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Graphene Oxide: A Convenient Metal-Free Carbocatalyst for Facilitating Amidation of Esters with Amines

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Abstract: Herein we report a graphene oxide (GO) catalyzed condensation of non-activated esters and amines, that can enable diverse amides to be synthesized from abundant ethyl esters forming only volatile alcohol as a by-product. GO accelerates ester to amide conversion in the absence of any additives, unlike other catalysts. A wide range of ester and amine substrates are screened to yield respected amides in good to excellent yields. The improved catalytic activity can be ascribed to the oxygenated functionalities present on the graphene oxide surface which forms H-bonding with the reactants accelerating the reaction. Improved yields and a wide range of functional group tolerance are some of the important features of the developed protocol.

Introduction

The peptide linkage (-CONH₂) i.e. the amide bond is ubiquitous in nature and is one of the most important functional groups amongst others in industries.¹ Amides are present as structural and functional units in natural products and synthetic polymers, and also as linkers in building functional nanomaterials and surfaces.² The pervasiveness and stability of amides make them attractive in organic synthesis. Thus, the quest for an effective method for amide synthesis is one of the hot topics in synthetic organic chemistry. Amongst different reactions for amide bond formation, the direct amidation is particularly useful.³ Primarily amides were prepared from carboxylic acids and amines using dehydrating agents, which generates large quantities of by-products.⁴ Efforts have been made to overcome this problem, but further development is necessary to avoid the usage of a large quantity of desiccating agents to improve the substrate scope, to sustain catalyst activity.⁵ Thus, to overcome these drawbacks and in search of simpler methods, a variety of substrates such as alcohols,⁶ aldehydes⁷, and acyl halides⁸ have been explored to a great extent for direct amidation of amines.

In this regard amidation of esters with amines is a potentially valuable method for synthesis of complex molecules having amide functionality. This is a simpler route for the synthesis of amides using esters since it produces only volatile alcohols as a by-product. Typically, stoichiometric amounts of promoters or metal mediators are obligatory in conventional amidation of esters. Recently, various effective catalytic processes were developed which produced the targeted amides along with only alcohol as a by-product. Usage of bases like NaOMe⁹ and DBU¹⁰ enables the ammonolysis of esters but it suffers from few drawbacks such as longer reaction times and requirement of a larger quantity of bases. Therefore, to avoid the excessive use of the base, use of a metal catalyst (Ru-MACHO¹¹), metal alkoxides in combination with additives $(Zr(OtBu)_4^{12}$ La $(OTf)_{3,}^{13}$ and $ZrCp_2Cl_2.)^{14}$ were used. The scarce availability and high costs of these rare-earth metals, high catalyst loading, and

requirement of additives increase the complexity of the protocol employed.

Recently carbon-based nanomaterials (activated charcoal, fullerenes, single- and multiwalled carbon nanotubes (CNT) and graphene oxide (GO)) have become promising substitutes for conventional metal-based catalysts for many organic transformations.¹⁵ Particularly, graphene-based materials have gained great attention due to their exceptional physical, chemical, thermal, mechanical and electric properties. ¹⁶ Besides, high surface area and biocompatibility have made them attractive for a wide range of catalytic processes. ¹⁷, ¹⁸

In 2010, graphene oxide (GO) was used for the first time by Bielawski et al. as a metal-free carbocatalyst for the aerobic oxidation of benzylic hydrocarbons ¹⁹ Afterward, GO has turned out to be a highly versatile heterogeneous carbocatalyst for various catalytic processes such as C-H bond activation, oxidation of alcohols,²⁰ oxidative bromination of anilines and phenols,²¹ aldol condensation and Knoevenagel reaction,²² aza-michael additions,²³ oxidative esterification of aldehydes and alcohols, ²⁴ esterification reaction,²⁵ synthesis of substituted coumarins,²⁶ synthesis of xanthenes and benzoxanthenes,²⁷ synthesis of β-enaminones,²⁸ synthesis of 1,5benzodiazepines.²⁹ Importantly, GO has replaced many metal-based catalysts for various organic transformations. The versatility of GO can be ascribed to the presence of different functional groups like hydroxyl (-OH), epoxy (-O-), and carboxyl (-COOH) embedded on its surface which accounts for oxidizing properties and acidity to the catalyst (pH 4.5 at 1 mg mL-1).30

Further, there are some reports on amide catalytic synthesis based on GO, such as GO catalyzed oxidative amidation of aldehydes and anilines,³¹ sulfonated reduced GO catalyzed amidation of carboxylic acids,³² Pd nanoparticles supported on GO,³³ GO supported Co species catalyzed Ester–Amide Exchange³⁴. Though these methodologies are advantageous they suffer from some disadvantages such as the use of toxic solvents, requirement of costly

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Catalyst (wt. %)

GO (20)

GO (20)

GO (20)

GO (20)

GO (20)

No catalyst

No catalyst

GO (5)

GO (10)

GO (15)

GO (25)

GO (20)

GO (20)

GO (20)

GO (20)

GO (20)

Graphite

Activated

carbon

CNT

Journal Name

Yield of 3a

(%)^b

NR

26

42

72

95

18

23

74

83

87

95

20

32

NR

10

34

18

22

25

Temp (°C)

RT

50

80

90

100

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transition metal catalysts which often include multistep synthesis and offer lower to moderate yields of desired products.

Thus, considering the drawbacks associated with the established amidation protocols and knowing the versatility of graphene oxide catalyst, herein we demonstrate a rapid and efficient amidation protocol in the presence of graphene oxide under solvent-free conditions.

Result and discussion

Initially, GO was prepared by following Improved Hummer's Method (IHM) 35 and characterized by several spectral techniques (ESI Fig. S1A-S1I). Further, to evaluate the catalytic activity of graphene oxide, Ethyl benzoate (1a, 0.1g, 1.0 mmol) and benzylamine (2a, 0.11, 1.2mmol) were selected as the model substrates for the desired transformation. Initially (1a, 0.1g, 1.0 mmol) was reacted with (2a, 0.11g, 1.2mmol) using 20 wt.% of GO at room temperature, but no product formation was observed even after 15h (Table 1, entry 1). It was noticed that the temperature played a crucial role for amide synthesis. At low temperatures (50 °C, 80 °C, and 90 °C) the rate of the reaction was very slow and the yields of the product **3a** isolated were 26, 42, and 72%, respectively (Table 1, entries 2-5). When the reaction was performed at 100 °C, and the yields obtained were significantly higher because upon increasing the temperature, the molecules move faster and thus collide more frequently, this accelerates the rate of reaction. Besides, the reaction was also performed at 120 °C and 130 °C in the absence of the catalyst, but poor yields of 3a were observed (Table 1, entries 6 & 7). We realized the catalyst also plays an important role in carrying out the reaction. The model reaction was then carried out with different amounts of the GO. As the amount of GO was increased from 5 to 20 Wt. %, the yield of 3a was also increased from 74 to 95% (Table 1, entries 8-10). The increased yield can be ascribed to the increased substrate-catalyst interactions which are responsible for the enhanced electrophilicity of the carbonyl carbon of the ester group via H-bonding. In addition, the small size, better dispersion, and the presence of oxygen functionalities would have assisted the GO to achieve the higher yields. Further, an increase in the catalyst loading (25 wt. %), show no improvement in the yield of product 3a (Table 1, entry 11). To achieve the best catalytic efficiency, the reaction was carried out in several solvents like DMF, DMSO, water, acetonitrile, toluene, and THF. It was observed that the formation of the product 3a was poor in the presence of polar solvents (DMF, DMSO, water, Acetonitrile, THF)) as well as a non-polar solvent (Toluene) (Table 1, entries 12-16), whereas the yield of product 3a was found to be highest in solvent-free conditions (Table 1, entry 5) Moreover, the model reaction was tried out with other carbon-based material like graphite, activated charcoal and carbon nanotube, which formed Nbenzyl benzamide in 18%, 22% & 25% respectively displaying low catalytic activity (Table 1, entries 17-19). Reduced graphene oxide (RGO) prepared by reduction of graphene oxide with N₂H₄ afforded 42% of the desired product (Table 1, entry 20)

Table 1: Optimization of reaction conditions for 3a^a



Solvent

Effect of temperature

Effect of catalyst loading

Effect of solvents

DMF

DMSO

Water

Acetonitrile

Toluene

Comparison with other catalysts

 20
 RGO
 100
 42

 ^aReaction Conditions:1a (1 mmol), 2a (1.2 mmol); time- 15 h; All reactions were performed in a sealed tube; ^bIsolated yield; NR: no reaction. CNT; carbon nanotube; RGO: reduced graphene oxide.

The substrate scope was investigated for structurally diverse esters and amines (Scheme 1). Various methyl and ethyl esters were examined where isopropyl benzoate substantially decreased the yield, and tertiary butyl benzoate offered low yield (27%) of the desired product (3a). Ethyl benzoates containing electron-withdrawing substituents gave the corresponding amides in excellent yield showing good reactivity (3b, 3c), whereas the reaction of esters having electrondonating groups required a more reaction time (18-20 h) to produce a good yield of corresponding amides (3d, 3e, 3f). Whereas ortho-substituted ethyl benzoate is also reactive despite its more hindered environment (3g & 3h). The triamidated product was achieved selectively when 3.6 Equiv. of benzylamine was used (3i). Furthermore, alkanoates such as ethyl phenylacetate and ortho and para-substituted phenyl ethyl acetate were also easily converted to the corresponding products providing excellent yields (3j-3n). Condensation of aliphatic α -hydroxy ester such as N-benzyl-2-hydroxy-2phenylacetamide with benzylamine proceeded smoothly with high chemoselectivity offering 30 in 82% yield since no esterification product was detected. Amidation of α , β unsaturated ester such as methyl cinnamate, underwent conversion efficiently without showing any side reactions like 1,4- addition, to produce corresponding amide **3p** in 89% yield. The reaction of an amide ester such as ethyl benzoylglycinate with benzylamine produced the corresponding amide in 94% yield without showing any transamidation product (3q). Moreover, in the case of diesters, the selective diamidation product was achieved (3r). The ethyl 2-(2-

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formylphenoxy)acetate selectively formed the amidated product of the ester group without affecting the formyl group present in it (3s). A simple aliphatic ester also underwent amidation effectively (3t-3w) and also turned out to be more reactive than aromatic substrates, especially those having electron-withdrawing substituents such as ethyl trifluoroacetate which could also be coupled efficiently (3x).



*Reaction conditions: Ester 1 (1.0 mmol), Amine 2 (1.2 mmol), GO (20 wt. %), temperature: 100 °C; 6-24 h, isolated yields, unless otherwise noted. bReaction was performed using 1(1 mmol), 2 (2,4 mmol), Reaction was performed using 1 (1 mmol), 2 (3.6 mmol), dReaction was performed at 80 °C.

Further, this methodology also applied to the reaction of ethyl benzoate with a variety of amines (Scheme 2). First, we have studied the reaction of ethyl benzoate with a wide range of benzyl amines providing corresponding secondary amides 5a-5f in good to excellent yields (79-95%). The reaction of ethyl benzoate also proceeded well with different primary aliphatic amines such as octyl amine, butyl amine to give amides 5g & 5h in excellent yields. Tert-butylamine could also be coupled and offered reasonable yields (5i). The free hydroxyl group was well tolerated as more nucleophilic nitrogen was preferred over the oxygen, evidenced by amidation of ethyl benzoate with ethanolamine to give corresponding amide 5i with 88% yield. The reaction proceeded successfully with cyclic amines, such as cyclohexylamine and cyclopropylamine to afford 5k & 5l in good yields. When ethyl formate was reacted with 4-nitro and 4cyano benzylamines, yields of products were reduced to 72%, and 76% respectively. The reduction in yields was due to the presence of electron-withdrawing substituents on benzylamine. (5m,5n). The reaction of ester was also extendable to electronically more nucleophilic but sterically hindered secondary amines afforded products 50-5t in good to excellent vields signifying the present conditions are also useful for the synthesis of tertiary amides. Moreover, aniline, 4-methoxy and 4-hydroxy aniline having lower nucleophilicity than aliphatic amines reacted with various ester under optimized conditions showing good yields of corresponding amides 5u-5w. Whereas, sterically hindered diphenylamine resulted in poor yield (52%) of 5x.



Scheme 1: Substrate scope of GO Catalysed amidation of different esters with benzyl amine^a



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with different amines^a

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^aReaction conditions: Ester 4 (1.0 mmol), amine 2 (1.2 mmol), GO (20 wt. %),

temperature: 100 °C; 8-24 h, isolated yields unless otherwise noted. ^bReaction

Scheme 3: GO-Catalysed Amidation of heteroaromatic esters with



GO (20 wt %).

 a Reaction conditions: ester 6 (1.0 mmol), amine 2 (1.2 mmol), GO (20 wt. %), temperature: 100 °C; 12–24 h, isolated yields unless otherwise noted.

This protocol was further utilized to obtain amides containing heterocyclic rings with excellent yield from their corresponding esters and amines (Scheme 3, 7a-7d).

Scheme 4: Intramolecular amidation



An intramolecular lactam formation could also be achieved effectively under optimized reaction condition (Scheme 4).

Scheme 5. GO catalyzed Direct Coupling of Protected Amino esters



[°]Reaction conditions: α - amino Ester (1.0 mmol), benzylamine (1.2 mmol), GO (20 wt. %), temperature: 100 °C; 24 h, isolated yields

To expand the application scope of this protocol, the reactions were tried out with BOC protected amino esters derivatives. The results

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5x; 52%; 36h

amines

was performed using 1 (2 mmol), 2 (1 mmol)

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showed that BOC protected amino esters were well tolerated providing corresponding amidated products in moderate to good yields, albeit slightly inferior to those of simple amides **Scheme 5.**

Reaction mechanism

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A plausible reaction mechanism has been suggested based on the above experimental results and literature reports 36,37,29 (Figure 2). It is apparent that the acidity of GO plays an important role in this transformation. The surface of GO nanosheet is decorated with hydroxyl, epoxy, and carboxyl functionalities which provide hydrophilicity as well as the acidic environment. The high surface area of GO is also responsible for the extensive surface accumulation of reactant molecules around the active functional groups causing the significant acceleration of the reaction rate. It is well documented that the carboxylic groups present on the edges of GO form intermolecular hydrogen bonding with the ester (intermediate 1). Due to hydrogen bonding, the carbonyl carbon of ester becomes more electrophilic. Thereafter, the nucleophile, amine attacks at the carbonyl carbon of ester to form the intermediate Followed by successive rearrangement results in 2. intermediate 3. Finally, the elimination of alcohol forms the desired product and regenerates GO catalyst (intermediate 4).



Figure 1: Plausible reaction mechanism

Comparative study of current methodology with previous reports

We compared the result obtained from the current catalytic protocol with that of previously reported methodologies, as shown in Table 2. Most of these methods depend on metalbased catalysts (entry 1-7), which causes many shortcomings such as the difficulty of waste disposal and metal contamination in the products. Moreover, these catalysts were homogeneous, hygroscopic, and difficult to handle. Non-metal catalyst loses its applicability under sustainable conditions: due to the large usage of a base (entry 8), and limited substrate scope (entry 9). Therefore, in comparison to these methodologies, the present protocol utilizes a cheap, metal-free, heterogeneous catalyst for the amidation of esters under sustainable and economic conditions (entry 10).

Table:2 Comparative study of current methodology with previous reports

Sr. no.	Catalyst used	Nature of catalyst	Reaction condition	Time (h)	Yield (%)
1	La(OTf)₃ (0.05- 5 mol%)	Metal	Rt-70 °C	1-48	79- >99 ¹³
2	Cal ₂ (10 mol%)	Metal	Solvent: toluene (110 °C)	4	45-89 ³⁸
3	Zr(Ot-Bu)4 910mol %), additive (20 mol%)	Metal	Solvent; toluene (60 °C)	1	50-99 ¹²
4	NaOMe (5 mol %)	Metal	Solvent; toluene (50 °)	20-48	70-99 ⁹
5	ZrCp ₂ Cl ₂ (10 mol%)	Metal	Solvent; Toluene (110 °C)	4-20	85 ¹⁴
6	Cu-Mn (C) (10 % w/w)	Metal	Solvent: THF (80 °C)	6	66-91 ³⁹
7	Ru-MACHO (10 mol%), tBuOk(20mol %)	Metal	Solvent; Toluene (120 °C); N ₂ atm	48	9411
8	CF ₃ CH ₂ OH (20 mol%) K ₃ PO ₄ (1 equiv)	Non- metal	Solvent; THF (2M), 90 °C	22	95 ⁴⁰
9	OSU-6	Non- metal	solvent-free 100 °C	6	91 ⁴¹
10	Graphene oxide (20 wt. %)	Non- metal	Solvent-free 80-100 °C	6-24	52-98 (Presen t work)

Gram Scale Amidation Reactions



1a, 1g (6.65mmol) 2a, 0.85g (7.99 mmol)

3a (1.29g, 92%)

To study the amidation reaction on larger scales, N-benzyl benzamide synthesized using gram quantities of material.

Recyclability study

Table 2: recyclability of the catalyst

Entry	1 st run	2 nd run	3 rd run	4 th run
The yield of 3a (%)	92	67	61	53

To evaluate the sustainability of the GO, a recyclability study was carried out. For this, the reaction of ethyl benzoate and benzylamine in the presence of GO was carried out at 100°C for 15h. After the completion of the reaction, the GO was separated and recovered by filtration and thoroughly washed with ethyl acetate and DI water to

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eliminate the traces of reaction mass, and dried under vacuum. The results showed that the recovered GO did not perform the same as the fresh GO. The results in Table 2 show the reduction in the catalytic activity of the recovered GO after each reaction. The literature reports reveal that primary amines reduced the GO into r- $GO.^{42}$ The decrease in the yield of product in the subsequent cycle illustrated the catalytic activity of GO reduced to some extent due to the participation of primary amines, which have been further confirmed by characterization.

Characterization of recovered graphene oxide after the fourth cycle:

FTIR spectroscopy depicted in Figure 2A shows the bands present at 2869 cm-1 (symmetric) and 2926 cm-1 (asymmetric) stretching modes was due to the splitting of $-CH_2$ band into two sub-bands. A band at 3416 cm-1 due to C-OH stretching was weaker compared to band Present in GO. The peak at 1606 cm-1 was due to O-H stretching or C=C stretching of graphene sheet. ^{43,44}



Figure 2A: FTIR spectra of recovered GO (GO4)

The XRD study of recovered GO (GO4) was performed as shown in **Figure 2B.** The characteristic diffraction peak of GO gets disappeared and new broad peak at $2\theta = 24^{\circ}$ corresponds to (002) plane which showed the formation of reduced GO and was found to be shifted to $2\theta = 24^{\circ}$ as compared to natural graphite (002) peak which is located at ~26.4° (**Figure 2B**). The shift of (002) peak could be ascribed to the presence of oxygenated functionalities. ⁴⁵



Figure 2B: X-ray diffraction pattern of recovered GO (GO4);

Further to check the quality of the recovered GO, Thermal gravimetric analysis (TGA) was performed (Figure 2C). a small

amount of weight loss was observed in recovered GO, signifying the small amount of water loss and removab of isome/oxygenated functional groups. From the results, it was concluded that although GO was gradually reduced, the oxygen-containing functional groups were not completely removed.⁴⁶



Figure 2C: Thermogravimetric analysis (TGA) of recovered GO (GO4);



Figure 2D: UV–Vis spectrum of recovered GO (GO4);

The recovered GO (GO4) was further characterized by UV–Vis spectrum as shown in **Figure 2D**. UV–Vis spectrum of recovered GO shows absorption peaks at 250 nm due to the reduction of GO signifies the electronic conjugation was restored in the graphene sheet. ⁴⁵

Morphology studies of GO4 were also examined by FE-SEM, TEM and SAED pattern (Figure 2E, 2F). Scanning electron microscopy (SEM) image of recovered GO (Figure 2E) revealed randomly aggregated and crumpled sheets loosely packed together. In the TEM image (Figure 2F) transparent area shows monolayer of the sheet, while dark shade shows a wrinkled structure that forms a thick layer of graphene sheets with several oxygen functionalities.

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Figure 2E: Scanning electron microscope (SEM) images of recovered GO (GO4); scale bar 1µm; **Figure 2F:** TEM image of recovered GO (GO4); scale bar 200 nm;

To further study the changes in the surface, characteristics of recovered GO, we also performed XPS analysis (Figure 2G). The bands at 284.6 and 532.2 eV corresponds to C1s and O1s, respectively ⁴⁷. In the case of reduced GO (GO4) O1s intensity decreased compared with that of GO (Figure S1H), suggesting the loss of oxygenated functionalities in GO.⁴⁸ The new peak at 400.0 eV was observed which corresponds to N1s, which may be due to the presence of nitrogen in the benzylamine, signifying the adsorption of benzylamine on GO.⁴⁹ The carbon to oxygen atomic ratio of GO and GO4 was found to be 2.21 and 5.91, respectively, indicating the reduction of functional groups of GO. The C1s spectrum of recovered GO (GO4) shows bands at 284.6, 285.7, 287.8, and 288.6 eV which corresponds to C-Sp², C-N, C-O-C, and C=O respectively (Figure 2H).⁴² It can be seen that intensity of all peaks of C-O decreased as compared to GO due to loss of oxygenated functional groups.



Figure 2G: XPS survey of recovered GO;



Figure 2H: C1s XPS Spectrum of recovered GO

Conclusions

In summary, graphene oxide (GO) serves as an excellent metalfree catalyst for the amidation of esters under the solvent-free reaction condition. A wide range of esters and amines were employed for the desired transformation under the optimized conditions. We have also studied selective amidation of various esters and amines when other functionalities were present. Additionally, low catalyst loading, simple workup procedure, high yield, are some added advantages of this synthetic methodology.

General:

Materials and Methods

Graphite flakes, natural (~325 mesh, 99.8%, Alfa Aesar), phosphoric acid (S D Fine Chem. Ltd.), sulphuric acid (98% assay with 99% purity, Merck), hydrochloric acid, 30% hydrogen peroxide, (S D Fine Chem. Ltd.), potassium permanganate (S D Fine), amines and esters were purchased from Sigma Aldrich, Spectrochem Pvt. Ltd, Loba Chemie, S. D. fine-chem. Ltd, India. All chemicals and solvents were used as received without further purification. The reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 GF245 precoated sheets and components were visualized using a UV-lamp at a wavelength of 254 nm or using KMnO₄ stain. Column chromatography was done using silica gel (230-400 mesh) and was performed.

Instrumentation

XRD analysis was carried out using a Shimadzu (Maxima 7000). FTIR spectra were recorded on Bruker Tensor 27 spectrometer with KBr pellets. The TGA thermograms were recorded on the Shimadzu 60H DTG apparatus. Raman analysis was carried out on a STR 500 confocal micro-raman spectrometer. UV-Visible spectra were recorded on a Perkin Elmer Lambda 25 UV–VIS spectrophotometer. A scanning electron microscope (SEM) was performed using Hitachi S-4800. Transmission Electron Microscopy (TEM) was done by using a PHILIPS model CM 200. X-Ray Photoelectron Spectroscopy (XPS) analysis was performed using a PHI 5000 Versa Probe II, FEI Inc. system. Melting points were recorded on the melting point

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apparatus (Sunder industrial products, Mumbai) and are uncorrected. Nuclear magnetic resonance spectra were recorded on Agilent (300 MHz or 400 MHz, 500MHz) instrument with DMSO-d⁶ or CDCl₃ as a solvent and TMS as an internal standard.

Experimental Section

Preparation of Graphene oxide (GO) by reported improved Hummer`s method (IHM)³⁵:

Graphene oxide was synthesized from natural graphite flakes by following Improved Hummer's method.³⁵

General Procedure for Direct Catalytic Amidation of Esters:

Ester (1.0 mmol) and aliphatic/aromatic amine (1.2 mmol) were heated at 80-120°C along with graphene oxide (20 wt. %) in 25mL of a sealed tube for the required time. After the reaction gets completed, the reaction mass was cooled to RT and then dissolved in ethyl acetate (10 mL). The GO was separated from the reaction mass by simple filtration. Most of the pure products were obtained directly after solvent evaporation under vacuum. In some cases, the crude reaction mass was subjected to column chromatography (solvent system- Hexane: Ethyl acetate) to get pure product.

Acknowledgments

Authors are greatly thankful to University Grants commission-UGC-CAS and Green Technology for providing financial assistance, SAIF IIT, Bombay for performing TEM analysis, and MRC, MNITJ Jaipur for Raman analysis. D D pal, TS XRD and XPS lab, IIT Kanpur for XPS analysis.

Conflict of interest

There are no conflicts to declare.

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New Journal of Chemistry Accepted Manuscript

View Article Online

DOI: 10.1039/C9NJ05283F

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