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ORIGINAL PAPER

Green and recyclable sulfonated graphene and graphene oxide nanosheet catalysts for the syntheses of 3,4-dihydropyrimidinones

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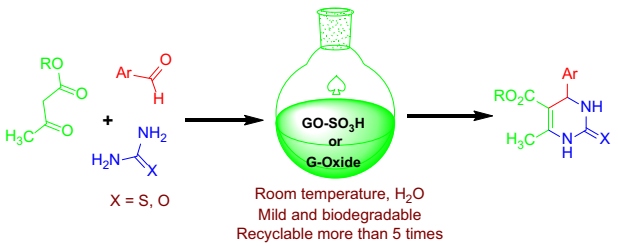
Abstract Sulfated graphene and graphene oxide were used successfully as the heterogeneous catalysts for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) through the reaction between ethyl acetoacetate, an aldehyde, and an urea or thiourea, at room temperature in the environmentally friendly solvent. The catalysts could be separated from the reaction mixture and reused at least five times without any considerable loss of the activity. Sulfonated graphene proved to be a more efficient catalyst compared with graphene oxide.

Graphical abstract



Keywords Sulfonated graphene · Graphene oxide · Dihydropyrimidinones · Multicomponent

Introduction

The chemistry of 3,4-dihydropyrimidin-2(1*H*)-ones(-thiones) (DHPMs) has come a long way since the pioneering works of Pietro Biginelli [1–4]. DHPMs and their derivatives have exhibited antibacterial and antifungal properties [5], antiviral activity [6], anti-inflammatory [7], anticancer agents [8–13], and antioxidative properties [14]. In addition, being potent calcium channel modulators, they display coronary dilation and antihypertensive effects [15–27]. DHPMs and well-known 1,4-dihydropyridine calcium channel modulators of the nifedipine-type reveal high structural similarity and similar biological profiles [15].

The classic approach to the synthesis of DHPMs is Biginelli reaction through the condensation reaction of ethyl acetoacetate, aromatic aldehyde, and urea under strong acidic conditions. Different synthetic strategies have been developed for the preparation of the DHPMs derivatives [28]. However, among the various acid catalysts, the solid acid catalysts and especially supported solid acids are attracting more consideration in organic transformations. These catalysts improve the atom efficiency of the reaction, simplify the process and workup, increase the lifetime (through reuse), and reduce the volume of waste. Reusability of the solid catalyst is another important issue in the organic chemistry. In the last decade, several nanosolid catalysts, such as graphite [29], sulfonated carbon [30], ZrO_2-nanopowder/sf/MWI [31], silica/Fe [32], and PVP-DVBl/CeO_2/H_2O [33], for this synthesis strategy have been reported.

Graphene was experimentally isolated in 2004, and became one of the most intriguing research prospects [34].

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Graphene represents a new class of carbon material, which has unique two-dimensional hexagonal atomic layer nanostructure and fascinating unusual properties. The application of graphene, as an ideal support in heterogeneous catalysis, has been grown significantly due to the integrated cost reduction for graphene production, high specific surface area, extraordinary thermal, and mechanical stability [35–37]. Given the importance of graphene, the large-scale use of graphene as support can be expected. In fact, graphene because of increasing the yield of catalysis recovery and more efficient process has been widely used as a support material for various catalytic applications in recent years [38–40].

There is no example on the use of sulfonated graphene (GO-SO_3H) and graphene oxide (GO) as catalyst for the synthesis of dihydropyrimidinones and -thiones. In continuation of our efforts to introduce new efficient methods for the synthesis of heterocyclic compounds [41–43], especially DHPMs skeletons [44], herein, we report a facile and straightforward method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thi)ones **4** via a one-pot condensation reaction between ethyl acetoacetate (**1**), (aromatic) aldehyde **2**, and urea or thiourea (**3**) in the presence of sulfonated graphene (GO-SO_3H) or graphene oxide (GO) in water at ambient temperature (Scheme 1).

Results and discussion

The synthesis of GO-SO_3H was accomplished in the three steps [45, 46]. The first step involved the synthesis and prereduction of GO using $NaBH_4$, the second step is sulfonation of reduced GO using the aryl diazonium salt of sulfanilic acid, and the third step consisted of postreduction using hydrazine.

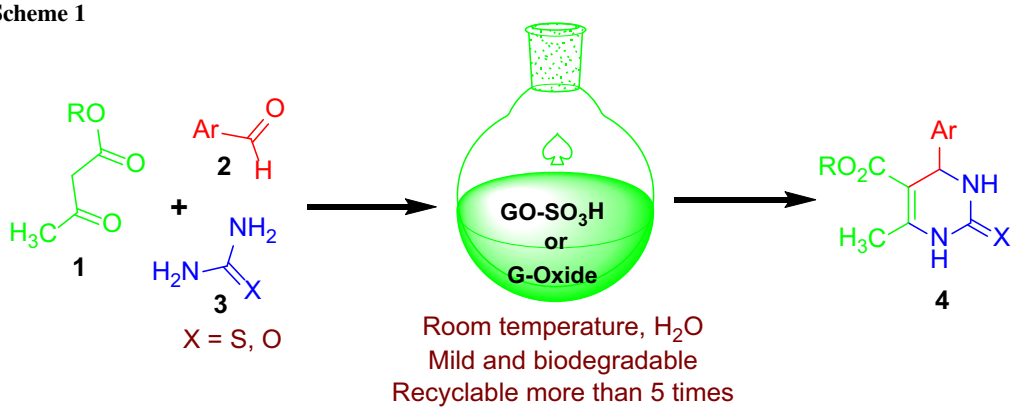
As shown in Fig. 1, the TEM image of the GO-SO_3H sample appears transparent, and shows a single layer graphene sheet. Figure 2 shows the XRD patterns of sulfonated graphene (GO-SO_3H) and graphene oxide (GO). In the XRD pattern of GO, the strong and sharp peak at $2\theta = 11.6°$ corresponds to an interlayer distance of 7.6 Å (d002). In the XRD pattern of GO, the graphite peak at 26.5° disappeared completely and confirmed the formation of GO. After reduction of GO by sodium borohydride and sulfonation of reduced graphene oxide, the diffraction peak at 11.6° associated with GO disappears, and the broad diffraction peak ranging centered at 24.2° appears, which suggested that GO was reduced to graphene with only a few layers [47]. CHNS analysis indicates the presence of sulfur in 4.83 % in GO-SO_3H nanosheets.

The effect of solvents was also examined for the above reaction, and the results indicated the solvent efficiency on the reaction. Performing the reaction of benzaldehyde, ethyl acetoacetate, and urea in various protic and aprotic solvents showed the efficiency of polar solvents, and preferentially water as the reaction solvent (Table 1). As can be seen in Table 1, of the solvents, polar solvents, among them water as the reaction solvent was selected because of its better efficiency, and green chemistry is preferred over other solvents.

The catalytic activity of GO and GO-SO_3H was evaluated for the synthesis of **4d**. As shown in Table 2, it was found that 0.01 g of GO or GO-SO_3H in H_2O is the best reaction condition (entry 3). It is important to note that while organic solvents, such as EtOH, gave similar yields. Furthermore, H_2O was selected as the solvent due to its accordance with the green chemistry principle.

The synthesis of the DHPMs involved the one-pot reaction between ethyl acetoacetate (**1**), (aromatic) aldehyde **2,** and urea or thiourea (**3**) in the presence of sulfonated graphene (GO-SO_3H) or graphene oxide (GO) in water at ambient temperature (Scheme 1). The reaction proceeded smoothly, and the product was separated from the reaction mixture in high yields and purity without any further work-up. Various aromatic aldehyde and urea or thiourea were used successfully in this reaction; the synthesized products are presented in Table 3.

Scheme 1



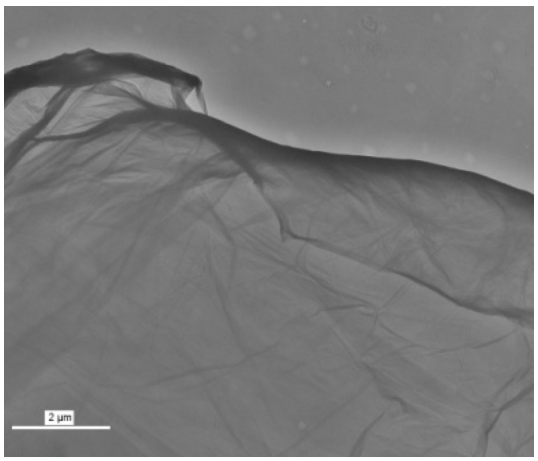


Fig. 1 TEM image of synthesized GO-SO_3H

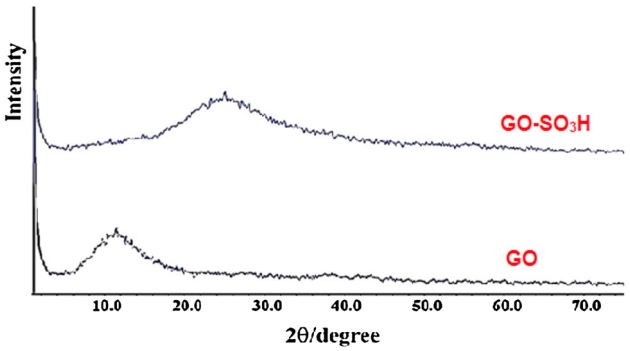


Fig. 2 X-ray diffraction (XRD) pattern of GO and GO-SO_3H

Table 1 Influence of the solvent on the yield of model 3,4-DHPM **4d**

Entry	Solvent	Time/min	Yields[a]/%	
			GO[b]	G-SO_3H[c]
1	Toluene	25	0	0
2	Dichloromethane	25	14	18
3	Chloroform	25	19	24
4	THF	25	29	35
5	Acetonitrile	25	68	73
6	Ethanol	25	76	82
7	Water	25	87	91

Reaction conditions: benzaldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol), and urea (3.00 mmol) in solvent and 0.01 g GO or GO-SO_3H as catalyst at room tempreature

[a] Isolated yield

[b] Graphene oxide nanosheets

[c] Sulfonated graphene nanosheets

As results show, electron-rich and electron-deficient substrates were reacted to synthesis the corresponding DHPMs under the optimized reaction conditions. As indicated in Table 3, the reaction proceeds efficiently and led to the products **4a**–**4m** in good yields.

Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency using this procedure (Table 3). Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in high to quantitative yields with high purity. Acid-sensitive furfural also worked well without the formation of any side products (Table 3, entry **4g**). Another important feature of this method is survival of a variety of functional groups, such as nitro, halide, hydroxyl, and methyl groups, under the reaction conditions. This method is even effective with aliphatic and α,β-unsaturated aldehydes, which normally show extremely low conversions in the Biginelli reaction (Table 3, entries **4g** and **4h**). Unlike most of the reported methods, this procedure does not require any additives or activators or anhydrous conditions. Some other methods require the use of toxic reagents in combination with Bronsted acids, such as hydrochloric acid and acetic acid, as additives [28]. This procedure not only preserves the simplicity of the Biginelli reaction, but also produces excellent yield of the products with high purity. Thiourea has been used with similar success to produce the corresponding thio derivatives of dihydropyrimidinones, which are also of much interest with respect to their biological activities (Table 3, entries **4j**–**4m**) [28]. Decreased reaction times and improved yields are realized as a result of the increased reactivity of the substrates on the surface of GO-SO_3H or GO. In addition, water is a medium that is fully compatible with green chemistry.

The reusability of the catalyst was also investigated with the same model reaction again studied under the optimized conditions. After the completion of the reaction, the catalyst was recovered according to the procedure described in the experimental section and reused. The catalyst could be reused at least six times with only a slight reduction in activity.

The changes in the structure of the recovered GO-SO_3H and GO were determined by Raman, XRD, and FT-IR methods. In addition, the XRD pattern of GO-SO_3H and GO is the same as Fig. 2. As can be seen in Fig. 3, the structure of the recycled catalyst does not change, and a very slight decrease in the reaction yield is may be due to the covering the surface of catalyst by impurities.

Experimental

All the reagent and solvents were obtained from Merck (Germany) and were used without further purification. Melting points were measured on an Electro Thermal 9100 apparatus.

Table 2 Effects of catalyst amount for the synthesis of 3,4-DHPM **4d**

Entry	Catalyst amount/g	Solvent	Time/min	Yields[a]/%	
				GO[b]	G-SO_3H[c]
1	0.005	Water	25	53	60
2	0.005	Ethanol	25	43	48
3	0.01	Water	25	87	91
4	0.01	Ethanol	25	76	82
5	0.02	Water	25	89	92
6	0.02	Ethanol	25	78	83
7	0.03	Water	25	90	92
8	0.03	Ethanol	25	78	84

Reaction conditions: benzaldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol), and urea (3.00 mmol) in solvent and GO or GO-SO_3H as catalyst at room tempreature

[a] Isolated yield

[b] Graphene oxide nanosheets

[c] Sulfonated graphene nanosheets

Table 3 One-pot synthesis of DHPMs derivatives in the presence of graphene oxide (GO) and sulfonated graphene (GO-SO_3H) in H_2O

Product	Ar	R	X	Time/min	Yields[a]/%		M.p./°C	
					GO[b]	GO-SO_3H[c]	Found	Reported [44]
4a	4-HO–C_6H_4	Et	O	20	87	93	226–228	226–228
4b	4-CH_3–C_6H_4	Et	O	20	81	92	215–217	215–217
4c	4-Cl–C_6H_4	Et	O	25	79	90	210–213	209–211
4d	C_6H_5	Et	O	25	85	91	199–201	200–203
4e	C_6H_5CH=CH	Et	O	30	77	89	234–236	237–239
4f	4-NO_2–C_6H_4	Et	O	35	80	88	206–208	207–209
4g	2-Furyl	Et	O	30	83	89	206–208	208–209
4h	Cyclohexyl	Et	O	35	79	83	237–239	236–238
4i	C_6H_5	CH_3	O	25	86	90	221–223	222–224
4j	4-HO–C_6H_4	Et	S	20	84	92	199–201	198–200
4k	3-NO_2–C_6H_4	Et	S	35	80	85	203–205	201–203
4l	4-NO_2–C_6H_4	Et	S	35	78	86	108–110	107–109
4m	2-Furyl	Et	S	30	79	86	183 (dec.)	184 (dec.)

Reaction conditions: aldehyde, ethyl acetoacetate, urea or thiourea, 0.01 g GO or GO-SO_3H, room temperature

[a] Isolated yield

[b] Graphene oxide nanosheets

[c] Sulfonated graphene nanosheets

Preparation of graphene oxide [47]

GO was prepared using a modified Hummer's method. Graphite powder (1.00 g, 325 mesh) and 23 cm^3 concentrated H_2SO_4 were added to a 250 cm^3 conical flask and the mixture stirred. Sodium nitrate (0.50 g) was added, and the resulting mixture was cooled to 0 °C. Under vigorous agitation, 3.00-g $KMnO_4$ was added slowly, and the mixture was stirred for 1 h, while the temperature was kept below 35 °C. Then, 45 cm^3 H_2O was added slowly to the reaction mixture, and the solution was stirred for 30 min at 90 °C. Next, 10.0 cm^3 H_2O_2 (30 % solution) and 140 cm^3 deionized water were added to the mixture. Then, resulting precipitate was centrifuged and washed repeatedly with 5 % HCl (3 × 15 cm^3) and EtOH, and vacuum dried at 60 °C. The GO was obtained as a brown powder.

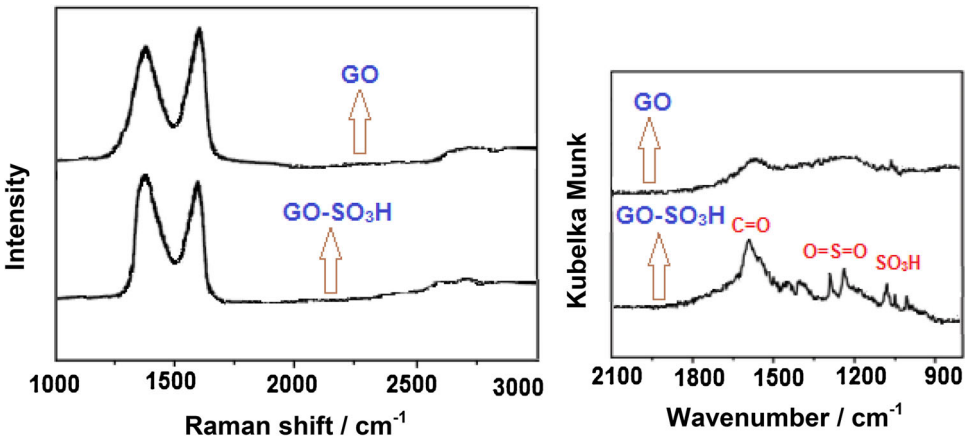


Fig. 3 FT-IR and Raman scattering spectra of GO and GO-SO_3H

Preparation of sulfonated graphene [49]

Graphene oxide (GO) was reduced using 0.60-g $NaBH_4$. The pH of the reaction mixture was adjusted to 9–10, and the temperature was kept constant at 80 °C. After 1 h, the partially reduced GO was centrifuged and washed with H_2O (5 × 15 cm^3). The reduced GO was dispersed in 75.0-g H_2O by sonication for 20 min. The aryl diazonium salt, which was prepared from the reaction of 0.02-g sodium nitrite and 0.5-g HCl (1 M) in 10.0-g H_2O in an ice bath, was added to the dispersed GO. After stirring in the ice bath for 2 h, the product was separated from the reaction media by centrifugation and washed with H_2O (3 × 10 cm^3). The resulting sulfated graphene oxide was dispersed in 75.0-g water and reduced using 2.00-g hydrazine in 5 cm^3 of H_2O at 100 °C for 2 h. The final product was obtained after rinsing with 50 cm^3 H_2O.

General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-(thi)ones 4a–4m

To a solution of ethyl acetoacetate (1.10 mmol), aldehyde (1.00 mmol), and urea or thiourea (3.00 mmol) was added, 0.01-g GO or GO-SO_3H dispersed in 3.00 cm^3 H_2O. The mixture was stirred at room temperature for 20–35 min. After completion of the reaction, which resulted in precipitation of the desired 3,4-dihydropyrimidin-2(1*H*)-(thi)ones **4a**–**4m**. The precipitated solid was filtered, dried, washed with petroleum ether to remove any residual starting material, and then recrystallized from ethanol to afford the pure product. The catalyst could be recovered after evaporation of the aqueous layer. After washing with EtOH and H_2O (2 × 4 cm^3) and drying at 300 °C, GO or GO-SO_3H separated as a black solid, and reused consecutive times in Biginelli reactions. Products were characterized by ^1H NMR, ^{13}C NMR, and CHN analysis data.

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References

1. Biginelli P (1891) Ber Deutsch Chem Ges 24:1317
2. Biginelli P (1893) Gazz Chim Ital 23:360
3. Biginelli P (1891) Ber Deutsch Chem Ges 24:2962
4. Biginelli P (1893) Ber Deutsch Chem Ges 26:447
5. Ashok M, Holla BS, Kumari NS (2007) Eur J Med Chem 42:380
6. Hurst EW, Hull R (1961) J Med Pharm Chem 3:215
7. Bahekar SS, Shinde DB (2004) Bioorg Med Chem Lett 14:1733
8. Blacquiere JM, Sicora O, Vogels CM, Cuperlovic-Culf M, Decken A, Ouellette RJ, Westcott SA (2005) Can J Chem 83:2052
9. Kato T, Chiba T, Abe Y (1984) 5-Carbamoyl-6-methyl-4-substituted-1,2,3,4-tetrahydro-2-thioxopyrimidines. Jpn Pat. 59190974, Oct 29, 1984; (1985) Chem Abstr 102:132067
10. Fewell SW, Smith CM, Lyon MA, Dumitrescu TP, Wipf P, Day BW, Brodsky JL (2004) J Biol Chem 279:51131
11. Rodina A, Vilenchik M, Moulick K, Aguirre J, Kim J, Chiang A, Litz J, Clement CC, Kang Y, She Y, Wu N, Felts S, Wipf P, Massague J, Jiang X, Brodsky JL, Krystal GW, Chiosis G (2007) Nat Chem Biol 3:498
12. Evans CG, Wisen S, Gestwicki JE (2006) J Biol Chem 281:33182
13. Wisen S, Androsavich J, Evans CG, Chang L, Gestwicki JE (2008) Bioorg Med Chem Lett 18:60
14. Magerramov AM, Kurbanova MM, Abdinbekova RT, Rzaeva IA, Farzaliev VM, Allakhverdiev MA (2006) Russ J Appl Chem 79:787
15. Kappe CO (2000) Eur J Med Chem 35:1043
16. Grover GJ, Dzwonczyk S, McMullen DM, Normadinam CS, Sleph PG, Moreland S (1995) J Cardiovasc Pharmacol 26:289
17. Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hedberg A, O'Reilly BC (1991) J Med Chem 34:806
18. Rovnyak GC, Atwal KS, Hedberg A, Kimball SD, Moreland S, Gougoutas JZ, O'Reilly BC, Schwartz J, Malley MF (1992) J Med Chem 35:3254
19. Atwal KS, Rovnyak GC, Kimball SD, Floyd DM, Moreland S, Swanson BN, Gougoutas JZ, Schwartz J, Smillie KM, Malley MF (1990) J Med Chem 33:2629
20. Atwal KS, Rovnyak GC, Schwatz J, Moreland S, Hedberg A, Gougoutas JZ, Malley MF, Floyd DF (1990) J Med Chem 33:1510

21. Baldwin JJ, Pitzenberger SM, McClure DE (1987) Substituted pyrimidinecarboxylates useful as calcium channel blockers. US Pat. 4675321, Jun 23, 1987; (1987) Chem Abstr 107:242619
22. Ertan M, Balkan A, Saraç S, Uma S, Renaud JF, Rollad Y (1991) Arch Pharm 324:135
23. Kastron VV, Vitolin RO, Khanina EL, Dubur GY, Kimenis AA, Kondratenko NV, Popov VI, Yagupolsky LM, Kolomeitsev AA (1988) Preparation of 2-oxo-4-(2′-difluoromethylthiophenyl)-5-methoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine having coronary-dilating activity. US Pat. 4738965, Apr 19, 1988; (1989) Chem Abstr 110:18547
24. Rovnyak GC, Kimball SD, Beyer B, Cucinotta G, DiMarco JD, Gougoutas J, Hedberg A, Malley M, McCarthy JP, Zhang R, Moreland S (1995) J Med Chem 38:119
25. Sujatha K, Shanmugam P, Perumal PT, Muralidharan D, Rajendran M (2006) Bioorg Med Chem Lett 16:4893
26. Yarim M, Sarac S, Kilic FS, Erol K (2003) Farmaco 58:17
27. Saraç S, Ciftçi M, Zorkun IS, Tunç O, Erol K (2007) Arzneim-Forsch/Drug Res 57:137
28. Kolosov MA, Orlov VD, Beloborodov DA, Dotsenko VV (2009) Mol Divers 13:5
29. Zhang Y-Q, Wang C, Li G-S, Li J-C, Liu H-M, Wu Q-H (2005) Chin J Org Chem 25:1265
30. Moghaddas M, Davoodnia A, Heravi MM, Tavakoli-Hoseini N (2012) Chin J Chem 33:706
31. Gopalakrishnan M, Sureshkumar P, Thanusu J, Kanagarajan V, Ezhilarasi MR (2008) Lett Org Chem 5:142
32. Martínez S, Meseguer M, Casas L, Rodríguez E, Molins E, Moreno-Manas M, Roig A, Sabastián RM, Vallribera A (2003) Tetrahedron 59:1553
33. Sabitha G, Reddy KB, Yadav JS, Shailaja D, Sivudu KS (2005) Tetrahedron Lett 46:8221
34. Novoselov KS, Geim AK, Morozov S, Jiang D, Zhang Y, Dubonos S, Grigorieva I, Firsov A (2004) Science 306:666
35. Schedin F, Geim A, Morozov S, Hill E, Blake P, Katsnelson M, Novoselov K (2007) Nature Mater 6:652
36. Novoselov K, Jiang SZ, Zhang Y, Morozov S, Stormer H, Zeitler U, Maan J, Boebinger G, Kim P, Geim A (2007) Science 315:1379
37. Wu J, Pisula W, Müllen K (2007) Chem Rev 107:718
38. Liu F, Sun J, Zhu L, Meng X, Qi C, Xiao F-S (2012) J Mater Chem 22:5495
39. Huang L, Wu B, Yu G, Liu Y (2011) J Mater Chem 21:919
40. Feng D, Gu ZY, Li JR, Jiang HL, Wei ZH, Zhou C (2012) Angew Chem Int Ed 124:10453
41. Hosseinzadeh-Khanmiri R, Moghimi A, Shaabani A, Valizadeh H, Seik WN (2014) Mol Divers 18:769
42. Moghimi A, Hosseinzadeh-Khanmiri R, Omrani I, Shaabani A (2013) Tetrahedron Lett 54:3956
43. Moghimi A, Hosseinzadeh-Khanmiri R, Shaabani A, Hamadani H (2013) J Iran Chem Soc 10:929
44. Hassanpour A, Abolhasani J, Hosseinzadeh-Khanmiri R (2014) J Korean Chem Soc 58:5
45. Xu Z, Dietrich J, Shaw AY, Hulme C (2010) Tetrahedron Lett 51:4566
46. Zhang Y-M, Fan X, Yang S-M, Scannevin RH, Burke SL, Rhodes KJ, Jackson PF (2008) Bioorg Med Chem Lett 18:405
47. Long D, Li W, Ling L, Miyawaki J, Mochida I, Yoon S-H (2010) Langmuir 26:16096
48. Si Y, Samulski ET (2008) Nano Lett 8:1679
49. Hummers WS, Offeman RE (1958) J Am Chem Soc 80:1339