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Green Synthesis of Benzimidazoles: Sustainable Graphene Oxide Catalyst for Bioactive Compound Design and Drug Discovery

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Abstract

We report a novel and eco-friendly method for synthesizing a series of benzimidazoles using 1,3,5-Tris(2-hydroxyethyl) isocyanurate-Cu(II) functionalized magnetic graphene oxide (MGO-THEIC-CuII) as a catalyst under microwave irradiation in ethanol. The newly synthesized compounds were thoroughly characterized by IR and NMR spectroscopy. Furthermore, their biological activities were assessed through antimicrobial activity and Brine-Shrimp lethality assays. The results demonstrate the efficacy and versatility of the developed green synthesis approach, which could have significant implications in the design of bioactive compounds. These findings open new avenues for the development of sustainable and efficient methodologies in drug discovery and related fields.

Keywords: Benzimidazole, Graphene Oxide, Biological Activity

INTRODUCTION.

Catalysts play a crucial role in driving green synthesis, and both homogeneous and heterogeneous catalysis have made significant contributions to societal progress. Heterogeneous catalysis[1], in particular, stands out as the preferred choice for large-scale industrial processes, especially those utilizing continuous flow systems.

This preference arises from its user-friendly nature, resilience and reduced susceptibility to common environmental factors like moisture and air. Heterogeneous catalysts, exemplified by carbocatalysts have garnered attention due to their cost-effectiveness and widespread availability. They have demonstrated efficacy in facilitating oxidative aromatization and the production of heteroaromatic compounds. A noteworthy newcomer in the realm of organic synthesis is graphene oxide (GO), a versatile carbocatalyst. GO, possessing a two-dimensional structure, boasts an abundance of oxygen-containing groups, making

its synthesis, functionalization, and chemical assembly more straightforward compared to its counterpart, graphene. The unique hydrophilic groups present in GO, allow it to easily disperse in liquid states, enabling chemical reactions and functional modifications. GO finds applications across diverse fields such as energy storage, advanced catalysis, sensing technology and environmental remediation[2]. The significance of N-heterocycles is evident across natural products, pharmaceuticals and synthetic materials which

covalently linked to polymers through esterification process[3]. Establishing efficient methodologies for crafting diverse N-heterocyclic derivatives remains a prominent goal in organic chemistry. Benzimidazoles, a subgroup of N-heterocycles, holds special importance due to their wide array of biological activities and material utility[4]. The synthesis of these compounds, particularly polycyclic benzimidazole derivatives, has garnered significant attention for its relevance in medicinal chemistry and organic material exploration.

Benzimidazole derivatives[5] serve as critical building blocks in pharmaceutical development, finding application in various therapeutic areas encompassing antiviral, anticancer, and antioxidant agents. Despite the existing approaches, challenges like extended reaction times and suboptimal yields persist. Consequently, there is a pressing need for the introduction of an efficient heterogeneous catalyst with excellent recyclability[6]. Parallel efforts have also focused on providing timely updates in the dynamic field of organic synthesis.

Varma's pioneering work in microwave-assisted organic synthesis (MAOS) using solid catalysts, exemplified by the 1,3,5-tris(2-hydroxyethyl)isocyanurate-Cu(II) functionalized magnetic graphene (MGO-THEIC-CuII) catalyst, has opened exciting avenues. This catalyst, distinguished by its high efficiency and reusability, has enabled the microwave-assisted synthesis[7,8] of benzimidazole derivatives, showcasing its potential in organic transformations

Our Lab and reagents Setup

We got all the chemicals we needed from Merck and Aldrich, the ones you can buy in stores. We didn't do anything special to them except for benzaldehyde, which we distilled ourselves right before using it. To look at the molecules, we used a machine called a Shimadzu FT-IR-8400S, which gives us cool pictures called infrared spectra. And when we wanted to see how things were separating, we used these thin plates covered in a special material called silica gel, kind of like when you draw on a wet surface. We made sure we really knew what we were working with by comparing the data we got from the IR and NMR pictures to what's already known in science from other samples or books

Modified Hummer Method for Preparation of GO

To prepare graphene oxide (GO), we started with natural graphite powders of extremely high purity (> 99.95%). The method we used was a modified version of the famous Hummer's method, which involves oxidizing graphite flakes. Here's how we did it: We took a 250mL flask and added 23mL of H_2SO_4 into it. We made sure to cool it down and then started stirring it. Next, we added 1g of graphite powder and 0.5g of $NaNO_3$ to the flask. We mixed them vigorously under the stirring process. Gradually, we introduced 3g of $KMnO_4$ into the mixture while using sonication to aid the process. To maintain the temperature, we carefully kept it below 20°C. After that, we continued stirring the mixture at room temperature. To further treat the mixture, we diluted the suspension and stirred it at 98°C. Then, we added 12mL of 32% H_2O_2 and 2mL of 32% HCl. Once all the steps were completed, we filtered the mixture and thoroughly washed it with deionized water to get rid of any impurities. The final step was to dry the product in a vacuum drying oven at 60°C for 24 hours before we could use it. By following this procedure, we successfully obtained graphene oxide from the natural graphite powders, and it was ready for further applications.

procedure for the preparation of (MGO-THEIC-CuII)

We started by adding 100 mg of graphene oxide (GO) and 200 mg of acetic anhydride into a round-bottom flask containing 10 mL of deionized water. The mixture was then subjected to ultrasonic mixing for 1.5 hours. After that, we introduced 300 mg of 1,3,5-tris(2-hydroxyethyl) isocyanurate (THEIC) into the mixture and continued ultrasonication for 2.5 hours[9].

To separate the resulting suspension, we employed a centrifuge at 12,000 rpm for 20-30 minutes. Following this, we added 20 mL of 9.6 M HCl to the separated mixture and let it stand at 80 °C for 1 hour. The solid that formed was isolated using the centrifuge again and then washed thoroughly with deionized water to remove any excess HCl or THEIC.

The final step involved drying the black solid at 50 °C for 24 hours under ambient air[8]. This process led to the formation of two types of functionalized GO-THEIC, one with magnetic nanoparticles and the other with $Cu(OAc)_2$. These newly designed catalysts proved to be efficient in synthesizing benzimidazole derivatives.

synthesis of benzimidazole derivatives using MGO-THEIC- Cu(II) catalyst.

We mixed 1 millimole of o-phenylenediamine (compound 2) with 1 millimole of various aldehydes (compound 3) and 0.02 grams of MGO-THEIC-CuII catalyst (compound 1). We then stirred the mixture under microwave irradiation for a suitable amount of time. To check if the reaction was complete, we used thin-layer chromatography (TLC)[9].

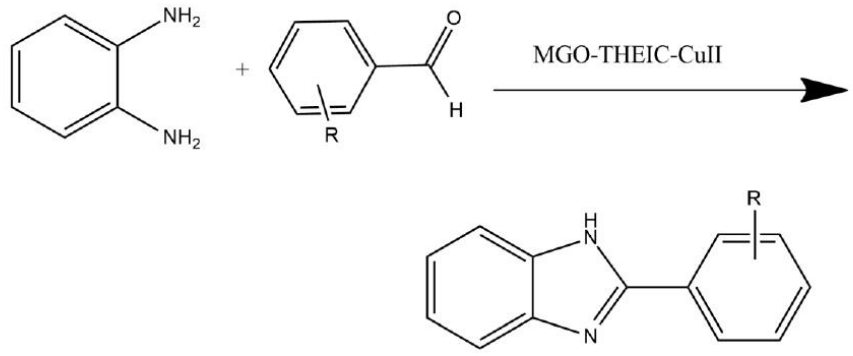
Once the TLC indicated that the reaction had finished, we dissolved the reaction mixture in hot ethanol. We then used an external magnet to recover the catalyst, which we washed, dried, and saved for reuse in subsequent reactions. The remaining mixture was recrystallized using ethanol, resulting in pure desired substituted benzimidazoles as the final product.

Results and discussion

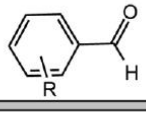
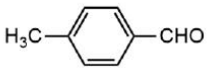
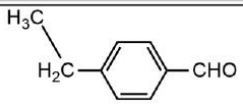
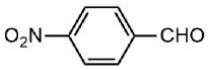
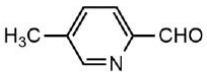
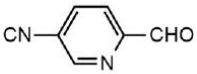
In this study, we investigated the catalytic abilities of MGO-THEIC-CuII in facilitating a two-component reaction between o-phenylenediamine and various aldehydes to efficiently synthesize substituted benzimidazoles. Our goal was to find a catalyst that could achieve a quantitative yield in a short reaction time.

To begin the experiment, we used 0.02 grams of the MGO-THEIC-CuII catalyst and carried out the reaction under microwave irradiation for different durations, ranging from 10 to 30 minutes. The reactions were carefully monitored to assess the efficiency of the catalyst in promoting the formation of substituted benzimidazoles.

The results of the experiment were promising and have been summarized in Table 1. We observed that using the MGO-THEIC-CuII catalyst led to excellent yields of the desired products, reaching a quantitative yield in the specified reaction time range. This suggests that the catalyst is highly effective in facilitating the synthesis of substituted benzimidazoles.



Synthesis By Catalytic Behaviour of GO.

S.N.		Time	%Yield
1.		15	91
2.		17	89
3.		8	98
4.		7	96
5.		5	97

Biological Activity and tests

Newly synthesized compounds were tested with purpose to check their toxicity by applying Brine-Shrimp lethality assay. Fresh eggs of Brine-Shrimp (Artemia salina), sold as a fish food, were purchased.

Antimicrobial activity assay

In our study, we conducted an antimicrobial activity test following the CLSI reference M7-A7 and M100-S16 broth microdilution methods, as previously described in our research (Ozkay et al., 2010).
For each chemical agent, we performed two readings of the minimum inhibitory concentration (MIC). To carry out the antibacterial and antimycotic assays, we dissolved the compounds in DMSO. We then prepared further dilutions of the compounds and standard drugs in the test medium at specific concentrations, ranging from 800 µg/mL to 1.5625 µg/mL, using Mueller-Hinton broth and Sabouroud dextrose broth[10].
To ensure that the DMSO solvent did not have any impact on bacteria or yeast growth, we conducted a control test. This control test involved inoculated broth supplemented with only DMSO at the same dilutions used in our experiments, and it showed no activity in the culture medium.

Brine-Shrimp lethality assay

In our study, we used a method called the Artemia salina 96-well assay to assess the cytotoxicity levels of various compounds. These compounds were prepared in a concentration range of 1.95 to 1000 µg/mL by dissolving them in DMSO.
To determine the LD50 values (the dose at which 50% of the organisms are affected) and the 95% confidence intervals for the compounds, we employed a computer program called LC50 (Version 1.5), which uses the Trimmed Spearman-Karber Method. This program allows us to analyze the data and calculate the toxicity levels accurately.

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