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Graphene oxide nanosheets promoted regioselective and green synthesis of new dicoumarols†

Saeed Khodabakhshi,*[a] Bahador Karami,*[a] Khalil Eskandari,[a] S. Jafar Hoseini[a] and Alimorad Rashidi[b]

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Graphene oxide (GO) was obtained by modified Hummers oxidation of graphite and used as a highly efficient, metal-free, non-oxidative, and recyclable catalyst to promote the condensation of 4-hydroxycoumarin and aryl glyoxals for synthesis of new dicoumarols. This method is completely in accord with green chemistry.

Introduction

Green chemistry by nanocatalysis has emerged as a sustainable alternative to the conventional methods.[1–3] Although various catalysts are used in chemical reactions, metal-free and heterogeneous catalysts have attracted considerable attention in recent years.[4,5] Among metal-free catalysts, graphene and graphene oxide (GO) are emerging as a new class of carbocatalysts.[6] Until now, however, the catalytic application of graphene and reduced-GO has focused primarily on the use of these materials as supports for catalytically active transition metals. Simplified structure of a single layer of graphene oxide (GO) was proposed (Fig. 1).[7]

The acidic and oxidative nature of the oxygen functionalities allows it to function as a solid acid or green oxidant. From a broader perspective, the unique properties inherent to well-defined nanosheets such as graphene and GO are suitable for facilitating a wide range of transformations and may offer extraordinary potential in the design of novel catalytic systems. GO and its related materials have advantages over many common catalysts. For example, stability, safety, insolubility in common solvents, and recyclability make them green catalysts for chemical reactions. However, the application of GO and other reduced-GO as catalysts in synthetic chemistry remains essentially unexplored.

Pharmaceutically, dicoumarol is a naturally occurring anti-coagulant that functions like warfarin as a vitamin K antagonist. Dicoumarol is the bridge substituted dimers of 4-hydroxy-coumarin which has been employed for the prevention and treatment of thrombosis. It is also used in biochemical experiments as an inhibitor of reductases.[8] According to the importance of some compounds containing coumarin nucleus in pharmaceutical research, the chemistry of this compounds have recently received special attention of chemists.[9,10] Although dicoumarol was firstly discovered in mouldy wet sweet-clover hay, several methods have been described in the literature for synthesis of dicoumarol derivatives. As a background, the total synthesis of dicoumarols starting from salicylaldehyde and formaldehyde,[11] biosynthesis of dicoumarol employing micro-organisms such as *Penicillium jenseni*,[12] and Knoevenagel condensation of 4-hydroxycoumarins with carbonyls using several catalysts[13–16] are some of them.

Organic synthesis on water has been well reviewed by Chanda and Fokin describing the heterogeneous reactions on the surface of water.[17] Water possesses many unique properties including safety and cheapness, thus, using water instead of organic solvents can efficiently help to finish the concerns about economic and environmental problems to the chemical reactions.[18] Besides, employing safe and recyclable catalytic systems is an important factor in the context of sustainable

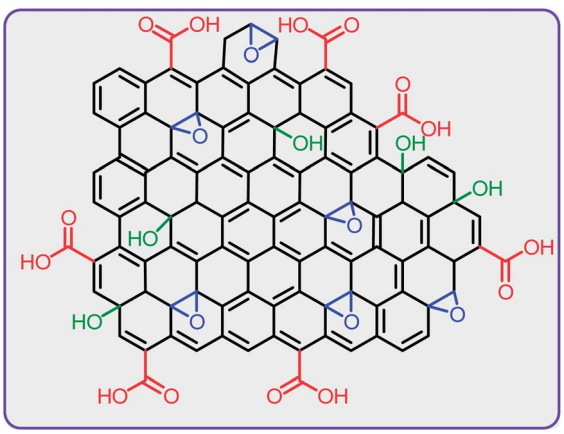

Fig. 1 Structural model of graphene oxide (GO).

[a]*Department of Chemistry, Yasouj University, P. O. Box 353, Yasouj, 75918-74831, Iran. E-mail: karami@mail.yu.ac.ir; Fax: +98 7412242167; Tel: +98 7412223048*

[b]*Nanotechnology Research Center, Research Institute of Petroleum Industry, Tehran, Iran*

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chemistry.[19,20] Accordingly, in this paper, we report the use of GO as a metal-free, eco-friendly and recyclable catalyst for the convenient synthesis of some dicoumarols containing aryloyl group in aqueous media.

Experimental

All chemicals were purchased from Merck and Aldrich. GO was prepared using modified Hummers method from flake graphite (Merck Company).[21] Aryl glyoxals were synthesized in accord with our previously reported method.[22] The reaction progresses were monitored by thin layer chromatography (TLC; silica-gel 60 F_{254}, *n*-hexane: AcOEt). IR spectra were recorded on a FT-IR JASCO-680 and the ^{1}H NMR spectra were obtained on a Bruker-Instrument DPX-400 and 300 MHz Avance 2 model. X-ray photoelectron spectroscopy (XPS) data were obtained with an ESCALab220i-XL electron spectrometer from VG Scientific using 300 W AlKα radiation. The varioEl CHNS was also used for elemental analysis. Scanning electron micrographs (SEM) were obtained using a Cambridge S-360 instrument with an accelerating voltage of 20 kV. The powder X-ray diffraction (XRD) pattern was obtained by a Bruker AXS (D8, Avance) instrument employing the reflection Bragg–Brentano geometry with CuKα radiation. The structure of the products was confirmed on the basis of IR, NMR spectroscopic data, and elemental analysis.

Preparation of GO

A flask containing graphite (1 g) and of $NaNO_3$ (0.75 g) was placed in the ice-water bath. H_2SO_4 (75 ml) was added with stirring and then $KMnO_4$ (4.5 g) was slowly added over about 1 h. After vigorously stirring for 5 days at room temperature, 5% H_2SO_4 (140 ml) aqueous solution was added over about 1 h with stirring, and the temperature was kept at 98 °C. The temperature was reduced to 60 °C, 3 ml of H_2O_2 (30 wt% aqueous solution) was added, and the mixture was stirred for 2 h at room temperature. As-prepared GO was suspended in ultra-pure water to give a brown dispersion, which was subjected to dialysis to completely remove residual salts and acids. Resulting purified GO powders were collected by centrifugation and air-dried. GO powders were dispersed in water to create 0.05 wt% dispersion. Then, the dispersion was exfoliated through ultrasonication for 1 h, which the bulk GO powders were transformed into GO nanoplatelets.

Synthesis of dicoumarols 3 (mentioned in Table 2)

A mixture of 4-hydroxycoumarin **1** (2 mmol), aryl glyoxals **2** (1 mmol) and GO (0.005 g) in H_2O (10 ml) was refluxed for an appropriate time mentioned in Table 2. The progress of the reaction was monitored by TLC. Upon completion of reaction, the mixture was poured on ice. After formation of precipitate, the solid was filtered off, dried, and dissolved in hot EtOH–THF (2 : 1) to separate the catalyst. Finally, the product **3** was afforded after recrystallization from EtOH–THF (2 : 1).

4-Flouro-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane (3b). M.p. 235–237 °C; IR (KBr) $\tilde{\nu}$ = 3500–3300, 3066.26, 2887, 1695, 1650, 1619, 1600, 1567, 1271, 1225, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.15 (s, 2H), 7.89 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.79–7.75 (m, 2H), 7.56–7.50 (m, 2H), 7.33–7.24 (m, 4H), 6.94 (t, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.91, 165.40, 152.41, 133.27, 132.00, 130.77, 130.65, 125.08, 124.56, 116.75, 116.35, 115.97, 115.68, 42.80; anal. calcd for $C_{26}H_{15}FO_7$: C, 68.12; H, 3.30. Found: C, 68.30; H, 3.22.

4-Methoxy-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane(3e). M.p. 265–267 °C; IR (KBr) $\tilde{\nu}$ = 3500–3300, 3076, 2978, 1684, 1650, 1620, 1601, 1571, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.22 (s, 2H), 8.00 (dd, 2H, J = 8.2, 1.6 Hz), 7.77–7.72 (m, 2H), 7.55–7.49 (m, 2H), 7.32–7.24 (m, 4H), 6.77–6.72 (m, 2H), 6.00 (s, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 193.13, 165.22, 163.55, 152.40, 133.08, 130.48, 128.30, 124.94, 124.57, 116.68, 116.48, 113.88, 55.46, 42.62; anal. calcd for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86. Found: C, 69.10; H, 3.69.

3-Methoxy-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane (3f). M.p. 205–207 °C; IR (KBr) $\tilde{\nu}$ = 3500–3300, 1693, 1655, 1619, 1602, 1567, 1273, 1427 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.16 (s, 1H), 8.00 (dd, 2H, J = 8.2, 1.6 Hz), 7.55–7.49 (m, 2H), 7.34–7.24 (m, 6H), 7.12 (t, 1H, J = 8.2 Hz), 6.94–6.90 (m, 1H), 6.00 (s, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.21, 165.28, 159.72, 152.40, 136.93, 133.17, 129.42, 125.03, 124.52, 120.26, 120.15, 116.73, 116.42, 112.46, 42.91; anal. calcd for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86. Found: C, 69.06; H, 3.65.

4-Chloro-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane (3g). M.p. 250–252 °C; IR (KBr) $\tilde{\nu}$ = 3500–3300, 3080, 2884, 1713, 1665, 1650, 1614, 1564, 1266, 1090, 767 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 11.10 (s, 2H), 7.85 (d, 2H, J = 6.0 Hz), 7.72 (d, 2H, J = 5.2 Hz), 7.62–7.52 (m, 4H), 7.31–7.25 (m, 4H), 6.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 196.16, 165.92, 163.33, 152.27, 135.90, 131.66, 131.24, 129.32, 125.94, 123.83, 123.45, 118.09, 115.87, 101.64, 42.92; anal. calcd for $C_{26}H_{15}ClO_7$: C, 65.76; H, 3.18. Found: C, 65.91; H, 3.03.

2-Naphthoyl[bis(4-hydroxycoumarin-3-yl)]methane (3h). M.p. 255–257 °C; IR (KBr) $\tilde{\nu}$ = 3550–3300, 1694, 1653, 1617, 1565, 1454, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.24 (s, 2H), 8.27 (s, 1H), 8.01 (dd, 2H, J_1 = 8.2, J_2 = 1.6 Hz), 7.83–7.72 (m, 4H), 7.54–7.43 (m, 4H), 7.33–7.23 (m, 4H), 6.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 177.38, 166.60, 163.65, 152.32, 134.48, 134.38, 131.82, 131.50, 129.13, 127.95, 127.54, 126.70, 124.15, 123.90, 123.33, 118.50, 115.78, 101.67, 43.14; anal. calcd for $C_{30}H_{18}O_7$: C, 73.47; H, 3.70. Found: C, 73.68; H, 3.75.

Results and discussion

GO sheets were synthesized by a modified Hummers method (* please see from Exp. section). Fig. 2 shows the XRD pattern of the bulk GO in dry state of GO. In the XRD pattern, the clear diffraction bands centered at $2\theta \sim 10^\circ$ correspond to the (002) plane of the GO with an interlayer spacing about 0.87 nm. With respect to that the pure graphite shows a diffraction peak at $2\theta = 26.3^\circ$ (inset in Fig. 2), corresponding to an interlayer spacing of about 0.335 nm, therefore, the elimination of the peak at 26.3° and the appearance of the peak at 10° confirm that GO has been completely oxidized.[23]

Scanning electron microscopy was used to observe the morphology of graphene oxide nanoplatelets. Fig. 3 is SEM

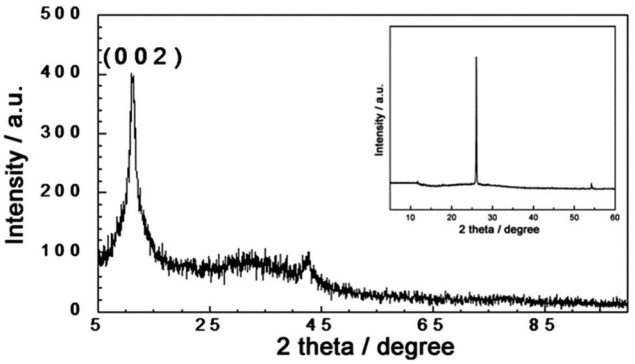


Fig. 2 XRD pattern of GO (inset shows XRD of graphite).

images of as-prepared GO nanoplatelets that shows crumpled thin layers with wrinkles and folds on the surface of GO. The upturned crinkly GO nanosheets can be attributed to a high-power ultrasound or a partial high-temperature environment created by the intense oxidization during the preparing process. X-ray photoelectron spectroscopy (XPS) was also used to characterize the functional groups present in GO.

As shown in Fig. 4, the overall XPS spectrum of the GO shows the typical peaks of C 1s and O 1s.

Fig. 5 also shows the C 1s signal of the prepared graphene oxide sheets that was fitted by four components at C=C (284.5 eV), C–O (286.4 eV), C=O (287.5 eV) and O=C–O (288.6 eV). In addition, the estimated C/O atomic ratio is 2.5, in agreement with the previous studies.[24]

Following our continuous interest to introduce new and safe methods in the field of organic synthesis,[25] we turned our attention towards the condensation of 4-hydroxycoumarin (**1**) and aryl glyoxals **2** in the presence of catalytic amounts of graphene oxide nanosheets (GO NSs) to produce dicoumarol derivatives **3** (Scheme 1).

To achieve this aim, several experiments were preliminary performed in order to find the simple reaction conditions for the synthesis of **3**. Therefore, the synthesis of **3a** was selected as a model.

As can be seen in Table 1, we found that the reaction proceeds slowly and cannot be completed after 120 min in the absence of the catalyst. Also, higher loadings of the catalyst did not show a marked influence on the product yield or reaction rate. In the next experiment, to demonstrate the effect of solvent or media on the reaction progress, we used several solvents which the results have been shown in Table 1. It should be also noted that 4-hydroxycoumarin is soluble in alcohol, acetone

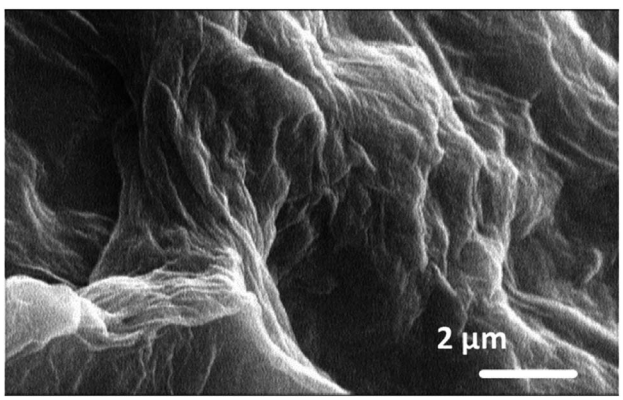


Fig. 3 SEM image of GO.

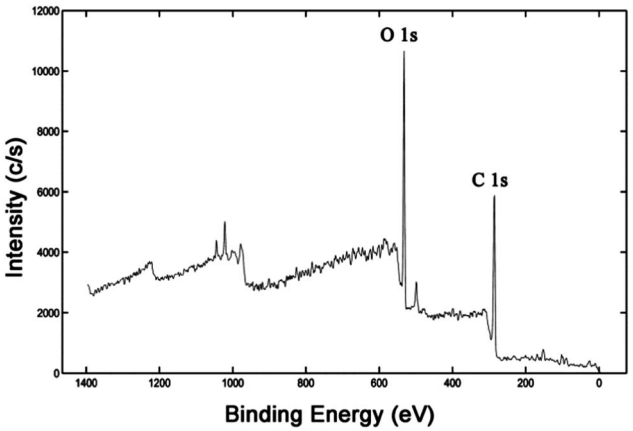


Fig. 4 Overall XPS spectra of GO.

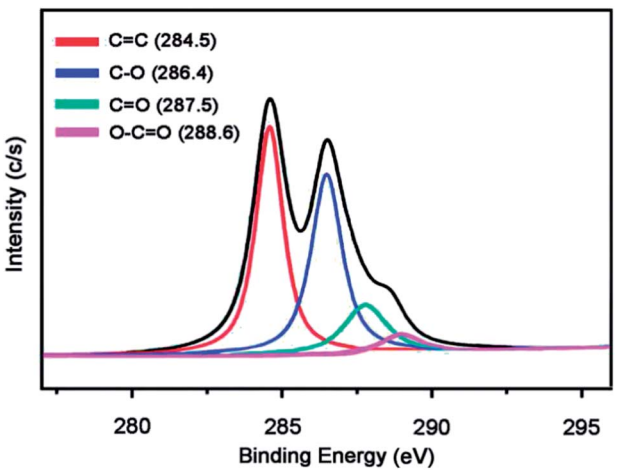
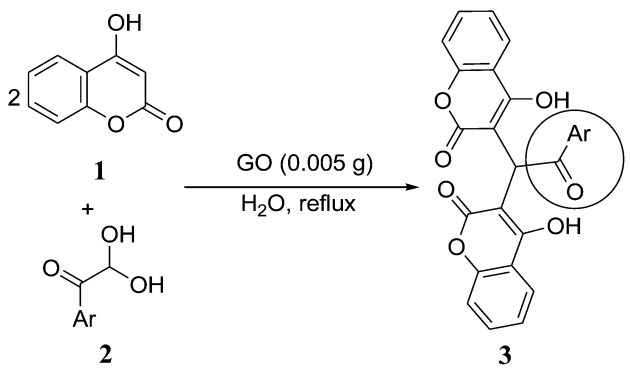


Fig. 5 C 1s XPS spectra of GO.



Scheme 1 Synthesis of dicoumarols catalyzed by GO.

Table 1 Effect of several conditions in synthesis of **3a** under reflux

Entry	Catalyst	Solvent	Time (min)	Yield (%)
1	Catalyst-free	H_2O	120	Trace
2	GO NSs (0.003 g)	H_2O	45	77
3	GO NSs (0.005 g)	H_2O	10	83
4	GO NSs (0.010 g)	H_2O	10	82
5	GO NSs (0.005 g)	Solvent-free	120	Trace
6	GO NSs (0.005 g)	MeOH	15	80
7	GO NSs (0.005 g)	EtOH	10	80
8	GO NSs (0.005 g)	THF	20	75
9	GO NSs (0.005 g)	CH_2Cl_2	120	50
10	GO NSs (0.005 g)	EtOH–H_2O (1/1)	10	83
11	Fe_3O_4 NPs (0.005 g)	H_2O	10	25
12	ZnO NPs (0.005 g)	H_2O	10	30
13	ZnO NWs (0.005 g)	H_2O	10	25
14	TiO_2 NPs (0.005 g)	H_2O	10	10
15	TiO_2 NWs (0.005 g)	H_2O	10	10

and ether, but it has low solubility in water. Nevertheless, considerable rate acceleration is mostly observed in reactions performed using protic solvents, such as EtOH, MeOH, and H_2O when compared to those in aprotic ones. However, water can be perfectly used, without hindering the yield. In addition, the reaction did not proceed under solvent-free conditions, so, it can show the importance of aqueous media for this type of reactions. Through screening, we found that this reaction was efficiently completed using GO (0.005 g) under reflux in H_2O about 10 min.

In another variation, to show the merit of GO with other catalysts, we surveyed the effect of some commonly nano-sized catalysts in the synthesis of model compounds. Despite the merits of nano Fe_3O_4, ZnO, and TiO_2, using them suffers from some disadvantages such as long reaction times and low yields. By using ZnO NPs, the reaction proceeded slowly. However, ZnO nanoparticles (NPs) seem to be better than nano Fe_3O_4 and TiO_2. Considering the results, it is clear that GO acts better rather than other ones from the aspect of productivity and reaction time.

In addition, from the environmental point of view, GO is a metal-free solid acid and using it is more reasonable than abovementioned catalysts which act as Lewis acids.

The scope of this unique synthesis was investigated after optimization. As can be seen in Table 2, the reaction proceeded effectively with different substitution on aryl glyoxal and it was not found to be dependent upon the electronic properties of the substituents.

It should be noted that the exact mechanism for this reaction is unclear, as there are not sufficient insights into the mechanistic aspects of the GO. In regard of recently published review explaining the possible mechanistic pathways for GO in organic reactions,[6] we think the probable active sites of the catalyst, in the present reaction, are acidic groups.

A simple plan for the GO catalyzed synthesis of **3** is suggested in Scheme 2. It seems that the reaction takes a place in three steps. It is reasonable to assume that the initial event involves the Knoevenagel condensation of the aryl glyoxal and 4-hydroxycoumarin. In the next steps, a Michael type addition to

Table 2 Synthesis of dicoumarols using GO (0.005 g) under reflux in H_2O[a]

Entry	Ar	Time (min)	Yield (%)	M.p. (°C)
3a	C_6H_5	10	83	177–175
3b	4-F-C_6H_4	10	75	273–235
3c	4-Br-C_6H_4	12	80	262–264
3d	4-NO_2-C_6H_4	10	80	270–272
3e	4-MeO-C_6H_4	8	77	265–267
3f	3-MeO-C_6H_4	12	73	205–207
3g	4-Cl-C_6H_4	15	80	250–252
3h	2-Naphthyl	5	85	255–257

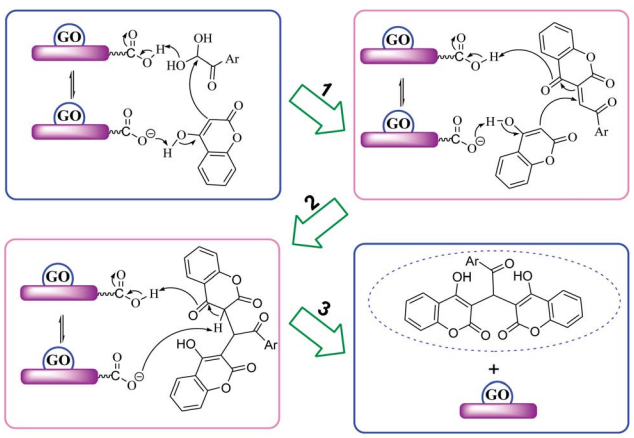
[a] Isolated yields.

the produced α,β-unsaturated ketone and subsequent enolization promoted by GO gives final products.

To strengthen the speculative mechanism, the effect of the catalyst on the reaction rate through using several samples with different concentrations of acid groups was investigated for synthesis of **3a**. In the first case, the reaction was conducted in the presence of pure graphite (0.005 g) and it was found that the reaction is not completed after 30 min. Using a sample with less acidic groups in which graphite has not been completely oxidized, led to an increase of production rate (completion: 17 min) in compression with pure graphite. By employing the completely oxidized graphite (0.005 g), the reaction proceeded well and the desired product was obtained in good yield and short reaction time (Table 1, entry 10). In another variation, to demonstrate the effect of acidic group on the rate of the reaction, the NaOH was used as catalyst, but the reaction did not proceed after 30 min.

Green chemistry principles emphasizes on the development of new methods for chemical transformations which are resource and energy efficient, practically simple and environmentally safe. The use of water instead of organic solvents is more reasonable because of its safety and cheapness. To investigate the reusability of GO in synthesis of dicoumarols **3**, the recyclability of GO was also investigated (Fig. 6).

The results show that the GO is usable for 4 times without appreciable loss in catalytic activity. Avoidance of organic



Scheme 2 Suggested mechanism for synthesis of **3** using GO.

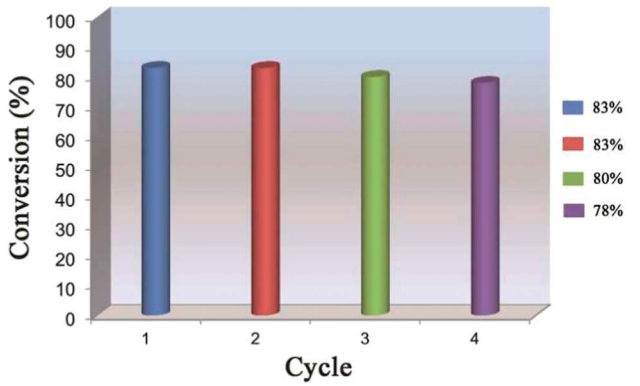


Fig. 6 Recyclability of GO in synthesis of 3a.

solvents and the use of a separable and recyclable catalyst are significant factors in agreement with sustainable chemistry.

Conclusions

To sum up, we have established an environmentally benign procedure to synthesize dicoumarols containing aryloyl group starting from 4-hydroxycoumarin with aryl glyoxals in H_2O. The reactions have been dramatically promoted by GO as a metal-free catalyst leading to good yield of desired products in short reaction times. Use of a safe and recyclable catalyst in water is completely compatible with sustainable chemistry. The simplicity of the protocol will be also beneficial to the sustainable synthesis of dicoumarols in the laboratory and in industry.

Acknowledgements

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