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Increased catalytic activity through ZnMo₇O₂₄/g-C₃N₄ heterostructured assemblies for greener indole condensation reaction at room temperature

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As an economical conjugated polymer, graphitic carbon nitride (g-C₃N₄) has recently attracted much attention due to its exciting chemical and thermal stability and easy availability. Herein, we constructed a metal-coordinated graphitic carbon nitride (M-g-C₃N₄) catalyst through simple impregnation and calcination methods and used it as a new heterogeneous catalyst for the efficient synthesis of bis (indolyl) methanes and trisindolines under mild conditions. This reaction is performed efficiently in water as an environmentally friendly solvent at ambient conditions. The ZnMo₇O₂₄/g-C₃N₄ nanocomposite was synthesized by a simple method by immobilizing Mo₇O₂₄(NH₄)₆·4H₂O and ZnCl₂ on the surface of g-C₃N₄ under hydrothermal conditions. It was characterized by FT-IR, EDS, and electronic scanning microscopy (SEM). The metal doping of Mo and Zn on the surface of graphitic carbon nitride leads to the formation of a green catalyst that gives good to excellent yields of products in short reaction times with an easy working procedure. In addition, the ZnMo₇O₂₄/g-C₃N₄ catalyst could be reused at least five runs without apparent loss of efficiency.

The indole derivatives are important nitrogen-containing compounds due to their diverse pharmacological activities^{1,2}. The indole alkaloids^{3,4}, from lysergic⁵ acid to vincristine⁶ are one of the largest classes of alkaloids⁷, and they possess extended biological activity and drug discovery⁸. Among various reactions of indole^{9,10}, the condensation reactions of indole with electron-deficient carbonyl compounds for the preparation of bis (indolyl) methanes and trisindolines has attracted and continues to attract interest in recent years^{11,12}. In this context, various articles have focused on the preparation of target compounds employing homo and heterogeneous catalysts such as acidic ionic liquid immobilized on silica¹³, LiClO₄¹⁴, silica sulfuric acid¹⁵, magnetic metal-organic framework¹⁶, graphene¹⁷, Protic solvents¹⁸ and heteropoly acids¹⁹. Although these methods have some advantages, most have fundamental weaknesses, such as harsh reaction conditions, volatile organic solvents, toxic reagents and solvents, limited substrate scope, expensive reagents, and catalyst overload. In recent years, the literature has also documented various green protocols, such as organocatalyst^{20,21}, ionic liquids²², deep eutectic solvents²³, ultrasounds²⁴, and Taurine²⁵ for the efficient synthesis of indole derivatives.

Carbon nanomaterials have become a new research hotspot in sensors, drug delivery, photocatalysis, and energy-saving^{26,27}. Graphite carbon nitrides (g-C₃N₄) as a fascinating conjugated polymer constructed from two-dimensional sheets with outstanding potential for catalytic and optoelectronic applications. Its physicochemical properties, such as resistance to acidic or basic media, extended chemical, and thermal stability, fascinating electronic properties, and unique structure, have elicited interdisciplinary research fascination^{28,29}. g-C₃N₄ consists of earth-abundant carbon and nitrogen elements with a high degree of density and is the most stable allotrope of carbon nitrides in the ambient atmosphere³⁰. It has rich surface properties due to its many nitrogen coordination sites suitable for catalytic applications^{31–34}. In addition, many free amino groups on the C₃N₄ backbone make these compounds rich in electron lone pairs easily bound to metal ions²⁵, doping g-C₃N₄ with metal and nonmetal ions showed significant improvement in their catalytic activity^{35–37}. Furthermore, graphitic carbon nitride can easily be obtained under solid-state conditions without organic solvents^{38,39} from inexpensive materials such as melamine or urea derivatives⁴⁰.

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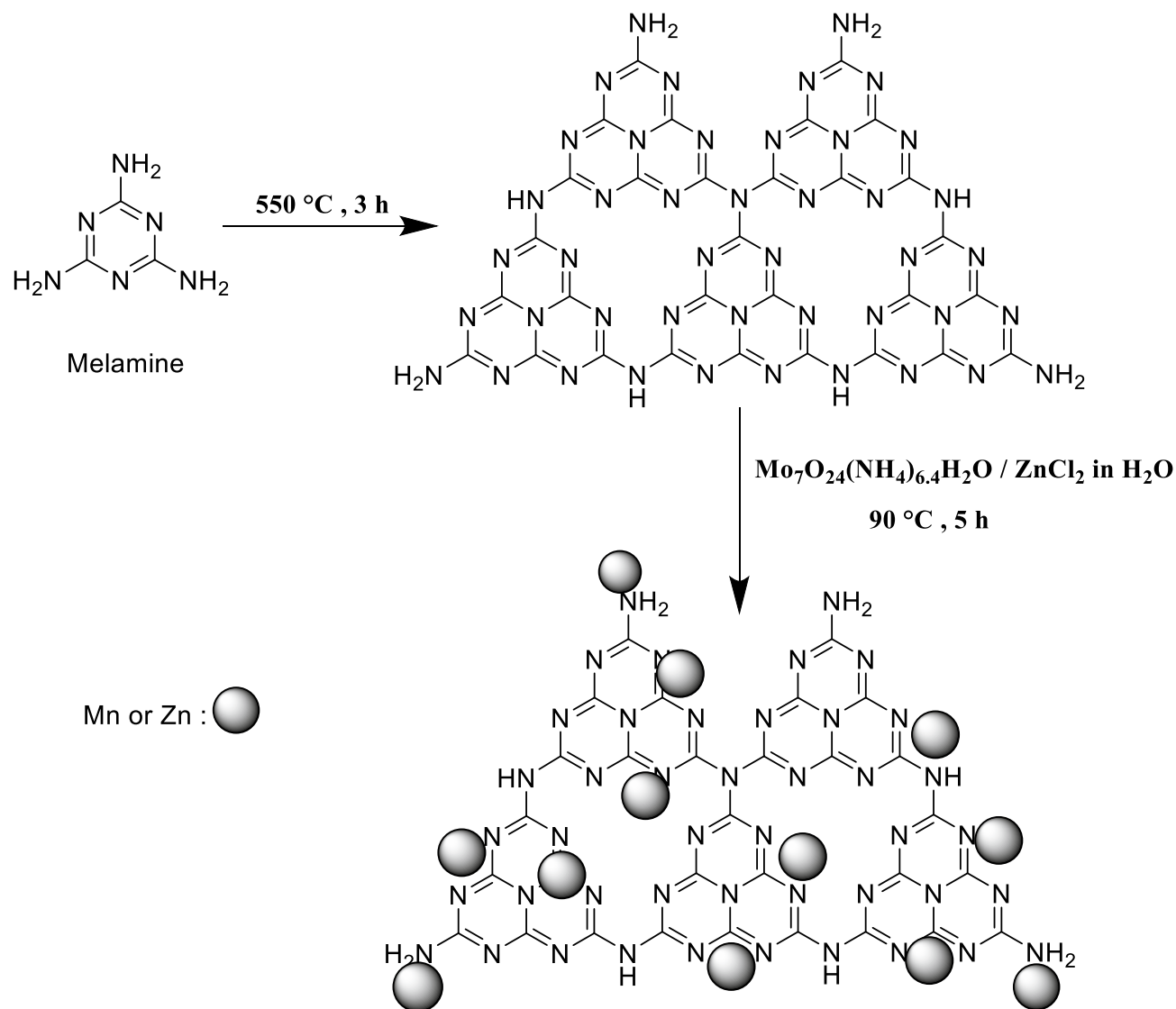


Figure 1. Synthesis of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$.

In continuation of our research by using green solvents and catalysts in organic transformations^{41,42} herein, we have reported a simple, mild, and general method for synthesizing indole derivatives in water in the presence of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ as a new separable and inexpensive heterogeneous composite.

Experimental

General. All chemicals, such as aldehydes, indole, ketones, isatin, $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, and ZnCl_2 were commercially available and used without further purifications. Solvents were purchased from commercial sources and distilled before use. The Buchi Melting point M-535 is used to determine melting temperatures.

Preparation of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$. The bulk $\text{g-C}_3\text{N}_4$ was prepared by thermal polymerization of melamine according to the reported procedure³⁸. In detail, 20 g of melamine in 150 mL crucible is heated to 550 °C with a heating rate of 5 °C min^{-1} and kept at 550 °C for 3 h in an air atmosphere. The resultant light yellow agglomerates were ground by an agate mortar for the next steps. The $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ composites were prepared by a facile chemical method. 0.5 g of $\text{g-C}_3\text{N}_4$ was dispersed in 50 mL deionized water using a stirrer for 10 min at room temperature. In the next step, 0.2 g of $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$ was dispersed in 20 mL of deionized water under stirring. In another flask, 0.2 g of ZnCl_2 was added to 20 mL of deionized water and dissolved by magnetic stirring. Then, $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$ and ZnCl_2 solutions were added to the $\text{g-C}_3\text{N}_4$ suspension, and a magnetic stirrer was used to stir the reaction mixture for 5 h at 90 °C. After completion of the reaction, the solvent was removed in a vacuum by rotary evaporator and was dried at room temperature for 12 h, and Blue-green powder $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ catalysts were obtained (Fig. 1).

General procedure for the synthesis of bis-indoles. Indole (1.0 mmol), aldehyde (0.5 mmol), and $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ (15 mg) in deionized water (1.0 mL) were stirred well using a magnetic stirrer, and TLC

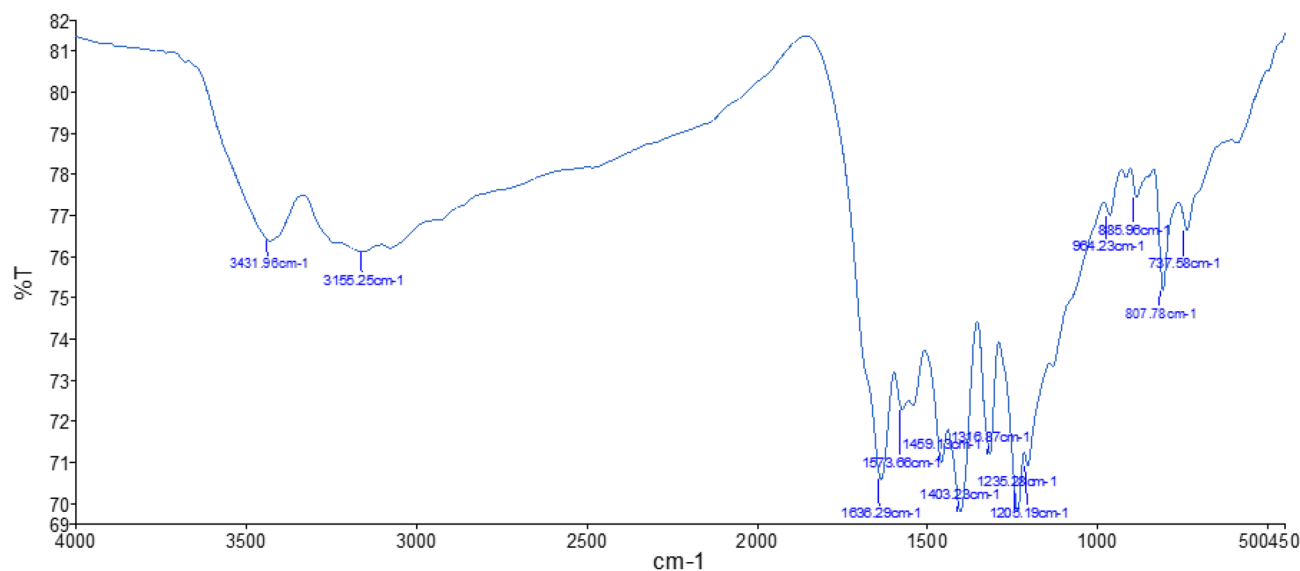


Figure 2. FT-IR spectra of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$.

assessed the progress of the reaction until the reaction completion. Then, ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture and centrifuged. The organic phase was removed under reduced pressure, and the crude product was purified by recrystallization in ethanol, ethyl acetate, or column chromatography to afford the corresponding products. All products were known and identified by melting point.

General procedure for the synthesis of trisindolines. A mixture of indole (1.0 mmol), isatin (0.5 mmol), and $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ (30 mg) in deionized water (1.0 mL) conditions was stirred at room temperature, and TLC tracked the reaction progress. After completion, the reaction mixture was diluted with water and ethyl acetate and centrifuged to give the crude product after evaporation of ethyl acetate. The crude product was purified by silica gel column chromatography or recrystallized in ethanol or ethyl acetate to afford the corresponding pure trisindolines (Supplementary Information).

Results and discussion

The co-condensation procedure was used to synthesize pure $\text{g-C}_3\text{N}_4$. The $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ nanocomposite was synthesized by immobilizing $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$ and ZnCl_2 on the surface of $\text{g-C}_3\text{N}_4$. The morphology and structure of nanocomposite were thoroughly characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FT-IR).

FTIR analysis was further carried out to identify the functional groups, and the results are shown in Fig. 2. The absorption peak at $3000\text{--}3500\text{ cm}^{-1}$ is related to the stretching vibration of NH and NH_2 groups in the $\text{g-C}_3\text{N}_4$ or adsorb water from the environment. The prominent characteristic peaks in the area 1636 , 1573 , 1403 , 1317 , and 1235 cm^{-1} represent the stretching vibrations of s-triazine or tri-s-triazine of $\text{g-C}_3\text{N}_4$ in the sample. Besides, the strong absorption peak at 807 cm^{-1} is the bending vibration of the s-triazine rings system.

The typical SEM microscopy analysis is presented in Fig. 3 to investigate the new nanocomposite's morphology. The SEM spectrum of the $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ catalyst indicates a series of thin sheets with wrinkles and irregular folding structures on the surface of $\text{g-C}_3\text{N}_4$.

The energy dispersive spectroscopy (EDS) technique is used for the qualitative analysis of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$. This pattern showed the Mo, Zn, and Cl elements are identified beside the C and N elements. As shown in Fig. 4, adopting Mo and Zn nanoparticles onto the $\text{g-C}_3\text{N}_4$ was efficacious. Also, the spectrum reveals that the scattering of these nanoparticles on the $\text{g-C}_3\text{N}_4$ substrates is uniform and acceptable.

After preparation and characterization of the $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ composite, the catalytic activity of the composite was evaluated in the preparation of bis(indolyl) methanes via the reaction 2-methylindole (1.0 mmol) and aldehyde (0.5 mmol) in the presence of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ as a catalyst in deionized water (1.0 mL) to optimize reaction parameters (Table 1). The greener synthesis of bis(indolyl) methanes was carried out in a 5 mL three-necked round flask equipped with a magnetic stirrer, and the mixture was vigorously stirred at room temperature.

The first finding indicated that the synthesis of bis(indolyl) methanes in the presence of the $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ (15 mg) in deionized water (1.0 mL) was accomplished within 120 min with quantitative yields. (Table 1, entry 3). First, the amount of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ on the model reaction was optimized, and the results are shown in Table 1. The maximum yields of 95% were obtained when the loaded amount of composite was 15 mg (Table 1, entry 3). As the loaded amounts of composite increased to 20 mg, the reaction yields did not increase (Table 1, entry 4). While the amount of composite is reduced to 5 and 10 mg, increased reaction time was needed to achieve the optimal results (Table 1, entries 1–2). Furthermore, composite elements such as $\text{g-C}_3\text{N}_4$ (Table 1, entry 14) and $\text{ZnMo}_7\text{O}_{24}$ (Table 1, entry 12) $\text{Na}_2\text{Mo}_7\text{O}_{24}$ (Table 1, entry 11) ZnCl_2 (Table 1, entry 13) gave reduced yields. The model reaction was performed in different polar and nonpolar solvents (Table 1, entries 5–10) to

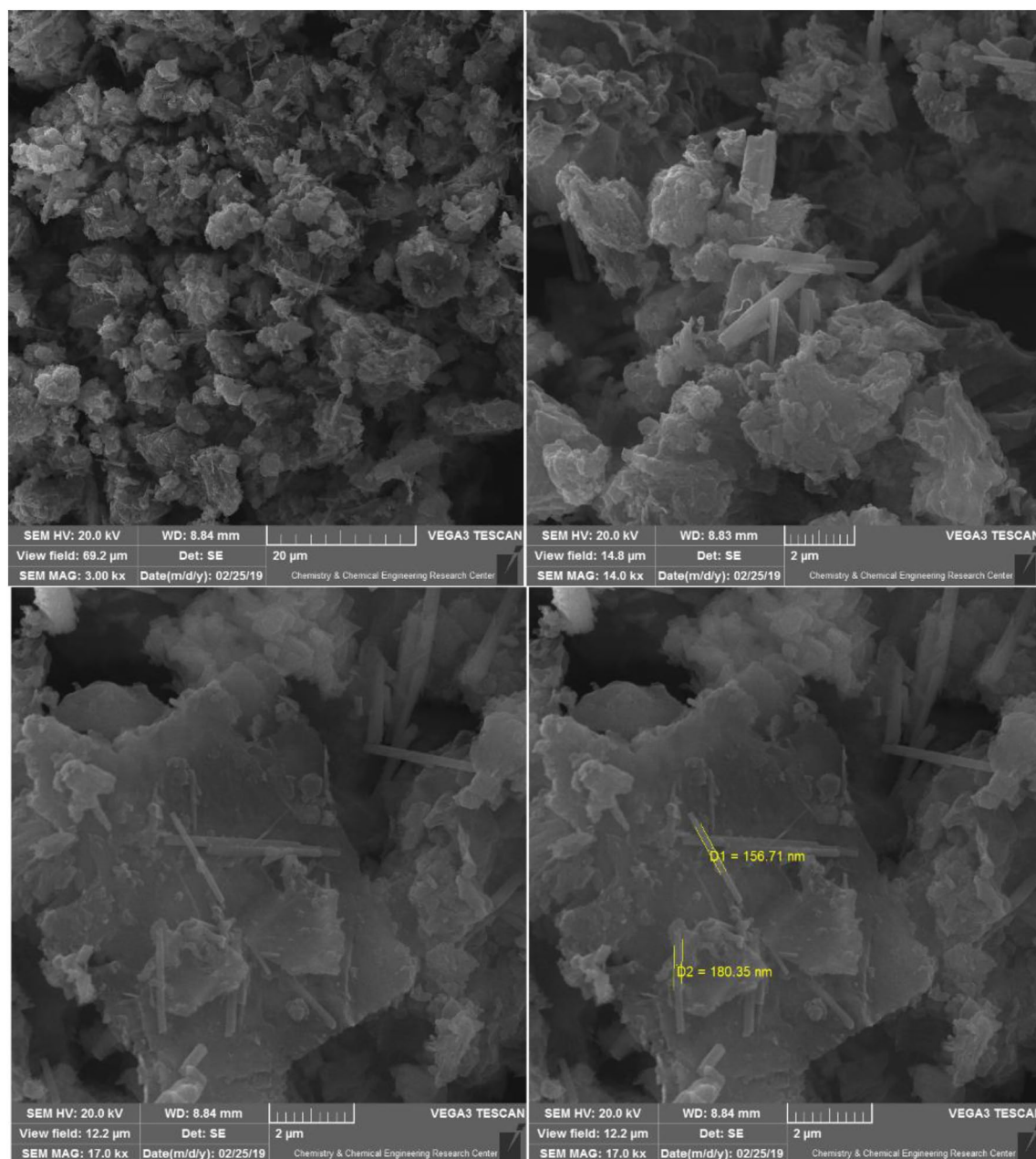


Figure 3. SEM images of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$.

optimize reaction conditions. The model reaction in organic solvents such as ethanol, dimethylformamide, and tetrahydrofuran in the presence of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ (15 mg) formed the expected product in lower yield.

The general nature of the procedure was confirmed by using structurally various aromatic and aliphatic aldehydes bearing electron-withdrawing and electron-donating substituents in the reaction with indole derivatives under the optimized conditions (Table 2). As seen in Table 2, different electron-donating or electron-withdrawing groups in the benzaldehyde ring proceeded well with 2-methylindole or indol, which gives good to excellent yields under short reaction times. It is necessary to mention that no remarkable reactivity differences were observed. In other words, the aromatic aldehydes with the electron-donating groups increased the yield slightly. They gave well to excellent results, while electron-withdrawing benzaldehyde derivatives did not reduce the reactivity. As an exception, the interaction of 2-hydroxy benzaldehyde and 2-methylindole yielded a lower yield (70%) than the other aldehydes. In addition, cyclohexanone generated the corresponding product in only a moderate yield under identical reaction conditions.

The heterocyclic spirooxindole skeleton, such as isatin containing core structure, has different biological activities and can function as synthons for naturally occurring alkaloids and pharmaceutically important drug molecules^{15,16}. Encouraged by this success, we extended this reaction of substituted isatin with indole derivatives to obtain trisindoline compounds with $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ as the catalyst (Fig. 5). Initially, indole (1.0 mmol) and isatin (0.5 mmol) reacted in the presence of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ as a catalyst in deionized water (1.0 mL). The

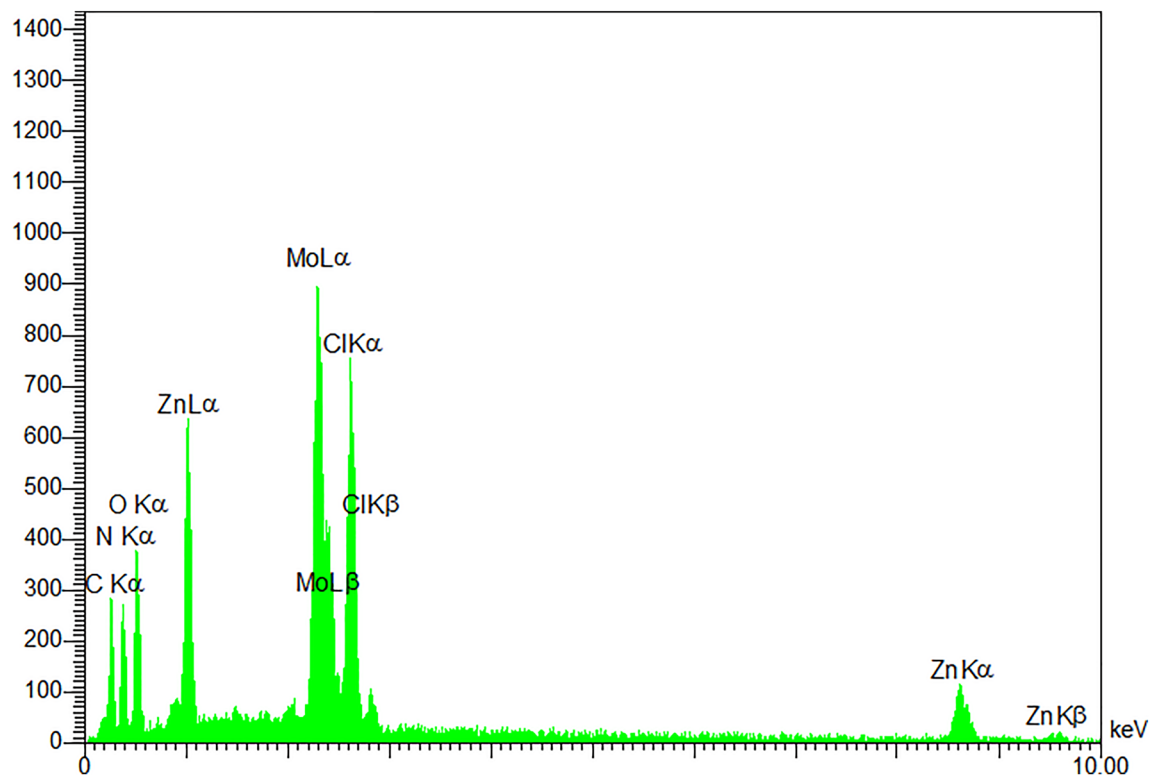
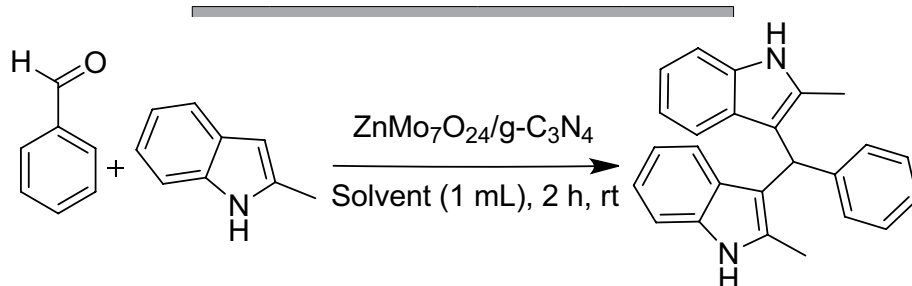
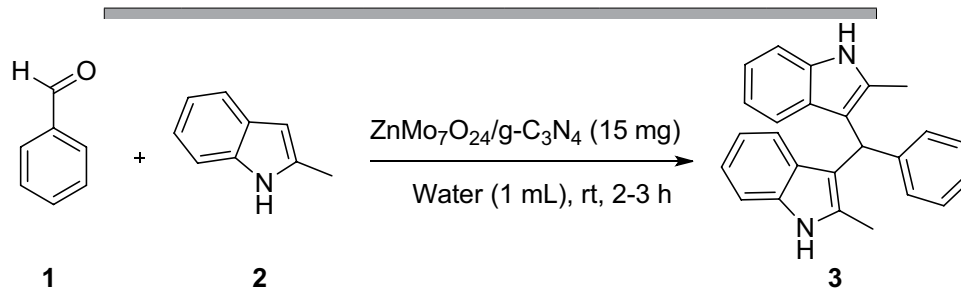


Figure 4. EDS spectrum of $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$.



Entry	$\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ (mg)	Solvents (1 mL)	Yields (%) ^a
1	5	Water	67
2	10	Water	86
3	15	Water	95
4	20	Water	95
5	15	Ethanol	84
6	15	DMF	76
7	15	THF	72
8	15	Toluene	45
9	15	Ethyl acetate	44
10	15	CH_3CN	56
11 ^b	15	Water	32
12 ^c	15	Water	75
13 ^d	15	Water	57
14 ^e	15	Water	–
15 ^f	–	Water	–

Table 1. Optimization of the synthesis of bis(indolyl) methanes. ^aIsolated yields. ^b $\text{Na}_2\text{Mo}_7\text{O}_{24}$. ^c $\text{ZnMo}_7\text{O}_{24}$ as a catalyst. ^d ZnCl_2 catalyst. ^e $\text{g-C}_3\text{N}_4$ as a catalyst. ^fWithout catalyst.



Entry	Aldehydes (R-CHO)	Indole	Products	M.P. (°C)	Yields (%) ^a
1	C ₆ H ₅ -	2-Methylindole	3a	120–121 118–120 ¹³	95
2	C ₆ H ₅ -	1-Methylindole	3b	182–184 181–183 ¹³	96
3	3-OMe-C ₆ H ₄	2-Methylindole	3c	237–239 236–238 ¹⁵	93
4	4-Cl-C ₆ H ₄	2-Methylindole	3d	229–230 228–230 ¹⁴	90
5	4-Me-C ₆ H ₄	2-Methylindole	3e	217–218 217–219 ¹⁴	95
6	4-OMe-C ₆ H ₄	2-Methylindole	3f	194–195 194–196 ¹⁴	79
7	2,4-Cl-C ₆ H ₃	1-Methylindole	3 g	136–138 210–212 ¹⁴	94
8	Thiophene-2-	1-Methylindole	3 h	147–149 148–150 ¹⁹	89
9	4-NO ₂ -C ₆ H ₄	2-Methylindole	3i	238–241 240–242 ¹⁹	91
10	C ₆ H ₅ -	Indole	3j	52–53 52–53 ¹⁷	95
11	4-Me-C ₆ H ₄	Indole	3 k	219–221 220–221 ¹⁷	95
12	3-NO ₂ -C ₆ H ₄	Indole	3 l	214–216 216–218 ¹⁹	85
13	2,4-Cl-C ₆ H ₃	Indole	3 m	103–105 103–106 ¹⁸	94
14	4-CO ₂ Me-C ₆ H ₄	Indole	3n	219–221 219–221 ¹⁹	91
15	Cyclohexanone	Indole	3o	184–186 184–187 ¹⁴	73

Table 2. The synthesis of bis (indolyl) methanes using ZnMo₇O₂₄/g-C₃N₄ as the catalyst. ^aIsolated yields.

results showed that 30 mg of catalyst at room temperature provided the optimum yield (92%) for the corresponding trisindoline within 180 min. The reaction of isatins and different indoles containing electron-donating and electron-withdrawing group substituent on nitrogen proceeded smoothly with good to excellent yields in 2.5–4 h.

Figure 6 shows the possible catalytic pathway for the ZnMo₇O₂₄/g-C₃N₄ catalyzed the synthesis of trisindoline. A Zn or Mo Lewis acid coordinates to carbonyl groups of Isatin 4, and the nucleophilic attack of indole 2 to activated carbonyls 4 creates the zwitterionic species 6. The resulting intermediate 6 undergoes dehydration to provide the coordinated intermediate 7, which can be captured by the second addition of indole 2 to furnish target product 5. We proposed porous graphitic carbon nitride (g-C₃N₄)-stabilized ZnMo₇O₂₄ materials as in protic solvents leading to highly organodispersible and colloidal stable carbon nitrides as bifunctional Lewis acid composite for condensation reaction.

An imperative topic for implementing a heterogeneous composite is its recovery and reusability. The ZnMo₇O₂₄/g-C₃N₄ catalyst could be separated by centrifugation after each run. To show the recyclability of the ZnMo₇O₂₄/g-C₃N₄, the composite was recycled five times, and the results are shown in Fig. 7. Figure 4 shows the corresponding yields of the reused composite for a 5a, which demonstrates that the catalytic activity of ZnMo₇O₂₄/g-C₃N₄ did not significantly decrease after being used five times. After the reaction completion, ethyl acetate was added, and the reaction mixture was centrifuged and dried under a vacuum, and used for the next cycle. The SEM and FTIR images of the reused composite after 5 cycles did not change the nanocomposite morphology.

Conclusion

In this study, we have reported a simple and efficient method for the synthesis of bis (indolyl) methanes and trisindolines derivatives using a novel heterogeneous catalyst, Mo₇O₂₄(NH₄)₆·4H₂O and ZnCl₂ supported on graphitic carbon nitride (g-C₃N₄). The outstanding features of this catalyst were good to excellent yield, short reaction times, simple separation, and easy work-up. The g-C₃N₄ is considered an inexpensive and high surface area support for synthesizing bis (indolyl) methanes and trisindolines derivatives. Also, the ZnMo₇O₂₄/g-C₃N₄ showed high stability and reusability over several reaction sets without significant catalytic activity and selectivity loss.

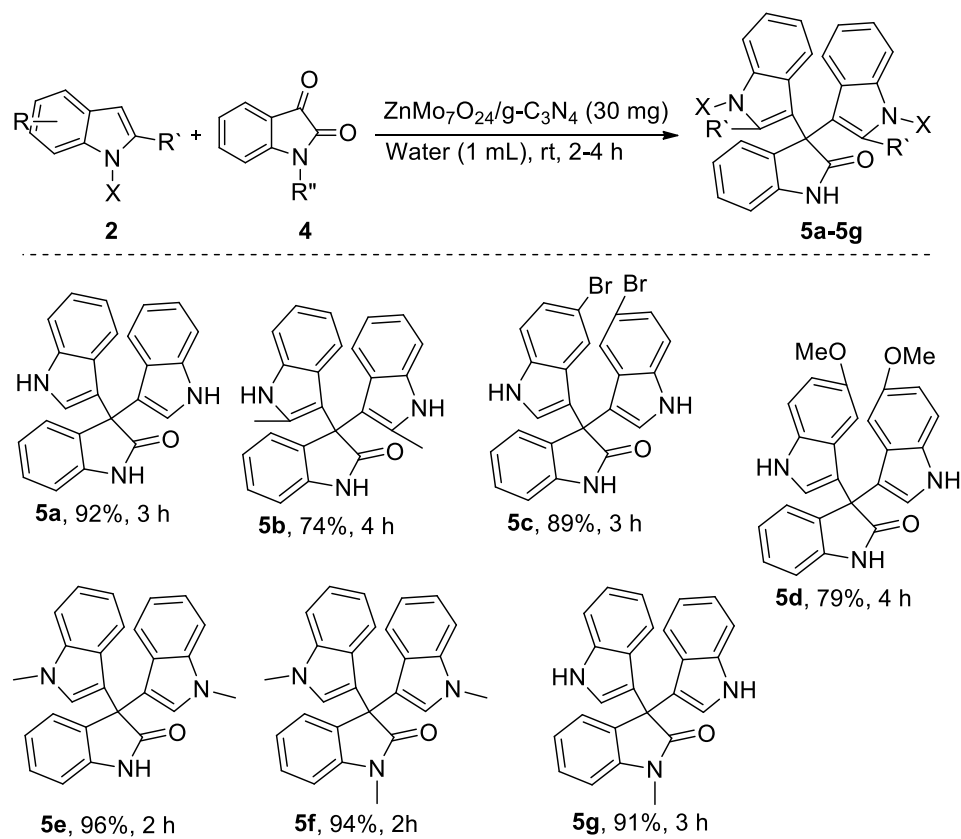


Figure 5. The synthesis of trisindoline using $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$ as the catalyst.

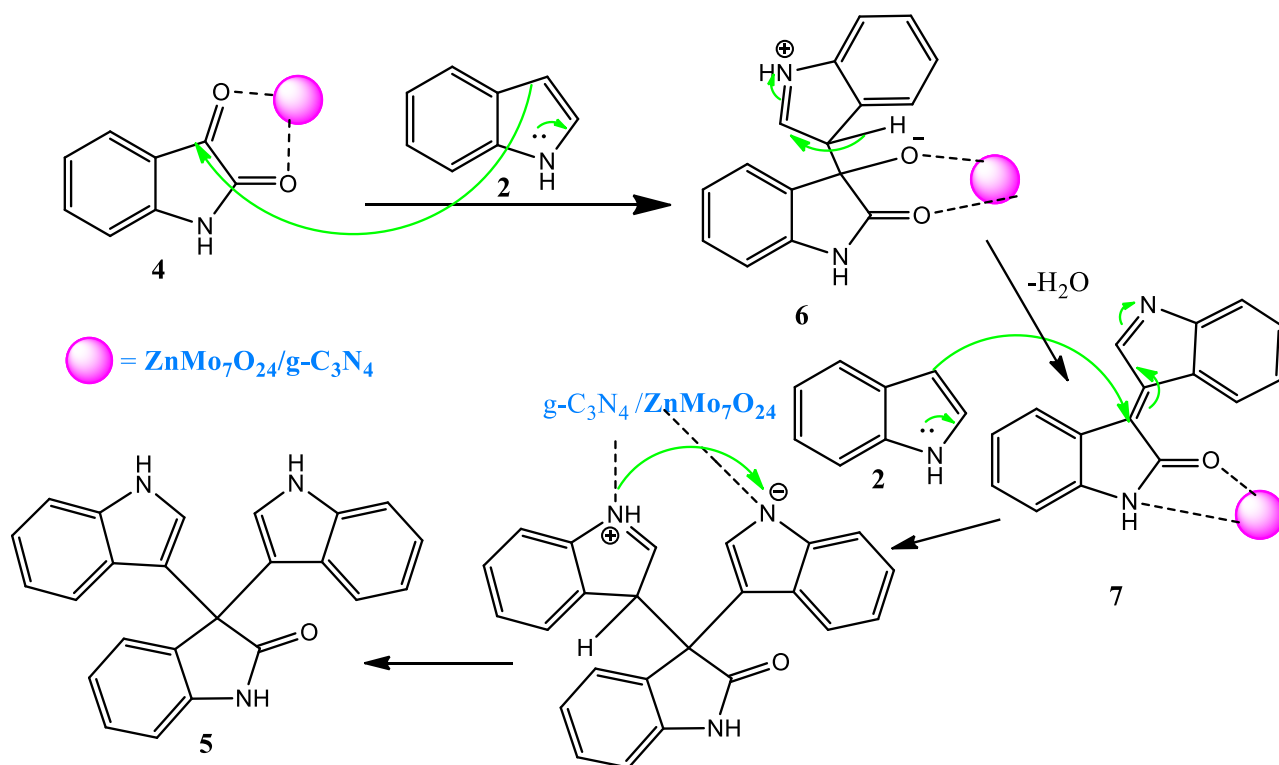


Figure 6. The possible reaction mechanism between isatin and indole for the synthesis of trisindoline catalyzed by $\text{ZnMo}_7\text{O}_{24}/\text{g-C}_3\text{N}_4$.

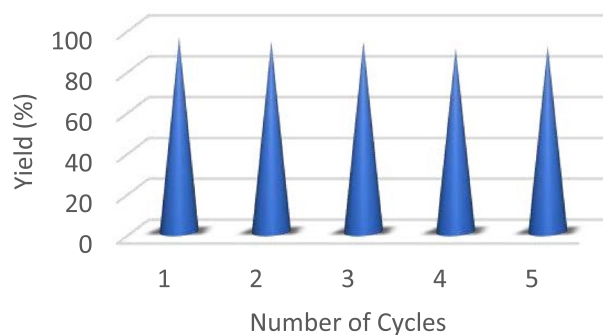


Figure 7. Recycling results of the ZnMo₇O₂₄/g-C₃N₄ for the synthesis of trisindoline.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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Competing interests

The authors declare no competing interests.

Additional information

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