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Efficient synthesis of trisphenols using reduced sulfonated graphene nanocatalyst under solvent free conditions

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ABSTRACT

This study reports a new methodology for the efficient synthesis of trisphenol compounds using the reaction of 2,6-bis(hydroxymethyl) phenols with phenols under heterogeneous conditions. A sulfonated reduced graphene oxide (RGO-SO_3H) nanocatalyst was used to promote the reaction under solvent-free conditions. A range of trisphenol compounds were produced in the presence of this catalyst system in good to excellent yields. In the presence of this catalyst system, a less amount of phenol is required, which improves the environment through its capability in synthesis of trisphenols. The RGO-SO_3H catalyst was reusable at least for 8 times in this process without a significant decrease in its catalytic activity.

***Keywords**: Trisphenol, 2,6-bis(hydroxymethyl) phenols, Sulfonated reduced graphene oxide, Solvent-free conditions.*

1. Introduction

Modern organic synthesis relies heavily on the design of efficient, clean and fast methodologies applying an appropriate catalyst, reagent and conditions [1-3]. The use of heterogeneous catalysis in organic reactions possesses many advantages in comparison with homogeneous counterparts especially on reusability and sustainability point of view [4-6]. Application of heterogeneous acid catalysts (solid acids) in acid-catalyzed organic reactions have some advantages, including easy application capabilities, decreased reactor and plant corrosion problems, and being more environmentally safe and available [7-9]. Thus, utilization of appreciate solid supports that allow the bond of acidic functional groups in order to prepare solid acid catalysts is the main subject in this field [10,11]. Among the used supports, graphene derivatives are good candidates because of the high surface area and stability of this material as the most important factors in the design of heterogeneous catalysts. Furthermore, the simple chemical modification of graphene using different functional groups allow generating special catalytic sites on the surface of this valuable material [12,13].

Since the discovery of the grapheme, it has been used extensively in many research fields [14-17] and in parallel with this line it has also been used as solid supports in the synthesis of heterogeneous catalysts [12,13,18,19]. In order to prepare solid acids based on graphene, it is functionalized by acidic groups such as -SO_3H and -CO_2H in different forms [12,13].

Recently, some graphene functionalized sulfonic acid catalysts were reported for application in acid-catalyzed reactions [20,21]. This catalyst system was used for synthesis of bisphenolic antioxidants and this important class of compounds was obtained in high isolated yields under solvent free conditions. In continuation of our program on synthesis of heterogeneous acid catalysts and their application in organic reactions [22-26], herein we disclose an efficient methodology for synthesis of trisphenols under solvent-free conditions using an acidic graphene nanocatalyst system.

Trisphenols are one of the important categories of polyhydroxy aromatic compounds, due to a range of biological activities associated with them. Several drugs based on trisphenols have been introduced for

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the treatment of diseases [27]. There are derivatives of trisphenols that show interesting antibacterial derivatives [28,29]. In addition to the biological activity, these compounds have been used as starting materials in synthesis of complex molecules such as calyx[4]arenes and crown ethers [30]. Several photophysical applications of trisphenols have been reported. For example, they have been used in organic photoluminscent devices and semiconductor industries [31,32].

In spite of the widespread application of trisphenols in organic synthesis and industries, there are rare methods for the efficient synthesis of these compounds [33-39]. Although the current methodologies for the synthesis of trisphenols have their advantages, some of them suffer from main limitations. In many cases, low yields of the products are obtained in long reaction times [28]. The use of corrosive, mineral acid catalyst or catalyst containing transition metals is main disadvantages of these synthetic methodologies [28,29]. One of the unavoidable problems in synthesis of trisphenols is the use of large excess phenols, which is unsuitable from the green chemistry point of view due to the toxicity of phenolic compounds in nature [33-35]. Importantly, most of the used methods have a tedious work-up process while a toxic solvent is used as reaction media [34-39]. Therefore, introduction of a new protocol that uses a highly efficient and reusable catalyst which is at the same time more environmentally benign as the conditions for the preparation of trisphenols is strongly recommended.

2. Experimental

2.1. Materials and apparatus

The chemicals and solvents were purchased from Sigma and Merck chemical companies. The known products were characterized by comparison of their spectroscopic and physical data with literature data. IR spectra were obtained as KBr pellets in the range of 400–4000 cm^{-1} on a Perkin-Elmer 781 spectrophotometer and on an impact 400 Nicolet FT-IR spectrophotometer. ^{13}CNMR and ^{1}HNMR spectra were recorded in DMSO-(d6) solvent using DRX-300 spectrometer at 75 and 300 MHz, respectively, and TMS as an internal standard. The elemental analyses (C, H, N) were performed using a Heraeus CHN Rapid analyzer. The SEM images of prepared catalysts were taken on a FE-SEM HitachiS4160 instrument. Melting points were determined using melting point IA 8103 apparatus. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

2.2. Preparation of graphene oxide nanosheets

Graphene oxide was obtained using a modified Hummer's protocol [40]. Graphite powder (10 g), sodium nitrate (5 g) and 230 mL of concentrated sulfuric acid (98%) were introduced into a 1 L round-bottom flask and stirred to the point of homogeneity. The obtained solution was stirred and slowly added 30.0 g of potassium permanganate during 1 h (exothermic reaction). Then, round-bottom flask was set to room temperature with a continuous stirring until a foam-like material was formed (about 2 h). At this stage, 400 mL of distilled water was added to it very slowly in order to avoid an uncontrolled temperature increase. The green-brownish liquid was then placed in the 98°C water bath for 15 min to obtain a dark suspension. Then, 1400 mL of deionized water and 100 mL of H_2O_2 (30%) were sequentially added to the mixture solution to terminate the reaction. The suspension was filtered and washed first with 500 mL of distilled water and 5% HCl solution. The graphite oxide powder was obtained after drying in vacuum at 60 ^{0}C for 12 h. The graphite oxide was dispersed in distilled water to make concentration of 0.5 mg mL^{-1}, and exfoliated by ultrasound (75 W) for 30 min to generate graphene oxide nanosheets, followed by centrifugation at 3500 rpm for 30 min to remove unexfoliated graphite oxide.

2.3. Preparation of sulfonated reduced graphene oxide nanocatalyst

First, reduced graphene oxide (RGO) was provided by the chemical reduction of graphene oxide using sodium borohydride ($NaBH_4$). 1.0 g of the GO in 700 mL of deionized water was dispersed by sonication (40 W) for 15 min. Then, 2.4 g of$NaBH_4$ was added into the round-bottom flask and heated at100 °C for 24 h. At this stage, the resulted material was washed several times with water and filtered under reduced pressure by vacuum pump over sinter glass and centrifugation at 3500 rpm for 15 min to obtain RGO nanosheets. Finally, sulfonated reduced graphene oxide nanosheets (RGO–SO_3H) was prepared from the hydrothermal sulfonation of RGO using H_2SO_4 (100%) at180°C. For providing the mentioned catalyst, 1.0 g of RGO was added into 50 mL of H_2SO_4. After sonication (40 W) for 15 min, the mixture was transferred into a round-bottom flask under nitrogen atmosphere and stirring to heat at 180°C for 24 h. Then, the prepared catalyst was washed with a large amount of deionized water and drying at 80°C for 12 h.

2.4. General procedure for the synthesis of trisphenols by using RGO-SO_3H nanocatalyst

In a 50 mL round bottom flask, a mixture of RGO-SO_3H (30 mg), BHMP (1 mmol), and 2,6-substituted phenol (3 mmol) was heated at 110 °C and stirred until TLC monitoring indicated no further progress (30–60 min according to Table 2). Then, the reaction mixture was cooled to room temperature. 5 mL acetonitrile was added to the mixture and the catalyst was removed by

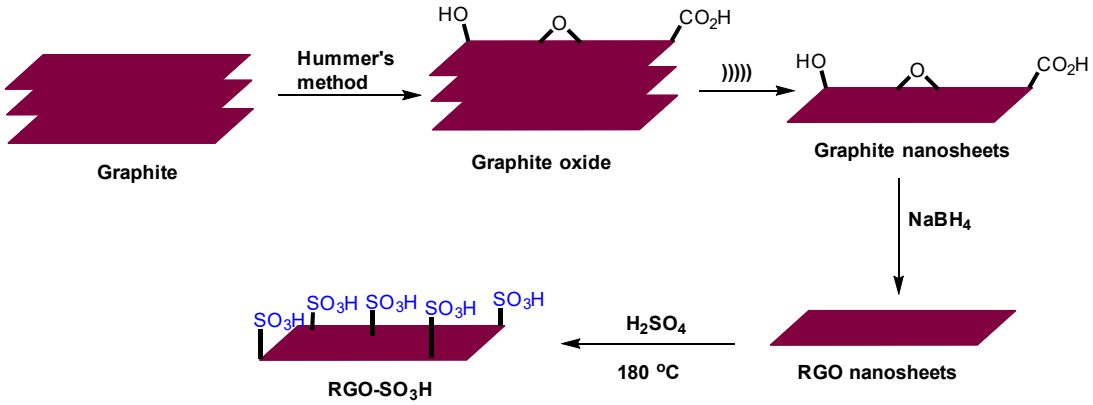
filtration. The filtrates were evaporated under reduced pressure. Then, the residue was suspended in boiling water (3×15 mL) and decanted to remove the unreacted phenolic reactant. The product was purified by column chromatography (hexane/ethyl acetate=3/1) to obtain the corresponding trisphenol.

3. Results and Discussion

The sulfonated reduced graphene oxide catalyst (RGO-SO_3H) was synthesized based on the procedure in the literature and the synthetic pathway is shown in Scheme 1 [25]. RGO-SO_3H was characterized using different microscopic and spectroscopic techniques. In order to illustrate the surface morphology and microscopic feature of the catalyst, the SEM images of RGO and RGO-SO_3H catalyst are shown in Fig. 1. The shown morphologies in SEM image of RGO exhibit that the large two dimensional nanosheets with layered structures reveal face to face stacking of sheets (Fig. 1). The comparison between SEM images of RGO and RGO-SO_3H shows significant differences in morphology of these materials.

The TEM image of the RGO-SO_3H is shown in Fig. 2. It was observable that the synthesized RGO-SO_3H exhibit a typical exfoliated and two-dimensional nanostructure with a rather and large flat and smooth flake-like morphology with several layers.

A comparison between the FT-IR spectra of both RGO and RGO-SO_3H is shown in Fig. 3. As shown, some new peaks appeared in the FT-IR of RGO-SO_3H, which confirms the functionalization of RGO with SO_3H groups. The peak at 3416 cm^{-1} is related to the presence of water on KBr pellets. Also, the presence of the peak at 1555 cm^{-1} shows that after chemical reduction at 100°C for 24 h, the RGO is still flake-like sheets. The FT-IR spectrum of RGO-SO_3H shows peaks related to C–O, carbonyl, and hydroxyl groups at about 1052, 1716, and 3408 cm^{-1}, respectively [20]. The symmetric stretching of the O=S=O fragment was observed at 1172 cm^{-1} [41]. Thus, the FT-IR data confirmed that the functionalization of RGO with H_2SO_4 and chlorosulfonic acids occurred to afford RGO–SO_3H catalyst.



Scheme 1. The synthetic route for the synthesis of RGO-SO_3H.

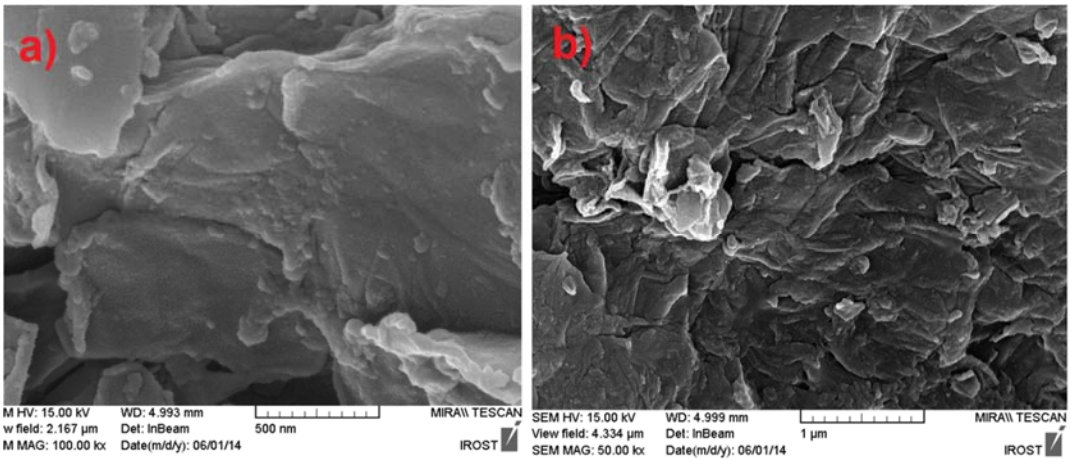


Fig. 1. The SEM images of RGO (a) and RGO-SO_3H (b).

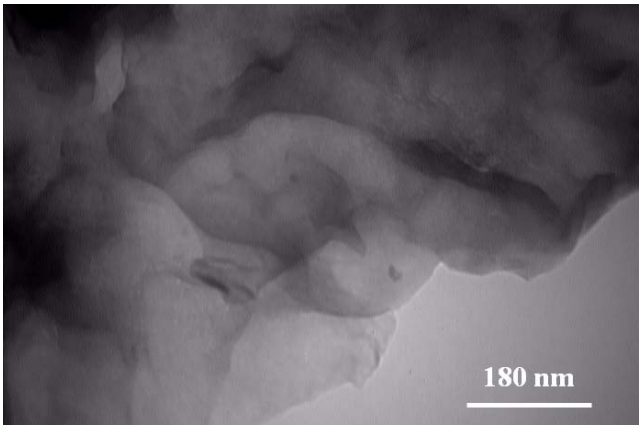


Fig. 2. The TEM image of RGO-SO_3H catalyst.

The total amount of the sulfonated groups was measured in the RGO-SO_3H catalyst using back acid–base titration. The back acid–base titration also showed that the density of sulfonated groups anchored on graphene layers for catalysts is about 2.15 mmol g^{-1}.

In this study, the catalytic applicability of RGO-SO_3H was evaluated in the synthesis of trisphenols. The reaction between 2,6-bis (hydroxymethyl) phenols(BHMP) and phenols was applied for the synthesis of trisphenolic compounds in the presence of RGO-SO_3H catalyst. The BHMP derivatives can be synthesized simply using the reaction of phenols and formalin [42].

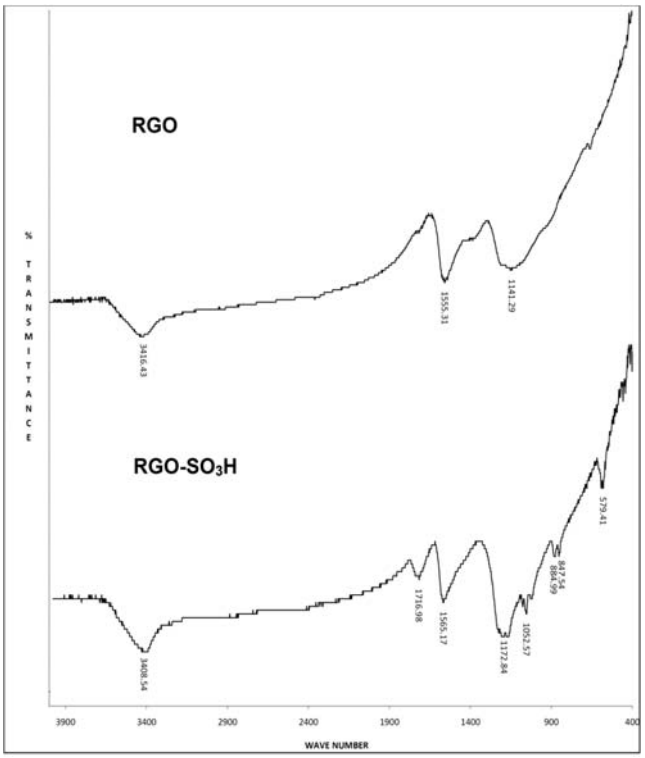


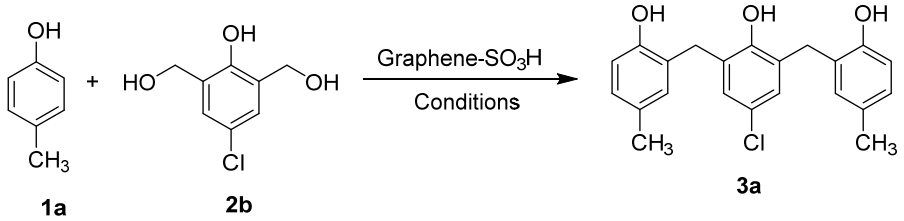
Fig. 3. A comparison between the FT-IR spectrum of RGO and RGO-SO_3H.

To find the appropriate conditions for the synthesis of trisphenols, a model reaction was selected and different conditions were used. Results of optimization study are shown in Table 1. As shown in Table 1, in the absence of the catalyst, about 8% of the product was obtained after 48h in *n*-hexane solvent (Table 1, entry 1). In the presence of 30 mg of the RGO-SO_3H catalyst, about 25% of trisphenol (**3a**) was produced (Table 1, entry 2). The type of solvent was changed, and in acetonitrile, ethanol and water about37, 48 and 64% of product was produced, respectively (Table 1, entries 3-5). Then, the solvent-free condition was used and at 60°C, about 28% of product was observed (Table 1, entry 6). By increasing the reaction temperature to 110°C, a remarkable improvement in reaction yield was observed so that at 110°C after 1h about 88% of product was isolated (Table 1, entries 7-9). The reaction yield and time were improved by increasing the ratio of phenol related to BHMP (Table 1, entries 10-12). Then, the catalyst loading was optimized and 30 mg of RGO-SO_3H was recognized as optimum (Table 1, entries 13-15). The optimized reaction conditions for efficient synthesis of trisphenols using the reaction of BHMP and phenols in the presence of RGO-SO_3H are shown in Scheme 2.

After optimization of the reaction conditions, in order to show the generality of this methodology in synthesis of other derivatives of trisphenols using reaction of BHMP and phenols, a range of these compounds were synthesized (Table 2). As shown in Table 2, it is possible to synthesize diverse trisphenols using reaction of BHMP and phenols using this methodology. All of the products were obtained in good to excellent yields under mild conditions. This procedure works for phenolic compounds bearing both electron-donating (**3b,c,d,f**) and electron-withdrawing groups (**3g,h**). Using this reaction, the acid sensitive double bond was tolerable and compound **3i** were obtained in 91% yield. Also, compound **3j** was synthesized using the reaction of 2-acetyl-5-fluorophenol and (5-fluoro-2-hydroxy-1,3-phenylene) dimethanol in 87% yield and the acetyl group remained unchanged during the reaction progress.

A plausible reaction mechanism for the reaction between BHMP and phenols for synthesis of trisphenol using RGO-SO_3H is proposed (Scheme 3). The BHMP is activated by protonation with solid acid catalyst, converting the hydroxy group to better leaving group. Nucleophilic attack of a phenol to the activated BHMP gives a bisphenolic intermediate which undergoes in subsequent nucleophilic reaction with other phenol in order to generate trisphenol product. The role of RGO-SO_3H catalyst is protonation of hydroxyl groups to active the BHMP substrate and produced hydroxy functionalized intermediates to participate in nucleophilic substitution reactions. After completion of the reaction, the catalyst can be reused using a simple filtration and used for next run.

Table 1. Optimization of the reaction conditions for synthesis of 2,2'-((5-chloro-2-hydroxy-1,3-phenylene)bis(methylene))bis(4-methylphenol) (**3a**) using the reaction of (5-chloro-2-hydroxy-1,3-phenylene) dimethanol (**2b**) and *p*-cresol (**1a**) in the presence of RGO-SO_3H catalyst.



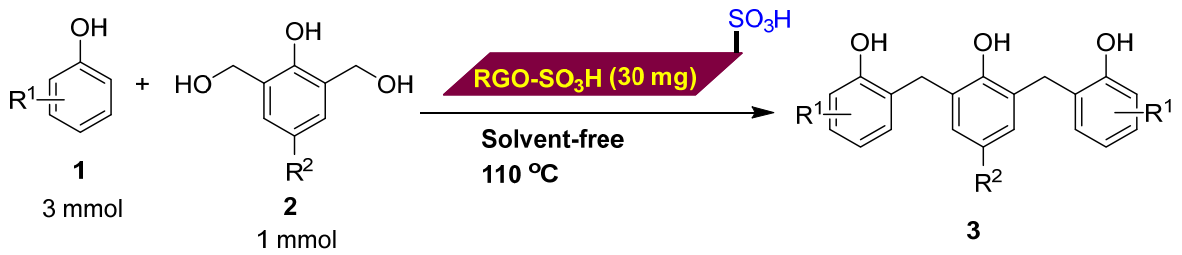
1a **2b** **3a**

Entry	Catalyst(mg)	Solvent (mL)	**1a** (mmol)	**2b** (mmol)	Temp.(°C)	Time	Yield (%)[a]
1	-	*n*-Hexane (10)	2	1	Reflux	48h	8
2	30	*n*-Hexane (10)	2	1	Reflux	5h	25
3	30	CH_3CN (10)	2	1	Reflux	4h	37
4	30	EtOH (10)	2	1	Reflux	5h	48
5	30	H_2O (10)	2	1	Reflux	2h	64
6	30	Solvent -free	2	1	60	5h	28
7	30	Solvent -free	2	1	80	2h	57
8	30	Solvent -free	2	1	100	1h	87
9	30	Solvent -free	2	1	110	1h	88
10	30	Solvent -free	2.5	1	110	45min	91
11	30	Solvent -free	3	1	110	30min	94
12	30	Solvent -free	3.5	1	110	30min	94
13	25	Solvent -free	3	1	110	1h	73
14	20	Solvent -free	3	1	110	2h	40
15	40	Solvent -free	3	1	110	30 min	93

[a]Isolated yields.

The reusability of the RGO-SO_3H catalyst was checked in the model reaction and it was observed that it is reusable at least for 8 times without significant decreasing in its catalytic activity. The yield of first run was 94% and the yield of eighth run was 80%.

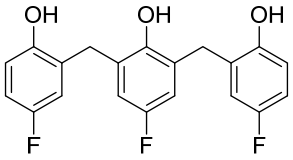
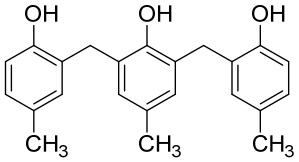
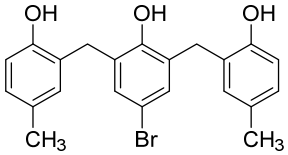
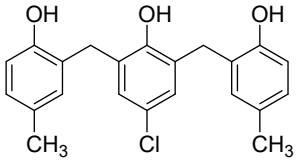
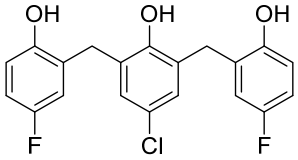
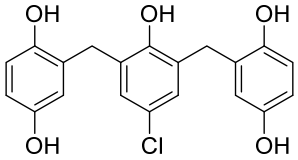
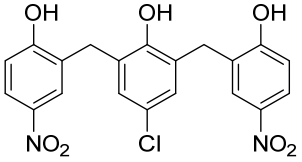
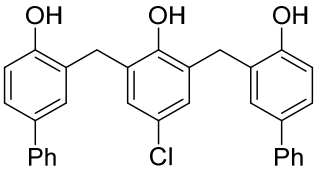
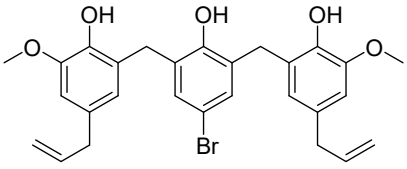
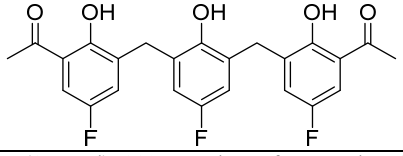
A comparison between the efficiency of RGO-SO_3H catalyst and other catalytic systems used in the synthesis of trisphenols is presented in Table 3. As shown, the RGO-SO_3H has good activity and efficiency in the synthesis of trisphenols in comparison with other reported catalysts.



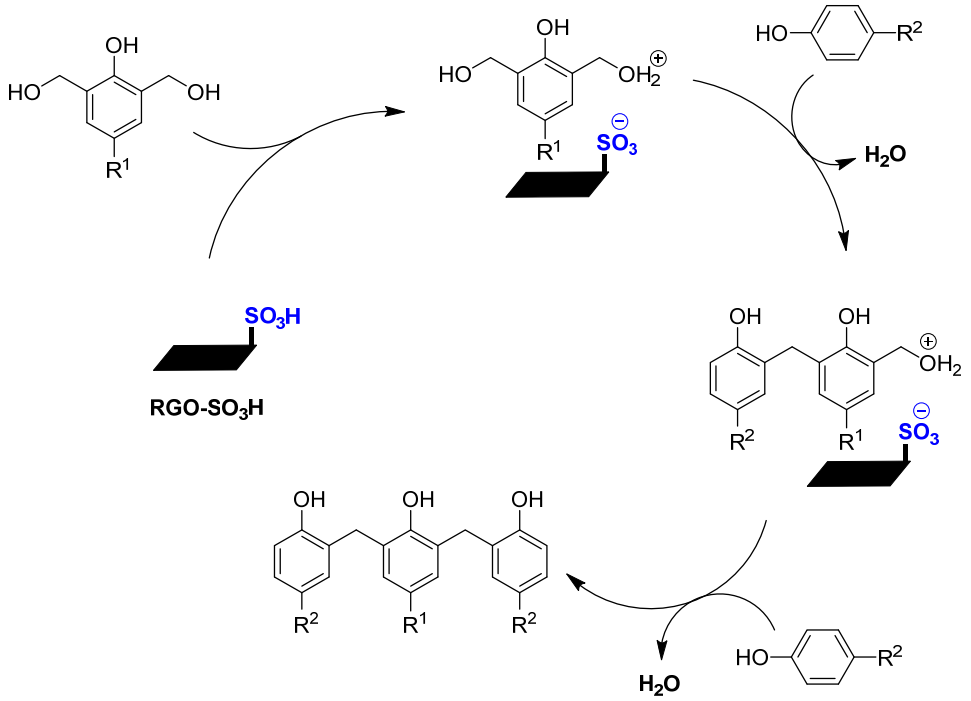
1 3 mmol **2** 1 mmol **3**

Scheme 2. Optimized reaction conditions for synthesis of trisphenols in the presence of RGO-SO_3H.

Table 2. Synthesis of trisphenol derivatives using reaction of BHMP and phenols in the presence of RGO-SO_3H.[a]

Entry	Trisphenol	Structure	Time(min)	Yield (%)[b]
1	**(3a)**		30	92
2	**(3b)**		30	95
3	**(3c)**		30	96
4	**(3d)**		30	94
5	**(3e)**		30	89
6	**(3f)**		30	92
7	**(3g)**		60	85
8	**(3h)**		40	88
9	**(3i)**		45	91
10	**(3j)**		55	87

[a]Reaction conditions: phenol (3 mmol), BHMP (1 mmol), 110°C, Solvent-free, catalyst (30 mg).
[b]Isolated yields.



Scheme 3. Proposed reaction mechanism for synthesis of trisphenols using RGO-SO_3H catalyst.

Table 3. A comparison between the catalytic activities of RGO-SO_3H catalyst in the synthesis of trisphenols.

Entry	Catalyst & conditions	Time (h)	Yield (%)	Ref.
1	HCl, Methanol	12h	68	[29]
2	$ZnCl_2$, Microwave	42s	90	[35]
3	Silica sulfuric acid, 1,4-dioxane	1.5 h	85	[36]
4	Tungstosilicic acid, H_2O	6h	85	[33]
5	3-methyl-1-(4-sulfobutyl)-1-H-midazol-3-iumhydrogensulfate, solvent-free, 80°C	20 min	90	[38]
6	RGO-SO_3H, Solvent-free, 110°C	30 min	88	This work

4. Conclusions

In conclusion, we have developed a new and efficient strategy for the synthesis of trisphenolic compounds using the reaction of 2,6-bis(hydroxymethyl) phenols and phenols using a solid acid catalyst. The sulfonated reduced graphene oxide as a high surface nano material with reusable capability was found to be an efficient catalyst for the synthesis of trisphenols in high isolated yields, low reaction times under solvent-less conditions. The catalyst system was reusable for 8 times with no significant decreasing in its catalytic applicability. We believed that this methodology possesses advantages for the synthesis of this class of compounds in comparison with existing methods.

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