1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide: as a novel and efficient nanocatalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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Abstract: The preparation, characterization and catalytic application of a novel 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide are 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 biginelli condensation of different aldehydes with urea and alkylacetoacetates under solvent-free conditions and at moderate temperature. Moreover, the significant advantages of this procedure are the stability, reactivity and reusability of the catalyst, 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.

Keywords: Graphene oxide, Multicomponent reactions, 3,4-dihydropyrimidin-2(1*H*)-ones, Biginelli reaction

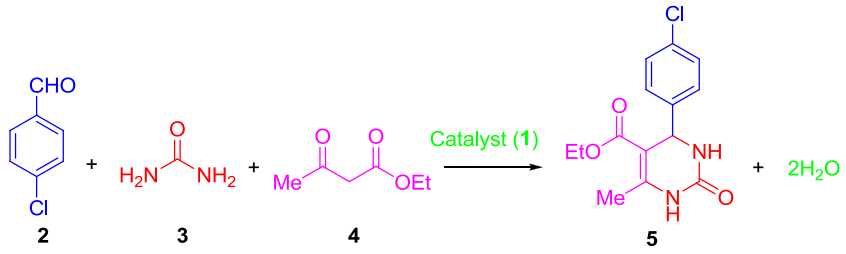
Introduction

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].

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. Considering that most of the atoms of the starting materials (three or more components) are incorporated into the final product, and that water is the byproduct for some MCRs, these reactions became synthetic tools found in a prominent position. MCRs have the advantage of conserving most of the atoms from the building blocks that are present in the product to generate libraries of compounds in an efficient manner [2-4]

In this context, many catalytic methodologies have been tested to improve MCR adduct formation, to reduce reaction times, to improve yields, selectivities and for more amenable reaction conditions, as noted in many recent reviews. Among MCRs, the Biginelli reaction (Scheme 1), announced by Pietro Biginelli in 1891, is a very elegant multicomponent methodology applied in the synthesis of 3,4-dihydropyrimidin-2(1H)-one or thione (DHPMs) derivatives. DHPMs usually have distinct biological activities and can be applied as calcium channel modulators,

adrenergic receptor antagonists, antibacterials, mitotic Kinesin inhibitors, antivirals, and others, as reviewed elsewhere [3].



Scheme 1 One-pot three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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.

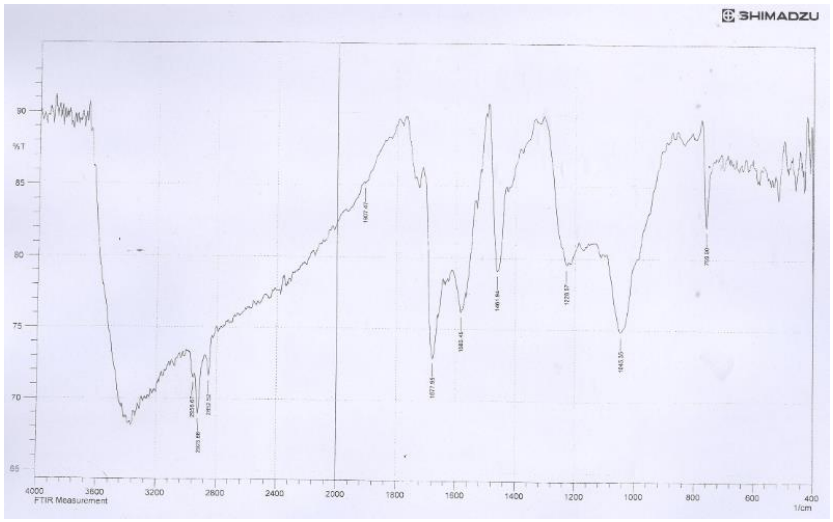


Figure 1. FT-IR of 1, 3, 5-Tris (2-hydroxyethyl) isocyanurate functionalized graphene oxide

To show the efficiency of the catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives (**5**), the reaction of 4-chlorobenzaldehyde (**2a**, 1 mmol), urea (**3**, 1.5 mmol) and ethyl acetoacetate (**4**, 1 mmol) was investigated as model reaction. The reaction conditions were optimized with regard to the best catalyst loading, different solvents and temperature for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives. The results have been summarized in Table **1**.

It was observed that low yields of the desired product (**5a**) were obtained in the presence of the catalyst under ultrasonic and ball-milling conditions (Table **1**, entries 1 and 2). Furthermore, the use of EtOH as solvent with 15 mg loading of the catalyst improved yield of the desired product (**5a**) under reflux conditions compared to other solvents (entries 3-5). The study of model reaction in solvent-free conditions showed that the yield of the desired product (**5a**) was increased significantly under similar reaction conditions with increasing temperature (entries 6-9 and 11). It was observed that product (**5a**) was obtained with higher yield and shorter reaction time under solvent-free conditions at 80 °C compared to other temperatures (entry 9). Also increasing of amount of the catalyst had no major effect on yield of the desired product (**5a**) (entry 10).

In order to demonstrate the scope of this protocol, the optimized reaction conditions were developed to other aromatic, heterocyclic or aliphatic aldehydes **2a-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 4-chlorobenzaldehyde (**2a**), urea (**3**) and ethyl acetoacetate (**4**) under different conditions[a]**.**

Entry	Amount of Catalysts **(1)**/mg	Solvent	Temp.(℃)	Time (min)	Yeild[b] (%)
1[c]	15	-	r.t	90	15
2[d]	15	EtOH	r.t	120	50
3	15	H_2O	Reflux	150	31
4	15	EtOH	Reflux	110	65
5	15	CH_2Cl_2	Reflux	180	10
6	15	Solvent-free	r.t	150	Trace
7	15	Solvent-free	45	60	12
8	15	Solvent-free	70	60	76
9	15	Solvent-free	80	40	95
10	20	Solvent-free	80	40	95
11	15	Solvent-free	90	40	95

[a] Reaction conditions: 4-chlorobenzaldehyde (**2a**, 1 mmol), urea (**3**, 1.5 mmol) and ethyl acetoacetate (**4**, 1 mmol) in the presence of 15 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 3,4-dihydropyrimidin-2(1*H*)-ones derivatives **5** from 4-chlorobenzaldehyde (**2a**), urea (**3**) and ethyl acetoacetate (**4**) under the optimized conditions[a].

Entry	Aldehyde **2**	Product **5**	Time (min)	Yeild[b] (%)
1	4-Chlorobenzaldehyde (**2a**)	**5a**	40	95
2	2,4-Dimethoxybenzaldehyde (**2b**)	**5b**	45	93
3	4-Hydroxybenzaldehyde (**2c**)	**5c**	70	91
4	4-Methylbenzaldehyde (**2d**)	**5d**	45	87
5	Thiophene-2-carbaldehyde (**2e**)	**5e**	30	80

[a] Reaction conditions: 4-chlorobenzaldehyde (**2a**, 1 mmol), urea (**3**, 1.5 mmol) and ethyl acetoacetate (**4**, 1 mmol) in the presence of 15 mg of the catalyst (**1**) under solvent-free conditions at 80℃.

[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 3,4-dihydropyrimidin-2(1*H*)-ones derivatives (5a-e)

In a 5 mL round-bottomed flask, 4-chlorobenzaldehyde (**2a**, 1 mmol), urea (**3**, 1.5 mmol) and ethyl acetoacetate (**4**, 1 mmol) and 15 mg of the catalyst (**1**) were added. The obtained mixture was stirred at 80 ˚C for times indicated in Table **2**. After completion of the reaction monitored by TLC (eluent: EtOAc: n-hexane), EtOH (4 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 80–95% yields based on the starting aldehyde. The separated catalyst was suspended in EtOH (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 3,4-dihydropyrimidin-2(1*H*)-ones derivatives. The reaction system was significantly affected by catalyst loading, temperature and solvent. The catalyst illustrated high efficiency and reactivity for the one-pot three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives using different aldehydes, urea and ethyl acetoacetate under solvent-free conditions. In addition, the catalyst could be recovered and reused with no decrease in its activity. Therefore, the significant advantages of this procedure are low catalyst loading, short reaction times, high to excellent yields, elimination of toxic organic solvents, simple workup, reusability of the catalyst and simple purification of the products.

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