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Synthesis of α-Imino Amidines and 2,3-Diamino Indolenines Using a One-Pot Graphene Oxide-Catalyzed Process

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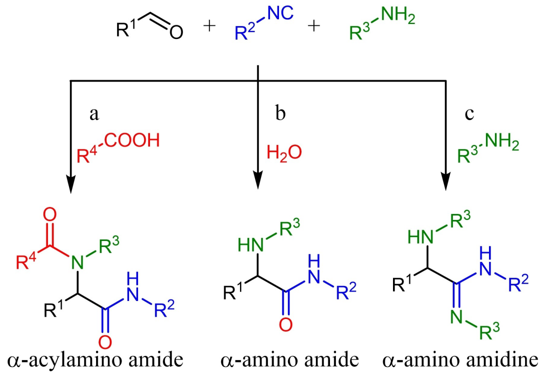
The acid-catalyzed three-component (3 C) UGI reaction of isocyanides, amines, and aldehydes generally gives α-amino amidines. Herein, we report the graphene oxide (GO)-promoted promoted 3 C Ugi reaction followed by a C–N bond oxidation to provide rapid access to α-imino amidines. GO plays a crucial role both in the multicomponent reaction and in the subsequent oxidation. Interestingly, α-imino amidines bearing electron-donating groups undergo spontaneous cyclization leading substituted 2,3-diamino indolenines. The scope of the process has been investigated with respect to all three components, and a comparison between the one-pot and sequential approaches is given. The major advantages of the developed methodology include one-pot synthesis, operational simplicity, high atom economy, broad substrate scope, multicomponent character, and applicability towards gram scale synthesis. Recovery and regeneration of GO and investigation of its real active sites has been performed by control experiments and X-ray photoelectron spectroscopy (XPS).

Introduction

The isocyanide-based Ugi reaction (U-4CR) combines 4 diversity inputs: isocyanides, aldehydes, primary amines and carboxylic acids, leading to peptide-like compounds.[1] Among multicomponent reactions (MCRs), U-4CR is by far the most exploited one, thanks to the several variants developed.[2] For instance, the intermediate nitrilium ion might be trapped by various nucleophiles rather than carboxylic acids, generating different products (Scheme 1).[3] When the nucleophile is an amine, α-amino amidines are obtained (Scheme 1, c). However, the reaction does not lead to acceptable product yields without using proper catalysts. Despite the pioneering work by MacFarland in the 60',[4] few catalysts have been reported so far,[5] with varying degrees of success in terms of yields and versatility (Scheme 2, a).



Scheme 1. Classical Ugi reaction and its variants.

In view of our continued efforts in the development of new synthetic methodologies using MCRs,[6] and following our recent interest on the use of graphene oxide (GO) as a heterogeneous catalyst for MCRs,[7] we planned to use GO for the synthesis of α-amino amidines **1** via this Ugi-type reaction. Contrary to what expected, the reaction between aldehydes, isocyanides and 2 equivalents of aromatic amines in the presence of GO, provided a mixture of α-amino amidines **1** and α-imino amidines **2**, as the result of an Ugi-type reaction and a partial C–N bond oxidation.

Moreover, studying the optimization of the reaction conditions, we noticed that the α-imino amidines **2** obtained by reacting electron-rich anilines, underwent spontaneous cyclization to give the corresponding indolenines **3** (Scheme 2, b). GO is a commercially available carbon-based material, well known for its applications in material science,[8] biomedicine,[9] and energy storage.[10] Recently, GO had been attracting much attention as catalyst in organic synthesis.[11] Thanks to its multifunctional character, GO can be considered as a multicatalytic system:[12] the π-conjugated domains provide interactions with aromatic compounds;[13] oxygenated functional groups furnish acidic properties (both BrØnsted and Lewis

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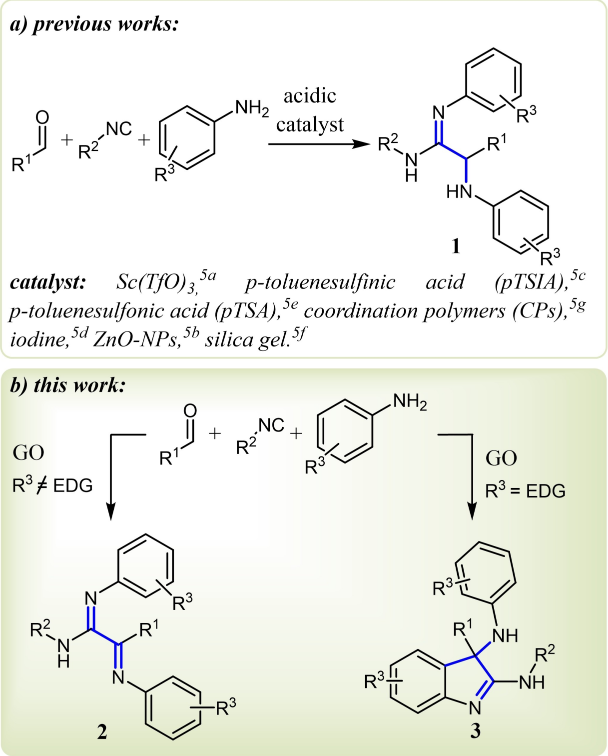


Scheme 2. Approaches for the three-component Ugi-type condensation reaction.

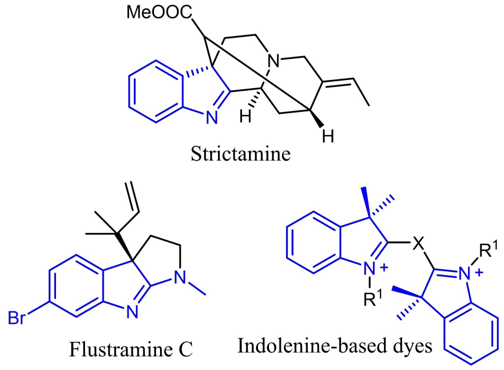


Figure 1. Natural substituted indolenine derivatives and indolenine-based dyes.

acidity)[14] and oxidant capacities;[15] internal structural defects and holes promote radical processes.[16] Based on the deep experience of our group on the diversity-oriented synthesis of heterocycles coupling MCRs and post-MCR cyclization,[6a,b,17] we were interested to further investigate these results.

Herein, we report the first GO-promoted one-pot multistep synthesis of α-imino amidines **2** and substituted 2,3-diamino indolenines **3**. The operational simplicity, the limited number of steps, the heterogeneous catalytic nature of the process and the possibility to partial recover and reuse GO, bring our approach close to the concept of the ideal eco-friendly synthesis.[18] The α-imino amidines **2** have never been reported in literature, though they can be considered useful synthetic intermediates, while the amino indolenines are privileged scaffolds, present in natural products,[19] bioactive compounds[20] and organic dyes[21] (Figure 1).

Finally, the investigation of the real active sites of GO using X-ray photoelectron spectroscopy (XPS) and the possibility to regenerate and reuse the catalyst are described.

Results and Discussion

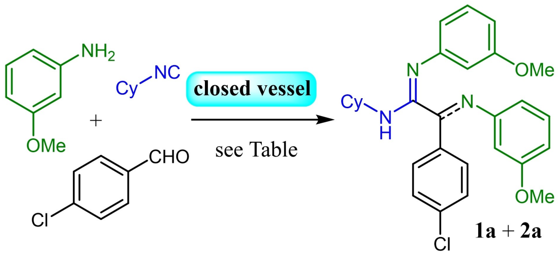
The reaction between 4-chlorobenzaldehyde, cyclohexylisocyanide and 3-methoxyaniline has been extensively optimized by varying several parameters, such as solvent, concentration, relative quantity of components, nature and amount of carbocatalyst, and temperature. The most significant experiments for the optimization are summarized in Table 1. Best results were obtained by using 30 mg mmol^{-1} of GO in a 2:1 mixture of CH_3CN/water at 30 °C (Table 1, entry 1). All other conditions tested furnished lower yields, even if no notable side products were observed. GO resulted mandatory for the occurrence of the reaction, as only traces of product were observed in the absence of the carbocatalyst (entry 2). Alcoholic solvents were detrimental (entry 4), as well as the absence of water as co-solvent (entry 5).

Increasing the amount of isocyanide (entry 6) or aniline (entry 7) did not influence the conversion and consequently the yield, while the temperature turned out to be crucial. Actually, an accurate temperature control is fundamental for the success of the reaction; in particular, performing reaction at 30 °C, allowed to achieve almost complete conversion and high yield; lower temperature decreased the yield (entry 8), while higher temperature (entry 9) increased just the oxidation of α-amino amidine **1 a** into α-imino amidine **2 a**.

To investigate the role of oxygen on the C–N bond oxidation, we performed the reaction under nitrogen atmosphere (N_2) as well as in open air, to ensure a constant presence of oxygen. In effect previous conditions involved the use of a closed vessel. Under N_2, the formation of compound **2 a** was not completely suppressed, even if it was formed in lower amount (entry 10). On the other hand, the reaction conducted in open air, furnished almost exclusively α-imino amidine **2 a** (entry 11). Finally, using reduced GO (rGO) as carbocatalyst, the desired products were obtained in poor yield, with a **1 a**:**2 a** ratio close to 1:1 (entry 3). These results show that both the nature of the carbocatalyst and the presence of oxygen influence the oxidation of the C–N bond.

To investigate this point more deeply, other experiments were carried out in open air by changing all three components (Table 2). The total yields were found to be comparable, excluding entry 4, where a third product was isolated too, the indolenine **3** (38% yield, general structure in Scheme 2). Instead, the nature of the substrates strongly influences the ratio between α-amino amidines **1** and α-imino amidines **2**. Aldehydes bearing electron donating groups prevent the C–N bond oxidation (entries 1–3), while those bearing electron withdrawing groups promote the formation of **2** (entry 4). While

Table 1. Control experiments and optimization of the GO-promoted 3 C Ugi reaction.[a]

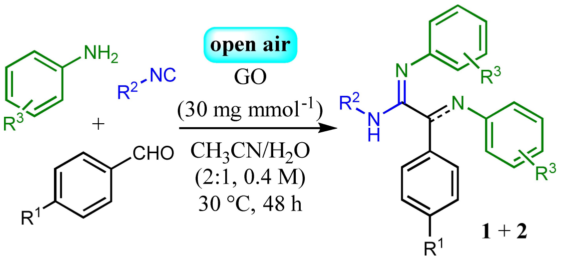


Entry[a]	Standard reaction conditions	Ratio **1a**:**2a**[b]	Yield (%)[d]
1	GO (30 mg mmol^{-1}), CH_3CN/H_2O (2:1, 0.4 M), 30 °C, 48 h	22:78	70
	Variation from standard conditions		
2	No GO	–[c]	4
3	rGO	58:42	34
4	*t*-BuOH as solvent	–[c]	20
5	CH_3CN as solvent	60:40	35
6	CyNC (3 eq)	70:30	50
7	*m*-MeO-aniline (3.3 eq)	65:35	55
8	20 °C	75:25	41
9	40 °C	12:88	66
10	under nitrogen	53:47	41
11	open air	5:95	59

[a] Selected results are reported; the full set of optimization data can be found in the ESI (Table S1); reaction conditions: 0.25 mmol of aldehyde (1 eq), CyCN (2 eq.) and aniline (2.2 eq); CH_3CN technical grade and deionized water; vial 10 mL; **1a** = α-amino amidine; **2a** = α-imino amidine; [b] Calculated by NMR after column chromatography; [c] not calculated; [d] Isolated yield.

the electronic effect of the aromatic aldehydes was more predictable, the influence of isocyanide structure was less obvious. When the reaction was carried out employing *t*-butylisocyanide, only α-amino amidine **1f** or **1g** was isolated, with no trace of C–N bond oxidation (entries 5 and 6). We postulate that a bulkier group, such as *t*-butyl, inhibits the molecule planarization, thus preventing the α-imino amidine formation (entry 5 versus entry 11 of Table 1). Considering that the C–N bond oxidation was substrate-dependent, we carried out a further optimization with the aim to find the experimental conditions to quantitatively convert the α-amino amidines **1** into the corresponding α-imino amidines **2**.

Table 2. Steric and electronic effects on the oxidation of the α-amino amidines **1**.



Entry	R^1	R^2	R^3	Ratio 1:2[a]	Yield (%)[b]
1	MeO	Cy	*m*-MeO	97:3	65 (**1b**+**2b**)
2	Me	Cy	*m*-MeO	75:25	67 (**1c**+**2c**)
3	H	Cy	*m*-MeO	71:29	70 (**1d**+**2d**)
4	NO_2	Cy	*m*-MeO	0:100	24[c](**1e**+**2e**)
5	Cl	*t*-Bu	*m*-MeO	100:0	69 (**1f**+**2f**)
6	Cl	*t*-Bu	*p*-Br	100:0	80 (**1g**+**2g**)

[a] Calculated by NMR after column chromatography; [b] Isolated yield; [c] the corresponding indolenine **3e** (38%) was isolated too.

Compound **1g**, obtained as pure α-amino amidine following the standard reaction conditions, was selected as model compound, and subjected to a short optimization. We found that slightly changing the concentration, the mixture of solvents and increasing the temperature up to 80 °C, we were able to produce quantitatively the α-imino amidine **2g** (Table 3, entry 1). Other control experiments were performed to investigate the catalytic activity and the role of GO and oxygen in the process.

The carbocatalytic oxidation carried out under argon atmosphere (entry 3) brought to partial conversion (**1g**:**2g** = 34:66), demonstrating that oxygen is important, although its absence does not completely suppress the reaction. Contrary to what expected, when reduced graphene oxide (rGO) was employed, total conversion was achieved (entry 2), though the concomitant presence of rGO and argon atmosphere dramatically dropped the conversion (entry 4). Again, no reaction occurred without GO (entry 5).

These results suggest that GO plays a dual role in the oxidation step, as previously reported in the literature by us[7] and others:[22] GO acts both as stoichiometric oxidant, thanks to the hydroxyl and epoxy groups, and as a catalyst in the aerobic oxidation of the substrate.

Therefore, the best way to obtain the α-imino amidine **2** as single product, seems to be the two-steps protocol. Following this approach, we moved on to establish the scope (Scheme 3).

Different isocyanides, aldehydes (including electron rich- and electron poor-aromatic and heteroaromatic ones) and anilines have been combined. The overall yields of the 3 C Ugi/oxidation protocol are good or, in most cases, excellent. Noteworthy, excellent yields were observed employing heteroaromatic aldehydes (**2o**, **2q**), substrates rarely used in this Ugi-type reaction. However, when pyrrole-2-carboxyaldehyde was used, the corresponding α-amino amidine **1p** was obtained in poor yield together with the unreacted imine **4p** (30 %).[23] To improve the conversion of the less reactive substrates, we slightly changed the reaction conditions of the oxidation step, applying a longer time and/or a higher reaction temperature (**2j**, **2m**, **2n**, **2q** and **2s**), affording the products in satisfactory yields. Unfortunately, with aliphatic amines (such as benzylamine and pyrrolidine) the reaction was unsuccessful and the desired amidines were not obtained. Studying the versatility of the process, it was realized that no α-imino amidine **2a** was obtained when **1a** was submitted to the oxidation step. Instead, the corresponding 3,3-disubstituted-2-amino-indolenine **3a** was isolated as major compound (Scheme 5). The formation of **3a** can be explained as the result of a C–N bond oxidation followed by a regioselective intramolecular electrophilic, aromatic substitution. Attracted by the unusual structure of scaffold **3**, the basic skeleton of which has previously been reported just once,[24] we further investigated the synthetic protocol, trying to elucidate the role of GO.

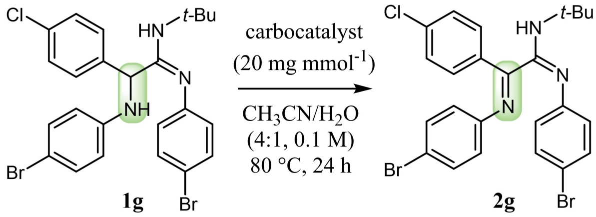
The pure α-imino amidine **2a** was reacted under the optimized conditions in the absence of carbocatalyst (Scheme 4). Compound **2a** was completely converted into the indolenine **3a**, demonstrating that, even if GO was crucial for the occurrence of oxidation reaction (see Table 3), the subsequent cyclization might take place spontaneously by heating.

After a short optimization (see ESI, Table S2), we found that the reaction conditions used for the synthesis of the α-imino amidines **2** were the best.

We also tried to perform the oxidation-cyclization process under microwave (MW) heating to shorten the reaction time, obtaining **3a** in comparable yield (66 %) after only 4 h. However, the desired compound was partially contaminated by byproduct **5a** (10 %) (Scheme 5). The latter compound might be formed through a water-promoted hydrolysis of the ketoimine moiety, which is obviously favored by harsh conditions. Therefore, we applied traditional heating for the scope of the reaction, to simplify the purification and isolation of the desired products **3**. It is noteworthy that 2-amino-3-hydroxy-indolenines, such as **5a**, are interesting structures with antimalaria activity,[25] relatively unexplored due to the lack of synthetic methodologies.[26]

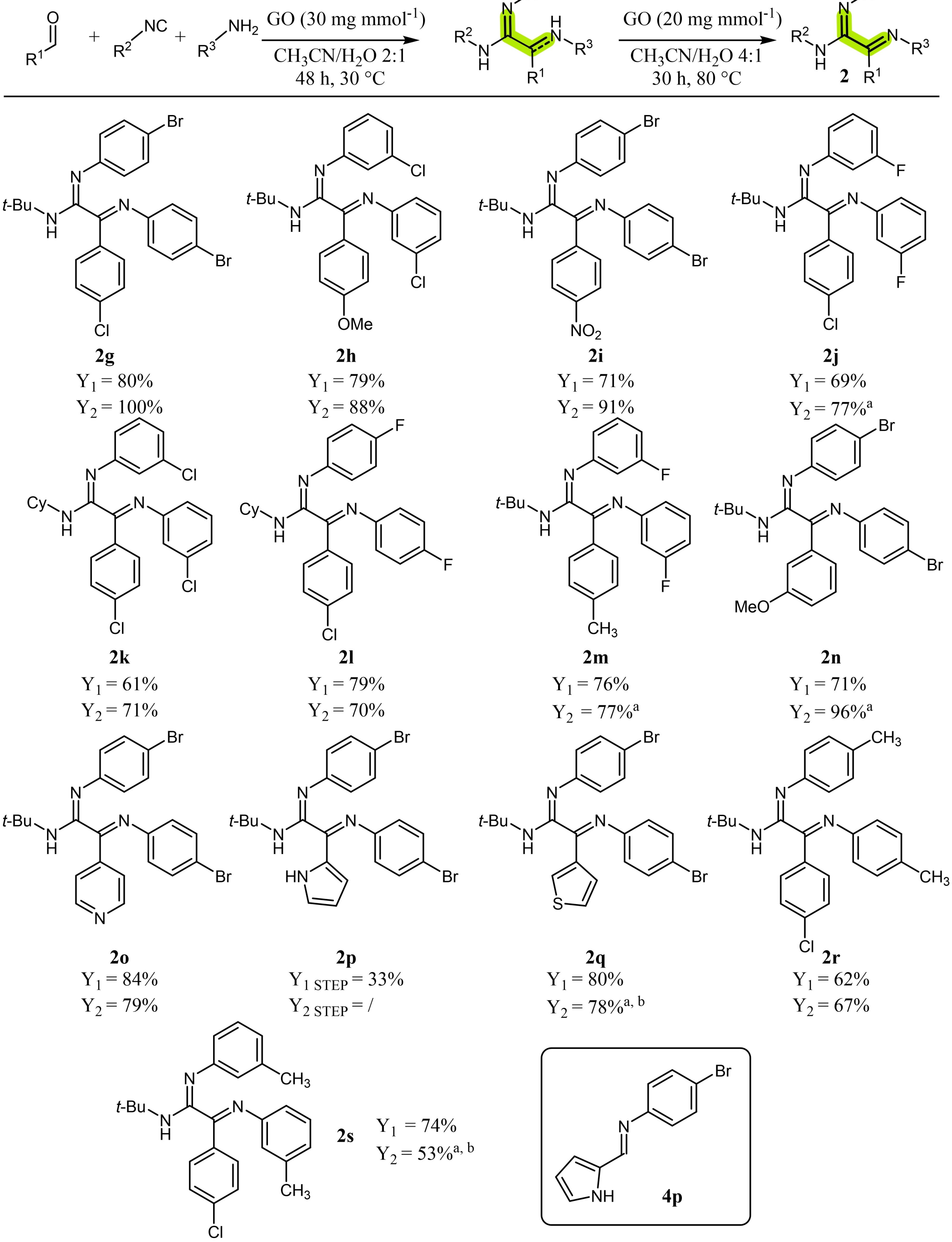
The MCR employing electron rich anilines proceeded smoothly with different substrates, including aromatic and

Table 3. Control experiments and mechanism investigation of oxidation step.



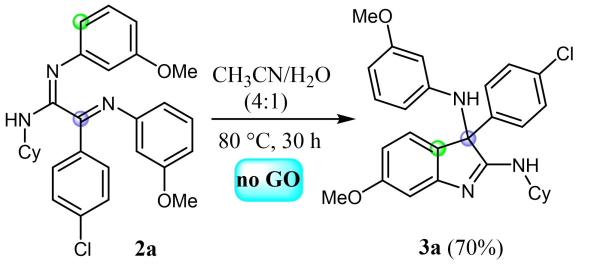
Entry	Carbocatalyst	Atmosphere	Ratio **1g**:**2g**[a]
1	GO	air	0:100
2	rGO	air	0:100
3	GO	argon	34:66
4	rGO	argon	79:21
5	No GO	air	100:0

[a] Calculated by NMR after column chromatography.



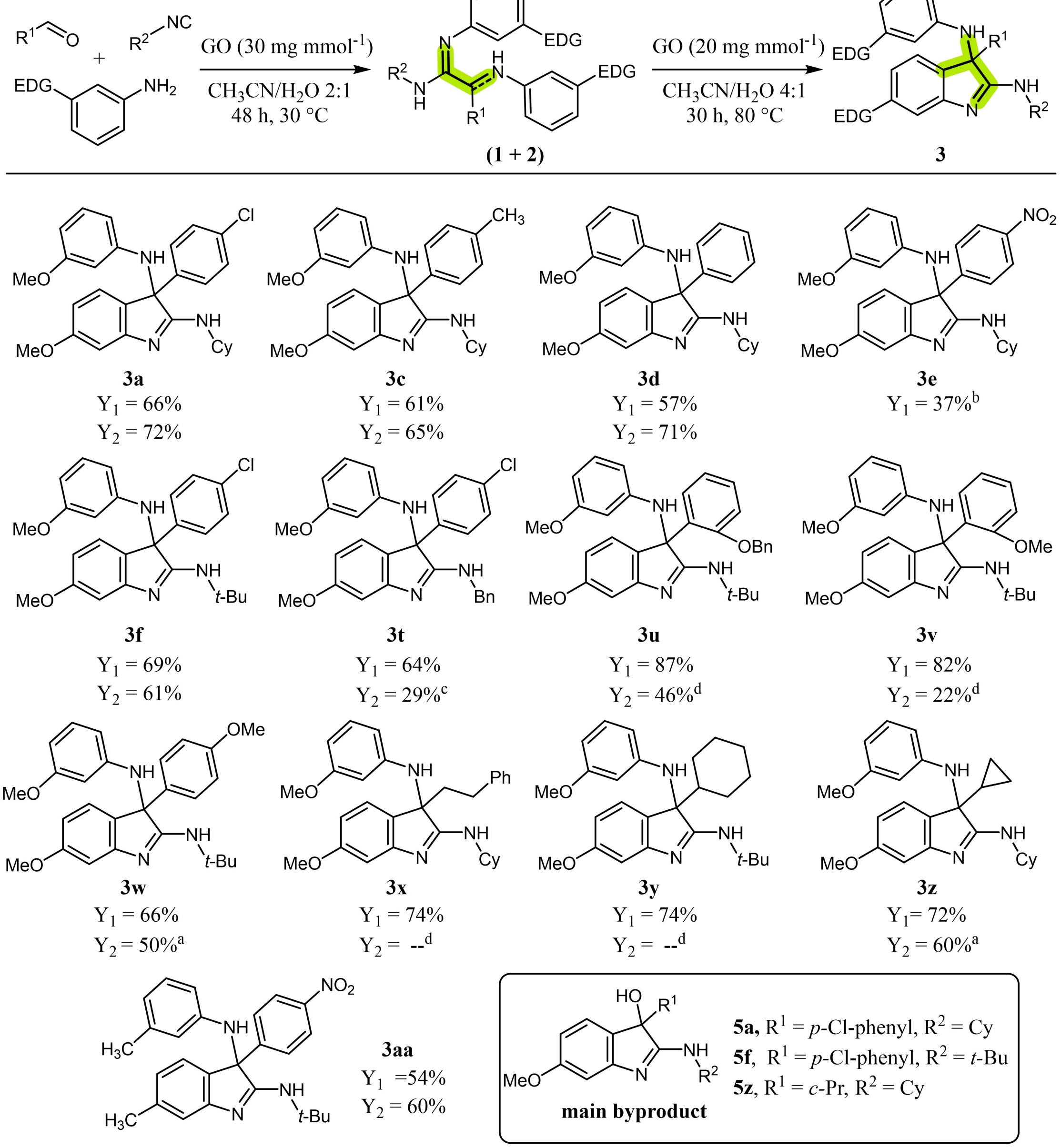
Scheme 3. Scope of carbocatalyzed preparation of α-imino amidines **2**. Different reaction conditions: a) 110 °C; b) 48 h.

aliphatic aldehydes and aliphatic isocyanides (Scheme 5). In other cases, the behavior of the oxidation-cyclization step was less evident: indolenines with R^1 as a phenyl (**3d**) or phenyls bearing poor donating groups (**3c**) and electron withdrawing groups (**3a**, **3f**) have been obtained in high yields, except for **3t**, for the synthesis of which benzyl isocyanide was used. In this case, the conversion was not complete, and the crude profile appeared very complex when the reaction was conducted under the optimized conditions. Running the reaction for only 6 h, we succeeded in isolating **3t** even if in low yield (29%). Moreover, for compound **3f**, a significant amount of byproduct **5f** was isolated after column chromatography: the steric hindrance of *t*-butyl group might have caused the partial hydrolysis with the loss of aniline portion. Instead, the oxidation-cyclization process was less efficient for compounds bearing electron donating groups (**1u**+**2u**, **1v**+**2v** and **1w**+



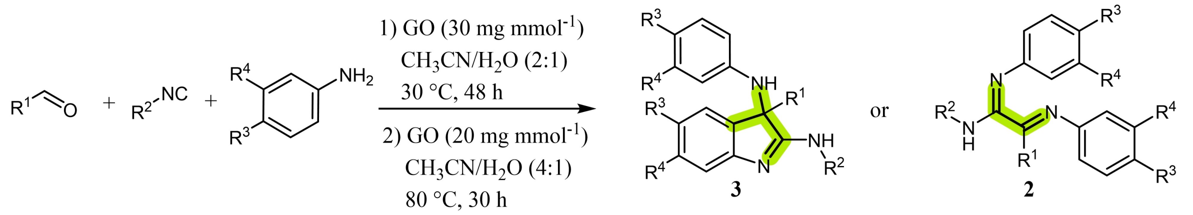
Scheme 4. Control experiment and mechanism investigation of cyclization step.

2w). To improve the conversion of these less reactive substrates, we applied longer time and/or higher reaction temperature: in this way indolenine **3w** was recovered in 50% yield after 48 h, together with starting material (20%). For compounds **3u** and **3v**, higher temperature (110 °C) and extended time were required for the occurrence of the reaction: the oxidation might be prevented by steric hindrance due to the alkoxy group in ortho position. Nevertheless, both reactions were not complete and starting materials were recovered after column chromatography (16% for **3u** and 34% for **3v**). The presence of a strong electron withdrawing group such as nitro allowed the direct formation of the indolenine when 3-methoxy aniline was employed (**3e**) in the MCR, or to achieve **3aa** in good yield even if aniline was not strongly activated. When



Scheme 5. Scope of the carbocatalyzed preparation of 3,3-disubstituted-2-amino-indolenines **3**. Y$_1$ = isolated yield of **1** + **2**. Y$_2$ = isolated yield of **3**. Different reaction conditions: a) 48 h; b) **3e** was directly obtained after the first step; c) 6 h; d) 110 °C, 48 h.

Table 4. Synthesis of a library of α-imino amidines **2** and of 3,3-disubstituted-2-amino indolenines **3** by the one-pot procedure.



Entry	R^1	R^2	R^3	R^4	Yield of 2[a]	Yield of 3[a]
1	*p*-Cl-Ph	*t*-bu	Br	H	**2 g** 72 (80)[b]	–
2	*p*-MeO-Ph	*t*-bu	H	Cl	**2 h** 81 (70)[b]	–
3	*p*-NO$_2$-Ph	*t*-bu	Br	H	**2 i** 70 (65)[b]	–
4	*p*-Cl-Ph	Cy	H	OMe	–	**3 a** 50 (48)[b]
5	H	Cy	H	OMe	–	**3 d** 65 (40)[b,c]
6	*p*-Me-Ph	Cy	H	OMe	–	**3 c** 46 (39)[b]
7	*p*-MeO-Ph	*t*-bu	H	OMe	–	**3 w**[e] 39 (33)[b]
8	*p*-NO$_2$-Ph	Cy	H	OMe	–	**3 e** 48 (37)[d]
9	*c*-Pr	Cy	H	OMe	–	**3 z** 39[f] (43)[b]

[a] Isolated yield after column chromatography; [b] the second yield in parentheses refers to the two-step procedure (Schemes 3 and 5); [c] the classical Ugi product (12 %) was isolated too; [d] the second yield in parentheses refers to the 3 C Ugi reaction (Scheme 5); [e] the second step was carried out at 110 °C; [f] the byproduct **5 z** (29 %) was isolated too.

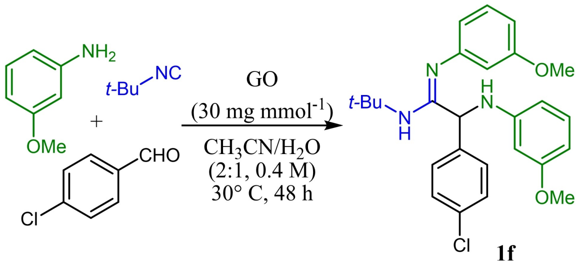
aliphatic aldehydes were used in the MCR, the oxidation-cyclization did not take place, even at 110 °C and starting material was completely recovered (**1 x** and **1 y**, see ESI), unless for compound **3 z**, which was obtained in good yield after heating for 48 h.

Having demonstrated the efficiency of this protocol, we decided to investigate the one-pot procedure leading to **2** or **3**, depending on the aniline used. First, we ran some experiments to establish whether the addition of GO was necessary after the first step (see ESI, Table S3). Having found that in some cases it improves the outcome, we chose to apply this protocol: as soon as the multicomponent reaction was complete, acetonitrile, water, and fresh GO (20 mg mmol^{-1}) were directly added to the reaction mixture, and the temperature was increased to 80 °C. A comparison with the previously reported two-step procedure showed that the one-pot protocol was superior or, at least, comparable, allowing the synthesis of the α-imino amidines **2** or the 3,3-disubstituted-2-amino indolenines **3** in shorter time and with minimum effort (Table 4). When benzaldehyde was used, a small amount of classical Ugi product was also isolated (entry 5). We guess that GO promotes the oxidation of the unreacted aldehyde, forming *in situ* benzoic acid, which reacts as fourth component in a classical Ugi reaction. This behavior has never been observed using the two-step procedure, thus it may occur over a long time. Contrary to what observed with the two–step protocol, during the one-pot synthesis of compound **3 z**, a significant amount of byproduct **5 z** (29 %) was recovered.

Then, we assessed the recyclability of the catalyst for both reaction steps. For the 3 C Ugi reaction, we carried out again the synthesis of **1 f**. As soon as it was complete, the product was recovered by dilution with a 1 : 1 mixture of CH$_2$Cl$_2$/EtOAc, followed by centrifugation at 7800 rpm for 5 min. This process was repeated five times. Then, GO was extensively washed, dried, and reused in a consecutive reaction. A significant deactivation of the GO catalyst was noticed from the very first run (Table 5, entries 1 and 2).

As previously reported by us,[7] GO shows poor recyclability when employed in MCRs involving anilines. X-ray photoelectron

Table 5. Efficiency comparison of recovered- and regenerated GO in 3 C Ugi reaction.



Entry	GO	Yield of 1f[a]
1	Fresh GO	69 %
2	GO recovered after 1st run	41 %
3	GO regenerated[b]	65 %
4	GO recovered after treatment with *m*-MeO-aniline	53 %

[a] Isolated yield after column chromatography; [b] GO after 1st run was regenerated by treatment with piranha solution as reported in literature.[22]

spectroscopy (XPS) analysis was performed to elucidate this behavior, investigating the structural modifications of GO-surface before and after the reaction (Figure 2). GOs recovered from the syntheses of compounds **1 f** and **1 g** have been collected and analyzed by XPS. Compounds **1 f** and **1 g** have been chosen in order to evaluate the behavior of electron-rich and an electron-poor anilines, which might chemically interact with GO surface in different ways.[27] The XPS results from recovered GO were compared with a blank GO that was kept at 30 °C in CH_3CN/H_2O (2:1) for 48 h.

The main modification observed by XPS involved the presence of heteroatoms (N, Cl, Br) associated to the reagents, that significantly increased after the reaction: N and Cl from being substantially absent on pristine and control GO (only 0.2% atomic N) were found to be about 3.0% and 1.1%, respectively, after the synthesis of **1 f**; as well as N, Br and Cl were found to reach 2.0%, 0.9% and 0.3% after the synthesis of **1 g**.

In the first case the ratio of expected abundances of heteroatoms in **1 f** (N:Cl 3:1) matched with the one found by XPS, suggesting that **1 f** was probably adsorbed or chemically bonded to GO after synthesis; conversely, in the second case the ratios of **1 g** (N:Br:Cl 3:2:1) were not strictly matching the product. Secondly, the overall oxidation of GO recovered after **1 f** appeared to be significantly reduced: the values of O/C ratio was 0.22 (~0.4 for blank GO), while after **1 g** the O/C increased to 0.37. These values must be carefully handled: given the significant presence of heteroatoms (N, Cl, Br) we may reasonably suppose a proportional amount of carbon related to reagent (i.e. *m*-MeO-aniline has 1 N, 1 O and 7 C), thus the GO has overall maintained the integrity of its structure and have simply incorporated (adsorbed or covalently bonded) the reagents. We further investigated this aspect by selectively put GO and each single reagent in contact (48 h, 30 °C) and obtaining some similar results observed when GO was employed in the MCR reaction. The amount of nitrogen on GO after *m*-MeO-aniline, *p*-Br-aniline and *t*-butylisocyanide increased up to 2.8%, 2.0% and 1.5% (see Figure 2), suggesting that the single reagent easily remain on GO, as also confirmed by the increase of Cl and Br in respective cases. The total amounts of heteroatoms in single reagent conditions were significantly lower compared to the complete reaction for the **1 f** synthesis, while it was almost equal for **1 g**. The grafting of organic molecules on GO surface was verified by infrared spectroscopy measurements. The FT-IR spectra of the GO recovered after MCR is shown in the ESI and compared to control GO. The presence of organic substances can be deduced by the appearance of sharp IR absorption peaks below 1700 cm^{-1}, not present for control GO.

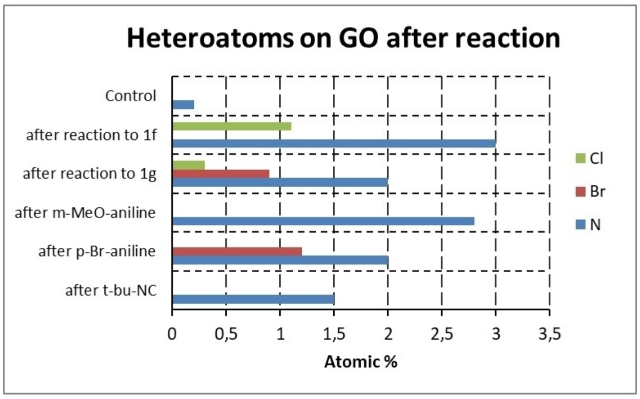


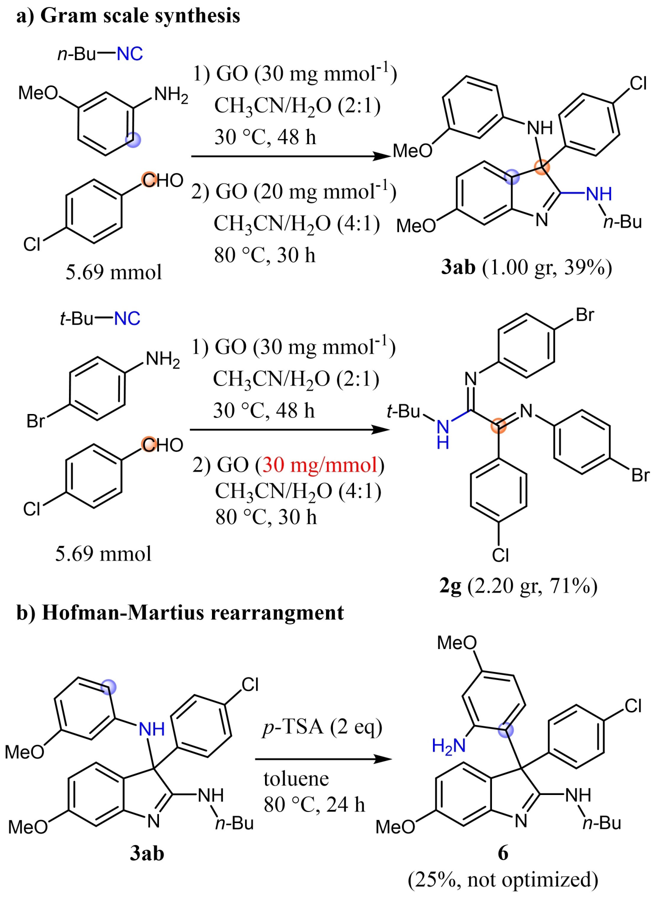
Figure 2. XPS heteroatomic composition of GO. Control: after treatment in CH_3CN/H_2O 2:1, 30 °C for 48 h; after *m*-MeO-aniline: after treatment with *m*-MeO-aniline in CH_3CN/H_2O 2:1, 30 °C for 48 h; after *p*-Br-aniline: after treatment with *p*-Br-aniline in CH_3CN/H_2O 2:1, 30 °C for 48 h; after *t*-butylisocyanide: after treatment with *t*-butylisocyanide in CH_3CN/H_2O 2:1, 30 °C for 48 h. For XPS spectra of GO see ESI, Tables S4 and S5 and Figure S1.

Based on these experimental results, the decrease in efficiency seems related to the partial passivation of the GO-surface due to covalent bonds with the organic substrates rather than by self-reduction. With the aim to reactivate the catalyst, we treated the recovered-GO with piranha solution (see ESI), and the regenerated-GO was analyzed by XPS (ESI, Table S5) and subsequently used in the 3 C Ugi reaction (Table 5, entry 3). Our data showed an almost complete recovery of GO reactivity, that can be associated to the removal from GO surface of residual molecules. XPS showed a significant decrease of heteroatoms after the regeneration (1.4%N and 0.3%Cl). To further demonstrate the passivation caused by the aniline component, the GO recovered after treatment with *m*-MeO-aniline was also tested, showing a slight reduction in the yield of **1 f** (entry 4). Based on our experimental findings, we suppose that GO promotes the Ugi-type reaction acting both as Brønsted acid and as a Lewis acidic carbenium catalyst, as previously reported for other MCRs involving amines and aldehydes.[7]

For what concerns the oxidation step, we have performed other experiments with the aim to investigate the reusability of GO. α-Amino amidine **1 g** was used as model compound and subjected to the oxidation reaction under the optimized conditions. GO was washed, recovered, analyzed by XPS and reused in a second run. Based on XPS analysis, the magnitude of GO reduction was significantly higher than GO after Ugi-type reaction, with a O/C ~0.1 after the reaction, with a similar amount of heteroatoms (2.1%N, 1.4%Br and 0.7%Cl) found after the synthesis of **1 g**.

Moreover, the relative N:Br:Cl ratios found by XPS, match perfectly the values for molecules **1 g** or **2 g** (ESI, Table S6 and Figure S2). Despite that, the yield of the second run did not dramatically drop furnishing **2 g** in 62%, thus maintaining its ability to promote the aerobic oxidation of the substrate.

Having established an efficient methodology, we further investigated its synthetic utility. First, the suitability of the one-pot protocol toward the gram scale was verified (Scheme 6, a). While the indolenine **3 ab** has been efficiently scaled up to 5.7 mmol using optimized reaction conditions, a slight increase of GO was required to obtain complete conversion of α-amino amidine **1 g** into the α-imino amidine **2 g**. Additionally, the resulting indolenine **3 ab** might be further elaborated: treated under acidic conditions, it underwent the Hofmann-Martius rearrangement to give the corresponding 3-aminoaryl-indolenine **6** (Scheme 6, b).[28]



Scheme 6. Gram scale reactions and product elaboration.

Conclusions

In conclusion, we have reported the GO-promoted multistep synthesis of α-imino amidines and 2,3-diamino indolenines. GO resulted crucial for both the 3 C Ugi reaction and subsequent C–N bond oxidation. Remarkably, the synthetic procedure can be performed as a one-pot synthesis, in gram scale, tolerating a broad variety of substrates. The present method is versatile and allowed the preparation of highly substituted complex structures under mild reaction conditions, without the need for inert atmosphere.

Although different synthetic procedures involving isocyanide towards amino-indolenines have already been reported,[24,29] our procedure avoids the use of transition metal catalyst, increasing the sustainability of the process. Furthermore, compare to the two-step procedure, the one-pot protocol decreases chemical wastes, avoiding purification of intermediates and simplifying practical aspects, providing access to variously substituted interesting scaffolds starting from simple commercial substrates. Processing requires a simple filtration to remove the catalyst and a column chromatography.

XPS and IR characterizations of carbon materials have proved covalent chemical modifications upon interaction with organic substrates and/or products during the 3 C Ugi reaction, leading to a partial inactivation of the GO. Interestingly, GO activity has been restored by treatment with piranha solution.

2,3-Diamino indolenines can find applications in medicinal chemistry, while α-imino amidines may be explored as useful intermediates for further synthetic elaboration, such as for natural products synthesis. Studies directed towards these goals are in progress and will be reported in due course.

Experimental Section

General procedure for the two-step synthesis of α-imino amidine 2g: suspension of GO (30 mg mmol^{-1}, 8 mg) in CH_3CN/H_2O 2:1 (0.4 M) in a vial is sonicated for two minutes. Then, 4-chlorobenzaldehyde (1.0 eq, 0.25 mmol, 35 mg), 4-bromoaniline (2.2 eq, 0.55 mmol, 95 mg) and *t*-butylisocyanide (2 eq, 0.50 mmol, 57 μL) were added in the vial. The reaction was stirred at 30 °C. After 48 h, the crude was filtered on celite by washing with a mixture of CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL), and concentrated. The residue was filtered on a short column of silica gel with PE/Acetone (from 97:3 to 95:5) and **1g** (109 mg, 80%) was directly submitted to the next step. A suspension of **1g** (1 eq, 0.11 mmol, 59 mg) and GO (20 mg mmol^{-1}, 2 mg) in CH_3CN/H_2O 4:1 (0.1 M) was sonicated in a vial for 2 minutes. The reaction mixture was stirred at 80 °C for 30 h. Then, the mixture was filtered on celite by washing with a mixture of CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL), and concentrated, obtaining **2g** (60 mg, 100%) as yellow oil. **2g** was characterized without further purification. $R_f = 0.44$ (PE/acetone 90:10); I.R.: $\tilde{\upsilon}$ (cm^{-1}) = 3410, 2963, 1622, 1588, 1580, 1566, 1506, 1479, 1452, 1390, 1361, 1317, 1262, 1248, 1216, 1201, 1177, 1164, 1092, 1069, 1007, 936, 902, 822, 778, 738, 700, 646, 631, 619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H, 2 CH Ar), 7.44 (d, J = 8.5 Hz, 2H, 2 CH Ar), 7.36 (d, J = 8.5 Hz, 2H, 2 CH Ar), 7.06 (d, J = 8.6 Hz, 2H, 2 CH Ar), 6.64 (d, J = 8.6 Hz, 2H, 2 CH Ar), 6.20 (d, J = 8.5 Hz, 2H, 2 CH Ar), 4.22 (s, 1H, NH), 1.45 (s, 9H, 3 CH_3 of *t*-bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (Cq imine), 149.5 (Cq amidine), 148.0 (Cq), 147.9 (Cq), 138.1 (Cq), 134.9 (Cq), 131.6 (2 CH Ar), 131.3 (2 CH Ar), 129.9 (2 CH Ar), 129.3 (2 CH Ar), 123.2 (2 CH Ar), 122.6 (2 CH Ar), 118.8 (Cq), 115.4 (Cq), 53.4 (Cq *t*-bu), 28.7 (3 CH_3 of *t*-bu).

General procedure for the one-pot synthesis of α-imino amidine 2g: a suspension of GO (30 mg mmol^{-1}, 8 mg) in CH_3CN/H_2O 2:1 (0.4 M) in a vial is sonicated for two minutes. Then, 4-chlorobenzaldehyde (1.0 eq, 0.25 mmol, 35 mg), 4-bromoaniline (2.2 eq, 0.55 mmol, 95 mg) and t-butylisocyanide (2 eq, 0.50 mmol, 57 μL) were added in the vial. The reaction was stirred at 30 °C. After 48 h, GO (20 mg mmol^{-1}, 5 mg), CH_3CN (1.6 mL) and H_2O (0.3 mL) were added and the reaction mixture was stirred at 80 °C for 24 h. The mixture was filtered on celite by washing with a mixture of CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL), and concentrated. The residue was purified by column chromatography with PE/acetone (from 97:3 to 90:10) and **2g** was isolated (99 mg, 72%), as yellow oil.

General procedure for the two-step synthesis of 2,3-diamino indolenine 3a: a suspension of GO (30 mg mmol^{-1}, 8 mg) in CH_3CN/H_2O 2:1 (0.4 M) in a vial is sonicated for two minutes. Then, 4-chlorobenzaldehyde (1.0 eq, 0.25 mmol, 35 mg), 3-methoxyaniline (2.2 eq, 0.55 mmol, 62 μL) and cyclohexylisocyanide (2 eq, 0.50 mmol, 62 μL) were added in the vial and the reactions was stirred at 30 °C for 48 h. After this time, the crude was filtered on celite by washing with a mixture of CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL). The residue was filtered on a short column of silica gel with PE/Acetone (from 95:5 to 94:6) to give a mixture of **1a** and **2a** (22/78 by NMR analysis, 80 mg, 70%), which was directly submitted to the next step. A suspension of **1a** and **2a** (1 eq, 0.06 mmol, 30 mg) and GO (20 mg mmol^{-1}, 1 mg) in CH_3CN/H_2O

4:1 (0.1 M) was sonicated in a vial for two minutes. The reaction mixture was stirred at 80 °C for 30 h. Then, the mixture was filtered on celite by washing with CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL). The residue was purified by column chromatography with PE/EtOAc (from 80:20 to 50:50) to give **3 a** (20 mg, 70 %) as pink solid; M. p. 184.8–192.8 °C (CH_2Cl_2); $R_f = 0.38$ (PE/acetone 75:25); I. R.: $\tilde{\upsilon}$ (cm^{-1}) = 3400, 3272, 2930, 2853, 2833, 1599, 1567, 1518, 1488, 1463, 1441, 1400, 1371, 1341, 1309, 1272, 1217, 1190, 1153, 1140, 1094, 1027, 1013, 1001, 983, 925, 891, 833, 813, 794, 771, 688, 648; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 2H, 2 CH Ar), 7.30 (d, J = 8.7 Hz, 2H, 2 CH Ar), 6.94 (t, J = 8.2 Hz, 1H, CH Ar), 6.92 (d, J = 8.1 Hz, 1H, CH Ar), 6.89 (d, J = 2.3 Hz, 1H, CH Ar), 6.38 (dd, J = 8.2, 2.3 Hz, 1H, CH Ar), 6.29 (dd, J = 8.2, 2.4 Hz, 1H, CH Ar), 6.10 (dd, J = 8.1, 2.2 Hz, 1H, CH Ar), 6.01 (t, J = 2.3 Hz, 1H, CH Ar), 4.98 (bd, J = 8.4 Hz, 1H, NH), 4.46 (s, 1H, NH), 3.95–3.85 (m, 1H, CH Cy), 3.77 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 2.00–1.84 (m, 3H, 3 H CH_2 Cy), 1.71–1.49 (m, 3H, 3 H CH_2 Cy), 1.45–0.97 (m, 4H, 4 H of CH_2 Cy); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (Cq), 161.5 (Cq), 160.6 (Cq), 157.2 (Cq), 146.2 (Cq), 141.0 (Cq), 134.2 (Cq), 130.0 (CH Ar), 129.4 (2 CH Ar), 128.7 (Cq), 126.8 (2 CH Ar), 123.0 (CH Ar), 108.2 (CH Ar), 107.4 (CH Ar), 105.7 (CH Ar), 103.7 (CH Ar), 101.1 (CH Ar), 72.5 (Cq), 55.5 (OCH_3), 55.1 (OCH_3), 51.2 (CH Cy), 32.9 (CH_2 Cy), 32.8 (CH_2 Cy), 25.6 (CH_2 Cy), 24.6 (CH_2 Cy), 24.5 (CH_2 Cy). HRMS (ESI^+): m/z calcd for $C_{28}H_{31}ClN_3O_2$ $[M+H]^+$: 476.2099. Found: 476.2112.

General procedure for the one-pot synthesis of 2,3-diamino indolenine 3 a: a suspension of GO (30 mg mmol^{-1}, 8 mg) in CH_3CN/H_2O 2:1 (0.4 M) in a vial is sonicated for two minutes. Then, 4-chlorobenzaldehyde (1.0 eq, 0.25 mmol, 35 mg), 3-methoxyaniline (2.2 eq, 0.55 mmol, 62 μL) and cyclohexylisocyanide (2 eq, 0.50 mmol, 62 μL) were added in the vial. The reaction mixture was stirred at 30 °C for 48 h. After TLC analysis, GO (20 mg mmol^{-1}, 5 mg) CH_3CN (1.6 mL) and H_2O (0.3 mL) were added and the reaction mixture was stirred at 80 °C for 30 h. Then, the mixture was filtered on celite by washing with CH_2Cl_2/EtOAc 1:1 (30 mL) and MeOH (5 mL). The residue was purified by column chromatography with PE/EtOAc (from 80:20 to 60:40) to give **3 a** (59 mg, 50 %) as pink solid.

Structural characterization of GO: X-Ray Photoelectron spectroscopy (XPS) spectra were acquired on GO tablets (100 Bar pressure) by a hemispherical analyser (Phoibos 100, Specs, Germany) using a non-monochromatic Mg Kα excitation set at 125 W (XR50, Specs, Germany). The residual pressure in analysis chamber was 10^{-8} mBar. Survey and high-resolution spectra was acquired with and overall energy resolution of 1.5 eV and 0.9 eV, respectively, measured on freshly sputtered silver (Ag 3d). The spectrometer was calibrated to the Au $4f_{7/2}$ peak at 84.0 eV.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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