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Guanidino-Graphene Catalysed Synthesis of Flavones via Aldol-Michael-Oxidation

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Guanidino-graphene has been synthesized by the reaction of bromoamine with reduced graphene oxide and characterized by FT-IR, Raman, TGA, powder XRD, TEM, SEM, and zeta potential. It is a cheap, heterogeneous and environmentally benign solid base catalyst used for cascade Aldol-Michael-oxidation in the synthesis of chalcone, flavonoids.

Keywords: Guanidinium Based Graphene/Heterogeneous Base/Cascade Reaction/Flavonoids.

1. INTRODUCTION

Carbocatalysis, a promising field, is widely available and inexpensive that has facilitated a broad variety of reactions.¹ The heterogeneous carbon materials offer many advantages such as easy work-up, recyclability and less waste production.^{2,3} Catalysts based on graphene have been regarded as potential solid catalysts because of high ratio of catalytically active surface area to weight.⁴ Graphene's precursor, graphene oxide, has been used as a powerful reagent for oxidizing various alcohols and alkenes, as well as hydrating alkynes, to their corresponding aldehyde or ketone compounds.⁵⁻⁷ Recently, amino-functionalized carbon have been synthesized by various methods^{8,9} and used for the transesterification of triglycerides,¹⁰ biomass conversion¹¹ and as an oxygen reduction electrocatalyst.¹² Hence, it would be interesting to develop an guanidino graphene as a solid base catalyst.

Earlier, GO has been directly used as a catalyst for synthesis of chalcone in which high amount of catalyst has been used.¹³ This prompted us to use chemically modified amino graphene as a solid base catalyst for the synthesis of flavonoids. Their synthesis has been carried out through a variety of procedures, but the most common one is performed via the Claisen-Schmidt condensation and subsequent intramolecular Michael addition to form flavanones followed by oxidation to form flavones between the reaction of substituted benzaldehydes and substituted 2-hydroxyacetophenones in basic or acidic media under homogeneous conditions. Various solid catalysts have been applied to flavanoid synthesis, such as magnesium oxide,¹⁴ alumina,¹⁵ hydrotalcites¹⁶ and natural

phosphates¹⁷ modified with NaNO₃¹⁸ or KF.¹⁹ Herein, we have synthesized a novel guanidine based graphene, and employed it as a catalyst in a one-pot cascade reaction for the synthesis of chalcone, flavanone and flavone which offers several benefits including atom economy, as well as minimum time, labor and resource management.

2. EXPERIMENTAL DETAILS

2.1. Preparation of Graphene Based Catalysts

Graphite oxide (GO) was prepared from natural graphite by the modified Hummers method.²⁰ GO (300 mg) was dispersed into ultrapure water (50 mL) and sonicated for 1 h followed by addition of NaHSO₃ (16.2 mmol). The mixture was heated at 100 °C under stirring and the suspension was filtered, washed several times with distilled water, redispersed into water under the assistance of ultrasonication for 5 min and filtered again by washing with distilled water several times to make the pH ~ 7. The filtrated r-GO was dried.

Under N_2 atmosphere, vacuum-dried r-GO (200 mg) was suspended into THF (50 ml) and excess of lithium diisopropylamide (2 M solution in heptane/THF) was added. The mixture was vigorously stirred continuously for 12 h at room temperature. Various bromoamines were vacuum dried for 4 h and then added to the r-GO solution. The mixture was continuously stirred for 14 h at room temperature. At the end of the reaction, product was filtered, rinsed with water and methanol in order to remove the unreacted amine (Scheme 1).

2.2. Reaction Procedure for Flavanoid Synthesis

A mixture of o-hydroxyacetophenone (1 mmol), corresponding aldehyde (1 mmol) and amino graphene (50 mg)

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Scheme 1. Synthesis of Amino grafted graphene.

were dissolved in xylene (1 ml) and was refluxed for 14 h. The progress of reaction was monitored by TLC. The reaction mixture was filtered and solvent was removed under reduced pressure. The products were isolated by column chromatography. Catalyst was recovered by simple filtration and rinsing with dichloromethane and methanol.

3. RESULTS AND DISCUSSION

3.1. Structure Characterisation and Morphology of Amino-Grafted Graphenes

Various functionalized graphenes used in this paper were prepared through the covalent attachment of alkylamine onto the reduced graphene sheet (r-GO). LDA works better for proton abstraction as compared to BuLi as it is more stable and offers a cleaner reaction. The r-GO sheet consist of large number of chemically reactive vacancies and sp^3 carbon atoms as compared to graphite and therefore, can be used for covalent attachment of desired molecules via C–C coupling reactions.

The structure of synthesized amino-graphenes has been confirmed by FT-IR, Raman, TGA, powder XRD, TEM, SEM, zeta-potential measurements. The nitrogen containing graphene possess basic character with $pK_a \sim$ 9–11. Among all the synthesized graphene, guanidine based graphene (Gdn-Graphene) was found to be most basic. FTIR spectra of as-synthesized amino-graphene indicate contributions from nitrogen functional groups. Peaks 3430–3420 cm⁻¹ contribute for N–H stretching, 1645 cm⁻¹ for C=N stretching, 1552–1546 cm⁻¹ for N– H bending, 1152–1132 cm⁻¹ for C–N stretching (Fig. 1). Absence of peaks at 1730 for $\nu_C=_0$, 1091 for ν_{C-0} indicates complete reduction of GO. N-bromoamines did not react with –COOH and –OH as no corresponding peaks were observed in IR.

In Raman spectroscopy, r-GO has two characteristic peaks around 1353 and 1576 cm⁻¹, corresponding to the defect-induced D band and G band respectively.²¹ A red-shifted G band after amino-grafting, attributed to slight reduction of C=C and introduction of new functional groups on the graphene sheets was observed.²² The maximum shifting was observed in case of compound **4d** in

which G band appear at 1589 cm⁻¹ ($I_D/I_G = 1.12$) which showed that maximum functionalization was achieved with guanidinium type of functionality (Fig. 2).

In powder XRD (Fig. 3), the diffraction peak of GO appears at 11.3° (001) with interlayer space (*d*-spacing) of 0.76 nm, while r-GO exhibits a new diffraction peak at $2\theta = 24.9^{\circ}$, demonstrating the formation of graphitic structures during the reduction of GO. However in the functionalized graphenes, the diffraction peak blue shifts to $2\theta = 22.9^{\circ}$ which is attributed to the intercalation of amino groups between the stacked graphene layers, corresponding to an increased *d*-spacing (3.87 Å).

Elemental analysis was used to give the detailed chemical information of graphene-based samples. Table I show that after amino grafting, the nitrogen content increased significantly from 0.32% to 3.7%, a 10-fold increase, which confirms the successful introduction of amine groups onto the surface of r-GO. Among the prepared graphenes nitrogen content was found to be maximum in guanidine based graphene (9.21%). The values of the elemental analysis were in good agreement with the theoretical calculated values.

We also examined the thermal stability of the prepared graphenes and compared it with r-GO using TGA under



Figure 1. FT-IR spectra of (a) NH₂-Graphene, (b) Gdn-Graphene.

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Figure 2. Raman Spectra of (a) r-GO, (b) Gdn-graphene.

a nitrogen flow over a temperature range of 25–900 °C with flow rate of 10 °C per min (Fig. 4). Generally for r-GO, there is nearly no weight loss below 145 °C, as the oxygen functionalities have been removed upon reduction of GO. On the other hand, after amino-grafting, a large weight loss appeared from 200–400 °C, which is attributed to the thermal decomposition of amine moiety covalently attached to the sheet. The results, thus, proves the successful functionalization of various amines on r-GO sheet. All of the other prepared graphenes show similar findings in thermo-gravimetric analysis.

Detailed surface morphology can be explained by TEM and SEM images (Fig. 5). As can be seen in TEM images, r-GO exist as few layers of graphene sheets and the similar sheet with greater degree of crumpling was achieved for amino-graphene. The crumpled sheet helped in two ways, firstly, made the reactants easily accessible to the active sites on both sides of the sheets which may also facilitate the diffusion of the product molecules,²³ and secondly,



Figure 3. XRD pattern of Gdn-Graphene (4d).

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 Table I.
 Elemental analysis of GO, r-GO and the prepared graphenes.

Sample	Н (%)	C (%)	N (%)
GO (1)	2.23	67.18	0.61
rGO (2)	0.81	73.70	0.32
$-NMe_2$ (4a)	2.32	71.30	3.70
$-NH_2$ (4b)	2.11	71.97	3.10
Mor-Graphene (4c)	2.70	71.60	3.60
Gdn-Graphene (4d)	2.90	71.90	9.21

helps in effective dispersion. SEM images display flowerlike curled characteristics of amino graphene.

The zeta potential measurements (Fig. 6) have been widely used to study surface charge on a variety of carbons materials. The zeta potential of r-GO is negative ($\zeta = -30$ to -38 mV) indicating the negatively charged state of exfoliated r-GO.²⁴ The observed zeta (ζ) potential for amino-grafted graphene (Gdn-graphene) is +32 mV indicating the presence of positively charged amine groups on the graphene sheet.

3.2. Synthesis of Chalcones, Flavanones and Flavones

The reaction with equimolar quantities of 2-hydroxyacetophenone (5) and anisaldehyde (6a) in presence of synthesized amino-graphene under reflux conditions, gave chalcone (7a), flavanone (8a) and flavone (9a) (Table II, entry 1) (Scheme 2). Absence of catalyst did not yield any product even after 24 h. The optimized reaction was conducted at 140 °C with 50 mg of catalyst (10 wt%), 1 ml solvent and 1 mmol of reactants. With different synthesized graphenes varying conversion rate were obtained.

Gdn-graphene dramatically improved the conversion to 98% in which product yields were 40% chalcone, 40% flavanone, 13% flavones in 14 h. Control experiment using GO produced only chalcone (\sim 35% yield) in xylene as solvent. Control experiment using guanidine hydrobromide gave only chalcone in 40% yield.



Figure 4. Thermo-gravimetric analysis of r-GO and Gdn-Graphene (4d).



Figure 5. TEM images of (a) r-GO, (b) Gdn-graphene (4d), (c, d) SEM images of Gdn-graphene (4d).



Figure 6. Zeta-potential curve of Gdn-graphene (4d).

The one pot synthesis of chalcone, flavanone and flavones starting with aldehyde and 2-hydroxy acetophenone as precursors has not been reported till now and usually metals are used for the oxidation purpose,^{25–28} herein, we report the synthesis using a metal free catalyst. Although, the results of different solid catalysts used so far has been compiled in the Table II.

During the course of above reaction, chalcone is formed (2-3 h), followed by flavanone (3-4 h). On further

Table II. Catalytic performance of the amino functionalized graphene with different amino loadings in the condensation of 2-hydroxyacetophenone and anisaldehyde.

	Catalyst	Time (h)	Temp (°C)	Solvent	% Conversion ^a	% Yield ^b		
Entry						Chalcone	Flavanone	Flavone
1	$(-NMe_2-G)$	16	130	Xylene	68	30	30	7
2	(-NH ₂ -G)	16	130	Xylene	50	20	19	9
3	(Mor-G)	16	130	Xylene	75	30	32	8
4	$(Gdn-G)^c$	16	130	Xylene	98 (80)	43	37	13
5	Guanidinium hydrobromide	24	130	_	45	35	_	_
6	GO	14	130	Xylene	35	35	_	_
7	MgO	12	160	DMSO	90	21	69	_
8	Hydrotalcite	2	60	CH_2Cl_2	90	87	_	_
9	KF/Natural phosphate	2	100	N-tetradecane	91	35	52	_
10	No catalyst	24	130	Xylene	-	-	-	-

Notes: Reactants = 1:1; Solvent = 1 mL; Amount of catalyst = 50 mg; Reaction time = 12-18 h; abased on substrate; bisolated yields; cyields after 3 runs.

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Scheme 2. Synthesis of chalcone (7), flavanone (8) and flavone (9) using amino-graphene.

prolongation of reaction by 3–6 h flavanone was oxidized to flavone. Flavanone and 2'-hydroxychalcone exist in equilibrium between the pH range 10.5 and 13,²⁹ therefore, both are present as end-products with Gdn-graphene while only chalcone was formed when GO (pH \sim 4) was used. The reaction with Gdn-graphene was performed under N₂ as well as O₂ atmosphere for 24 h, and no change in yield was observed. Therefore, we suggested graphitic structure is responsible for the oxidative dehydrogenation and not molecular oxygen. A number of oxygen groups

 Table III.
 Reaction of 2'-hydroxyacetophenone and different aldehydes

 with guanidine based amino graphene (4d).

			% Yield ^b			
Entry	Aldehyde	% Conversion ^a	Chalcone	Flavanone	Flavone	
1	а	70	30	30	8	
2	b	95	42	38	15	
3	с	98	43	37	13	
4	d	65	29	29	6	
5	e	40	7	26	6	
6	f	72	28	33	9	
7	g	75	28	35	10	
8	h	80	10	46	20	

Notes: Reactants = 1:1; Solvent = 1 mL; Amount of catalyst = 50 mg; Reaction time = 12-18 h; ^{*a*}based on substrate; ^{*b*}isolated yields.

Table IV. Reaction of 2'-hydroxyacetophenone and anisaldehyde with guanidine based amino graphene (4d) in different solvents.

			% Yield ^b			
Entry	Solvent	% Conversion ^a	Chalcone	Flavanone	Flavone	
1	Xylene	98	43	37	13	
2	DMF	80	32	39	7	
3	Toluene	65	31	15	18	
4	Ethanol	45	23	12	5	
5	No solvent	65	15	22	25	

Notes: Reactants = 1:1; Solvent = xylene (1 ml); Reflux; Amount of catalyst = 50 mg; Reaction time = 12-18 h; ^{*a*} based on substrate; ^{*b*} isolated yields.

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and defects are induced upon oxidation of graphite which experimentally remain on the surface of graphene even after the reduction of GO.³⁰ These defects trap molecular oxygen and help in oxidation.³¹

Flavone formation occurred due to these trapped oxygen molecules in graphene defects via radical mechanism, which was proved by the addition of radical quencher NaN₃ (no flavone appeared). To test its reusability, the catalyst was removed from the reaction mixture by filtration and dried to remove water and soluble impurities. The isolated catalyst was used directly in the next run by adding the same amount of starting material as the initial run. After 5 consecutive runs, Gdn-Graphene still provided an average conversion of 80%. Raman spectrum of the used catalyst show same peaks as before. However, XRD reveal an extra peak at 18° which might arise due to some reactants adsorbed on graphene surface still after washing.

The reaction was explored by using different solvents and substituents on the aromatic ring (Tables III, IV). The substituents have found to have a great impact on the selectivity of product. With electron-withdrawing substituents at para-position of aldehyde favour higher selectivity towards flavanone unlike other solid base catalysts.³² The reaction worked best in non-polar solvents as the graphite sheet is hydrophobic in nature so reactants get solvated by polar solvents and thus, may interfere with the catalytic process.

4. CONCLUSION

In conclusion, a useful catalytic cascade synthesis of chalcone, flavonones and flavones with guanidino graphene based catalyst in non-polar solvent has been developed. Several factors play a decisive role: substituents, solvents and amount of catalyst. The advantages of this solid catalyst over other basic heterogeneous catalysts are the high catalytic turnover, low catalyst loading, simplicity of the catalyst preparation, ready availability, low price of the precursors, and the ease of reuse. These results open the way to the use of inexpensive solid as a basic catalyst for the applications in other organic reactions. Owing to this reaction, the reasonable timings, eco-friendly conditions, recyclability of guanidino graphene and excellent yields proves this method superior over other methods.

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