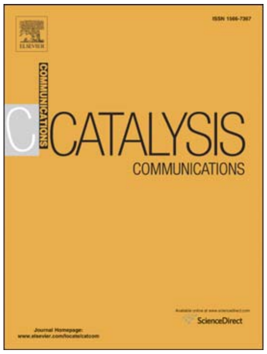

Supported molybdenum on graphene oxide/Fe_3O_4: An efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep eutectic solvent under microwave irradiation

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Catalysis Communications

Supported molybdenum on graphene oxide/Fe_3O_4: an efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep eutectic solvent under microwave irradiation

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ABSTRACT

Magnetically separable graphene oxide supported molybdenum (Fe_3O_4/GO-Mo) nanoparticles were prepared and characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), fourier transform infrared spectroscopy (FT-IR), and vibrating sample magnetometry (VSM) techniques. The synthesized heterogeneous material was found to exhibit high catalytic activity in one-pot, three-component reaction of isatins, malononitrile and anilinolactones using choline chloride (ChCl)/urea as a green solvent under microwave irradiation. It provided an efficient method for the synthesis of spiro-oxindole dihydropyridines in high to excellent yields. The catalytic system can be successfully reused eight times with a small decrease of its catalytic performance.

Keyword: Graphene oxide; Magnetic nanoparticles; Deep eutectic solvents; Multi-component reaction; Spiro-oxindole dihydropyridines; Microwave irradiation

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1. Introduction

From the viewpoint of green chemistry, the design of novel, efficient and clean reaction protocols using supported nanocatalysts in environmentally benign solvents to synthesize fine chemical and pharmaceutical products via multicomponent reactions (MCRs) has recently gained significant interest from academia and industry. In this context, carbon materials such as activated carbon [1], carbon nanofibers [2], carbon nanotubes (CNTs) [3-4] and graphene oxide (GO) [5-7] as promising supports have attracted significant attention as they are inexpensive and readily obtained. Particularly, GO as a novel nanocomposite has become one of the most widely used catalyst support due to its intriguing properties such as large surface area, high mechanical strength, unique layered structure, excellent physicochemical stability, and high flexibility. Most importantly, GO has abundant surface functional groups such as hydroxyl, carbonyl, epoxide and carboxylic acid, which makes GO as a fascinating support to provide covalent attachment of various specific groups. Despite their excellent catalytic performance in some organic reactions, some traditional separation methods such as filtration or high-speed centrifugation were usually required for the recycling of catalysts, thus limiting their wide use. In order to solve this problem, magnetic separation occurred as an intriguing alternative to filtration or centrifugation because it reduces loss of catalyst and makes the recovery and reusability of catalyst easier by magnetic force after completion of the reaction [8-10]. Thus, the incorporation of magnetic components into GO is most favoured and will provide high catalytic activity and improve separation capability [11-12]. Next, since conventional hazardous organic solvents pollute our environment severely, replacement of these toxic solvents by green and environmentally benign media is also of key relevance. Recently, deep eutectic solvents (DESs) have emerged as substitutes of conventional volatile organic solvents thanks to their advantages of low toxicity, nonvolatility, low flammability, biodegradability, simple and cheap preparation [13-14]. Besides, one pot, MCRs are becoming important tools for the rapid and efficient construction of structurally diverse complex molecules with excellent atom and step economy [15]. In addition, microwave irradiation has become particularly popular in recent years and a large number of organic reactions can be performed in improved yields, shorter reaction time and milder conditions under microwave irradiation [16]. With these aspects of green synthesis in mind, the development of microwave-promoted multicomponent reactions in environmentally benign media by use of a reusable magnetic nano-catalyst might be one exciting and desirable direction.

Synthesis of multi-heterocyclic compounds has received great attention in recent years because they show structural complexity and diversity. The importance of this type of molecule in pharmaceutical industry, material sciences and coordination chemistry has been demonstrated [17]. 1,4-Dihydropyridines represent an important class of calcium-channel modulating agents and have experienced widespread use in the treatment of cardiovascular disease [18]. They are useful as anti-Alzheimer's disease agent [19], calcium antagonists [20], TGFβ/Smad inhibitors [21] and anticancer drugs [22]. Additionally, the dihydrofuran skeleton is another important heterocyclic scaffold and it constitutes the structural subunit of many natural compounds and exhibits a broad range of biological properties [23]. The synthesis of spiro-heterocycles presents an interesting synthetic challenge due to their structural rigidity and complexity. Spirooxindoles, especially those spiroannulated with heterocycles at the 3-position, have been reported to possess good biological activities [24]. Based on the importance of these structural frameworks, the development of a simple procedure for the straightforward construction of spiro-heterocyclic compounds including the 1,4-dihydropyridine moiety and dihydrofuran framework using simple and readily available starting materials is highly desirable and valuable for medicinal chemistry and drug discovery.

By considering the above-mentioned points and continuing our efforts to develop environmentally benign synthetic methodologies [254-29], herein, we report for the first time, magnetically separable molybdenum immobilized to Fe_3O_4/graphene oxide as catalyst for the synthesis of spiro-oxindole dihydropyridines via one pot multi-component reaction of isatins, malononitrile and anilinolactones in ChCl/urea under microwave irradiation.

2. Experimental

2.1 General information

See in supporting information.

2.2 Synthesis of Fe_3O_4/GO nanocomposite

Magnetite-graphene oxide was prepared according to the modified method reported by Islam and co-workers [30]. 100 mg of GO was dispersed into 100 mL of deionized water with sonication for 1 h. 2.0 g of $FeCl_3$ and 0.75 g of $FeCl_2$ were added to 125 mL of deionized water with stirring for 30 min at room temperature. The aforementioned two systems were then mixed together, and stirred at 85 °C for 30 min. The mixture was adjusted to a pH of 10.0 with 25 % ammonia solution, and stirred for 45 min. The resultant Fe_3O_4 decorated GO suspension was cooled to room temperature and separated from the solution with the aid of an external permanent magnet, washed with distilled water and dried in a vacuum oven at 60 °C for 12 h.

2.3 Amine-functionalized of Fe_3O_4/GO

The obtained nano Fe_3O_4/GO (0.5 g) was dispersed in 10 ml water by sonication for 30 min at room temperature. Dopamine hydrochloride (0.5 g) dissolved in water (5 mL) was added, and the resulting mixture was again sonicated for 2 h. The prepared amine-functionalized magnetic nanoparticles were separated by magnetic decantation, and then washed with water and ethanol, and dried under vacuum at 60 °C for 2 h.

2.4 Immobilization of molybdenum on magnetic Fe_3O_4/GO

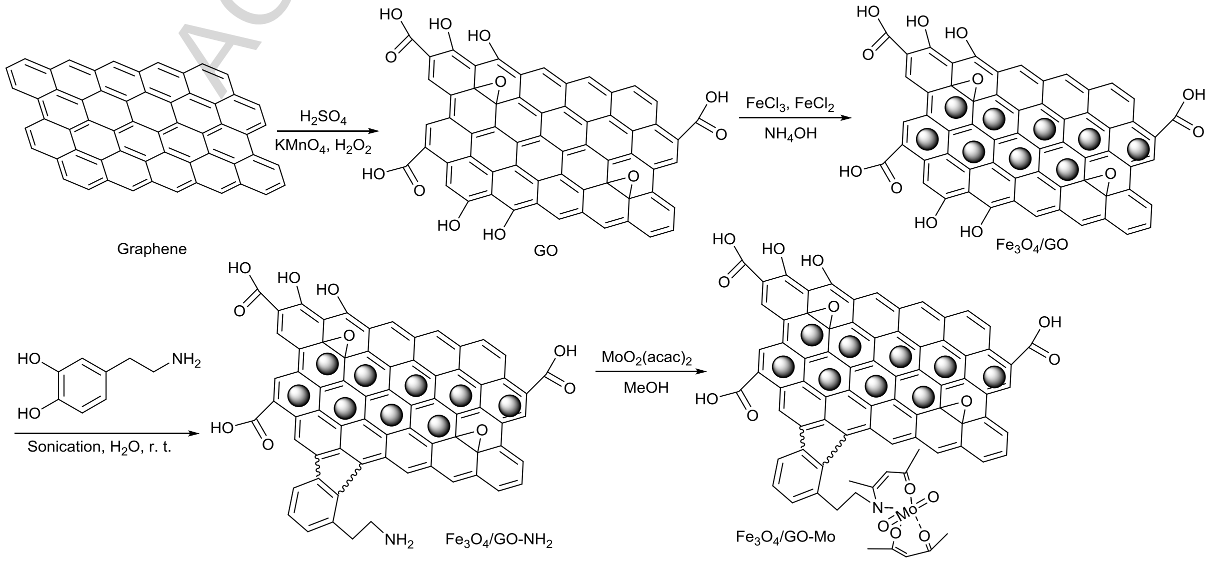
Amine-functionalized nano-Fe_3O_4/GO (0.5 g) was ultrasonically dispersed in dry MeOH (15 ml), bis(acetylacetonato)dioxomolybdenum (1.0 mmol) was added to the reaction mixture. The reaction mixture was then refluxed for 24 h. The catalyst was harvested with the aid of a magnet, washed several times with water and ethanol, and dried under vacuum at 60 °C for 2 h.

2.5 General procedure for synthesis of spiro-oxindole dihydropyridines

A mixture of isatin (1 mmol), malononitrile (1 mmol), anilinolactones (1 mmol) and Fe_3O_4/GO-Mo (20 mg, 0.015 mmol of Mo) in ChCl/urea (1 ml), was stirred under microwave irradiation at 90 °C for an appropriate time. After completion of the reaction as indicated by TLC, the catalyst was separated by external magnet and washed with acetone followed by water, and dried under vacuum and reused directly for the next round of reaction. After that, water (5 mL) was added to the reaction mixture to dissolve DES. The formed solid product was collected by filtration and recrystallized from ethanol (5 mL) to afford the pure product. The filtrate, consisting of the aqueous phase containing the DES, was evaporated under reduced pressure and then dried in vacuum at 100 °C to recover the DES for subsequent cycles.

3. Results and discussion

As shown in Scheme 2, the catalyst Fe_3O_4/GO-Mo was prepared in a four-step process. At first, graphene oxide (GO) was synthesized by oxidation of graphite powder according to a slightly modified Hummer’s method [31]. The synthesized graphene oxide was suspended into water and treated with $FeCl_3$ and $FeCl_2$ to obtain black colored Fe_3O_4/GO nanocomposites. High specific surface area of GO along with easily accessible oxygen-donating groups on GO sheets provided a better support for anchoring of Fe_3O_4 NPs. Amine-functionalized Fe_3O_4/GO NPs were prepared by sonicating Fe_3O_4/GO with dopamine in water [32-33]. Furthermore, the addition of bis(acetylacetonato)dioxomolybdenum into the Fe_3O_4/GO suspension in MeOH yielded magnetically separable Fe_3O_4/GO-Mo nanocomposites.



Scheme 1 Preparation of Fe_3O_4/GO-Mo

The XRD patterns of graphite, GO, and Fe_3O_4/GO-Mo are presented in Fig. 1. The original graphite shows a sharp characteristic diffraction peak at 2θ = 26.5^o, corresponding to the (002) crystal plane. After the oxidation treatment, the (002) diffraction peak for graphite shifted to lower angle at 2θ = 12.5 ^{o}C, indicating the formation of GO. The main peaks in Fe_3O_4/GO-Mo at 2θ = 30.1º, 35.5º, 43.5º, 57.0^o and 62.6^o corresponding to the diffractions of (220), (311), (400), (511) and (440), show the characteristics of Fe_3O_4 (JCPDS 19-0629), which implied that the crystal structure of the Fe_3O_4 core was still well-maintained after functionalization [34]. But no significant diffraction peak characteristic of Mo was detected, which was likely due to its low concentrations and poor crystallinity. The elemental composition of the Fe_3O_4/GO-Mo sample was determined by energy dispersive spectrum (EDS) analysis. The result indicates (Fig. S1 in supporting information) that the prepared catalyst contains C, N, O, Fe, and Mo element. It was revealed that Mo had been successfully immobilized on the surface of GO. The amount of Mo and Fe in Fe_3O_4/GO-Mo catalyst was found to be 7.70% and 55.2% respectively based on inductively coupled plasma mass spectrometry (ICP-MS) analysis.

The surface modification of the Fe_3O_4/GO-Mo nanoparticles was also investigated by X-ray photoelectron spectroscopy (XPS) analysis (Fig. S2 in SI), which shows the characteristic peaks for C 1s (284.8 eV), N 1s (399.5 eV), O 1s (530.0 eV), Fe 2p (711.6 eV), and Mo 3d (235.0 eV). Furthermore, the high-resolution narrow scan for Mo 3d displays energy peaks of Mo 3d5/2 and Mo 3d3/2 at 232.0 and 235.1 eV, respectively, which corresponded to the characteristic of Mo at a VI oxidation state. It clearly indicates that Mo complex has been successfully introduced on GO.

The magnetic property of the Fe_3O_4/GO-Mo was measured by using vibrating sample magnetometry (VSM) at room temperature. Magnetic measurement indicates the magnetic behaviour of the prepared Fe_3O_4/GO-Mo and the saturation magnetization value was found to be 28.6 emug^{-1} (Fig. S3 in SI). A suitable magnetic property of the prepared Fe_3O_4/GO-Mo fulfils our aim to develop a more efficient and easily separable catalyst for organic reactions.

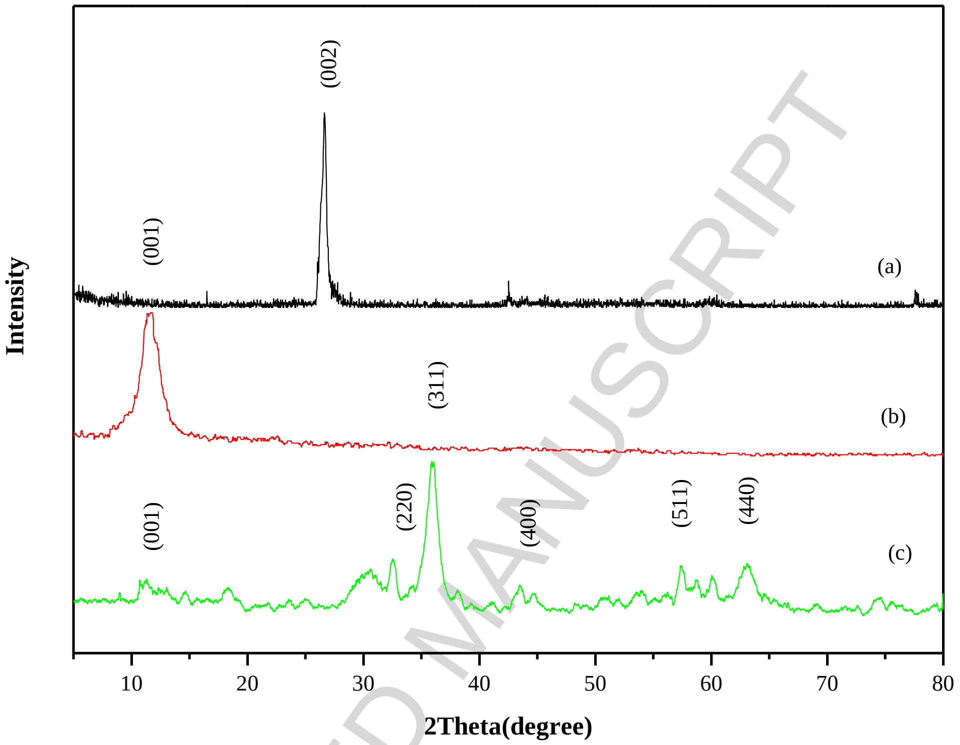


Fig. 1 XRD pattern of graphite (a), GO (b), and Fe_3O_4/GO-Mo (c)

The TEM images of GO, Fe_3O_4/GO and Fe_3O_4/GO-Mo are shown in Fig. S4 (in SI) and Fig. 2, respectively. The TEM image of Fe_3O_4/GO shows that Fe_3O_4 nanoparticles are distributed homogeneously throughout the graphene oxide surface. This image is the direct proof of the formation of Fe_3O_4/GO by chemically deposited Fe_3O_4 on GO. The TEM image of the Fe_3O_4/GO-Mo shows that the graphene oxide sheets are decorated with large quantities of Fe_3O_4 and molybdenum NPs. The average size of these particles was estimated to be about 30 nm, which is also in accordance with the result calculated by the Debye–Scherrer's equation by XRD data. The SEM image of Fe_3O_4/GO (Fig. 5 in SI) and Fe_3O_4/GO-Mo (Fig. 3) confirms that these nanoparticles are uneven-sized particles and most of the particles have a quasi-spherical shape.

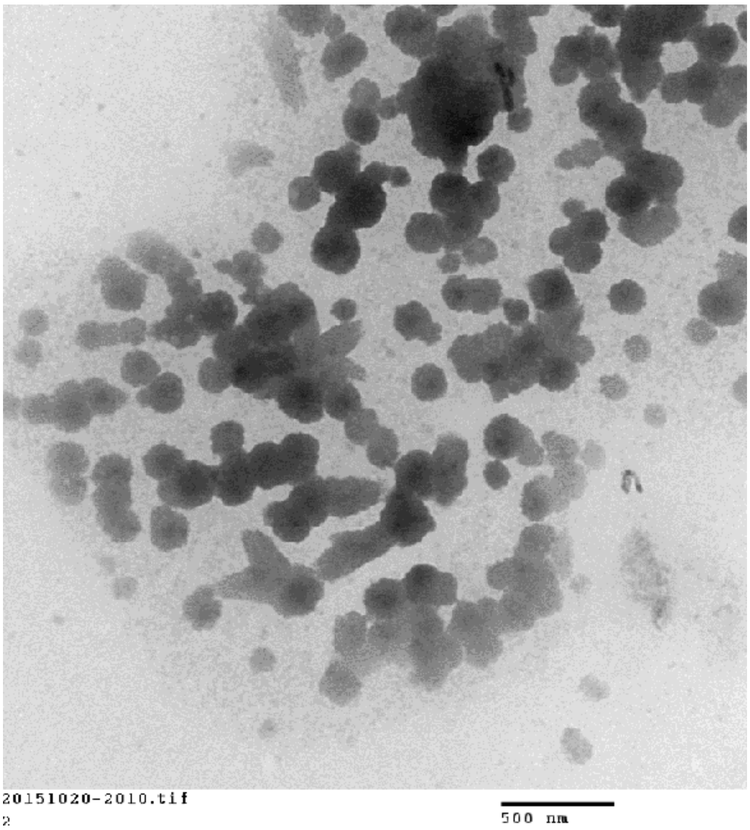


Fig. 2 TEM images of Fe_3O_4/GO-Mo.

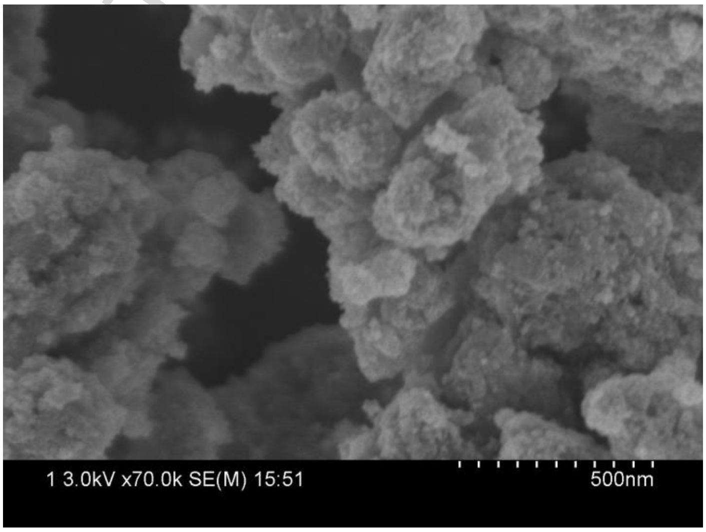


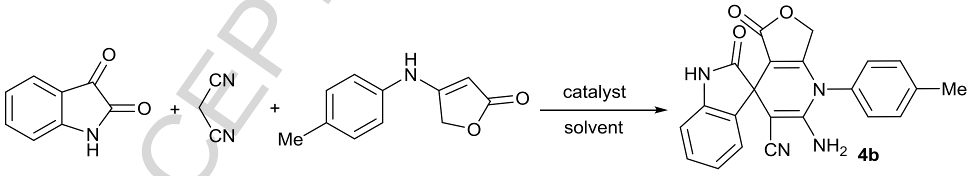
Fig. 3 SEM image of Fe_3O_4/GO-Mo.

The catalytic activity of the prepared catalyst was then evaluated in the model reaction of isatin, malononitrile and 4-(*p*-tolylamino)furan-2(5*H*)-one. As shown in Table 1, the desired product **4c** was obtained in 40% yield using 1.5 mol% Fe_3O_4/GO-Mo at 90 ^{o}C in glycerol for 1 h under microwave irradiation (Table 1, entry 1). Ghahremanzadeh and co-workers reported that this reaction was performed in the presence of a catalytic amount of manganese ferrite nanoparticles in PEG-400 to give product **4c** in

83% yield [35]. To further improve the yield, various reaction parameters were evaluated systematically. Some solvents were first screened and ChCl/urea was proved to be optimal and gave **4c** in 96% yield (entry 10). Control experiments confirmed that, in the absence of any catalyst or the presence of Fe_3O_4 or GO, only trace amount of the targeted product was detected (Table 1, entries 11-13). Other metal supported on graphene oxide/Fe_3O_4 such as Zn, Sn, Mn, Cu and Co were examined for this reaction, but unfortunately afforded unsatisfactory results (entries 14-18). In addition, we also investigated the influence of not having microwave irradiation on the model reaction (entry 19). It was found that the reaction under heating condition without microwave irradiation needed longer time and the yield of the expected product was lower than under microwave irradiation. The effect of microwave power on the reaction was also examined. The results showed that 500 W was the appropriate power for this reaction. The catalyst loading had a dramatic effect on reaction outcomes. When the amount of catalyst was reduced to 1.0 mol%, the yield of product **4c** dropped to 89%. A further increase of the amount of catalyst to 2 mol% did not affect the yield. A survey of the temperature was also conducted. The desired product **4c** was only formed in 54% yield at 70 ^{o}C. And decreasing the temperature to room temperature did affect the reaction efficiency and only traces of expected product were obtained (entry 26). However, the yield of the product was not improved as the reaction temperature increased from 90 ^{o}C to 100 ^{o}C.

Table 1

The effect of reaction condition on the reaction of isatin, malononitrile, and 4-(*p*-tolylamino)furan-2(5*H*)-one^{a}



Entry	Catalyst	Solvent	MW (W)	Temp (^{o}C)	Time (min)	Yield (%)^{b}
1	Fe_3O_4/GO-Mo	Glycerol	500	90	60	40
2	Fe_3O_4/GO-Mo	EtOH	500	reflux	60	62
3	Fe_3O_4/GO-Mo	H_2O	500	90	60	trace
4	Fe_3O_4/GO-Mo	ChCl/L-(+)-tartaric acid (2:1)	500	90	60	trace
5	Fe_3O_4/GO-Mo	ChCl/glucose (1:2)	500	90	60	trace
6	Fe_3O_4/GO-Mo	ChCl/fructose (1:2)	500	90	60	17
7	Fe_3O_4/GO-Mo	ChCl/itaconic acid (1:1)	500	90	60	21
8	Fe_3O_4/GO-Mo	ChCl/citric acid (1:2)	500	90	60	53
9	Fe_3O_4/GO-Mo	ChCl/glycerol (1:2)	500	90	60	67
10	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	90	50	96
11	Fe_3O_4	ChCl/urea (1:2)	500	90	120	trace
12	GO	ChCl/urea (1:2)	500	90	120	trace

13	No	ChCl/urea (1:2)	500	90	120	trace
14	Fe_3O_4/GO-Zn	ChCl/urea (1:2)	500	90	60	35
15	Fe_3O_4/GO-Sn	ChCl/urea (1:2)	500	90	60	60
16	Fe_3O_4/GO-Mn	ChCl/urea (1:2)	500	90	60	83
17	Fe_3O_4/GO-Cu	ChCl/urea (1:2)	500	90	60	71
18	Fe_3O_4/GO-Co	ChCl/urea (1:2)	500	90	60	47
19	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	0	90	240	93
20	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	200	90	120	91
21	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	300	90	120	93
22	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	400	90	90	94
23	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	600	90	50	96
24[c]	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	90	90	89
25[d]	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	90	50	96
26	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	25	120	trace
27	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	70	90	54
28	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	80	90	81
29	Fe_3O_4/GO-Mo	ChCl/urea (1:2)	500	100	50	94

[a] Reaction was performed with isatin (1 mmol), malononitrile (1 mmol), and 4-(*p*-tolylamino)furan-2(5*H*)-one (1 mmol), catalyst (20 mg, 0.015 mmol of Mo) in 1 ml solvent otherwise specified in the Table.

[b] Isolated yields.

[c] Catalyst (0.01 mmol of Mo).

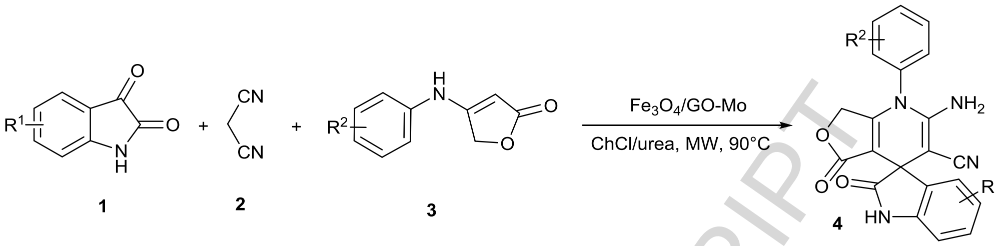
[d] Catalyst (0.02 mmol of Mo).

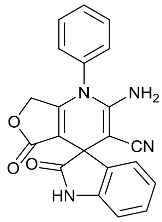
Having established the optimized reaction conditions, the scope and generality of this protocol were explored and representative results are displayed in Table 2. Firstly, isatin was fixed as the substrate to test various substituted anilinolatctones. It was found that anilinolactones bearing electron-neutral, electron-rich or electron-poor groups on benzene ring reacted with isatin and malononitrile to produce the desired products **4a-4f** in high yields. It was noted that anilinolactones possessing halogenated functional groups such as Cl and Br were well-tolerated and led to a beneficial effect on the reaction outcome, which allowed for easy further functionalization. However, the target product was not formed when the reaction was carried out using 4-(pyridin-2-ylamino)furan-2(5*H*)-one.

Subsequently, various isatins with electron-rich or electron-poor groups on the benzene ring were also tested. In most cases, this three-component reaction proceeded smoothly and the expected products were obtained in high yields. In contrast, no product was observed under above conditions when 4-bromoindoline was used as a substrate.

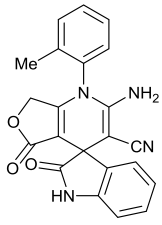
Table 2

Scope of substrates for synthesis of spiro-oxindole dihydropyridine derivatives[a].

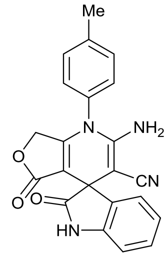




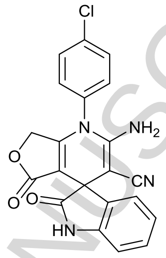
4a, 50 min, 87%



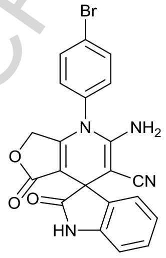
4b, 120 min, 88%



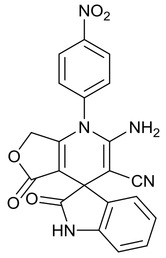
4c, 50 min, 96%



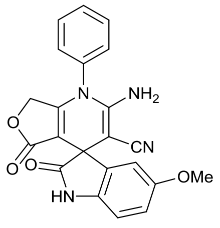
4d, 50 min, 90%



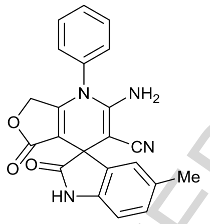
4e, 50 min, 89%



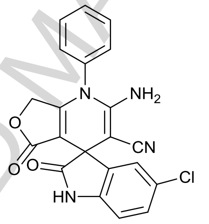
4f, 50 min, 88%



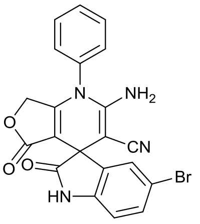
4g, 60 min, 91%



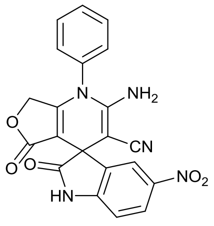
4h, 50 min, 94%



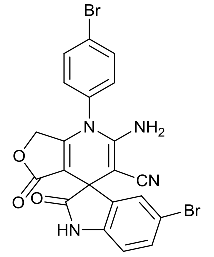
4i, 50 min, 88%



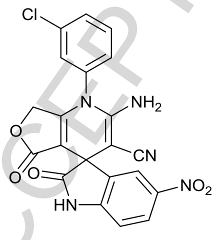
4j, 70 min, 86%



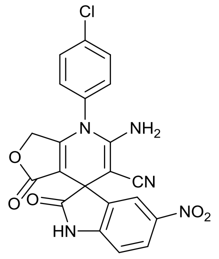
4k, 50 min, 95%



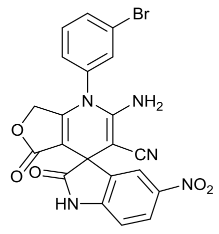
4l, 80 min, 85%



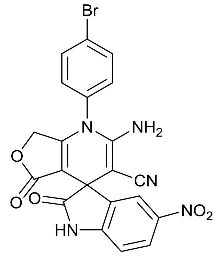
4m, 50 min, 92%



4n, 50 min, 93%



4o, 60 min, 93%



4p, 80 min, 85%

[a] Reaction conditions: isatins (1 mmol), malononitrile (1 mmol), and anilinolactones (1 mmol) in ChCl/urea (1 ml), MW 500 W, 90 °C.

Finally, we investigated the recovery and reusability of the catalytic system in the model reaction. After completion of the reaction, the reaction mixture was cooled to room temperature, the catalyst was separated magnetically, and washed with acetone followed by water, and dried under vacuum. Then, water was added to the reaction mixture to dissolve DES. The formed solid product was collected by filtration. The water of the aqueous phase containing the DES, was evaporated under reduced pressure in order to recover the DES. The recover DES and catalyst were reused in the model reaction for the next round. It was found that the catalytic system could be reused up to eight consecutive catalytic runs without a significant change in catalytic activity (Fig. 4). The amount of Mo and Fe leaching was also determined by ICP-MS analysis and found that the Mo and Fe contents after eight cycles were 0.82 and 0.66 ppm in ChCl/urea, respectively. This result confirmed that only a slight loss of the catalyst occurred during the course of work-up process.

In order to prove the heterogeneous nature of the catalyst, a hot-filtration test was performed. The catalyst was separated from the reaction mixture (after 30 min associated with approximate 50% conversion) using an external magnet. The progress of the reaction was monitored after removal of the catalyst. No further improvement of the yield of product was observed even after an extended time (1.5 h), indicating that the catalyst was stable under the reaction conditions and no leaching of the active species from the support.

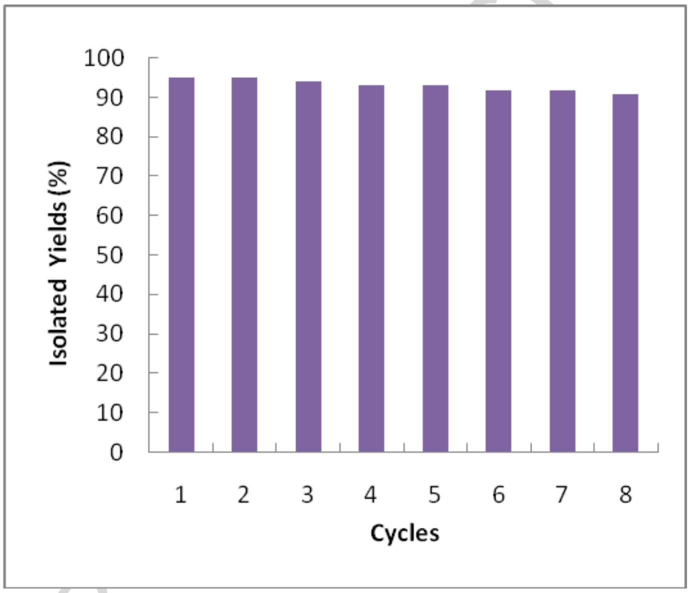


Fig. 4 Reusability of the Fe_3O_4/GO-Mo in ChCl/urea catalytic system in the model reaction. Reaction conditions: isatin (10 mmol), malononitrile (10 mmol), and 4-(*p*-tolylamino)furan-2(5*H*)-one (10 mmol), catalyst (200 mg) in ChCl/urea (10 ml).

4. Conclusion

In summary, we have developed a new type of magnetically separable graphene oxide supported molybdenum (Fe_3O_4/GO-Mo) catalyst and demonstrated that it was an efficient heterogeneous catalyst for synthesis of spiro-oxindole dihydropyridines via one-pot, three-component reaction of isatins, malononitrile and anilinolactones in ChCl/urea under microwave irradiation. Moreover, catalytic system could be easily recovered and reused eight times without significant loss of activity, conferring great potential for industrial application.

Acknowledgments

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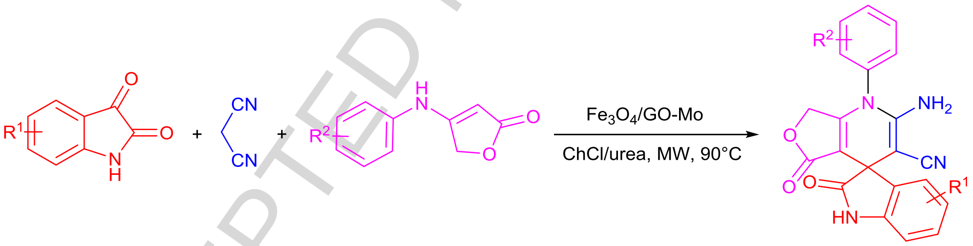
- **Graphical Abstract:**

Supported molybdenum on graphene oxide/Fe_3O_4: an efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep eutectic solvent under microwave irradiation

Mo Zhang, Yu-Heng Liu,* Ze-Ren Shang, Hai-Chuan Hu and Zhan-Hui Zhang*



Highlights

- Preparation of a new magnetic graphene oxide supported molybdenum catalyst.
- It showed high catalytic activity for the synthesis of spiro-oxindole dihydropyridines.
- The catalyst could be easily isolated by magnetic decantation.
- The catalyst was reused several times without any significant loss in catalytic activity.