Metal-Free Sustainable Synthesis of Amides via Oxidative Amidation Using Graphene Oxide as Carbocatalyst in Aqueous Medium

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Abstract

We describe an efficient, clean and metal-free procedure for the synthesis of amides via oxidative amidation of aldehydes with anilines using graphene oxide (GO) as a recyclable catalyst and KBrO₃ as a mild oxidant in aqueous medium under microwave irradiation. GO nanosheets were prepared and characterized by XRD, TEM, SEM, and FT-IR, analyses. GO showed high compatibility with KBrO₃ in water and offered high TOF value $(1.30 \times 10^{-3} \text{ mol g}^{-1} \text{ min}^{-1})$. GO oxygen functionalities catalyze the oxidative amidation effectively in mild condition with high recyclability. A plausible mechanism was proposed by the isolating the intermediate.

Graphic Abstract



Keywords Carbocatalyst \cdot Oxidative amidation \cdot Metal-free synthesis

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1 Introduction

Amide bond linkage has attracted a fair amount of interest on account of their efficacy in pharmaceuticals, agrochemicals, natural products and organic materials [1–3]. The vital importance of amides has led to them being encountered through the advancement of diverse synthetic protocols. Traditionally used protocol involves the direct reaction of amines with activated carboxylic acid derivatives [4]. Although these methods are suitable for certain synthetic applications but many of these procedures are associated with one (or more) disadvantages such as stoichiometric amount of high molecular weight of by products, low functional group tolerance and poor atom economy. The oxidative amidation of aldehydes with amines is



one of the most efficient and expedient alternative strategy due to abundant starting materials [5-11].

A guarded study would necessitate that this alternative path tolerate some obstructs owing to their limited utility due to the exploitation of metal as catalysts, use excess amount of oxidants, non-compatible solvent, long reaction time, tedious workup and low selectivity. Further, the affianced catalytic systems are non-recoverable, hence tumbling the turn over frequency (TOF) observed, which is vital from the industrial vision. While some metal free modifications have been accredited for upliftment of the reaction condition [12], but somewhere down the line it still require the broad adaptability. Therefore, further development of the catalytic system will require advanced materials that can facilitate straight access to amides by metal-free oxidative amidation employing mild oxidant is of high genuine interest.

Carbon materials at nanoscale have been made an intense impact. It is the chemical genius of carbon that it can create different nanostructures with entirely different properties [13, 14]. Particularly, graphene oxide (GO) nanosheets illustrated ubiquitous concern due to high surface area, presence of oxy functionalities like hydroxyl (-OH), carboxylic (-COOH), carbonyl (C=O), epoxide groups (C-O-C) on both accessible sides, easy availability, chemical functionalization, good water-dispersion and high cell compatibility. These advantages lead to advance magnetic, optoelectronic and catalytic materials [15–17]. Among them graphene oxide (GO) nanosheets widely acceptable metal-free carbocatalyst in various organic transformations such as oxidation, hydration, alkylation reaction, redaction etc. [18-22]. Additionally, prologue of water [23] carbon based materials [24-28] and in this metal free oxidative amidation added imperative endeavor in this vicinity.

Inspired by our previous work on catalytic application of carbon-based nanostructures and development of sustainable protocols [29–33], herein, we describe metalfree oxidative amidation of aldehydes with amines using GO as a recyclable catalyst and KBrO₃ as a mild oxidant in water with some fascinating mechanistic deliberation under microwave irradiation. (Scheme 1).



Scheme 1 Metal-free oxidative amidation

2 Results and Discussion

GO were synthesized by simple one-pot chemical route [29] and well characterized by XRD, TEM, SEM and FT-IR analyses. XRD patterns of GO are given in Fig. 1. For GO, a sharp characteristic peak is observed due to (001) reflection [34].

In SEM analyses, GO nanosheets displayed a crumpled and wrinkled surface (Fig. 2). The nanosheets stacked together to form a typical multi-layer structure due to presence of p-p interaction. Further, the wrinkled structure of GO nanosheets affords a huge surface area.

TEM analyses of GO also augment the results obtain by SEM (Fig. 3). From the FT-IR spectrum of GO (Fig. 4), the peaks at 3465, 1721, 1368 and 1030 cm⁻¹ of GO could be



Fig. 1 XRD patterns of GO



Fig. 2 SEM image of GO



Fig. 3 TEM image of GO



Fig. 4 FT-IR of GO

assigned to the –OH stretching, C=O stretching, O–H deformation and C–O stretching vibrations respectively. A broad peak at around 1209 cm⁻¹ corresponds to C–O–C vibration. Further, four absorption peaks ranging from 1438 to 1568 cm⁻¹ observed due to the aromatic C=C stretching of GO nanosheet [35].

Now we have employ as prepared GO as a metal-free catalyst for oxidative amidation of aldehydes. For that purpose reaction of benzaldehyde (2.0 mmol) and aniline (2.0 mmol) was chosen as a model reaction using KBrO₃ as a mild oxidant in water under microwave irradiation. When the reaction was carried out in the absence of the catalyst, no desired product was formed as determined. Thus the preliminary attempts were focused on the competent assessment of different catalyst systems. As shown in Table 1, reaction produced low yield of desired product in the presence of 10 wt% PTSA. Further, moderate yields were observed in the presence of other metal-free catalyst. In order to develop sustainable metal-free catalyst, the study of catalytic aptitude of GO and rGO were studied. The best result in terms of turnover frequency (TOF: number of moles of product produced per gram of catalyst used per min [29, 31]) attained by GO nanosheets catalyst (10 wt% loading, TOF = 1.30×10^{-3} mol g^{-1} min⁻¹). Inferior yield was observed in the presence of rGO as compared to GO due to the presence of lower functional site, which confirmed the active role of GO's oxygen functional groups in the reaction. It was evidently designated from Table 1 that 10 wt% of catalyst loading was adequate to catalyze the reaction, excessive amount of catalyst did not affect the yield remarkably. The use of diverse oxidant illustrated that KBrO3 was found to be the most efficient oxidant to generate desired product 3a with good selectivity. The model reaction was also studied with different equivalent of KBrO₃ (2 equiv., 4 equiv. and 6 equiv.). Best results were found with four equiv. of KBrO₃. Evidently, in the absence of any oxidant poor yield of the product was observed. The reaction was also investigated in various solvents, such as H₂O, MeOH, DMSO, THF, DCM and CHCl₃.

As shown in Table 1, water was superior solvent as contrast to other organic solvents. It appears that a large amount of oxygen-containing groups on GO nanosheets can improve its dispersion in aqueous media. Due to this higher catalytic sites were available for the reaction and gave high yield of products compared to many other catalytic systems. Moreover, KBrO₃ act as an admirable oxidant in water due to its high extent of solvolysis in water with respect to other solvents [36].

The catalytic activity of GO was found fourfold higher than the conventional method (Table 1). Due to difference in dielectric properties of materials and by volumetric dielectric heating nanomaterials selectively absorbs MW in the reaction mixture [37]. Thus, they can works as a catalyst as well as susceptor [38] and serve as an internal heat source for the reactions which enhance overall catalytic activity of nanomaterials in MW. During the optimization of the reaction condition, the model reaction was also studied by varying microwave power (300, 400, and 500 W) and temperature. It was concluded that 400 W power output at 80 °C was required to accomplish maximum conversion to product. To exclude the possibility of radical reaction pathway, TEMPO (2.2.6.6-tetramethylpipridine-N-oxyl) was added to the reaction as a radical inhibitor. No Inhibition of reaction was observed by adding TEMPO which ruled out the radical process nature of the reaction.

Next we examined the scope of the reaction with respect to diverse aldehydes and anilines under the optimized conditions. The results are summarized in Table 2. However, aldehydes were liable to be oxidized to acids, no amount

S. no.	Catalyst	Solvent	Oxidant	Time (min)	Yield (%) ^a	TOF $(\times 10^{-3} \text{ mol g}^{-1} \text{ min}^{-1})^{\text{b}}$
1.	_	H ₂ O	KBrO ₃	40	_	n.c.
2.	PTSA (p-Toluenesulfonic acid) (10 wt%)	H_2O	KBrO ₃	40	37	0.420
3.	MeSA (Methanesulfonic acid) (10 wt%)	H_2O	KBrO ₃	40	49	0.556
4.	I ₂ (10 wt%)	H_2O	KBrO ₃	40	46	0.522
5.	KI (10 wt%)	H_2O	KBrO ₃	40	41	0.464
6.	NaI (10 wt%)	H_2O	KBrO ₃	40	39	0.444
7.	GO (10 wt%)	H_2O	KBrO ₃	30	86	1.30
8.	rGO (reduced graphene oxide) (10 wt%)	H_2O	KBrO ₃	40	48	0.545
9.	GO (5 wt%)	H_2O	KBrO ₃	40	47	1.11
10.	GO (20 wt%)	H_2O	KBrO ₃	30	86	0.579
11.	GO (10 wt%)	H_2O	H_2O_2	30	Trace	n.c.
12.	GO (10 wt%)	H_2O	TBHP	30	43	0.650
13.	GO (10 wt%)	H ₂ O	NaClO ₃	30	Trace	n.c.
14.	GO (10 wt%)	H_2O	NaBrO ₃	30	47	0.711
15.	GO (10 wt%)	H_2O	_	30	14	0.131
16.	GO (10 wt%)	MeOH	KBrO ₃	30	27	0.408
17.	GO (10 wt%)	DMSO	KBrO ₃	30	21	0.319
18.	GO (10 wt%)	THF	KBrO ₃	30	18	0.273
19.	GO (10 wt%)	DCM	KBrO ₃	30	16	0.242
20.	GO (10 wt%)	CHCl ₃	KBrO ₃	30	14	0.212
21.	GO (10 wt%) ^c	H_2O	KBrO ₃	12 h	56	0.354
22.	GO (10 wt%) ^c	H_2O	KBrO ₃	40	26	0.028

Table 1 Comparison of catalytic activity of GO with other catalytic systems for the oxidative amidation (3a)

n.c. Not calculated

Reactions are performed on benzaldehyde (2.0 mmol) and aniline (2.0 mmol) in water with different catalysts and oxidant under microwave irradiation

^aIsolated yield

^bTOF is defined as the number of moles of product produced per gram of catalyst used per min

°Conventional method, reaction at 120 °C

of acids were examined in our method, which shows that KBrO₃ chemoselectively oxidized imines rather than the aldehydes. Additionally, replacing the aldehydes with corresponding carboxylic acids did not give the desired amides. Therefore, the possibility of oxidation of aldehydes to carboxylic acids in this oxidative amidation was also being ruled out. A series of aromatic aldehydes and anilines with both electron donating and electron withdrawing substituents such as halo, methoxy, methyl, hydroxy, etc. were successfully produced corresponding product in excellent yields. We found as compared electron donating substituted aldehydes, electron withdrawing substituted aldehydes gave better yield. However, Ortho substitute aldehydes and anilines gave moderate yields due to the steric hindrance. Further, at the expense of time up to 60 min, heterocyclic aldehydes also afforded good yields. Probably due to the electronic factors, unpublishable results were obtained with the aliphatic counter parts of the reactants.

Although the accurate mechanism of this transformation is uncertain, but on the bases of literature survey and considering our whole experimental finding a plausible mechanistic pathway for oxidative amidation of aldehydes with amines was outlined in Scheme 2. The reaction may proceed via any of the two possible pathways as represented in Scheme 2. GO nanosheets can serve as an acidic catalyst for the two possible pathways (Path A and B). In path A, GO served as a acid catalyst for the reaction of benzaldehyde with aniline through acid sites coordinated to the oxygen of carbonyl groups to form imine intermediate A. Then, intermediate A oxidize by KBrO₃ in further step affording the oxaziridine intermediate **B**. Thermal rearrangement of oxaziridine [39-42] intermediate gave amides 3a as a desired product. In path B, GO facilitate the formation of hemiaminal intermediate C via direct coupling of benzaldehyde with aniline, which was afterward oxidized by KBrO₃ to form corresponding amide 3a. Although, we isolate the imine intermediate A in controlled conditions (See ESI), but the





Reactions are performed on benzaldehydes (2 mmol), anilines (2 mmol), $KBrO_3$ (4 eq.) and 10 wt% GO in water under microwave irradiation



Scheme 2 Plausible mechanism for oxidative amidation

exact mechanism of this reaction remains uncertain and both pathways could be possible.

To confirm the heterogeneous nature of GO nanosheet in the reaction, the model reaction was carried out again under similar reaction conditions with the catalyst procured from a previous cycle. After 15 min, the catalyst was separated from the reaction mixture. The reaction was continued with the filtrate for another 60 min and the reaction conversion was monitored for every 5 min. It was observed that further increment in conversion was not observed even after 60 min. These results revealed that the oxidative amidation was occurring only due to the solid GO catalyst.

Recycling experiments were performed by choosing the benzaldehyde (2.0 mmol) and aniline (2.0 mmol) as a model reaction in water under microwave irradiation using GO as a solid catalyst. The reaction was started with the addition of $KBrO_3$ as a mild oxidant. When the reaction was completed, the reaction mixture was filtered and the solid mass (product + catalyst) was dried. Then, the solid mass was dissolved in ethanol and the dispersed catalyst was recovered by filtration. The recovered catalyst was washed with water and ethanol and reused in succeeding 8 reaction cycles without



Fig. 5 Recyclability of GO nanosheet

any significant loss in its catalytic activity (Fig. 5). The reason is that the characteristics obtained from SEM and TEM of fresh and used catalysts are similar (Fig. S3 and S4; see ESI), which suggest the retention of structure and morphology of GO after repeated use as catalyst.

3 Experimental Section

3.1 General

General part including used instruments is provided in ESI.

3.2 Preparation of Graphene Oxide (GO)

Graphene oxide (GO) was prepared by the oxidation of graphite flakes according to our previously reported method [17] (See ESI).

3.3 Catalyst Activity Measurement

The model reaction was examined to check the catalytic activity of GO benzaldehyde (2 mmol), aniline (2 mmol), KBrO₃ (4 eq.) and 10 wt% GO were taken in 8 mL water in a 10 mL round-bottom flask. The flask was placed in the microwave cavity and subjected to irradiation for appropriate time at 80 °C using a maximum power of 400 W. The complete conversion of reactants into products was checked by TLC. On completion of reaction, the resulting solid mass (product + catalyst) was dried. Then, the solid mass was dissolved in ethanol and the dispersed catalyst was recovered by filtration. The as obtained solution was concentrated to generate the crude product. The crude product was purified by crystallization from ethanol.

4 Conclusion

In conclusion, we illustrated GO as a competent metal-free carbocatalyst for oxidative amidation of aldehydes with amines using KBrO₃ as a mild oxidant in aqueous medium under microwave irradiation. No other oxidative side products like acids were produced in this process with amides. This atom-economical protocol, includes a much milder procedure, does not involve any tedious work-up for purification, avoids hazardous reagents/byproducts and the target molecules were obtained in good to excellent yields. The protocol will promote newer area of environmental research, based on innovation, aimed at developing environmentally sound catalysts and techniques and would be useful in introduction of newer, cleaner and economical synthetic procedures.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- 1. Greenberg A, Breneman CM (2000) The amide linkage: Structural significance in chemistry. Biochemistry and material science. Wiley-VCH, New York
- Cupido T, Tulla-Puche J, Spengler J, Albericio F (2007) Curr Opin Drug Discov Dev 10:768–783
- Ghose AK, Viswanadhan VN, Wendoloski JJ (1999) J Comb Chem 1:55–68
- 4. Valeur E, Bradley M (2009) Chem Soc Rev 38:606-631
- 5. Yoo WJ, Li CJ (2006) J Am Chem Soc 128:13064-13065
- 6. Seo Y, Marks TJ (2008) Org Lett 10:317-319
- 7. Ghosh SC, Ngiam JSY, Seayad AM, Tuan DT, Chai CLL, Chen A (2012) J Org Chem 77:8007–8015
- 8. Li Y, Jia F, Li Z (2013) Chem Eur J 19:82-86
- Whittaker AM, Dong VM (2015) Angew Chem Int Ed 54:1312–1315
- 10. Bhattacharya S, Ghosh P, Basu B (2018) Tetrahedron Lett 59:899–903
- Acosta-Guzmán P, Mateus-Gómez A, Gamba-Sánchez D (2018) Molecules 23:2309–2382
- 12. Mahesh M, Panduranga V, Prabhu G, Kumar R, Venkata Ramana P, Sureshbabu VV (2017) Synth Commun 47:716–721
- 13. Lee J, Jaeyun K, Taeghwan H (2006) Adv Mater 18:2073-2094
- Rodriguez NM, Chambers A, Terry R, Baker K (1995) Langmuir 11:3862–3866
- 15. Zhu Y, Murali S, Cai W, Li X, Suk JW (2010) Adv Mater 22:3906–3924
- 16. Loh KP, Qiaoliang B, Goki E, Manish C (2010) Nat Chem 2:1015–1024

- 17. Compton OC, SonBinh TN (2010) Small 6:711-723
- Jia HP, Dreyer DR, Bielawski CW (2011) Tetrahedron 67:4431–4434
- Dreyer DR, Jia HP, Bielawski CW (2010) Angew Chem Int Ed 49:6813–6816
- Dreyer DR, Jia HP, Todd AD, Geng J, Bielawski CW (2011) Org Biomol Chem 9:7292–7295
- 21. Jia HP, Dreyer DR, Bielawski CW (2011) Adv Synth Catal 353:528-532
- 22. Sengupta D, Ghosh S, Basu B (2017) Curr Org Chem 21:834-854
- 23. Olivier SM, Li CJ (2012) Chem Soc Rev 41:1415–1427
- Brahmayya M, Suen S-Y, Dai SA (2018) J Taiwan Inst Chem Eng 83:174–183
- Kumari S, Shekhar A, Mungse HP, Khatri OP, Pathak DD (2014) RSC Adv 4:41690–41695
- Mirza-Aghayan M, Ganjbakhsh N, Tavana MM, Boukherroub R (2016) Ultrason Sonochem 32:37–43
- Rostamnia S, Doustkhah E, Golchin-Hosseini H, Zeynizadeh B, Xin H, Luque R (2016) Catal. Sci Technol 6:4124–4133
- Soul J-F, Miyamura H, Kobayashi S (2013) Chem Asian J 8:2614–2626
- Dandia A, Sharma A, Parewa V, Kumawat B, Rathore KS, Sharma A (1902) RSC Adv 5(2015):91888–91889
- Dandia A, Parewa V, Kumari S, Bansal S, Sharma A (2016) Green Chem 18:2488–2499
- Dandia A, Gupta SL, Indora A, Saini P, Parewa V, Rathore KS (2017) Tetrahedron Lett 58:1170–1175

- 32. Dandia A, Parewa V, Rathore KS (2012) Catal Commun 28:90-94
- Dandia A, Parewa V, Gupta SL, Sharma A, Rathore KS, Sharma A, Jain A (2015) Catal Commun 61:88–91
- Qian Z, Cheng Y, Zhou X, Wu J, Xu G (2013) J Colloid Interface Sci 397:103–107
- Paredes JI, Villar-Rodil S, SolisFernandez P, Martinez-Alonso A, Tascon JMD (2009) Langmuir 25:5957–5968
- 36. Wei D, Hoseney RC (1995) Cereal Chem 72:58–63
- 37. Polshettiwar V, Varma RS (2010) Green Chem 12:743-754
- Chemat F, Esveld DC, Poux M, Di-Martino JL (1998) J Microwa Power Electromagn Energy 33:88–94
- Lattes A, Oliveros E, Riviere M, Belzecki C, Mostowicz D, Abramskj W, Piccinni-Leopardi C, Germain GV, Meerssche M (1982) J Am Chem Soc 104:3929–3934
- 40. Wenglowsky S, Hegedus LSJ (1998) J Am Chem Soc 120:12468-12473
- 41. Aube J (1997) Chem Soc Rev 26:269-277
- Leung CH, Voutchkova AM, Crabtree RH, Balcells D, Eisenstein O (2007) Green Chem 9:976–979

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