Article

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Magnetic Graphene Oxide Anchored Sulfonic Acid as a Novel Nanocatalyst for the Synthesis of N-aryl-2-amino-1,6-naphthyridines

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Magnetic graphene oxide functionalized with sulfonic acid (Fe_3O_4-GO-SO_3H) was used as a new recyclable nanocatalyst for one-pot synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives under solvent free conditions. The catalyst could be easily recovered from the reaction mixture by an external magnet and reused without significant decrease in activity even after 4 runs. This nanocatalyst exhibited better activities to other commercially available sulfonic acid catalysts.

Keywords: Magnetic nanocatalyst; Sulfonic acid; N-aryl-2-amino-1,6-naphthyridines.

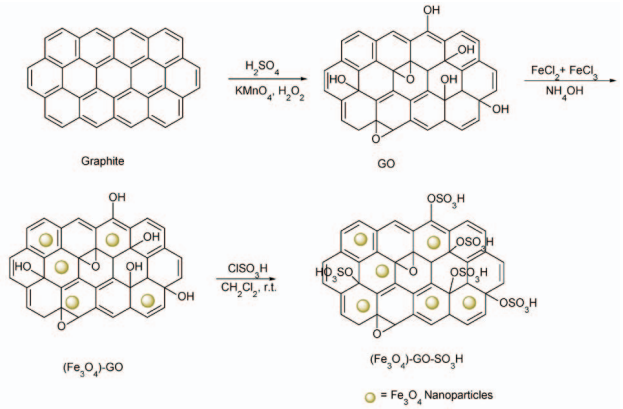
INTRODUCTION

Acid catalysts are used in a variety of industrial organic reactions, including aldol condensations, acylations, nucleophilic additions, hydrolyses, and others. However, use of soluble or liquid acids (homogeneous catalysts) has been inhibited in manufacturing synthesis because of difficulty in their waste neutralization, separations, reactor corrosion, and reusability. Consequently, the need for solid acid catalysts has arisen.[1]

GO, as a basic material for the preparation of individual graphene sheets in bulk-quantity, has attracted great attention in recent years.[2-4] In addition, the very large specific surface area, the abundant oxygen containing surface functionalities, such as epoxide, hydroxyl, and carboxylic groups, and the high water solubility afford GO sheets great promise for many more applications.[2,3] For instance, the GO nano-sheets modified with polyethylene glycol have been employed as aqueous compatible carriers for water-insoluble drug delivery.[2] The intrinsic oxygen-containing functional groups were used as initial sites for deposition of metal nanoparticles, such as Fe_3O_4, on the GO sheets, which opened up a novel route to multifunctional nanometer scaled catalytic, magnetic, and electronic materials.[5-8]

However, there are no reports about the functionalization of magnetic graphene oxide with sulfonic acid groups. Hence, for the first time the present work illustrates the immobilization of sulfonic acid groups on magnetic graphene oxide (Scheme I) for its use as recyclable, solid acid catalyst for the synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives.

Scheme I Preparation of (Fe_3O_4)-GO-SO_3H



It should be noted that [(Fe_3O_4)-GO-SO_3H] exhibits much better catalytic properties (activity and recyclability) than porous solid acids such as -SO_3H functionalized ordered mesoporous silica and other -SO_3H functionalized nanoparticles (Fe_3O_4) in acid-catalyzed reactions. This ac-

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tive solid acid catalyst in the presence of a magnetic field was easily recovered and exhibited good recyclability.

Over the past few years, naphthyridine derivatives have received considerable attention because of their wide range of biological and pharmaceutical activities, such as antitumor, anti-inflammatory, and antifungal properties.[9-11] These compounds are very useful in the treatment of hypertension, myocardial infarction, hyperlipidemia, cardiac arrhythmia, and rheumatoid arthritis.[12-14]

In view of these useful properties, and since we were interested in the synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives, a literature survey revealed that there are only a few reports for the synthesis of these compounds. El-Subbagh et al. have reported the synthesis of 1,6-naphthyridine derivatives through the two component reaction of α,β-unsaturated ketones and cyanoacetamide in butanol.[10] Recently, Shu-Jiang Tu et al.[15] reported the synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives through three component reaction between α,β-unsaturated ketones, aniline, and malononitrile using microwave irradiation in the presence of acetic acid as catalyst.

However, these methods are time-consuming and use large amount of toxic solvents, and reagents. Thus, the development of a green, simple, efficient, and general method for the synthesis of these widely used organic compounds, from readily available reagents, remains one of the major challenges in organic synthesis.

Therefore in this work, magnetically recoverable catalyst [(Fe_3O_4)-GO-SO_3H] have been used as new acidic catalyst for the one-pot synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives under solvent free conditions.

RESULTS AND DISCUSSION

At first the (Fe_3O_4)-GO was prepared according to the reported method in the literature with some modifications.[16] Then, the magnetic graphene oxide was reacted with chlorosulfonic acid to prepare the (Fe_3O_4-GO-SO_3H) as a new nanocatalyst. The prepared (Fe_3O_4)-GO-SO_3H was characterized with SEM, IR, XRD and acid-base titration.

In FT-IR spectra the band in the region of 1036 and 1153 cm^{-1} is attributed to the stretching vibrations of the (S=O) and the peak appeared at about 3367 cm^{-1} is due to the stretching of OH groups in the SO_3H (Fig. 1).

The structural properties of the synthesized nanocatalyst were analyzed by XRD (Fig. 2). (Fe_3O_4)-GO-SO_3H showed a sharp diffraction peak at 34.90° which originated from the diffraction GO on its (002) layer planes. Also, synthetic nanocatalyst showed some low intensity diffraction peaks that were indexed to cubic Fe_3O_4. In general, the XRD peaks of nanocatalyst were indexed to (002), (311), (400), (422) and (511) planes of a cubic unit cell of magnetite, appearing at 34.90°, 45.53°, 56.21°, 64.01° and 67.29°, respectively.

Also the SEM (Fig. 3) showed that the embedded nanoparticles were presented as uniform particles with rod morphology.

At first, for optimization of the reaction conditions, 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one

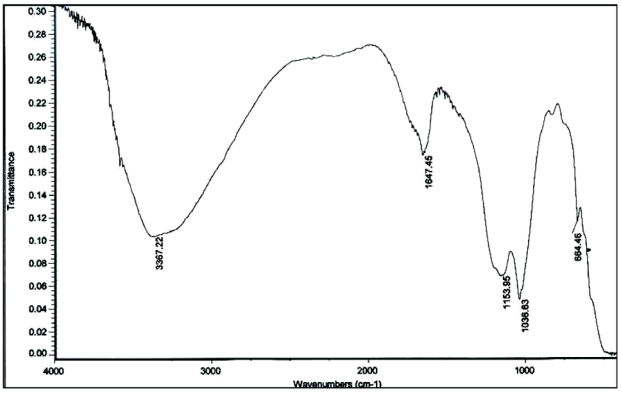


Fig. 1. The IR spectra of (Fe_3O_4)-GO-SO_3H.

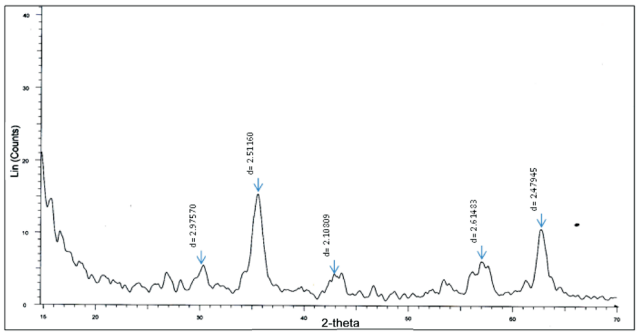


Fig. 2. The XRD patterns of (Fe_3O_4)-GO-SO_3H.

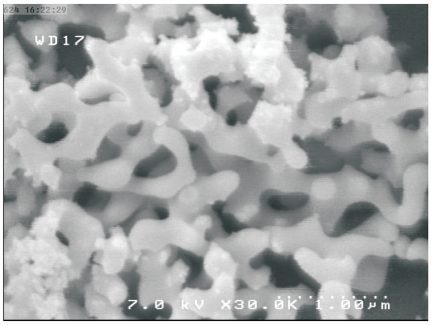
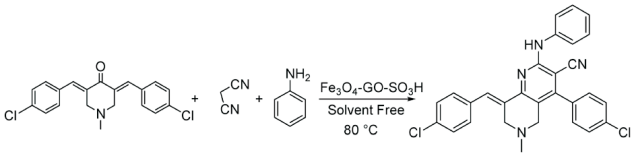


Fig. 3. The SEM image of (Fe_3O_4)-GO-SO_3H.

(0.33 mmol), aniline (0.33 mmol), and malononitrile (0.33 mmole) were used as model reactants under solvent-free conditions (Scheme II).

Scheme II Model reaction for the optimization



In order to show the unique catalytic behavior of (Fe_3O_4)-GO-SO_3H and to compare its activity with other catalysts, this reaction was performed in the presence of catalytic amount of $H_3PW_{12}O_{40}$, $HClO_4/SiO_2$, $NaHSO_4/SiO_2$, $NaHSO_4$, MCM-41, $(\alpha$-$Fe_2O_3)$-MCM-41, $(\alpha$-$Fe_2O_3)$-MCM-41-SO_3H and nanocrystalline metal oxides such as CuO and Fe_3O_4 nanoparticles. It was observed that only acidic catalysts were able to catalyze this reaction. Hence, it seems that the (Fe_3O_4)-GO-SO_3H is the most effective catalyst for this purpose, leading to the synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives in higher yields and shorter reaction times. The efficiency of this catalyst is due to the high surface area and strong acidity of -SO_3H groups (Table 1).

A comparison of the performance of the (Fe_3O_4)-GO-SO_3H in various solvents is shown in Table 2. Among the solvents tested (DMF, acetonitrile, methanol, ethanol, water) and solvent-free conditions the latter gave the highest yields with shorter reaction times.

After optimization of the reaction condition, a variety of aromatic aldehydes, possessing both electron-donating and electron-withdrawing groups were employed for N-aryl-2-amino-1,6-naphthyridine formation and the results indicated that for 3,5-dibenzylidenepiperidin-4-one bearing different functional groups, the reaction proceeded smoothly in all cases. It is worthwhile to note that 3,5-dibenzylidenepiperidin-4-one with electron-withdrawing groups reacted rapidly whereas those with electron-rich groups, required longer reaction times. Electron-withdrawing groups on the phenyl rings induce greater electronic positive charge on the corresponding β-atoms than electron donating moieties (Table 3).

The plausible mechanism is shown in Scheme III. Because of high surface area of magnetic nanocatalyst, the reactants are absorbed easily toward the nanocatalyst, and accompanied by the inherent Brönsted acidity of -SO_3H and

Table 1. Comparing the efficiency of different catalysts in the synthesis of **6d**

Entry	Catalyst*	Time (min)	Yield (%)
1	No catalyst	180	Trace
2	$H_3PW_{12}O_{40}$	180	45
3	$HClO_4/SiO_2$	180	50
4	$NaHSO_4/SiO_2$	180	47
5	$NaHSO_4$	240	35
6	CuO NPs	300	Trace
7	Fe_3O_4 NPs	360	Trace
8	Acetic acid, MW, 110 ºC, 200W	5	96 [15]
9	MCM-41	180	Trace
10	$(\alpha$-$Fe_2O_3)$-MCM-41	180	Trace
11	$(\alpha$-$Fe_2O_3)$-MCM-41-SO_3H	130	95 [17]
12	(Fe_3O_4)-GO-SO_3H	61	96

* Catalytic amount of all compared catalysts is 50 mg per 0.33 mmol of reactants

Table 2. Solvent screening for the synthesis of **6d**

Entry	Solvent	Reaction condition	Time (min)	Yield (%)
1	DMF	reflux	180	75
2	CH_3CN	reflux	180	50
3	CH_3OH	reflux	180	10
4	C_2H_5OH	reflux	180	60
5	H_2O	reflux	180	-
6	-	Solvent-free	61	96

Scheme III A plausible mechanism for the synthesis of N-aryl-2-amino-1,6-naphthyridine in the presence of (Fe_3O_4)-GO-SO_3H

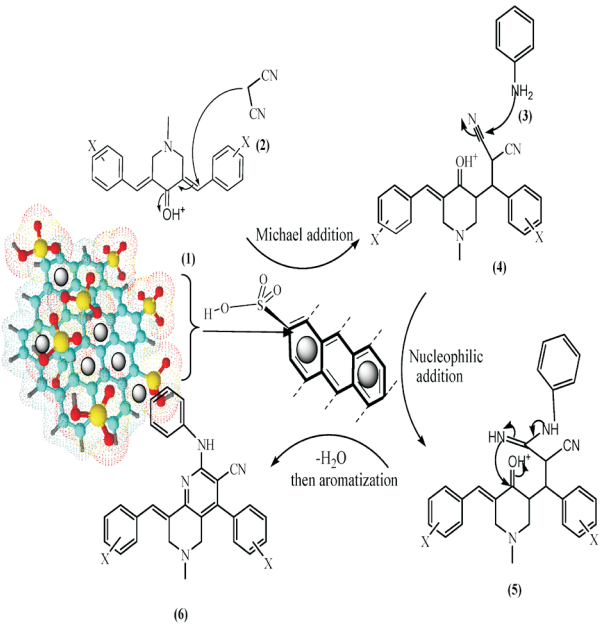
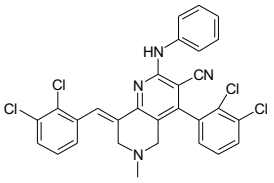
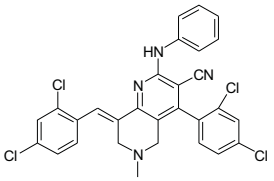
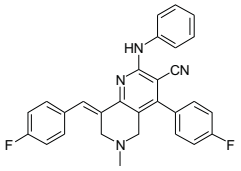
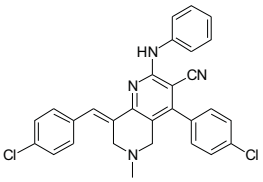
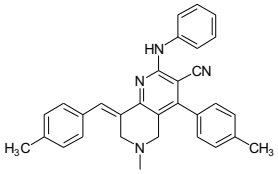
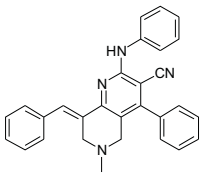
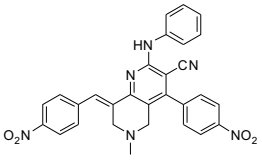
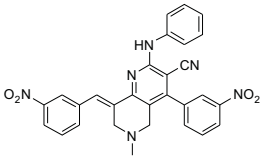
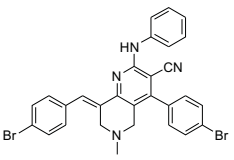


Table 3. The reaction time (min) and the yield (%) of N-aryl-2-amino-1,6-naphthyridine product

Entry		Product	Time (min)	Yield* (%)	M.P (°C) Found	M.P (°C) Reported
1	6a		35	95	221-223	-
2	6b		26	95	239-240	-
3	6c		56	93	244-245	244-246 [15]
4	6d		61	96	254-255	253-255 [15]
5	6e		65	84	233-235	233-235 [15]
6	6f		60	87	229-231	229-231 [15]
7	6g		45	96	243-245	243-245 [15]
8	6h		50	90	243-245	244-247 [15]
9	6i		50	93	268-269	268-270 [15]

Lewis acidity of the Fe^{3+}, which both are capable of bonding with the carbonyl oxygen of the 3,5-dibenzylidenepiperidin-4-one moiety. Afterwards, the Michael addition between activated 3,5-dibenzylidenepiperidin-4-one (**1**) and malononitrile (**2**) occurs, and then nucleophilic addition of aniline (**3**) to one of the cyano groups in the intermediate (**4**) results in the formation of the intermediate (**5**). Subsequently, through cyclization, and aromatization, the product (**6**) is formed. In other words, ionic intermediates (**4**, **5**) are generated inside the nanocatalyst because of the strong polarity of the $–SO_3H$ and Fe^{3+} groups. Using this magnetic nanocatalyst, the reaction rates and yields under the reaction condition are enhanced.

Finally, because of the magnetic property of the catalyst and in the presence of an external magnet, catalyst was transferred onto the magnet steadily and the reaction mixture turned clear within 10 s. Thus, the catalyst was collected effectively and the recovered catalyst was used in subsequent runs without observation of any significant decrease in activity even after 4 runs (Fig. 4).

EXPERIMENTAL

Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}CNMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts (δ) were reported relative to TMS, and coupling constants (*J*) were reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential. X-ray powder diffraction (XRD) was carried out on a Philips X'Pert diffractometer with CoKα radiation.

Preparation of (Fe_3O_4)-GO-SO_3H. To (Fe_3O_4)-GO (1 g), chlorosulfonic acid (0.5 g, 4.5 mmol) in 5 mL dichloromethane was added dropwise at room temperature during 30 min. After completion of the addition, the mixture was mechanically stirred for more 30 min until HCl was removed from reaction vessel. The mixture was then filtered and washed with CH_2Cl_2 to give (Fe_3O_4)-GO-SO_3H as brown powder.

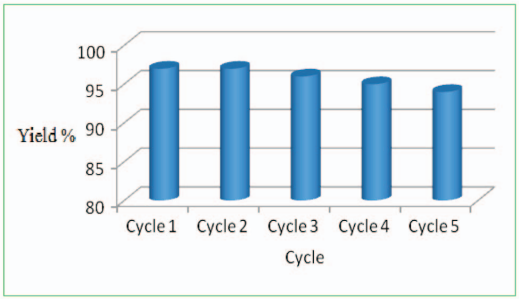


Fig. 4. Catalyst recovery at the end of the reaction.

General Procedure for the synthesis of 3,5-dibenzylidenepiperidin-4-one.[10] In a 50-mL reaction vial, a mixture of the 4-piperidone (10 mmol), the appropriate aldehyde (20 mmol), 10% NaOH (1 mL) and 95% EtOH (30 mL) was stirred at room temperature for 0.5-2 h. The separated solid was collected by filtration and recrystallized from ethanol for further purification.

General Procedure for the synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives. To the mixture of 3,5-dibenzylidenepiperidin-4-one (0.33 mmol), aniline (0.33 mmol), and malononitrile (0.33 mmol) was added (Fe_3O_4)-GO-SO_3H (50 mg); it was then stirred at 80 °C for an appropriate period of time (Table 3). After completion of the reaction (monitored by thin-layer chromatography, TLC; petroleum ether and EtOAc, 1:1), the ethanol was added to the reaction mixture and the catalyst was collected with an external magnet. Then, the mixture was filtered and the product was further purified by recrystallization from EtOH/H_2O (1:1) to give the pure product.

CONCLUSIONS

In summary, the new (Fe_3O_4)-GO-SO_3H nanocatalyst was prepared directly through the reaction of chlorosulfonic acid with (Fe_3O_4)-GO and used as a magnetically recoverable catalyst for an efficient one-pot synthesis of N-aryl-2-amino-1,6-naphthyridine derivatives under solvent free conditions. The catalyst was separated with an external magnet, and used in subsequent runs without observation of significant decrease in activity even after 3 runs. This new prepared catalyst exhibited better activities to other commercially available sulfonic acid catalysts.

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REFERENCES

1. Corma, A.; Garcia, H. *Adv. Synth. Catal.* **2006**, *348*, 1391.
2. Li, D.; Muller, M. B.; Gilje, S.; Kaner, R. B.; Wallance, G. G. *Nat. Nanotechnol.* **2008**, *3*, 101.
3. Park, S.; Ruoff, R. S. *Nat. Nanotechnol*. **2009**, *4*, 217.
4. Tung, V. C.; Allen, M. J.; Yang, Y.; Kaner, R. B. *Nat. Nanotechnol*. **2009**, *4*, 25.
5. Liu, Z.; Robinson, J. T.; Sun, X.; Dai, H. *J. Am. Chem. Soc*. **2008**, *130*, 10876.
6. Lomeda, J. R.; Doyle, C. D.; Kosynkin, D. V.; Hwang, W.; Tour, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 16201.

7. Muszynski, R.; Seger, B.; Kamat, P. V. *J. Phys. Chem. C* **2008**, *112*, 5263.
8. Xu, Y.; Liu, Z.; Zhang, X.; Wang, Y.; Tian, J.; Huang, Y.; Ma, Y.; Zhang, X.; Chen, Y. *Adv. Mater.* **2009**, *21*, 1275.
9. (a) Dukat, M.; Fiedler, W.; Dumas, D.; Damaj, I.; Martin, B.; Rosecrans, J. A.; James, J. R.; Glennon, R. A. *Eur. J. Med. Chem*. **1996**, *31*, 875. (b) Romero, F. M.; Ziessel, R. *Tet. Lett.* **1995**, *36*, 6471. (c) Heller, M. U.; Schubert, S. *J. Org. Chem*. **2002**, *67*, 8269. (d) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *10*, 3553. (e) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn*. **1990**, *63,* 80.
10. El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-Obaid, A. M. *J. Med. Chem*. **2000**, *43*, 2915.
11. Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem*. **2002**, *45*, 2501.
12. El-Kashef, H. S.; Geies, A. A.; Kamal El-Dean, A. M.; Abdel-Hafez, A. A. *J. Chem. Technol. Biotechnol.* **1993**, *57*, 15.
13. Haglid, F. *Ark. Kemi*. **1967**, *26*, 489.
14. Skotnicki, J. S. *Chem. Abstr.* **1990**, *113*, 78372 (US Patent 4,902,685).
15. Han, Z.-G.; Miao, C.-B.; Shi, F.; Ma, N.; Zhang, G.; Tu, S.-J. *J. Comb. Chem*. **2010**, *12*, 266.
16. Kassaee, M. Z.; Motamedi, E.; Majdi, M. *Chem. Eng. J.* **2011**, *172*, 540.
17. Rostamizadeh, S.; Azad, M.; Shadjou, N.; Hasanzadeh, M. *Catal. Commun*. **2012**, *25*, 83.

