

1,3,5-Tris (2-hydroxyethyl) isocyanurate - Cu(II) functionalized magnetic graphene oxide (MGO-THEIC-CuII): a highly efficient and recoverable nanocatalyst for the one-pot synthesis of substituted benzimidazoles under microwave irradiation

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Abstract

In this paper, we have synthesized a series of benzimidazoles from a new, highly efficient and green method. The reaction is performed in ethanol, by using 1,3,5-Tris (2-hydroxyethyl) isocyanurate-Cu(II) functionalized magnetic graphene oxide (MGO-THEIC-CuII), which has done under microwave irradiation. All compounds have been well characterized by IR and NMR spectral data.

introduction

Catalysts are one of the main contributors to green synthesis. Homogeneous and heterogeneous catalysis made enormous contributions to the improvement of society. Both types possess several advantages, however, heterogeneous catalysis appears to be more suitable for the large scale industrial processes, which prefer continuous flow systems. Easy handling, robustness, lower sensitivity to common conditions (e.g. moisture, air etc.), longer shelf life, are the most important advantages of using heterogeneous catalysts.¹ The use of carbocatalysts is attractive owing to their low cost and high natural abundance. Carbocatalysts have been demonstrated in the oxidative aromatization and preparation of heteroaromatic compounds such as pyridine, imidazole, and pyrimidine. Recently, graphene oxide (GO) has attracted attention as a new carbocatalyst in organic synthesis. Graphene oxide (GO) is a 2D carbon material with abundant oxygen-containing groups at the edge (e.g. carboxyl) and surface defects (e.g. hydroxyl and epoxy groups). Comparing with graphene, GO is much easier to be synthesized, functionalized and chemically assembled. GO has been widely applied in multidisciplinary fields, including energy storage, advance catalysis, sensitive detectors and environmental pollutant management.² The existence of various types of hydrophilic groups allows GO to be easily exfoliated, when it is in the liquid state. These active groups can be used to induce chemical reactions and provide GO with additional functional groups after the modification, thereby increasing the flexibility and diversity of GO applications. For example, GO layers can be intercalated or cross-linked with primary aliphatic amines, amino acids, diaminoalkanes, boronates, acyl chloride, and isocyanates, or they can be covalently linked to polymers through esterification.³

N-Heterocyclic moieties are widely exist in natural products, pharmaceutical agents, and synthetic materials. Development of diverse N-heterocyclic derivatives, for efficient synthesis, is of great interest in the field of organic chemistry. Among the Nheterocycles, benzimidazoles are important

because of their broad spectrum of biological activities and interesting material applications. The synthesis of polycyclic benzimidazole derivatives has attracted much attention, as is concluded from their applications in the fields of medicinal chemistry and organic material science.⁴ Benzimidazole derivatives are really useful intermediates or subunits of the development of pharmaceutical or biological interest. Benzimidazole derivatives considered as the important class of bioactive molecules in the field of drugs and pharmaceuticals. Benzimidazole derivatives have found the application in diverse therapeutic areas including antiulcer, antihypertensive, antiviral, antifungal, anticancer, anti-histaminic, antitubercular, antiallergic, antioxidant, antimicrobial and in vitro anti-HIV-1 activities etc. A compound containing benzimidazole and benzene rings have been used extensively for pharmaceutical purposes since 1960. 1-H-Benzimidazole rings, which exhibit remarkable basic characteristics due to their nitrogen content, comprise the active substances for several drugs. A number of biological activities have been attributed to these compounds. This ring system is presented in numerous antiparasitic, anthelmintic and anti-inflammatory drugs. Moreover, some benzimidazole nucleosides, particularly 5,6-dichloro- benzimidazole-1- β - D ribofuranoside (DRB) and its 2-substituted derivatives show some activities against human cytomegalovirus. It is also recognized that 5,6-dinitrobenzimidazole can substitute 5,6-dimethylbenzimidazole into the vitamin B12 molecule in *Corynebacterium diphtheriae* and 2-trifluorobenzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. They have relationship with the DNA base purines and they are also inhibitors of photosynthesis, and some exhibit appreciable herbicidal activity. Most recently, antiprotozoal activity of substituted 2-trifluorobenzimidazoles has been reported, consistent with several earlier studies on the anti-giardial activity of various benzimidazole derivatives.⁵ Nevertheless, many of these approaches suffer from a long reaction time, low yield, acidic media, tedious work-up, and excessive use of reagents and catalysts. Therefore, introducing a new efficient heterogenous catalyst contain good recyclability is of prime importance.⁶

On the other hand, several efforts have been dedicated on providing regular updates on the ever-increasing growth of research field in organic synthesis, with a recent example, which focuses on the application of microwaves in catalysis. Varma introduced the application of solid catalysts to microwave-assisted organic synthesis (MAOS). Since then, a broad array of new heterogeneous catalytic applications has been reported and reviewed periodically. There are several advantages of using solid catalysts in MAOS in order to ensure the environmentally benign preparation of the desired products.⁴ In continuation of our ongoing efforts to develop efficient catalysts for different MCRs, we report herein the catalytic application of a 1,3,5-Tris (2-hydroxyethyl) isocyanurate-Cu(II) functionalized magnetic graphene (MGO-THEIC-CuII), as a new, highly efficient and recoverable catalyst, for the synthesis of benzimidazoles derivatives under microwave irradiation.^{7,8}

Experimental

Reagents and Apparatus

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer. Analytical TLC was performed using Merck 0.2 mm silica gel 60F-254Al-plates. All compounds were characterized by IR and NMR spectral data as compared with those obtained from authentic samples or reported in the literature.

General procedure for the preparation of the GO

Graphene oxide (GO) was prepared from natural graphite powders via a modified Hummer's method through oxidation of graphite flakes (>99.95% purity).

First, 23 mL of H₂SO₄ was added into a 250 mL flask, and then cooled followed by stirring. 1 g of graphite powder and 0.5 g of NaNO₃ were subsequently added under vigorous stirring. Then, 3 g of KMnO₄ was added gradually under sonication and the temperature of the mixture was kept below 20 °C. The mixture was stirred at room temperature. The diluted suspension was stirred at 98 °C, followed by addition of 12 mL of H₂O₂ 32% and 2 mL of HCl 32%. Finally, the mixture was filtered and washed with deionized water repeatedly to remove any impurities. The product was dried at 60 °C for 24 h in a vacuum drying oven prior to use.

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

The above GO (100 mg) and acetic anhydride (200 mg) were added into a round bottom flask charged with 10 mL deionized water. The mixture was ultrasonically mixed for 1.5 h. Then, 1,3,5-tris(2-hydroxyethyl) isocyanurate (THEIC) (300 mg) was added into a mixture and again ultrasonication for 2.5 h. Next, the obtained suspension was separated using centrifuge (12000 rpm) for 20-30 minutes and then 20 mL of HCl 9.6 M was added into the above-mentioned suspension. The resulting mixture was allowed to stand for 1 h at 80 °C. The resulting solid was isolated by using centrifuge, washed completely with deionized water to remove excess of HCl or THEIC. Finally, the black solid was dried at 50 °C for 24 h under air.⁸ The two types of functionalized GO-THEIC with magnetic nanoparticles and Cu(OAc)₂ were designed and characterized as a new and efficient catalyst for benzimidazole derivatives synthesis.

General experimental procedure for the synthesis of benzimidazoles derivatives catalysed by MGO-THEIC-Cu(II)

A mixture of o-phenylenediamine (1 mmol, **2**), various aldehyde (1 mmol, **3**), and MGO-THEIC-CuII (0.02 g, **1**) had been stirred under microwave irradiation for an appropriate period of time. After completion of the reaction as indicated by TLC, the reaction mixture had been dissolved in hot ethanol and the catalyst was recovered by external magnet, washed, dried and

then reused in successive reaction. The reaction mixture had been recrystallized with ethanol to afford pure desired substituted benzimidazoles.

Results and discussion

The catalytic ability of the MGO-THEIC-CuII was evaluated in catalyzing a two-component reaction between o-phenylenediamine, various aldehyde, for the efficient synthesis of substituted benzimidazoles. It was found that the quantitative yield can be achieved when the reaction was carried out in the presence of 0.02 g catalyst for 10-30 min under microwave irradiation. The results have been summarized in Table 1.



Table 1. Synthesis of benzimidazole derivatives in the presence of MGO-THEIC-Cu(II)

Entry	3	Time (min)	Yield (%)
1		15	89
2		10	98
3		5	96
4		5	91
5		5	100

The MGO-THEIC-CuII were easily separated with an external magnet and the recovered catalyst was reused for at least six runs without significant degradation in catalytic activity and performance.

Conclusion

In this experiment, the catalytic application of functionalized superparamagnetic graphene-oxide has been demonstrated for the synthesis of a wide range of benzimidazole derivatives. The progress of reaction had been significantly affected by catalyst loading, reaction time and

solvent. The catalyst illustrated high efficiency for synthesis of substituted benzimidazole derivatives using a variety of aldehydes and o-phenylenediamine in EtOH under microwave irradiation conditions. Therefore, the attractive features of this procedure are low catalyst loading, avoiding the use of toxic reactive reagents for modification of the catalytic activity, short reaction times, high yields, elimination of toxic organic solvents, reusability and re-activity of the catalyst and simple procedure.

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