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ARTICLE TYPE

Synthesis of 2,3-dihydroquinazolinones and quinazolin-4(3*H*)-one catalyzed by Graphene Oxide nanosheets in aqueous medium: "on-water" synthesis accompanied by carbocatalysis and selective C-C bond cleavage

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Graphene oxide (GO) nanosheet catalyzed new and straightforward strategies for the construction of 2,3-dihydroquinazolinones and quinazolin-4(3H)-one starting from anthralinamide (2-aminobenzamide) and aldehyde/ketone in aqueous medium at room temperature have been materialized. This catalyst is also found to be efficient towards the expedient construction of quinazolin-4(3H)-one starting from anthranilamide and β-ketoester/1,3-diketone following selective C-C bond cleavage of β-ketoester/1,3-diketone at some elevated temperature under metal and oxidant free conditions.

Introduction

N-Heterocyclic compounds are considered to be the most profuse and integral scaffolds that are found in a large number of bioactive natural products, synthetic drugs and pharmaceuticals.[1] Among the diversified N-heterocyclic compounds, 2,3-dihydroquinazolinones and quinazolin-4(3*H*)-one are vastly significant class of heteroaromatic compounds that are ubiquitous in the field of pharmaceuticals, therapeutically potent and biologically active .[2] Owing to the large number of applications of these heterocyclic moiety, synthesis of these compounds is largely an affair of interest. Some attempts for the synthesis of these compounds have been reported in the literature in recent decades and reported methods[3] though claim good results in many instances, still development of efficient, simple, metal free approach using recyclable catalysts that offers a huge substrate scope and covers up most of the features of green chemistry[4] is desirable and of course in demand.

Recalling the previously developed methods and their shortcomings which have included the application of hazardous organic solvents, strongly acidic conditions, expensive moisture-sensitive catalysts, extended reaction times, high reaction temperatures, and also tedious work-up conditions, we intended to devise a new and simple catalytic method for the cyclocondensation reaction of anthranilamide and carbonyl compounds involving a carbocatalyst, graphene oxide (GO) nanosheets. After successful accomplishment to design both 2,3-dihydroquinazolinones and quinazolin-4(3*H*)-one, we proceeded to another synthetic route for the construction of the oxidized product (quinazolin-4(3*H*)-one) starting from anthranilamide and 1,3-diketones/ *β*-ketoesters *via* selective C-C bond cleavage of 1,3-diketones/ *β*-ketoesters involving the same catalyst in aqueous medium under oxidant free condition.

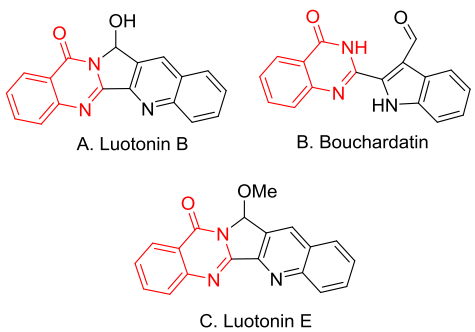

Fig. 1 Quinazolin-4(3*H*)-one based natural products

Now-a-days selective C−C bond cleavage is an important and essential topic in the field of organic synthesis[5], which allows the

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construction of a new C−C bond directly from inert starting materials. It was well demonstrated by the work of Yashuro et al, where camphorsulfonic acid was employed to furnish quinazolin-4(3*H*)-one moiety from 1,3-dicarbonyl compounds in ethyl lactate-water medium at 100 ^{o}C.[6] Furthermore, selective C-C bond cleavage was also realized during the formation of quinazolin-4(3*H*)-one from *β*-ketoesters employing phosphorous acid in ethanol medium[7]. Despite having some advances in this field , the development of selective C−C bond cleavage by catalytic mode is a challenging problem in organic chemistry involving metal-free and oxidant free strategies .[9] To conquer these challenges, we devised a new strategy for the C-C bond cleavage under metal and oxidant free conditions and successfully developed another synthetic protocol for the construction of quinazolin-4(3*H*)-one derivatives from anthranilamide and 1,3-diketone/*β*-keto ester allowing selective cleavage of C-C bond of 1,3-diketone/*β* -keto ester in presence of GO nanosheets.

In continuation of our ongoing research[10] in developing new catalytic system for the construction of various biologically significant molecules with the aid of sustainable chemistry, GO nanosheets being a carbocatalyst[11] was found to be the most efficient for our desired transformations. Recently, GO nanosheets has attracted enormous interest to the development of composite materials and catalysts[12], due to their remarkable physical, chemical, electrical characteristics and a very high specific surface area to weight[13].In the field of organic synthesis, nanostructured polycarbon acids are considered to be more vigorous in aqueous media which facilitates us to report GO nanosheets, a readily available, inexpensive and efficient carbocatalyst[11] that enhances the latitude of our current research.

Result and discussion:

Preparation of the carbocatalyst i.e. GO nanosheets was done by the slight modification of known methods[14]. XRD study and FTIR (Fig. 2) spectrum were recorded to identify the nature of various chemical functionalities present on the graphene oxide nanosheets and its dispersion in water. Various functional groups on GO nanosheets were appeared on oxidation of graphite powder. These functional groups are bonded on either edges and or basal planes of graphitic layers. Furthermore, trapped water molecules are suspected to be present between these layers and responsible for expansion of the interlayer spacing in graphene oxide nanosheets. An intense and broad peak appeared at 3424 cm^{-1} corresponds to the stretching mode of an O–H bond and suggests the abundance of hydroxyl groups in graphene oxide. The strong band at 1722 cm^{-1} represents carboxylic acid and carbonyl groups. FTIR bands at 1224 cm^{-1} and 1053 cm^{-1} are appeared due to the presence of C–OH and C–O of epoxy groups respectively, in GO nanosheets.

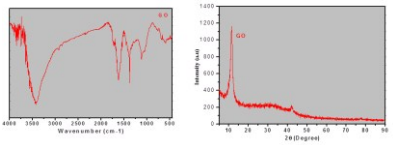

Fig. 2 FTIR and XRD pattern of GO nanosheets

HRTEM and FESEM images (Fig. 3) of GO nanosheets disclose that graphene oxide is composed of a few layers, resulting in a high surface area responsible for efficient catalytic activity.

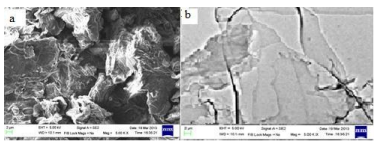

Fig 3. FESEM and TEM images of GO nanosheets

For the sake of validation of graphene oxide nanosheets to be the key for inferring the reactions in aqueous media, we have carried out screening tests employing a series of catalysts and solvents. Model substrate for the initial screening was anthranilamide (1) and *m*-nitrobenzaldehyde (2) as described in Table 1. Some of previously discussed methods involves the cyclocondensation of anthranilamide with aldehyde using p-sulfonic acid calix[4]arene[15], Fe_3O_4 nanoparticles[16], Sulfamic acid functionalized, piperidine-4-carboxylic acid- Fe_3O_4 nanoparticles[17] (Fe_3O_4-SA-PPCA nanoparticles), ionic-liquids[18],2-(Nmorpholino)ethanesulfonic acid (MES) in aqueous ethanol[19] suffer from one or more disadvantages as previously mentioned. Therefore, we have intended to design a simple, efficient, new and green route for the cyclocondensation reaction with a larger substrate scope. Our initial attempts involved reaction with, polyethylene glocol-SO_3H (PEG-SO_3H) reduced graphene oxide (RGO), polyethylene glycol-SO_3H-bearing solid acid catalyst (PEG-SAC), SnO_2 quantum dots, and nano $CuFe_2O_4$. In most of the cases time required for the generation of the desired product was more as well as the isolated yield was not sufficient. Hence, the search of appropriate catalyst was in demand. When the reaction was carried out in presence of nano GO, it was found that the desired product was obtained in higher yield than before (Table 1, entry 8). Result encouraged us to perform the reaction involving GO and it was found that these GO nanosheets offered maximum yield of the product within minimum period of time in aqueous medium. When 25 mg GO nanosheets was applied, it was found to be the most effective in promoting the formation of desired product with maximum yield (Table 1, entry 11) and shorter reaction time. The recyclability of GO nanosheets was also very high in aqueous media. After the reaction, GO nanosheets could be recycled easily and castoff in the next run. The recyclability chart of the catalytic potential of GO nanosheets is shown in Fig. 5 (recovery amount 90% after 5th run). Elemental analysis of fresh GO nanosheets provided - C 62.01% and H 2.84% respectively and in recycled GO it was found to be 61.98% and 2.86% respectively. The XRD image of

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recovered GO nanosheets is also identical with the XRD image of fresh GO (Fig. 4).

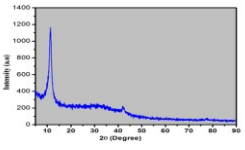
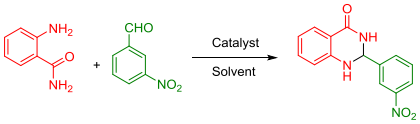


Fig. 4 XRD pattern of recovered GO nanosheets

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Catalyst Free	Water	100	10	trace
2	Catalyst Free	EtOH	Reflux	10	trace
3	PEG–SO_3H (10 mg)	Water	80	2	65
4	RGO (25 mg)	Water	r.t	0.5	-
5	PEG-SAC (25 mg)	Water	r.t	0.5	30
6	SnO_2.QDs (10 mol%)	EtOH	Reflux	10	-
7	Nano $CuFe_2O_4$ (10 mol%)	EtOH	Reflux	10	-
8	Graphene Oxide nanosheets (10 mg)	EtOH	Reflux	3	80
9	Graphene Oxide nanosheets (10 mg)	Water	80	0.5	85
10	Graphene Oxide nanosheets (15 mg)	Water	r.t	0.25	85
11	**Graphene Oxide nanosheets (25 mg)**	**Water**	**r.t**	**0.25**	**93**

[a]Reaction conditions: anthranilamide (1 mmol), meta- nitrobenzaldehyde (1 mmol)

[b] Isolated yields of pure products

In order to predict the active site present in GO, we have designed the model reaction taking various small molecules like benzoic acid, ethylene glycol, meso-1,2-diphenylethane-1,2-diol, sulphuric acid, styrene oxide, stilbene oxide and 2-iodophenol as the catalyst (Table 2). Among the applied catalysts, benzoic acid and sulphuric acid have proven their efficiency while benzoic acid showed its extra potential towards the desired transformation. Therefore, carboxylic acid functional group present in GO is assumed to be the active reaction centre and responsible for the desired transformations.

Utilizing the optimized reaction condition, synthesis of compound **3a-k** (involving electronically varied aromatic, aliphatic and heteroaromatic aldehydes **2**) was achieved with an excellent yield (Table3).

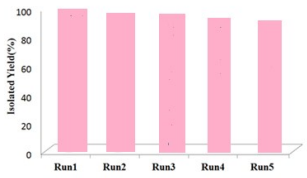


Fig.5 Reusability study of GO nanosheets

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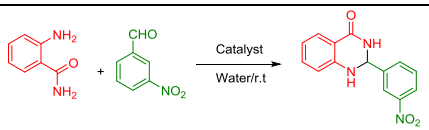
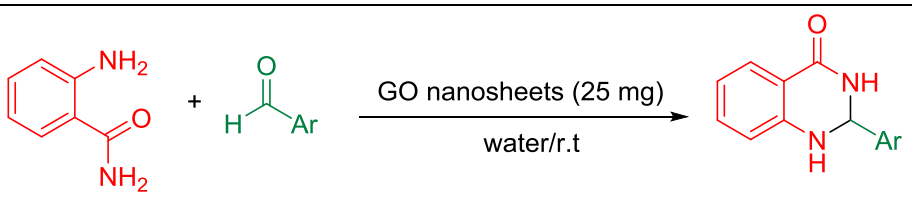
Table 2 Reactions for Evolution of Active Site in Catalyst (GO)



Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Benzoic acid (10 mol%)	Water	r.t	0.25	65
2	Ethylene glycol (10 mol%)	Water	r.t	0.25	-
3	1,2-diphenylethane-1,2-diol (5mol%)	water	r.t	0.5	-
4	H_2SO_4 (13 mol%)	Water	r.t	0.25	25
5	Styrene Oxide (10 mol%)	Water	r.t	0.5	-
6	Stilbene Oxide (10mol%)	water	r.t	0.5	-
7	2-iodophenol (10 mol%)	Water	r.t	0.5	-

Table 3 Synthesis of diversified 2,3-dihydroquinazolinone derivatives [a]



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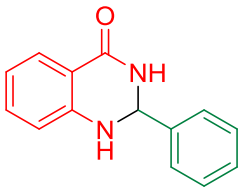
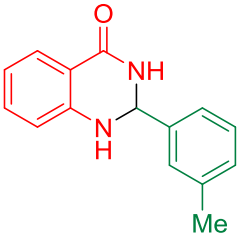
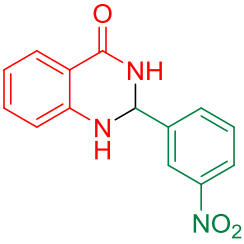
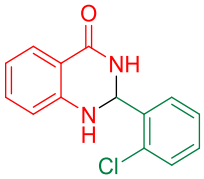
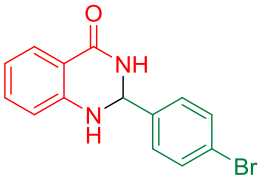
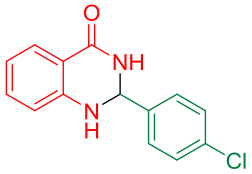
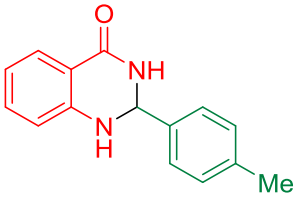
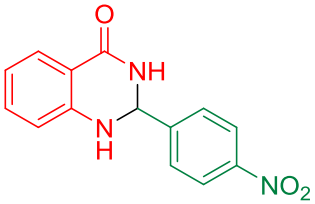
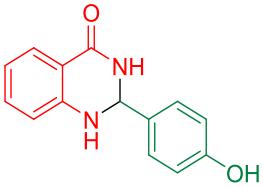
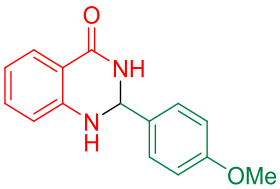
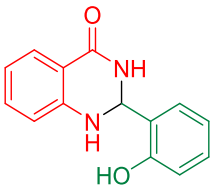
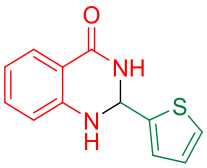
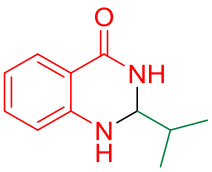
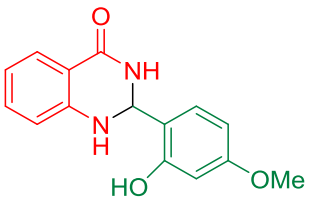
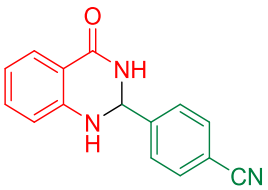
 **3a**, 20min, 94%	 **3b**, 25min, 92%	 **3c**, 10min, 96%
 **3d**, 12min, 95%	 **3e**, 12 min, 95%	 **3f**, 12min, 95%
 **3g**, 20 min, 92%	 **3h**, 12 min, 97%	 **3i**, 25min, 88%
 **3j**, 20min, 89%	 **3k**, 25min, 89%	 **3l**, 15min,90%
 **3m**, 25min, 88%	 **3n**, 25min, 87%	 **3o**,15min, 92%

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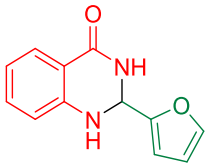
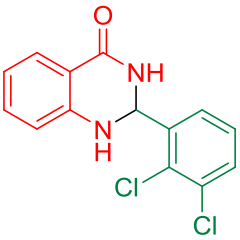
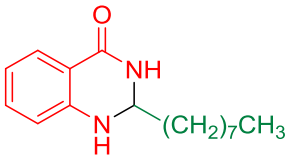
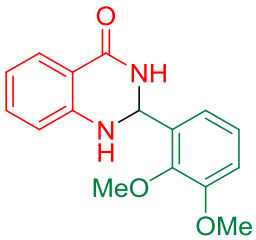
 **3p**, 15min, 90%	 **3q**, 20min, 94%	 **3r**, 30min, 85%
 **3s**, 25min, 89%		

[a]Reaction conditions: anthranilamide (1 mmol), aldehyde (1 mmol), GO nanosheets (25 mg), 3 ml H_2O at r.t for stipulated time

To further explore the substrate scope, various ketones[20] (**4**) were then investigated as depicted in Table 4. A wide range of activated as well as unactivated ketones, with electron-deficient and electron-rich aryl groups, cyclic & acyclic ketones were highly compatible under the developed protocol and provided excellent yield of the corresponding products (**5a-l**) at room temperature.

In all cases, the progress of the reaction was monitored by TLC. The structures of the desired products were characterized by ^1H , ^{13}C NMR and IR spectral data. The X-ray crystal structure of 2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**3h**) (Fig. 6), 2-methyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**5a**) (Fig. 7) and 1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'*H*)-one (**5j**) (Fig. 8) further confirmed the product identity.

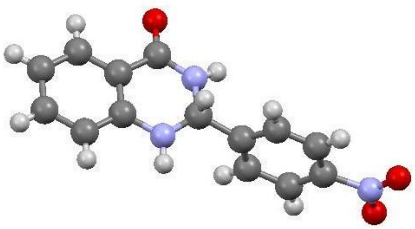


Fig.6 Single crystal structure of compound **3h** (CCDC) 1057348

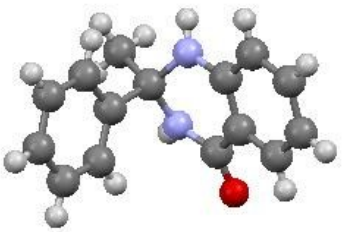


Fig. 7 Single crystal structure of compound **5a** (CCDC) 1416677

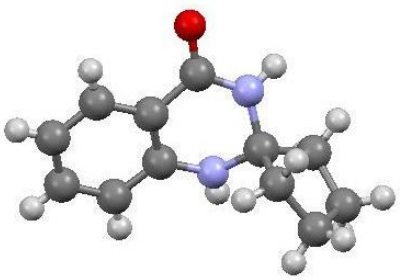


Fig. 8 Single crystal structure of compound **5j** (CCDC) 1057349

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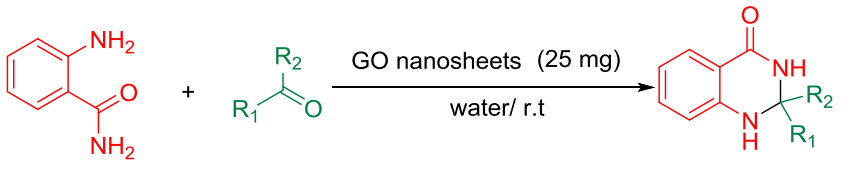
Table 4 Synthesis of diversified 2, 3-dihydroquinazolinones derivatives[a]



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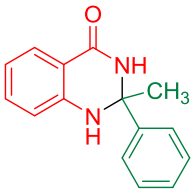
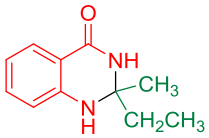
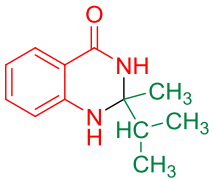


5a, 35min, 86%



5b, 40min 85%



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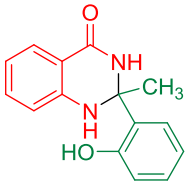

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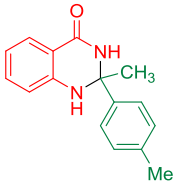

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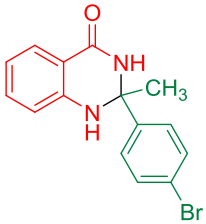

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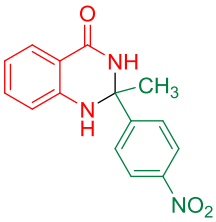
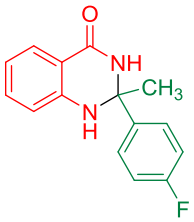
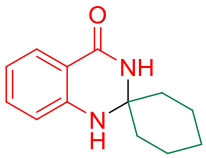


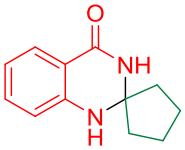
5g, 30min,89%



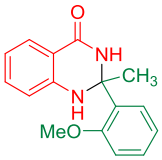
5h, 30min, 87%



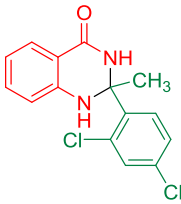
5i, 20min, 95%



5j, 20min, 95%



5k, 35min,83%



5l, 30min, 85%

[a]Reaction conditions: anthranilamide (1 mmol), ketone (1 mmol), GO nanosheets (25 mg), 3 ml H_2O at r.t for stipulated time

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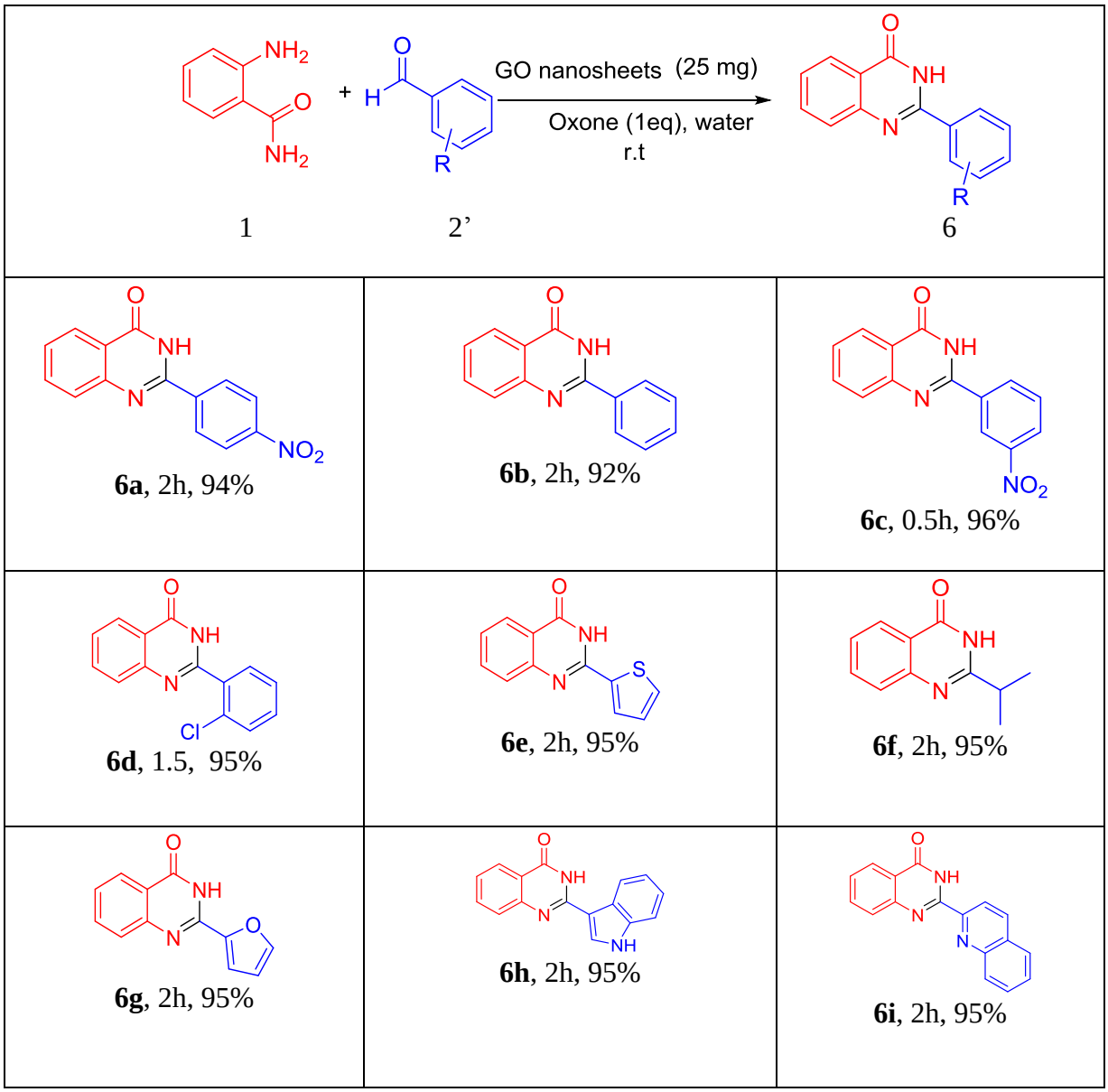
Result obtained applying the developed protocol in the cyclocondensation of anthranilamide and carbonyl compounds encouraged us to further extend this methodology for the synthesis of quinazolin-4(3*H*)-one derivatives and the oxidized products[21] (**6a-i**) were realized when the reaction was carried out in presence of oxone (Table 5). In this case, GO nanosheet solely was unable to provide the oxidized product at room temperature. Employing oxone with GO, led us to achieve the desired transformation (involving electronically varied nature of aldehydes **2'**) at room temperature. Interestingly, during this reaction condition no side product was evolved through the oxidation of the starting material rather the reaction has produced only the targeted molecule. In this study also, the progress of the reaction was monitored by TLC. The structures of all the products were well characterized through the analysis of ^{1}H , ^{13}C NMR and IR spectral data.

Table 5 Synthesis of diversified quinazolin-4(3*H*)-one derivative



[a]Reaction conditions: anthranilamide (1 mmol), aldehyde (1 mmol), GO nanosheets (25 mg), Oxone (307 mg), 3 ml H_2O at r.t for stipulated time

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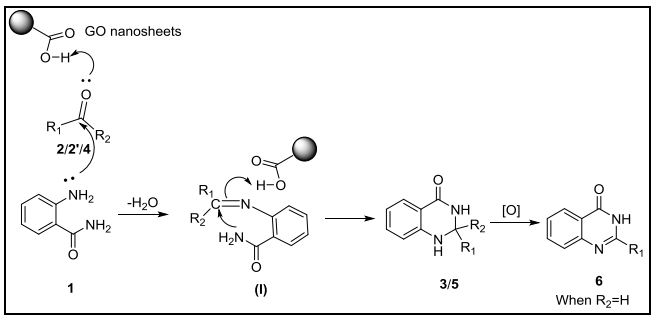
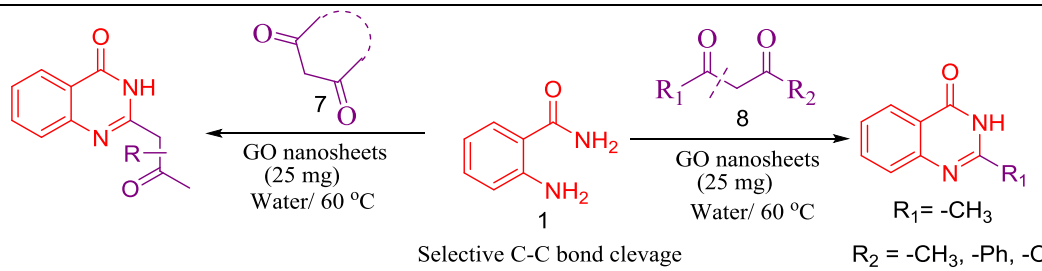
We then tried to understand the insight of the reaction which is represented in **Scheme 1**. The first step involves the condensation of anthranilamide (**1**) with aldehyde/ketone (**2**/**2**'/**4**) promoted by the catalyst (GO nanosheets) to produce imine intermediate (**I**). The imine part of the intermediate **I** could be activated by the catalyst and intermediate **I** subsequently converted into 2,3-dihydroquinazolinone (**3**/**5**) by intramolecular nucleophilic attack by the nitrogen of amide functionality on the imine carbon. In presence of oxidizing agent (oxone), this 2,3-dihydroquinazolinone then undergoes oxidation and converted into quinazolin-4(3*H*)-one (**6**).

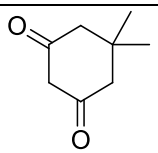
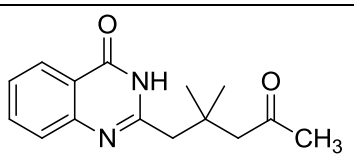


Scheme 1: Plausible reaction pathway for the formation of 2,3-dihydroquinazolinones and quinazolin-4(3*H*)-one

After successful effort to achieve the quinazolin-4(3*H*)-one from anthranilamide and aldehyde molecules, we then concentrated to the formation of the same compound starting from anthranilamide and 1,3-diketones (both cyclic and acyclic) *via* C-C bond cleavage applying the same catalyst. Treatment of anthranilamide with either acetyl acetone, benzoyl acetone or *β*-keto ester (ethyl acetoacetate), offered the same compound, 2-methylquinazolin-4(3*H*)-one with different yields (Table 6). Obtained results on analysis, gave the idea about the selective cleavage of C-C bond and also indicated that reactivity of the acetyl group is higher than that of the benzoyl group under the imposed reaction condition. Reason of higher reactivity of acetyl group in the present study is not clear; it may be due to the presence of graphitic layers of GO (catalyst) which enhances the electrophilicity of acetyl group more effectively than benzoyl group i.e. acetyl group is more exposed than benzoyl group towards nucleophilic attack under the experimental condition. When cyclohexane-1,3-dione was treated with anthranilamide in the presence of GO nanosheets (25 mg) in water at 60 °C for 8 h, product 2-(4-oxopentyl)quinazolin-4(3*H*)-one was generated in 85% yield (Table 6, entry 2). Interestingly, cyclohexane-1,3-dione exhibited a higher reactivity than 5,5-dimethylcyclohexane-1,3-dione (Table 6, entry1). In contrast, cyclopentane-1,3-dione, which contains a five-membered ring, did not give the desired products when treated with anthranilamide (Table 6, entry 3) even after raising the temperature (100 °C) and time period (18 h).

Table 6 Formation of quinazolin-4(3*H*)-one derivatives *via* C-C bond cleavage



Sl. No.	1,3-diketones/ *β*-keto ester	Product	Yield (%)	Time (h)
1		 **7a**	69	8

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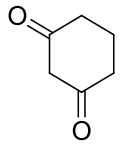
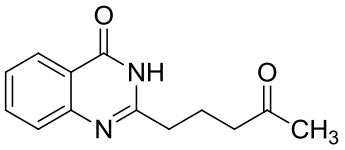
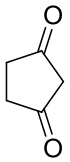
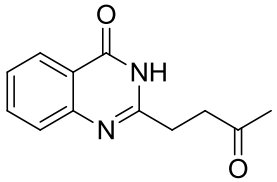
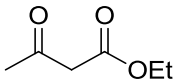
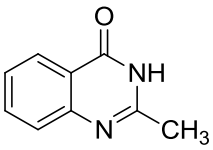
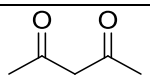
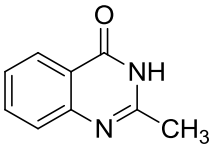
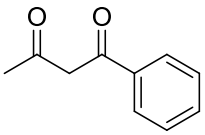
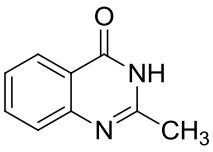
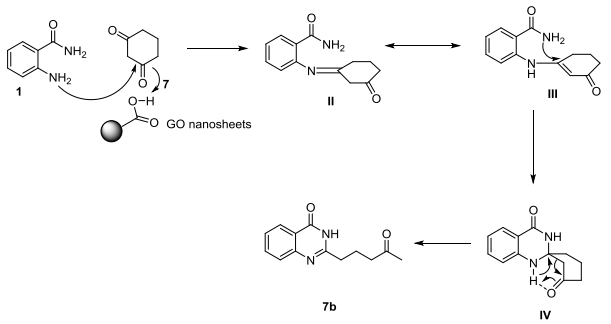
2		 **7b**	85	7
3		 **7c**	ND	18
4		 **8a**	95	6
5		 **8b**	98	6
6		 **8c**	80	6

[a]Reaction conditions: anthranilamide (1 mmol), 1,3 diketone/*β*-keto ester (1 mmol), GO nanosheets (25 mg), 3 ml H_2O at 60 ^oC for stipulated time. ND-not detected

GO nanosheets catalyzed condensation reaction of anthranilamide (**1**) with 1, 3-diketone (**7**) involves selective scission of C-C bond, which follows the course of producing a ketamine intermediate (**II),** tautomerization of **II** generates another intermediate enaminone (**III**). This enaminone subsequently undergoes intramolecular nucleophilic addition to generate **IV** and finally C-C bond cleavage reaction leads to the generation of the desired product (**Scheme 2**).



Scheme 2: Plausible reaction pathway for the formation of quinazolin-4(3*H*)-one *via* and oxidant free C-C bond cleavage

Experimental Section:

Preparation of GO

Natural graphite powder is used for the synthesis of GO nanosheets. Graphite powder (1000 mg) and $NaNO_3$ (1000 mg) were added to 35ml of concentrated H_2SO_4 (98%) under vigorous stirring in a 250 ml conical flask placed in an ice bath. The whole mass was converted to black slurry (it takes 2 min), then $KMnO_4$ (5000 mg) was added slowly to the slurry maintaining the reaction temperature between 15 ^oC and 20 ^oC. After 3 h, the entire system was taken out of the ice bath and diluted with 100 ml water and then further stirred for 3 h at ambient temperature. 200 ml hot water was added to the above reaction mixture followed by 30% H_2O_2 until the excess permanganate and manganese dioxide had been reduced to colourless soluble manganese sulfate. The resultant yellow precipitate was washed with distilled water several times and then was subjected to centrifuge to get the pure graphene oxide powder. After repeated centrifugation, salts and ions results from the oxidation process can be removed from GO suspensions. The GO nanosheets sample was collected and dried at 60^oC for 24 h. The GO

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nanosheets were characterized using XRD, FTIR, FESEM and TEM images.

General Procedure for the synthesis of 2, 3-dihydroquinazolinones:

Anthranilamide(**1**) (1 mmol) was added to aldehyde/ketone (**2** or **4**) derivative (1 mmol) in aqueous medium (3 ml water) followed by GO nanosheets (25 mg) at room temperature. The mixture was then stirred for the required period of time (indicated by TLC). After completion of each reaction, product and the catalysts separated from reaction system by simple filtration. The crude product was then dissolved in EtOH (3 ml) and this allows separation of minute quantity of the catalyst through filtration and crystallization of the crude product from EtOH furnished pure compound. All compounds were well characterized by ^{1}H, ^{13}C NMR and FT-IR analysis.

General Procedure for the synthesis of quinazolin-4(3*H*)-one:

Anthanilamide (**1**) (1 mmol) was added to aldehyde (**2'**) (1 mmol) in aqueous medium (3 ml water) followed by GO nanosheets (25 mg) and oxone (307 mg) at room temperature. The mixture was then stirred for the required period of time (indicated by TLC). After completion of each reaction, crude product was separated from reaction system by simple filtration. The crude product was then dissolved in EtOH (3 ml) and filtered. Finally crystallization of crude product from EtOH offered the pure compound. All compounds were well characterized by ^{1}H, ^{13}C NMR and FT-IR analysis.

Anthanilamide (**1**) (1 mmol) was added to 1,3-diketones (**7** or **8**) derivative (1 mmol) in aqueous medium (3 ml water) followed by GO nanosheets (25mg) at 60 ^{o}C. The mixture was then stirred for the required period of time (indicated by TLC). After completion of each reaction, the crude product mixture was extracted with ethyl acetate (2x3ml) and finally purified by column chromatography (eluent- ethyl acetate/petroleum ether: 1:4). All compounds were well characterized by ^{1}H, ^{13}C NMR and FT-IR analysis.

Conclusion:

We bring to completion developing the catalytic protocol which is applicable to the formation of both 2,3-dihydroquinazolinones and quinazolin-4(3*H*)-one. Firstly, cyclo-condensation reaction of anthranilamide and aldehyde/ketone using GO nanosheet offers various advantages like operational simplicity, extensive substrate scope, low catalyst loading, low thermal energy and high product yield. Use of water as the reaction medium and application of green oxidant make this protocol truly a practical one in synthetic chemistry and superior to the previously developed methodologies as it swathes most of the features of sustainable chemistry. Finally, formation of quinazolin-4(3*H*)-one *via* selective cleavage of C-C bond of 1,3-diketones under metal free and oxidant free condition is the most eye-catching feature of this work and will be considered much efficient relative to the previously developed methods in terms of product yield, catalyst loading and mild reaction condition. To the best of our knowledge this is the first application of a carbocatalyst (GO nanosheet) for the selective scission of C-C bond. Application of reusable nanosheets as the catalyst in organic synthesis extends the scope and may contribute further to progress in chemical research.

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