

CHAPTER 8

Graphene Oxide (GO)-Catalyzed Green Synthesis of Medicinally Privileged O-Heterocycles

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Abstract: Developing greener and metal-free synthetic approaches for preparing synthetically and medicinally valuable organic compounds is an urgent necessity in the context of green chemistry and sustainable development. Since 2010, the versatile and multifunctional two-dimensional graphene-based carbon nanomaterial, graphene oxide (GO), has garnered significant attention as a highly efficient, metal-free heterogeneous catalyst for a wide range of organic transformations. Due to its non-toxicity, biocompatibility, recyclability, low cost, and ease of accessibility, graphene oxide (GO) has been extensively explored for designing greener alternatives to many conventional metal-catalyzed organic reactions. Being decorated with multiple oxygenated functional groups, such as carboxyl, hydroxyl, and epoxy/ether groups, GO has been primarily exploited as an oxidant and a solid acid catalyst.

Meanwhile, GO has also received significant attention in developing greener synthetic routes to access medicinally privileged heterocyclic compounds, including O-heterocycles. These GO-catalyzed synthetic protocols offer several greener advantages, including cost-effectiveness, high atom economy,

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the use of green solvents or solvent-free conditions, shorter reaction times, excellent yields, energy conservation, operational simplicity, and catalyst recyclability.

This chapter highlights the utility of GO as an effective, recyclable, and eco-friendly catalyst for synthesizing various oxygen-containing heterocycles of medicinal interest under metal-free and greener conditions.

Keywords: Graphene oxide, Metal-free, Eco-friendly, Carbocatalyst, Bioactive, O-Heterocycles

1. Introduction

Heterocyclic compounds are indispensable in drug design and development due to their widespread inherent biological and pharmacological activities [1-5]. In many USFDA-approved drugs, heterocyclic compounds containing nitrogen, oxygen, and sulfur atoms are the fundamental building blocks [6-7]. Additionally, both naturally occurring and synthetic oxygen-containing heterocycles have played a significant role in ancient medications and in the design of modern, novel therapeutics [8-10]. Despite many effective metal-catalyzed synthetic protocols, metal-free, viable, and greener approaches for medicinally privileged O-heterocycles are highly desirable in the pharmaceutical industry to minimize cost, environmental impact, and health issues [11-18].

Recently, graphene oxide (GO), an oxidized derivative or precursor of the miracle 2D carbon nanomaterial graphene, has gained massive attention from academia and industry as an efficient, metal-free, and eco-friendly ‘carbocatalyst’ for organic synthesis, including heterocyclic synthesis [19-26]. Various reported chemical oxidation methods are used to prepare graphene oxide (GO), utilizing either graphite powder or flakes as the precursor. However, the Hummers’ and Tour methods are the two most popular methods widely used for preparing GO [Figure 1] [23, 27-29].

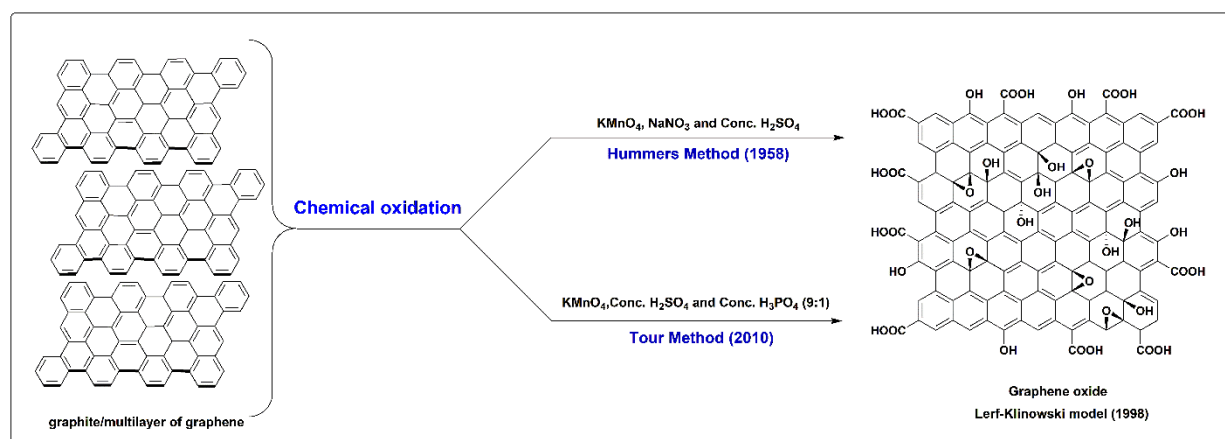


Figure 1: Chemical oxidation methods for the preparation of GO.

Graphene oxide (GO) is decorated with multiple oxygenated functionalities, namely, hydroxyl, carboxylic, carbonyl, phenolic, and epoxides/ether groups, on its surfaces and edges and inherits exceptional physicochemical properties [23-29]. Additionally, its large surface area, exclusive surface morphology bearing both sp^2 and sp^3 -hybridized carbon atoms, and the presence of defects, Brønsted/Lewis acidic and basic sites, zigzag edges, carbon vacancies, polarity, and strong chemisorption properties contribute to its excellent catalytic activity [19, 20, 23-29]. Furthermore, GO is non-toxic, metal-free, biocompatible, easily accessible, and recyclable, making it a convenient and eco-friendly heterogeneous catalyst for organic synthesis [19-26, 30]. Due to its diverse oxygenated acidic functional groups, GO has been extensively utilized as an oxidant and a solid acid catalyst in many organic reactions [19-26, 30]. Notably, GO-catalyzed synthetic approaches offer several advantages, such as using green solvents or solvent-free reaction conditions, low-cost, selective, room-temperature reaction conditions, shorter reaction time, and catalyst recyclability [19, 24-26, 30]. Furthermore, these metal-free approaches provide a solution to mitigate metal contamination issues in active pharmaceutical ingredients (APIs) containing heterocyclic scaffolds, which are prepared using toxic metal catalysts.

This chapter aims to provide an overview of GO-catalyzed metal-free and greener synthetic approaches for various bioactive O-heterocycles.

2. GO-catalyzed green synthesis of various bioactive coumarin derivatives under metal-free conditions

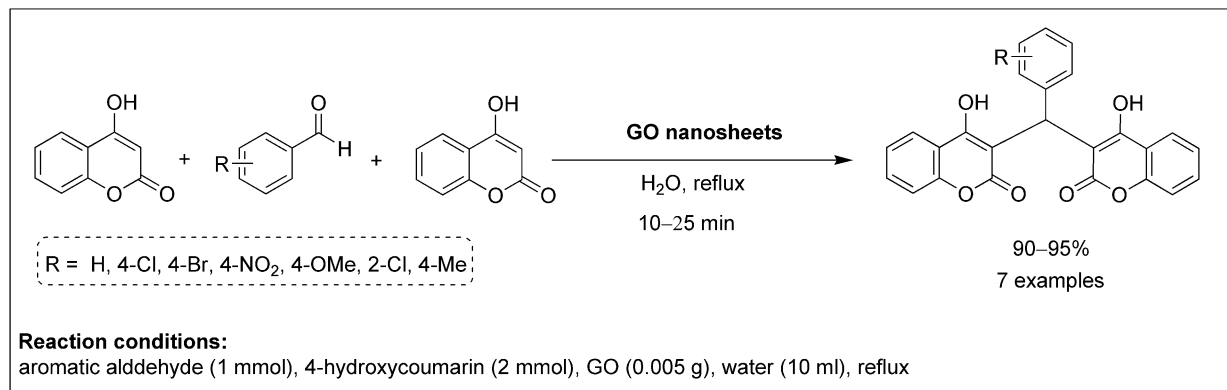
Coumarins are widely found in nature and exhibit a broad spectrum of pharmacological activities, e.g., antiviral, anti-inflammatory, antibacterial, anti-fungal, anti-cancer, anti-HIV, and anti-convulsant activities [31-34]. Besides, hybrid coumarin derivatives have been recognized as promising anticancer agents [33, 34]. Consequently, there is a growing trend in synthesizing novel multi-structural analogs of coumarin, including bis-coumarin, pyranocoumarins, benzylbarbiturocoumarins, and benzylpyrazolyl coumarins, under metal-free and environmentally friendly conditions, for use in synthetic and medicinal applications. [35-38].

2.1. Synthesis of *bis*-4-hydroxy coumarins

Over the decade, the synthesis of *bis*-coumarin under green conditions has gained considerable interest due to its extensive biological and pharmacological properties [37, 38].

Graphene oxide (GO) has been utilized as a metal-free, recyclable, and environmentally friendly nanocatalyst for preparing a range of diversely substituted *bis*-4-hydroxycoumarin derivatives under metal-free and greener conditions [39]. The synthesis of *bis*-4-hydroxycoumarin involved a one-pot reaction of an aromatic aldehyde and two molecules of 4-hydroxycoumarin in the presence of a catalytic amount of GO nanosheets (Scheme 1). The reactions were performed in water under reflux conditions and required only 10 to 25 minutes to deliver the desired products in excellent yields (90-95%). This GO-catalyzed method was highly effective for various aromatic aldehydes bearing electron-donating (-Me, -OMe) and electron-withdrawing (-Cl, -Br, -NO₂) groups to access their corresponding *bis*-4-hydroxycoumarin derivatives in outstanding yields. Interestingly, the electronic effects of the

substituents did not affect the yields. In addition, the catalyst GO was reusable for the reaction even after four consecutive runs. The impressive catalytic efficacy of GO for these reactions is attributed to its unique physicochemical properties, including high surface area, wrinkled layers, and acidic functional groups.

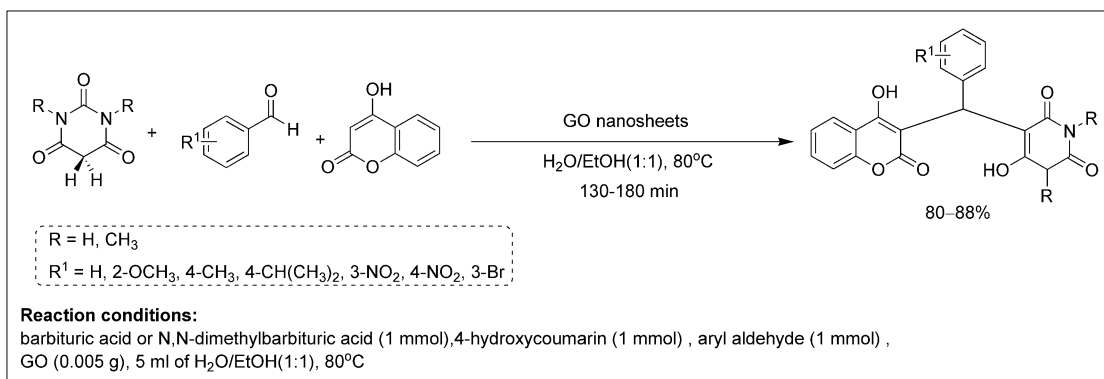


Scheme 1: Water-mediated green synthesis of *bis*-4-hydroxycoumarins catalyzed by GO.

2.2. Synthesis of novel benzylbarbiturocoumarin derivatives

Hybrid heterocycles with two or more different biologically active heterocyclic scaffolds are highly attractive in medicinal chemistry due to their enhanced pharmacological activities and therapeutic potential [40]. Barbituric acid is well-known for its biological and pharmacological activities. It also has numerous synthetic applications as a building block for organic synthesis and the preparation of pharmaceuticals [41, 42]. Therefore, synthesizing a hybrid scaffold based on bioactive coumarin and barbituric acid has excellent prospects for developing novel hybrid scaffolds, such as benzylbarbiturocoumarins [42].

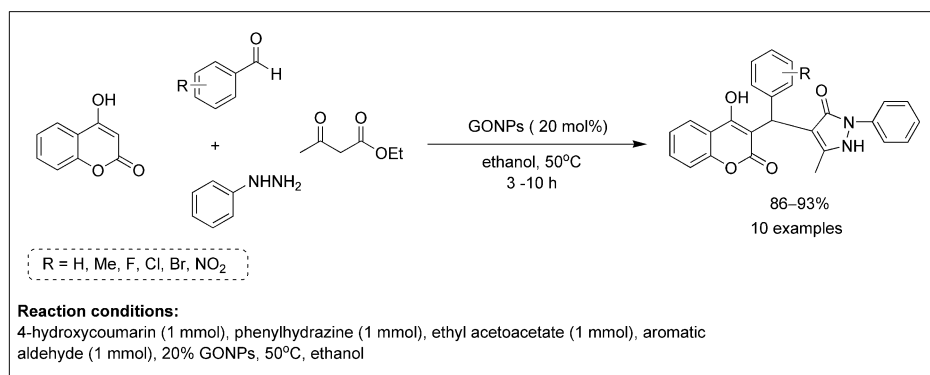
The synthesis of novel benzylbarbiturocoumarin derivatives using GO nanosheets as an efficient, metal-free, eco-friendly, and recyclable catalyst under green conditions has been reported [42]. The reactions involved a one-pot, three-component reaction among barbituric acid/*N*, *N*-dimethylbarbituric acid, an aromatic aldehyde, and 4-hydroxycoumarin (Scheme 2). The reactions were carried out in H₂O/EtOH (1:1) at 80 °C in the presence of a catalytic amount of GO nanosheets (0.005g). A wide range of aromatic aldehydes bearing electron-donating (-Me, -OMe, isopropyl) and electron-withdrawing (-Cl, -Br, -NO₂) substituents were successfully reacted with barbituric acid, *N*, *N*-dimethylbarbituric acid, and 4-hydroxycoumarin, affording the target products in good yields (80-88%). Notably, 1-naphthaldehyde was also reactive in producing its corresponding naphthylbarbiturocoumarin under this greener method. In this protocol, the catalyst GO was recyclable for five consecutive reactions without losing its catalytic activity, highlighting its economic and environmental advantages. The presence of Brønsted acidic and Lewis basic sites, attributed to epoxy and carboxyl groups on GO, is reported to be responsible for its admirable catalytic activity in facilitating the reactions.



Scheme 2: Metal-free synthesis of novel benzylbarbiturocoumarin derivatives in water catalyzed by GO.

2.3. Synthesis of novel benzylpyrazolyl coumarin derivatives (BCDs)

The green synthesis of novel hybrid heterocycles, benzylpyrazolyl coumarin derivatives containing a coumarin and pyrazole scaffold, has also been achieved using mesoporous graphene oxide nanoparticles (GONPs) as an effective, eco-friendly, recyclable, and heterogeneous acid catalyst [43]. The reactions involved a one-pot, four-component approach using phenylhydrazine, ethyl acetoacetate, an aromatic aldehyde, and 4-hydroxycoumarin as the substrates accessing bioactive benzylpyrazolyl coumarin (Scheme 3). The reactions were executed in green and renewable solvent ethanol at 50 °C in the presence of a catalytic amount of GONPs. A variety of aromatic aldehydes containing electronically diverse substituents were highly reactive under this protocol and delivered their corresponding target products in good to excellent yields (86-93%). It is worth mentioning that GONPs were prepared using renewable resources, specifically dry table sugar, as the precursor, under microwave heating and thermal annealing. The meticulous characterization by various spectroscopy and microscopy analytical techniques revealed that the prepared GONPs have many similarities in chemical structure and elemental composition with GO prepared from graphite/graphene. Different physical characteristics, such as specific surface area, porosity, and acidic chemical functional groups of GONPs, played the leading roles in their catalytic activity to facilitate the reactions.



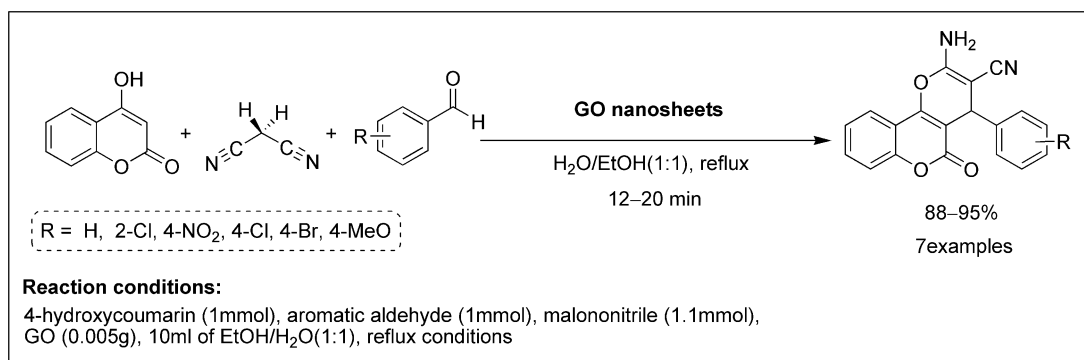
Scheme 3: Green synthesis of benzylpyrazolyl coumarins (BCDs) using GONPs as a metal-free catalyst.

3. Synthesis of bioactive 4*H*-pyran and chromene derivatives

Due to widespread biological and synthetic potential, synthesizing various 4*H*-pyran derivatives has also gained substantial interest in synthetic and medicinal chemistry [44, 45]. Furthermore, the synthesis of fused pyran rings with various biologically active heterocyclic scaffolds, such as pyranocoumarins, pyranoquinolines, pyranochalcones, and chromenes, is highly attractive in synthetic research due to their noteworthy therapeutic values [46].

3.1. Synthesis of bioactive pyranocoumarins

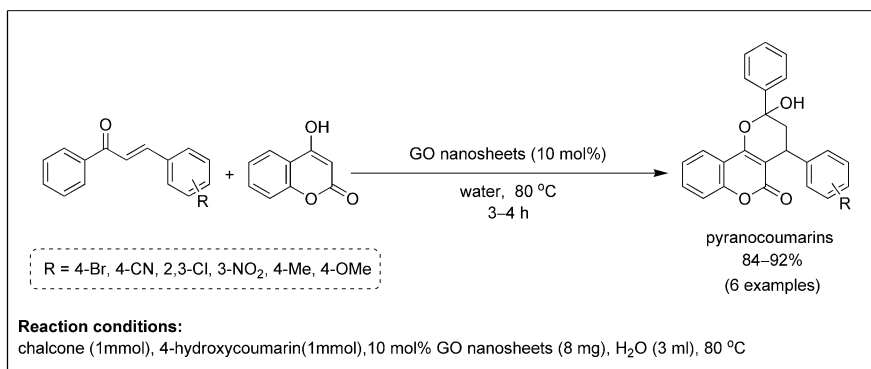
An efficient GO-catalyzed metal-free and greener multicomponent approach for synthesizing various diversely substituted pyranocoumarin derivatives has been reported [39]. This method was associated with a condensation reaction of an aromatic aldehyde, 4-hydroxycoumarin, and malononitrile in H₂O/EtOH (1:1) under reflux conditions in the presence of a catalytic amount of GO nanosheets (Scheme 4). Various aromatic aldehydes with electronically diverse substituents were tolerable under the optimized reaction conditions of this method. Moreover, the yields of desired products from these aldehydes were highly admirable. Under this protocol, 1-naphthyl aldehyde was also reactive and produced its corresponding pyranocoumarin derivative in high yield (88%). Notably, all these reactions required only 12 to 20 minutes to complete. Here, the acidic functional groups (-COOH groups) of GO also played a crucial role in activating the substrates for the reactions.



Scheme 4: Metal-free synthesis of pyranocoumarins in green reaction media catalyzed by GO.

N. Kausar and coworkers have reported a highly efficient, metal-free, and water-mediated GO-catalyzed greener protocol for preparing pyranocoumarins using chalcone and 4-hydroxycoumarin as precursors [46]. The reactions were carried out in water at 80 °C in the presence of 10 mol% of the catalyst, GO (Scheme 5). Mechanistically, the reactions involved a Michael-type addition between chalcone and 4-hydroxycoumarin, followed by an intramolecular cyclization to access the desired product. The carboxylic functional groups of GO facilitate the reactions by activating the reactants. Various chalcones with aryl groups containing electron-deficient and electron-rich substituents were compatible under this method and provided the desired products in good to excellent yields (84-92%). One chalcone bearing a thiophenyl ring was also reactive under this protocol, affording its corresponding pyranocoumarin product in good yield (84%). This method was also scalable, and the

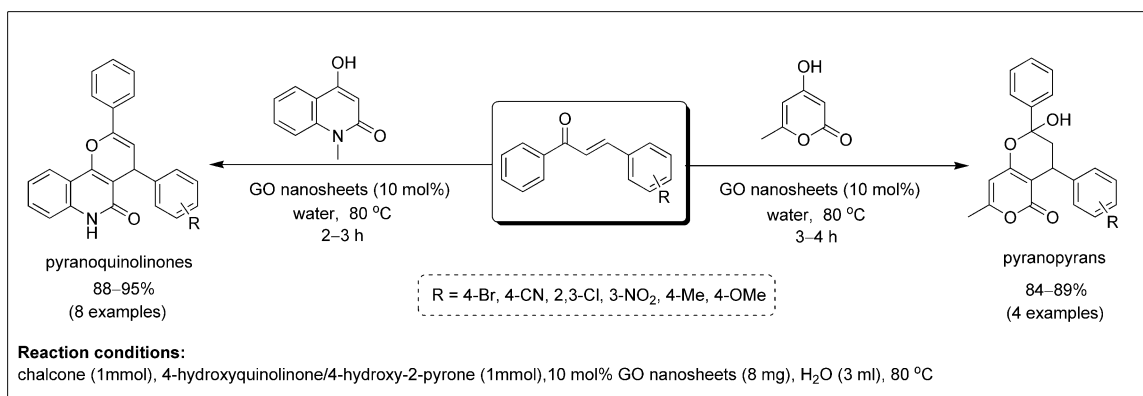
catalyst GO was reusable after five consecutive runs, highlighting the greener features of this present method.



Scheme 5: Metal-free and green synthesis of pyranocoumarin derivatives in water using GO as a recyclable catalyst.

3.2. Synthesis of bioactive pyranoquinolines and pyranopyrans

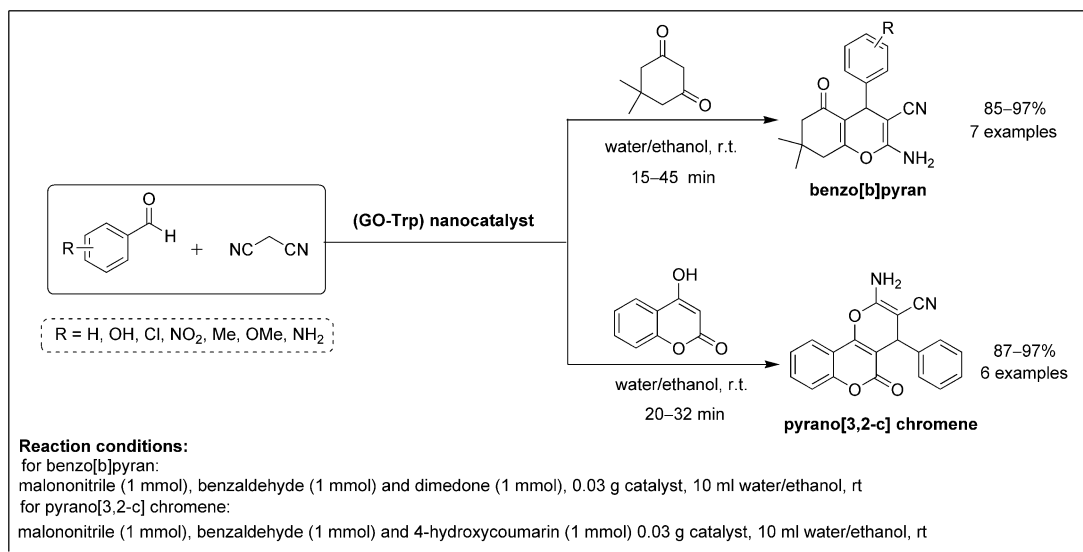
N. Kausar and coworkers have also reported the synthesis of two different derivatives of fused 4H-pyran, namely, pyranoquinolines and pyranopyrans, by employing GO nanosheets as a metal-free, recyclable, and green catalyst [46]. The formation of pyranoquinolines involved the reaction of 4-hydroxy-1-methylquinolinone with various chalcones in water in the presence of a catalytic amount of GO nanosheets (Scheme 6). The reactions proceeded *via* a Michael addition and sequential intramolecular cyclization and dehydration steps to form the target products. A range of chalcones bearing electron-donating (-Me, -OMe) and electron-withdrawing (-Cl, -Br, -CN, -NO₂) groups were highly compatible with this protocol and delivered their corresponding pyranoquinolines in good to excellent yields (88-95%). On the other hand, the pyranopyrans were obtained by the reaction of 4-hydroxy-6-methyl-2H-pyran-2-one with chalcones in the presence of GO nanosheets under similar reaction conditions (Scheme 6).



Scheme 6: Green synthesis of pyranoquinolines and pyranopyrans in water catalyzed by GO nanosheets.

3.3. Synthesis of bioactive benzo[b]pyran and pyrano[3,2-c] chromene derivatives

Due to the presence of diversified oxygenated functional groups, GO can be smoothly chemically modified, and its chemical properties can be tuned to produce novel catalytic systems. Very recently, a new heterogeneous acid-base biocatalyst, based on graphene oxide (GO) modified with the essential amino acid tryptophan (GO-Trp), has been developed and utilized to synthesize several pyran derivatives [47]. This biocatalyst, GO-Trp, was highly efficient in preparing various benzo[b]pyran and pyrano[3,2-c]chromene derivatives with outstanding yields and high purity. Moreover, the catalyst was recyclable for five consecutive runs to synthesize pyran derivatives without losing its catalytic efficacy. The formation of benzo[b]pyran derivatives required the use of malononitrile, benzaldehyde, and dimedone as reactants. Conversely, the reaction of malononitrile, benzaldehyde, and 4-hydroxycoumarin resulted in the formation of pyrano[3,2-c]chromene derivatives. In both cases, the reactions were performed via one-pot, three-component reaction strategies in a water/ethanol solvent at room temperature in the presence of GO-Trp (Scheme 7). Therefore, using GO-Trp as an effective, safe, recyclable, and green catalyst, the reactions become more environmentally friendly than the previously reported methods.

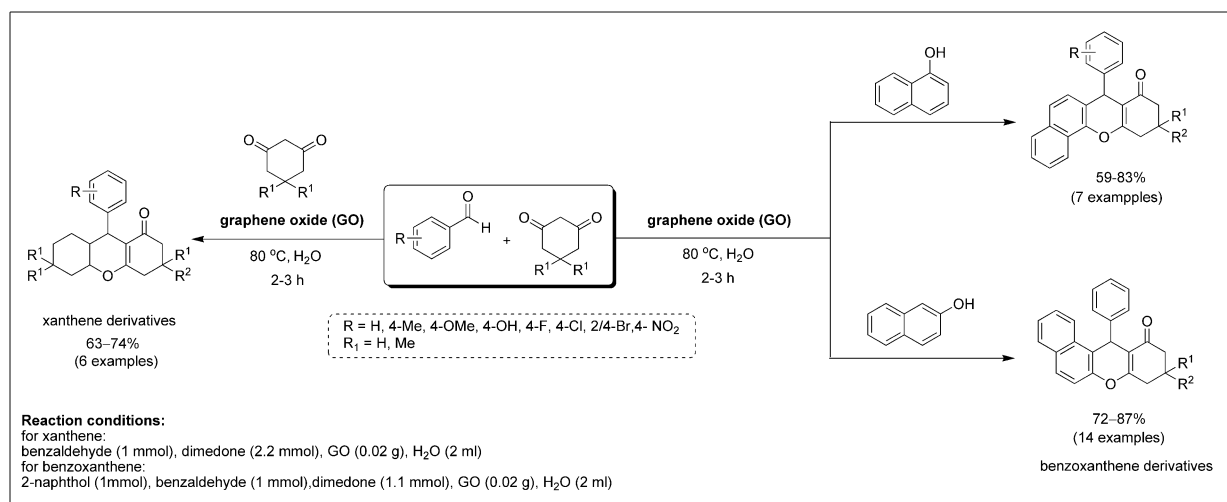


Scheme 7: Green synthesis of pyran derivatives using a novel heterogeneous GO-based biocatalyst (GO-Trp).

4. Synthesis of xanthenes and benzoxanthenes

Xanthenes are one of the privileged oxygen-containing heterocyclic scaffolds bearing dibenzo[*b,e*]pyran nuclei and exhibit a broad spectrum of pharmaceutical properties [48, 49]. Xanthene derivatives are also widely used in fluorescent dyes, sensors, and other industrial applications [49]. Benzoxanthene derivatives have also garnered considerable attention due to their impressive therapeutic properties and broad applicability as photosensitizers in photodynamic therapy (PDT) [49]. Consequently, many synthetic protocols have been reported for their synthesis [50].

Graphene oxide has also been utilized as a solid acid catalyst for the synthesis of a wide range of diversified xanthene and benzoxanthene derivatives *via* a one-pot, three-component condensation reaction involving an aryl aldehyde, a 1,3-diketone or dimedone, and 1-naphthol or 2-naphthol [51]. The xanthene derivatives were obtained by reacting one molecule of an aryl aldehyde and two molecules of dimedone in water at 80 °C in the presence of a catalytic amount of GO (Scheme 8). On the other hand, benzoxanthene synthesis involved a condensation reaction of an aryl aldehyde, 1,3-diketone, and 1-naphthol or 2-naphthol in water at 80 °C in the presence of a GO catalyst (Scheme 7). In both cases, various aromatic aldehydes bearing electron-donating and electron-withdrawing groups were successfully employed for the reactions to afford their corresponding xanthene and benzoxanthene derivatives. Interestingly, this GO-catalyzed greener method was highly efficient in obtaining desired products from different substituted benzaldehydes in good yields. In addition, the catalyst GO was recoverable and reusable for multiple reactions without losing its catalytic activity.



Scheme 8: Metal-free synthesis of xanthene and benzoxanthene derivatives in water catalyzed by GO.

5. Conclusion

In summary, this chapter provides an overview of the exciting catalytic efficiency of GO for preparing a broad range of medicinally important O-heterocycles and their functionalized derivatives under metal-free and greener reaction conditions. These GO-catalyzed protocols offer several advantages, including easy catalyst preparation, operational simplicity, a broad substrate scope, high yields, shorter reaction times, the use of green solvents such as water and ethanol, and ambient reaction conditions. However, the catalytic application of GO in the synthesis of O-heterocycles is limited. Therefore, there is a prospect for exploring GO in the preparation of more derivatives of oxygen-containing heterocycles in the future.

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