectrum (EDS) confirmed the presence of Ce, Cu, O, N and C species in the structure of the nanocomposite (Fig. 3).

Magnetic properties of nanocomposites before
Fig. 1. XRD pattern of (a) CeO$_2$/CuO, and (b) CeO$_2$/CuO@N-GQDs@NH$_2$

Fig. 2. SEM images of (a) CeO$_2$/CuO, and (b) CeO$_2$/CuO@N-GQDs@NH$_2$

Fig. 3. EDS spectra of (a) CeO$_2$/CuO, and (b) CeO$_2$/CuO@N-GQDs@NH$_2$
and after their being decorated with N-GQDs were tested by vibrating-sample magnetometer (VSM) (Fig. 4). The lower magnetism of the as-synthesized CeO₂/CuO@N-GQDs@NH₂ compared to the CeO₂/CuO nanocomposite was ascribed to the antiferromagnetic behavior of N-GQDs as a dopant.

FT-IR spectra of CeO₂/CuO, CeO₂/CuO@N-GQDs and CeO₂/CuO@N-GQDs@NH₂ nanocomposite are indicated in Fig. 5. The absorption peak at 3300 cm⁻¹ is related to the stretching vibrational absorptions of OH. The peaks at 509, 663 cm⁻¹ corresponded to Cu-O and Ce-O, respectively. The characteristic peaks at 3400 cm⁻¹ (O-H stretching vibration), 1660 cm⁻¹ (C=O stretching vibration), and 1101 cm⁻¹ (C-O-C stretching vibration) appear in the spectrum of Figure 5b. The peak at approximately 1475-1580 cm⁻¹ is attributed to C=C bonds. The peaks at 1560 and 3350 cm⁻¹ are related to the bending and stretching vibrational absorptions of N-H, respectively (Fig 5c).

The BET specific surface area of CeO₂/CuO and CeO₂/CuO@N-GQDs@NH₂ nanocomposites was measured by the nitrogen gas adsorption-desorption isotherms (Fig. 6). Based on the results, the BET specific surface area of CeO₂/CuO was improved from 1.72 to 9.82 m²/g after modification with N-GQDs, therefore, more active sites were introduced on CeO₂/CuO@N-GQDs@NH₂ surface.

Thermogravimetric analysis (TGA) considers
the thermal stability of the CeO₂/CuO@N-GQDs@NH₂ nanocomposites (Fig. 7). These nanoparticles show suitable thermal stability without a significant decrease in weight. The weight loss (2.14%) at temperatures below 200 °C is due to the removal of physically adsorbed solvent and surface hydroxyl groups. The curve displays a weight loss about 12.98% from 200 to 600 °C that is attributed to the oxidation, degradation of N-GQD and decomposition of the organic spacer grafting to the N-GQD surface.

X-ray photoelectron spectroscopy (XPS) analysis of CeO₂/CuO@N-GQDs@NH₂ nanocomposite is shown in Figure 8. In the wide-scan spectrum of nanocatalyst, the predominant components are Cu 2p (940-970 eV), Ce 3d (883.8 eV), O 1s (530.6 eV), N 1s (400 eV), and C 1s (286.3 eV).

At first, we investigated three-component reaction of formaldehyde, 4-methylaniline and dimedone as a model reaction. The model reactions were performed by pTSA, BF₃·SiO₂, ZrOCl₂, Et₃N, CeO₂/CuO, CeO₂/CuO@N-GQDs and CeO₂/CuO@N-GQDs@NH₂ nanocomposite. The best results were gained in EtOH and we found the convincing results in the presence of CeO₂/CuO@N-GQDs@NH₂ nanocomposite (4 mg) at room temperature (Table 1).

To investigate the scope and limitation of this catalytic process, formaldehyde, aromatic amines and dimedone or N, N-dimethyl-barbituric acid were chosen as substrates (Table 2). Investigations of the reaction scope revealed that various aromatic amines (bearing electron-withdrawing and electron-donating groups) can be utilized in this protocol.
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Fig. 8. X-ray photoelectron spectroscopy (XPS) analysis of CeO2/CuO@N-GQDs@NH2 nanocomposite

Table 1. Optimization of the reaction conditions using different catalysts a

<table>
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<tr>
<th>Entry</th>
<th>Catalyst (amount)</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield %</th>
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<tr>
<td>1</td>
<td>none</td>
<td>EtOH</td>
<td>400</td>
<td>NR</td>
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<td>2</td>
<td>pTSA (4 mol%)</td>
<td>EtOH</td>
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<tr>
<td>3</td>
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<td>350</td>
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<td>4</td>
<td>ZrOCl2 (5 mol%)</td>
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<td>400</td>
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<td>60</td>
<td>93</td>
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<tr>
<td>13</td>
<td>CeO2/CuO@N-GQDs@NH nanocomposite (4 mg)</td>
<td>CH3CN</td>
<td>95</td>
<td>82</td>
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a Isolated yield

Table 2. Synthesis of bis-spiropiperidines using CeO2/CuO@N-GQDs@NH2 a

<table>
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<th>Entry</th>
<th>R</th>
<th>di carbonyl compound</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield %</th>
<th>m.p °C (Found)</th>
<th>m.p °C [ref]</th>
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<tr>
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<td>4-Cl</td>
<td>dimedone 4a</td>
<td>4a</td>
<td>60</td>
<td>88</td>
<td>216-218</td>
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<td>2</td>
<td>4-Br</td>
<td>dimedone 4b</td>
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<td>224-226</td>
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<td>dimedone 4d</td>
<td>4d</td>
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<td>85</td>
<td>187-189</td>
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<td>5</td>
<td>2,3-dichloro</td>
<td>dimedone 4e</td>
<td>4e</td>
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<td>85</td>
<td>250-252</td>
<td>—</td>
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<tr>
<td>6</td>
<td>4-CH3</td>
<td>dimedone 4f</td>
<td>4f</td>
<td>120</td>
<td>93</td>
<td>198-200</td>
<td>199-201 [15]</td>
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<td>N,N-dimethyl-barbituric acid 5a</td>
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<td>11</td>
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<td>140</td>
<td>90</td>
<td>247-249</td>
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</table>

a Isolated yield


31
The reusability of the CeO₂/CuO@N-GQDs@NH₂ nanocomposite catalyst was examined for the model reaction and it was found that the product yields decreased to a small extent on each reuse (run 1, 93%; run 2, 93%; run 3, 92%; run 4, 92%; run 5, 91%, run 6, 91%).

A plausible mechanism for the preparation of bis-spiropiperidines is shown in Scheme 2. The spirocyclization looks to proceed as a domino sequence of Knoevenagel, Michael, and double Mannich reactions. The well-known reaction of dimeredone with formaldehyde leads to the formation of the standard dimeredone–formaldehyde adducts. In cycle, this undergoes two consecutive Mannich reactions with aniline to produce the spiro-piperidine. The amino groups distributed on the surface of CeO₂/CuO@N-GQDs activate the C=O and C≡N groups through hydrogen bonding [37-40].

CONCLUSION

We have reported an efficient method for the synthesis of bis-spiropiperidines using CeO₂/CuO@N-GQDs@NH₂ nanocomposite as a superior catalyst at room temperature. The new catalyst is characterized by SEM, FT-IR XRD, EDS, TGA, BET, VSM and XPS. The current method provides obvious positive points containing environmental friendliness, reusability of the catalyst, low catalyst loading and simple experimental.

ACKNOWLEDGEMENT

The authors are grateful to University of Kashan for supporting this work by Grant NO: 159196/XXX.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES


