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One-pot synthesis of benzopyranophenazines using graphene oxide dichlorotriazine (GO-DCT) under microwave irradiations

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Abstract. An efficient synthesis of benzopyranophenazines is presented by one-pot four-component reaction of hydroxynaphthoquinone, *o*-phenylenediamine, benzaldehydes, and malononitrile with graphene oxide dichlorotriazine (GO-DCT) as an efficient nanocatalyst under microwave irradiation in ethanol. The catalyst was characterized by Fourier-transform infrared spectroscopy (FT-IR), X-Ray powder Diffraction (XRD), Energy Dispersive Spectroscopy (EDS), Atomic Force Microscopy (AFM), and Scanning Electron Microscopy (SEM). Atom economy, experimental simplicity, wide range of products, low amount of catalyst loading, reusability of the catalyst, excellent yields in short reaction times, and applying the microwave methodology as an efficient and green method are some of the substantial features of this method.

1. Introduction

Phenazines have a number of pharmacological activities including anti-tumor [1], antimycobacterial [2], anti-proliferative, [3] antibiotics [4], antifungal [5], and anti-inflammatory [6]. Some phenazines isolated from *Streptomyces* (a marine bacterium) are described with biological significance (Figure 1) [7-10]. Therefore, seeking efficient and economical methods for the preparation of phenazines through multicomponent reactions (MCRs) is a valuable area of research in organic and medicinal chemistry. Recently, reports have been developed on synthesis of phenazines using *p*-TSA [11], glacial acetic acid [12], 1,4- diazabicyclo[2.2.2]octane (DABCO), [13,14], thiourea-based organocatalysts [15], caffeine [16], theophylline [17], *L*-proline [18], 1-butyl-3-methylimidazolium hydroxide ([Bmim]OH) [19], Et_3N [20], pyridine [21], and oxalic acid [22]. However, some of the reported methods suffer from drawbacks including long reaction times, generating a large amount of waste, unpleasant reaction conditions, use of toxic, and non-reusable catalyst. Therefore, to avoid these restrictions, the discovery of an efficient and retrievable catalyst with high catalytic activity for the synthesis of benzopyranophenazines is still favored. Recently, Graphen Oxide (GO) has attracted significant interest as the catalyst in organic synthesis [23,24]. Graphene and graphen oxide have large specific surface area, high surface-to-volume ratio, and chemical stability [25,26]. The graphene oxide is an effective platform for the construction of functionalized graphene platelets that can potentially confer improved mechanical, thermal, and electronic properties. Both small molecules and polymers have been covalently tethered to graphene oxide's highly reactive oxygen functionalities, or non-covalently at-

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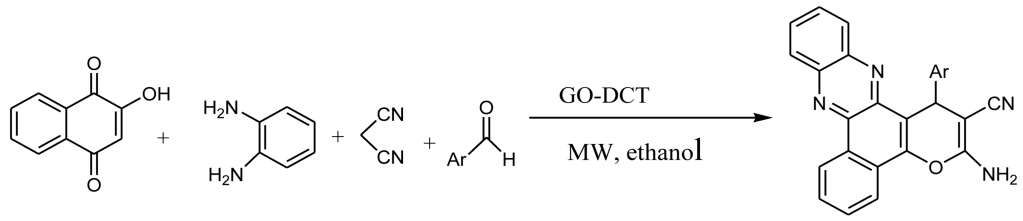


Scheme 1. Synthesis of benzopyranophenazines using graphene oxide dichloro triazine (GO-DCT) under microwave irradiations.

tached on the graphene surfaces, for potential use in sensors, polymer composites, paper-like materials, photovoltaic applications, and drug-delivery systems [27-31]. Herein, we wish to report the use of graphene oxide dichloro triazine (GO-DCT) as an efficient catalyst for the preparation of benzopyranophenazines by a multicomponent reaction of hydroxynaphthoquinone, *o*-phenylenediamine, benzaldehydes, and malononitrile under microwave irradiation (Scheme 1).

2. Experimental section

2.1. Chemicals and apparatus

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 MHz spectrometer using DMSO-d_6 as solvent. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Fourier transform infrared (FTIR) spectra were recorded on WQF-510, spectrometer 550 Nicolet. The Energy-Dispersive X-ray Spectroscopy (EDS) measurements were performed by SAMX analyzer. The AFM of GO nanosheets were measured using a Scanning Probe Microscope (SPM-9600, Shimadzu). Powder X-Ray Diffraction (XRD) measurements were carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation ($\lambda = 1.54056$ nm). SEM images were taken by MIRA3-TESCAN.

2.1.1. Preparation of graphene oxide dichlorotriazine (GO-DCT)

At first, GO was prepared from graphite powder through the improved hummers method as starting material [32]. 0.5 g graphite powder was dispersed into 200 mL H_2SO_4 (98%), sonicated for 2 h at 50°C, and stirred for 24 h. Then, 10 g $NaNO_3$ was added into stable dispersion and the mixture of reaction was placed in ice-water bath under stirring for 1 h. 30 g KMnO4 was added slowly and stirred for 24 h. Then, 200 mL H_2O and 60 mL H_2O_2 were added into the mixture of reaction. The color of the reaction material was light brown, which was filtrated and washed with water and dried in oven. The obtained GO (1 g) was dispersed in 10 mL $CHCl_3$; then, 0.5 g 2,4,6-trichloro-1,3,5-triazine was added and stirred for 24 h at room temperature. The obtained solution was filtrated and washed with $CHCl_3$ and dried in oven.

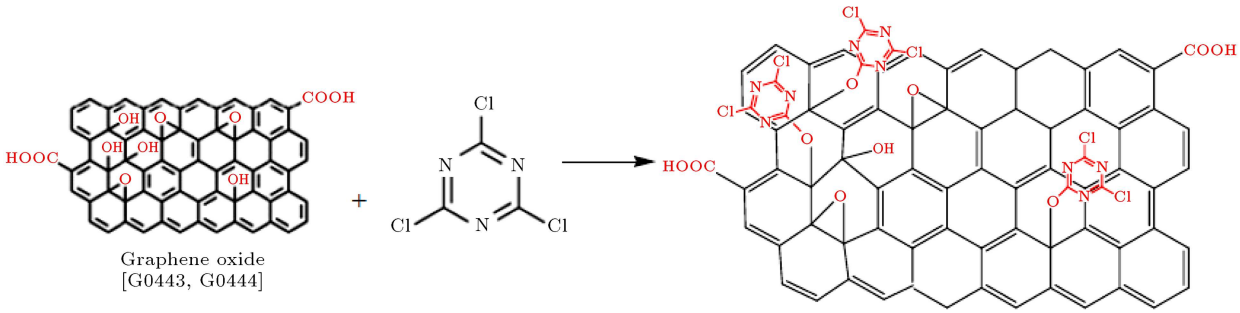
2.1.2. Preparation of benzopyranophenazines

A mixture of hydroxynaphthoquinone (1 mmol), *o*-phenylenediamine (1 mmol), an aldehydes (1 mmol), malononitrile (1.5 mmol), and graphene oxide dichlorotriazine (GO-DCT) (8 mg) in EtOH (15 mL) was irradiated inside microwave oven at the power level of 500 W for the appropriate time. After completion of the reaction (TLC), hot ethanol (10 mL) was added. The catalyst was insoluble in hot ethanol, and it could be recycled by centrifuging. The solvent was evaporated and a solid was obtained to afford the benzopyranophenazines. The pure products were characterized by comparison of their physical data (melting points, IR, and H NMR) with those of known compounds in the literature.

2.1.3. Spectral data of products

3-Amino-1-(4-cyano-phenyl)-1H-benzo[a]pyrano[2,3-c]phenazine-2- carbonitrile (**5h**):
Yellow solid, m.p.: 288-290°C; IR (KBr, ν, cm^{-1}): 3322, 3176, 3045, 2831, 2182, 2139, 1644, 1622, 1584, 1483, 1455, 1444, 1392, 1383, 1355, 1337, 1292, 1256, 1160; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 5.42 (s, 1H, CH), 7.23 (s, 2H, NH_2), 7.38 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.42 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.83-8.08 (m, 4H, Ar-H), 8.12-8.15 (m, 1H, Ar-H), 8.17-8.22 (m, 1H, Ar-H), 8.42 (d, 1H, $J = 7.6$ Hz, Ar-H), 9.17 (d, 1H, $J = 7.2$ Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 37.3, 57.9, 113.8, 115.3, 118.3, 122.1, 124.3, 125.5, 126.3, 127.8, 128.2, 128.6, 129.0, 129.2, 130.1, 130.3, 130.6, 130.8, 139.9, 140.1, 140.7, 141.4, 145.6, 146.5, 159.5; Anal. Calcd. for $C_{27}H_{15}N_5O$: C, 76.22; H, 3.55; N, 16.46; Found: C, 76.18; H, 3.43; N, 16.35.

3-Amino-1-(4-methoxy-phenyl)-1H-benzo[a]pyrano[2,3-c]phenazine-2- carbonitrile (**5m**):
Yellow solid, m.p.: 268-269°C; IR (KBr, ν, cm^{-1}): 3315, 3174, 3048, 2829, 2180, 1652, 1620, 1585, 1487, 1465, 1450, 1394, 1384, 1350, 1330, 1293, 1258, 1163; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 3.84 (s, 3H, OCH_3), 5.83 (s, 1H, CH), 6.65 (d, 2H, $J = 7.6$ Hz, Ar-H), 6.90 (d, 2H, $J = 7.6$ Hz, Ar-H), 7.35 (s, 2H, NH_2), 7.85-7.93 (m, 4H, Ar-H), 7.98-8.40 (m, 3H), 9.10 (d, 1H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 37.5, 55.2, 58.3, 112.1, 115.2, 115.5, 120.2, 120.4, 121.4, 125.2, 127.0,



Scheme 2. Preparation routes of graphene oxide dichloro triazine (GO-DCT).

129.1, 129.3, 129.7, 130.1, 130.5, 130.8, 130.9, 140.3, 141.2, 141.9, 146.4, 147.3, 159.4, 160.5; Anal. Calcd. for $C_{27}H_{18}N_4O_2$: C, 75.34; H, 4.21; N, 13.02; Found C, 75.25; H, 4.15; N, 12.93.

3. Results and discussion

The process for the preparation of graphene oxide dichlorotriazine (GO-DCT) catalyst is schematically described in Scheme 2. Graphene Oxide nanosheets (GO) were prepared using a modified Hummer's method and subsequently functionalized with dichlorotriazine.

XRD patterns of graphene oxide dichlorotriazine (GO-DCT) are shown in Figure 1. The characteristic peaks in the spectrum are in agreement with the standard XRD pattern of functionalized-graphene oxides [29-33].

The morphology of graphene oxide dichlorotriazine was investigated by Scanning Electron Microscopy (SEM) as shown in Figure 2. The SEM image of graphene oxide dichlorotriazine nanoplatelets showed crumpled thin layers with wrinkles and folds on the surface of GO.

The FT-IR spectra of graphene oxide and graphene oxide dichlorotriazine are shown in Figure 3. The FT-IR spectrum of GO demonstrates the characteristic oxygen-containing groups. The characteristic peaks at 3443 cm^{-1} (O-H stretching vibration), 1704 cm^{-1} (C=O stretching vibration), and 1126 cm^{-1} (C-O-C stretching vibration) appear in the spectrum of GO [33]. The peak at approximately 1659 cm^{-1} is attributed to C=C double bonds. Figure 3(b) shows the FT-IR spectrum of graphene oxide dichlorotriazine. The intense peaks appearing at around 619, 1123, and 1580 cm^{-1} are attributed to stretching vibrations of C-Cl, C-O, and C=N bonds. These basic characteristic peaks verify that dichlorotriazine is coated on the surface of graphene oxide.

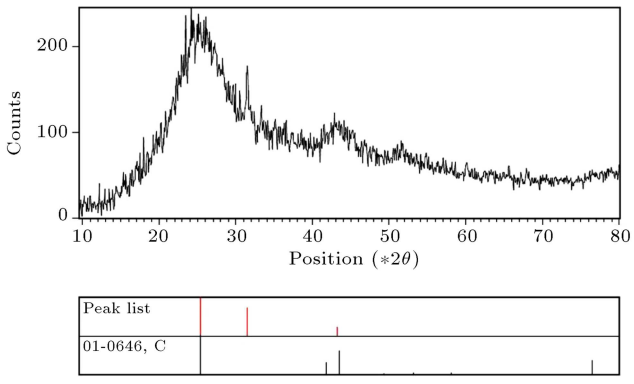


Figure 1. The XRD pattern of graphene oxide dichlorotriazine (GO-DCT).

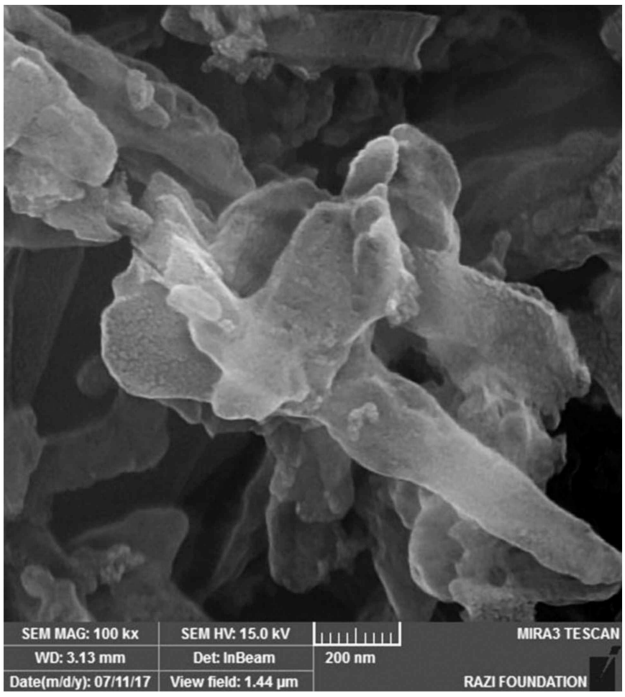


Figure 2. SEM image of graphene oxide dichlorotriazine (GO-DCT).

Figure 4 shows the EDS spectra of graphene oxide dichlorotriazine. The presence of elements such as carbon, oxygen, nitrogen, and chlor was confirmed by EDS spectroscopy.

Atomic Force Microscopy (AFM) was utilized to observe the morphology of GO nanosheets and measure their thickness. The AFM images of GO and graphene oxide dichlorotriazine easily confirm the wrinkled two-

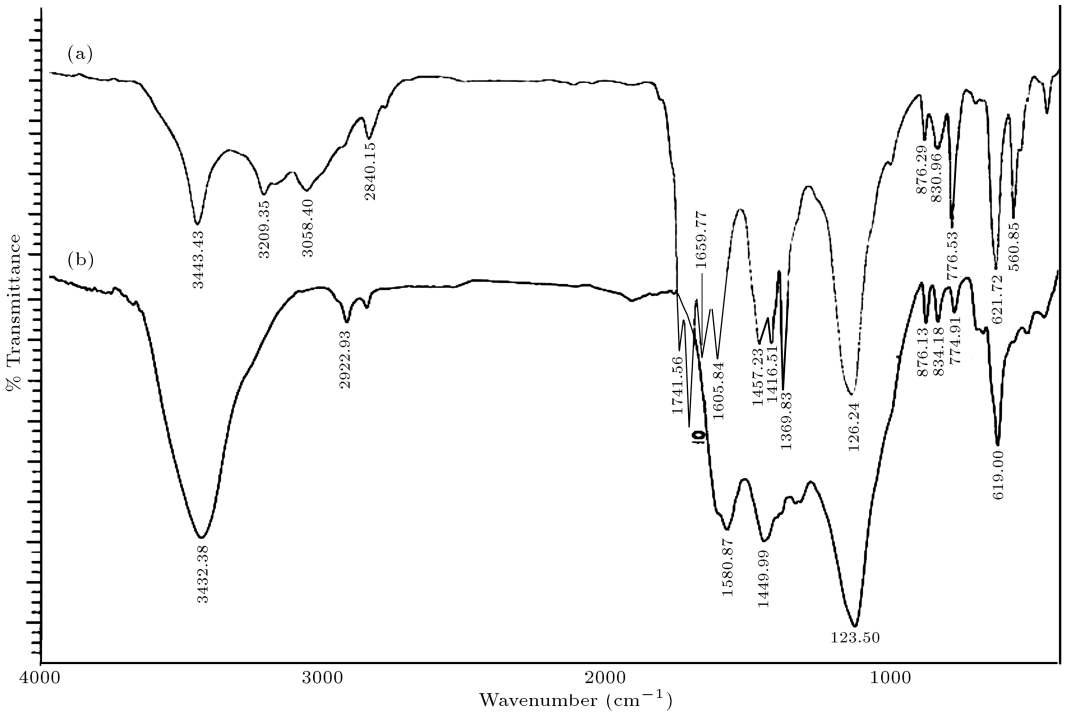


Figure 3. FT- IR spectrum of graphene oxide (a) and graphene oxide dichlorotriazine (b).

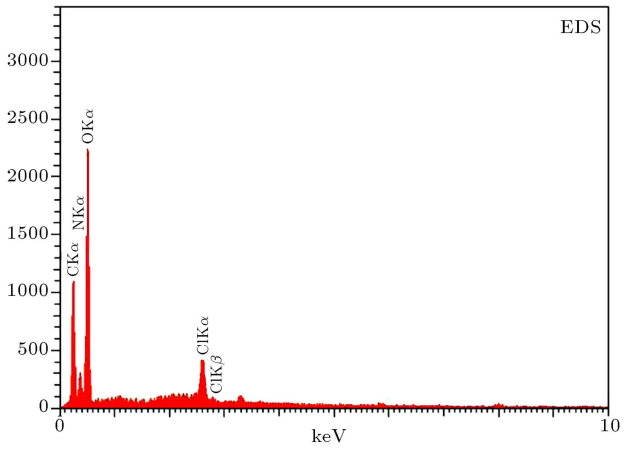


Figure 4. EDS spectrum of graphene oxide dichlorotriazine (GO-DCT).

dimensional characteristic of the GO nanosheets. The images show that the thickness of GO is approximately 0.9 to 1.5 nm, corresponding to structures with one to two layers (Figure 5(a) and (b)).

Initially, we focused on systematic evaluation of different catalysts for the model reaction of hydroxynaphthoquinone, *o*-phenylenediamine, 4-chlorobenzaldehyde, and malononitrile under different conditions. To obtain the ideal reaction conditions for the synthesis of compound **5b**, we studied some other catalysts and solvents, which are shown in Table 1. Screening of diverse catalysts such as $NiCl_2$, imidazole, $ZrOCl_2$, *P*-TSA, GO, and GO-DCT revealed GO-DCT as the most effective catalyst to perform this reaction under microwave irradiation in ethanol. In further studies on the catalyst loading, we recognized that yield of compound **5b** remained almost the same when 8 mg of GO-DCT was used (Table 1). Use of lower catalyst loading (6 mg) afforded **5b** in 89% yield. The results illustrated that the microwave certainly affected the reaction system. It could reduce the reaction time and increase the yield of the products (Table 2). When the reaction was carried out under reflux conditions, it gave low yields of products and took longer reaction times, while the same reaction was carried out under microwave irradiation to give excellent yields of products in short reaction times. Therefore, it was observed that the reaction in the presence of 8 mg GO-DCT and under microwave irradiation gave the best result as the obtained product was 96% isolated yield during 10 minutes.

The results show that the present catalytic method is extensible to a wide diversity of substrates to create a variety-oriented library of benzopyranophenazines. From the above observation, it is important to mention that electron-withdrawing groups increase the rate of reaction and give better yields than electron-donating groups (Table 2).

We investigated reusability of the GO-DCT as catalyst for the preparation of product **5b** and it was found that product yields were reduced to a small extent in each reuse (run 1, 96%; run 2, 96%; run 3, 96%; run 4, 95%; run 5, 95%, run 6, 94%). After completion of the reaction, the nanocatalyst was easily separated using centrifuging. The catalyst was washed

Table 1. Optimization of reaction conditions using different catalysts under different conditions[a].

Entry	Solvent (conditions)	Catalyst	Time (min)	Yield (%)[c]
1	EtOH (reflux)	No catalyst	400	Trace
2	EtOH (reflux)	$NiCl_2$ (5 mol%)	400	42
3	EtOH (reflux)	$ZrOCl_2$ (5 mol%)	500	45
4	EtOH (reflux)	imidazole (7 mol%)	400	35
5	EtOH (reflux)	*p*-TSA (8 mol%)	250	53
6	EtOH (reflux)	GO (15 mg)	250	57
7	H_2O (reflux)	GO-DCT (15 mg)	150	46
8	DMF (reflux)	GO-DCT (15 mg)	150	55
9	CH_3CN (reflux)	GO-DCT (15 mg)	150	64
10	EtOH (reflux)	GO-DCT (15 mg)	150	75
11	H_2O (MWI: 400 W)[b]	GO-DCT (10 mg)	15	56
12	DMF (MWI: 400 W)	GO-DCT (10 mg)	15	68
13	CH_3CN (MWI: 400 W)	GO-DCT (10 mg)	15	79
14	EtOH (MWI: 300 W)	GO-DCT (8 mg)	10	86
15	EtOH (MWI: 400 W)	GO-DCT (8 mg)	10	96
16	EtOH (MWI: 500 W)	GO-DCT (8 mg)	10	96
17	EtOH (MWI: 400 W)	GO-DCT (6 mg)	10	89
18	EtOH (MWI: 400 W)	GO-DCT (10 mg)	10	96
19	EtOH (MWI: 400 W)	GO (12 mg)	10	81

[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), O-phenylenediamine (1 mmol), 4-chlorobenzaldehyde (1 mmol), and malononitrile (1.5 mmol) as a model reaction;

[b]Microwave irradiation;

[c]Isolated yield.

Table 2. Synthesis of benzopyranophenazine derivatives.

Entry	*R*	Product	Time (min)	Yield (%)[a]	m.p/°C found (reported)
1	H	**5a**	10	92	297-300 (298-300) [34]
2	4-Cl	**5b**	10	96	290-292 (288-290) [34]
3	2-Cl	**5c**	10	93	299-302 (301-303) [34]
4	4-Br	**5d**	10	97	282-284 (283-285) [34]
5	4-F	**5e**	10	98	273-276 (274-276) [34]
6	3-NO_2	**5f**	10	93	277-281 (278-279) [34]
7	4-NO_2	**5g**	10	98	280-282 (281-283) [34]
8	4-CN	**5h**	10	91	288-290
9	4-$N(Me)_2$	**5i**	15	84	261-263 (261-263) [34]
10	4-Me	**5j**	15	86	293-295 (293-294) [34]
11	2-OMe	**5k**	15	82	268-270 (270-272) [34]
12	3-OMe	**5l**	15	84	239-241 (240-242) [34]
13	4-OMe	**5m**	15	82	268-269
14	2,4-dichloro	**5n**	10	97	306-309 (308-310) [34]

[a]Isolated yield.

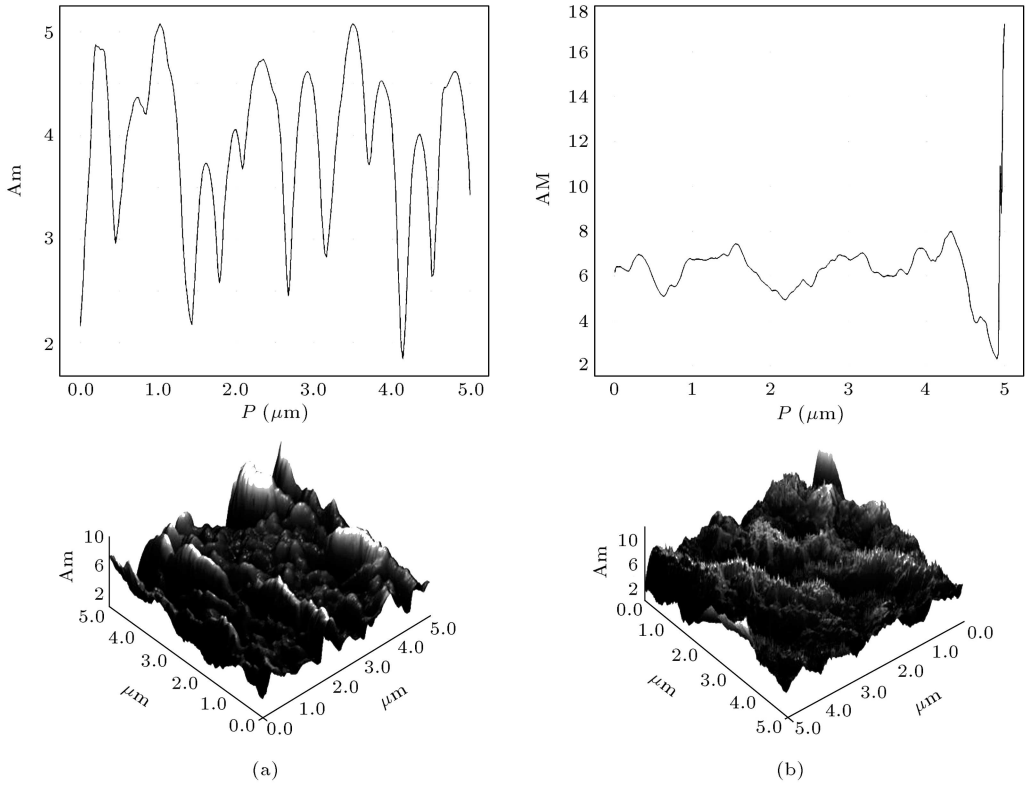


Figure 5. AFM of graphene oxide (a) and graphene oxide dichlorotriazine (b).

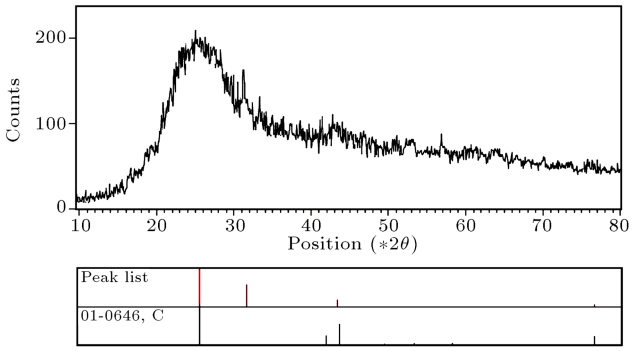


Figure 6. XRD patterns of graphene oxide dichlorotriazine catalyst after 5 runs.

four times with ethanol and dried at room temperature for 24 h.

In order to investigate the structural change of catalyst, the XRD pattern of recovered catalyst was provided (Figure 6). The result showed that there was no structural change after the reaction.

A proposed mechanism for the synthesis of benzopyranophenazines using GO-DCT is shown in Scheme 3:

(i) The initial condensation of hydroxynaphthoquinone with *o*-phenylenediamine afforded intermediate **I**;

(ii) Knoevenagel condensation of malononitrile and benzaldehydes formed intermediate **II**;

(iii) The Michael addition of intermediate **I** to intermediate **II** formed intermediate **III**, which in the subsequent cyclization and tautomerism afforded the corresponding products.

In this mechanism, the surface atoms of GO-DCT behaved as the centers where chemical reactions could be catalytically stimulated. The proposed mechanism has been supported in the literature [15,19,34]. Therefore, the superior performance of GO-DCT can mainly be attributed to many active sites such as –OH, –COOH, and triazines groups.

4. Conclusions

We developed a straightway and efficient method for the preparation of benzopyranophenazines using GO-DCT as an efficient catalyst under microwave irradiation. The method offers several advantages including rapid assembly of medicinally privileged heterocyclic molecules, use of easily available substrates, high yields, shorter reaction times, reusability of the catalyst, low amount of catalyst, and use of microwave irradiation as a valuable and powerful technology.

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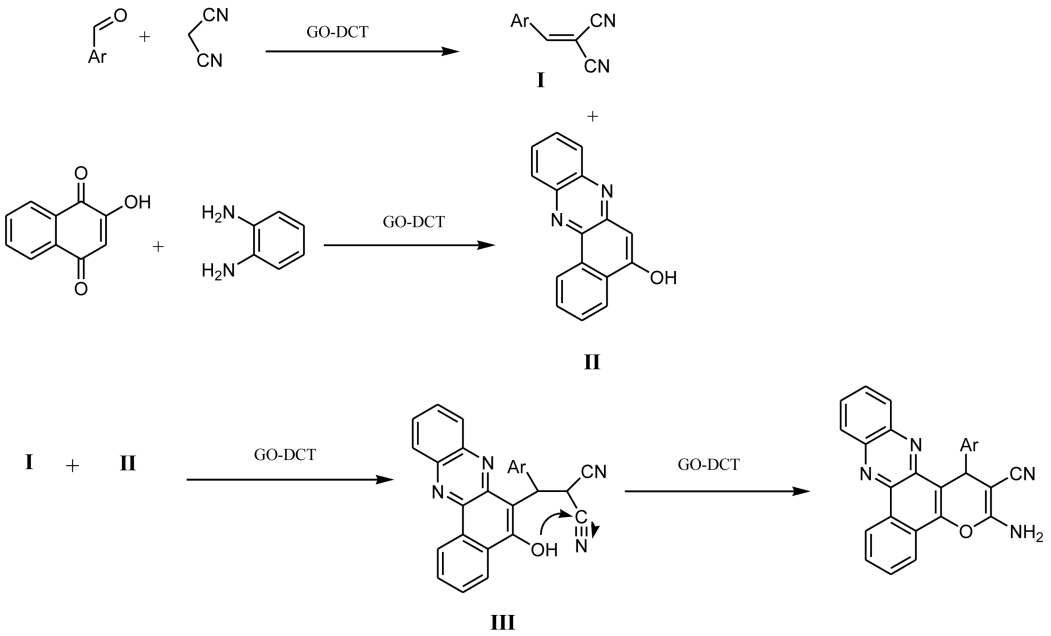

Scheme 3. A proposed mechanism for the synthesis of benzopyranophenazines.

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