The one-pot three component synthesis of imidazole derivatives by using of 1,3,5-Tris (2-hydroxyethyl) isocyanurate-functionalized graphene oxide as a novel and efficient nanocatalyst

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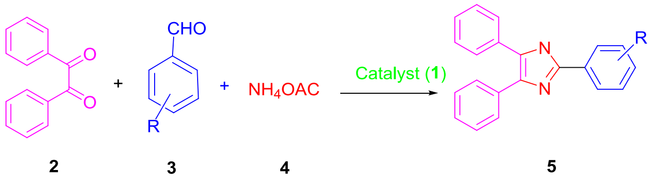
Abstract: The preparation, characterization and catalytic application of a novel 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide is described. The catalyst was characterized by nitrogen adsorption-desorption analysis, scanning electron microscopy (SEM) and Fourier transform infrared (FTIR) spectroscopy. The thermal stability of the material was also determined by thermal gravimetric analysis (TGA). The catalytic application of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide nanocatalyst was then investigated in the synthesis of imidazole derivatives from benzil, different aldehydes and ammonium acetate under solvent-free conditions in short reaction times and good to excellent yields. The significant advantages of this procedure are low loading of the catalyst, avoiding the use of toxic transition metals, short reaction times, high to excellent yields, easy separation and purification of the products and reusability of this nanocatalyst.

Keywords: Heterogeneous catalyst, Multicomponent reactions, Imidazoles, Green chemistry, Graphene oxide.

Introduction

In recent years, graphene has become a popular material, attracting attention in the fields of chemistry, physics, and materials science because of its optimal electronic, thermal, and mechanical properties. Graphene oxide (GO) is a derivative of graphene, but they have differing properties. Sheets of GO possess numerous oxygen-containing functional groups: hydroxyl and carboxyl groups are located around the edges, whereas carbonyl and epoxide groups are in the center. The existence of various types of hydrophilic groups allows GO to be easily exfoliated when it is in the wet 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 with polymers through esterification [1].

The use of heterogeneous catalysts has become highly desirable in recent years, because they incorporate many green chemistry principles [2]. On the other hand, multicomponent reactions (MCRs) offer high atom economy and bond-forming efficiency for the synthesis of diverse and complex molecules especially heterocyclic compounds in a fast and often experimentally simple procedure. The imidazole ring systems are one of the most important heterocyclic moieties found in a large number of natural products and pharmacologically active compounds. Hence, their role in biochemical processes is very significant [3-5]. In the recent years, a few methods have been described for the one-pot multicomponent synthesis of 2,4,5-trisubstituted imidazole derivatives from benzoin in the presence of different catalysts. These include graphene oxide–chitosan composite, molecular iodine, *p*-toluenesulfonic acid (PTSA), *N*-methyl-2-pyrrolidonium hydrogen sulphate, PEG-400 and 2,6-dimethylpyridinium trinitromethanide {[2,6-DMPyH]C(NO2)3}. However, there are much more catalytic methodologies starting from benzil. For example, catalysts such as KH_2PO_4, *p*-dodecylbenzenesulfonic acid (PDBSA), glyoxalic acid, L-proline, Zn-proline, $InCl_3{\cdot}3H_2O$, $KAl(SO_4)_2$, $ZnCl_2$, $FeBr_2$, $FeCl_3.6H_2O$, nano-In_2O_3, $NiCl_2.6H_2O/Al_2O_3$, $FeCl_3/SiO_2$, Wells-Dawson heteropolyacid supported on silica (WD/SiO_2), zirconium modified silica gel, ZrO_2-supported-β-cyclodextrin, and ionic liquids [2]. However, many of the reported synthetic protocols for the synthesis of imidazoles have limitations in terms of the use of excess amounts of expensive or toxic catalysts, formation of byproducts and unsatisfactory yields, lengthy reaction times, difficult work-up, unavoidable metal pollution, significant amounts of waste materials, and low selectivity.



Scheme 1 One-pot three-component reaction of benzil (**2**) and different aldehydes **3** with NH_4OAc (**4**)

Results and discussion

The catalyst was characterized with some techniques such as infrared (IR) spectroscopy, thermal gravimetric analysis (TGA), powder X-ray diffraction (PXRD), transmission electron microscopy (TEM) and scanning electron microscopy (SEM). FT-IR spectroscopy was performed for the confirmation of the formation of ester bond between GO and 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate.

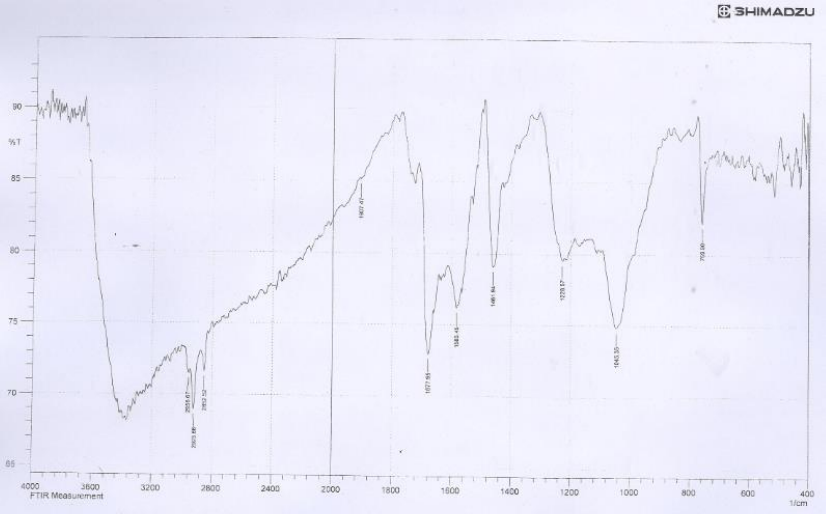


Figure 1. FT-IR of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide

To show the efficiency of the catalyst (**1**) for the synthesis of 2,4,5-trisubstituted imidazoles (**5**), the reaction of benzil (**2**, 1 mmol), 4-chlorobenzaldehyde (**3a**, 1 mmol) and ammonium acetate (**4**, 2.5 mmol) was investigated as the model reaction. The reaction conditions were optimized with regard to the best catalyst loading, different solvents and temperature for the synthesis of trisubstituted imidazole derivatives. The results have been summarized in Table **1**. It was observed that only 60% and 50% of the desired trisubstituted imidazole (**5a)** were formed in the presence of catalyst even under reflux conditions in EtOH & H_2O (Table **1**, entries 1 and 2). Moreover, using of ultrasonic and ball-milling conditions had no significant effect on the yield of the desired product (**5a**) (entries 3-4). Interestingly, the use of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide with 2 mg loading afforded the desired product (**5a**) in higher yield and shorter reaction time under solvent-free conditions compared to reflux conditions in solvent (entries 5 and 7). Increasing of amount of the catalyst had no significant influence on the yield of the desired product (**5a**) (entry 6). Therefore, optimize temperature in the model reaction was selected at 110 °C.

In order to demonstrate the scope of this protocol, the optimized reaction conditions were developed to other aromatic, heterocyclic or aliphatic aldehydes **3a-e**. The results are summarized in Table **2**. After completion of the reaction (monitored by TLC), EtOH was added and the catalyst was easily isolated from the reaction mixture by simple filtration during recrystallization of the products. As it can be seen, high to excellent yields were obtained under the optimized conditions in short reaction times for the desired products **5a-e.**

Table 1 Optimization of conditions in the reaction of benzil (**2**), 4-chlorobenzaldehyde (**3a**) and NH_4OAc under different conditions[a].

Entry	Amount of Catalysts **(1)**/mg	Solvent	Temp.(˚C)	Time (min)	Yeild[b] (%)
1	2	EtOH	Reflux	90	60
2	2	Water	Reflux	120	50
3[c]	2	-	r.t	60	Nil
4[d]	2	EtOH	r.t	120	65
5	2	Neat	110	8	94
6	5	Neat	110	8	95
7	2	Neat	100	12	85

[a] Reaction conditions: Benzil (**2**, 1 mmol), 4-Chlorobenzaldehyde (**3a**, 1 mmol), and NH_4OAc (**4**, 2.5 mmol) in the presence of 2 mg of the catalyst (**1**). [b] Isolated Yields. [C] The reaction was done in Ball-milling. [d] Under ultrasonic conditions

Table 2 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide (**1**) catalyzed one-pot three-componet synthesis of 2,4,5-trisubstituted imidazoles **5** from benzil (**2**), different aldehydes **3** with NH_4OAc (**4**) under the optimized conditions[a].

Entry	Aldehyde **3**	Product **5**	Time (min)	Yeild[b] (%)
1	4-Chlorobenzaldehyde (**3a**)	**5a**	8	94
2	4-Hydroxybenzaldehyde (**3b**)	**5b**	12	90
3	4-Methoxybenzaldehyde (**3c**)	**5c**	20	90
4	4-Nitrobenzaldehyde (**3d**)	**5d**	15	84
5	3-Nitrobenzaldehyde (**3e**)	**5e**	10	88

[a] Reaction conditions: Benzil (**2**, 1 mmol), 4-chlorobenzaldehyde (**3a**, 1 mmol), and NH_4OAc (**4**, 2.5 mmol) in the presence of 2 mg of the catalyst (**1**) under solvent-free conditions.

[b] Isolated Yields.

Experimental

General

All the solvents, chemicals and reagents were purchased from Merck, Fluka and Aldrich. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer by the method of KBr pellet.

Preparation of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide

100 mg GO and 200 mg of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate were added into a 50 mL round bottom flask charged with 10 mL deionized water. The mixture was ultrasonically mixed for 4h, and then 20 mL of HCl 9 M was then added into the abovementioned suspension. The resulting solution was allowed to stand at 80 °C for 2 h. The resulting solid was isolated by centrifugation and then washed completely with water (30 mL). Finally, it was dried at 50 °C for 24 h under air.

General procedure for synthesis of 2,4,5-trisubstituted imidazole derivatives (5a-e)

In a 5 mL round-bottomed flask, benzil (**2**, 1 mmol), aldehyde **3** (1 mmol), ammonium acetate (**4**, 2.5 mmol) and 2 mg of the catalyst (**1**) were added. The obtained mixture was stirred at 110 ˚C for times indicated in Table **2**. After completion of the reaction monitored by TLC (eluent: EtOAc: n-hexane), EtOH (3 mL) was added and the obtained mixture was heated and filtered off to separate the solid catalyst **1**. Water was added dropwise to the filtrate at 50 ˚C to give pure crystals of the desired products **5a-e** in 84–94% yields based on the starting aldehyde. The separated catalyst was suspended in EtOAc (1mL) for 30 min and the filtered. The obtained white powder was heated in an oven at 70 ˚C for 1 h and reused for successive runs.

Conclusions

We have introduced the catalytic application of a containing 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide (**1**) in the synthesis of imidazole derivatives. The reaction system was significantly affected by catalyst loading, reaction temperature and solvent. The catalyst illustrated high efficiency and reactivity for the one-pot three-component synthesis of substituted imidazole derivatives using a variety aldehydes, benzil and NH_4OAc under solvent-free conditions. In addition, the catalyst could be recovered and reused with no decrease in its activity. Therefore, the attractive features of this procedure are simple procedure, low catalyst loading, short reaction times, high yields, elimination of toxic organic solvents, simple workup, reusability of the catalyst and simple purification of the products.

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References

1. Wei. S. Hung, Chi. H. Tsou, M. D. Guzman, Q. F. An, Y. L. Liu, Y. M. Zhang, C. C. Hu, K. R. Lee, J. Y. Lai, *Chem. Mater*., 2014, **26**, 2983-2990.

2. M. G. Dekamin, E. Arefi, A. Yaghoubi, *RSC Adv.*, 2016, **6**, 86982-86988.

3. (a) V. Estevez, M. Villacampa, J. C. Menendez, *Chem. Soc. Rev.*, 2014, **43**, 4633-4657; (b) K. R. Reddy, K. Rajgopal, C. U. Maheswari, M. L. Kantam, *New J. Chem*., 2006, **30**, 1549-1552.

4. (a) S. S. K. Boominathan, C. Y. Chen, R. J. Hou, P. J. Huang, J. J. Wang, *New J. Chem*., 2015, **39**, 6914-6918; (b) E. Gopi, T. Kumar, R. F. S. Menna-Barreto, W. O. Valenca, E. N. da Silva Junior, I. N. N. Namboothiri, *Org. Biomol. Chem.*, 2015, **13**, 9862-9871.

5. (a) A. Patel, S. Y. Sharp, K. Hall, W. Lewis, M. F. G. Stevens, P. Workman, C. J. Moody, *Org. Biomol. Chem.*, 2016, **14**, 3889-3905; (b) H. Naeimi, D. Aghaseyedkarimi, *New J. Chem*., 2015, **39**, 9415-9421.