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Graphene Oxide (GO)–catalyzed Multi–component Reactions: Green Synthesis of Library of Pharmacophore 3–Sulfenylimidazo[1,2–a]pyridines

Samir Kundu and Basudeb Basu*

Department of Chemistry, North Bengal University, Darjeeling 734013, India

E–mail: basu_nbu@hotmail.com, Fax: +91 353 2699001

Abstract:

Green carbocatalyst graphene oxide (GO) has been successfully utilized for selective and expedient synthesis of biologically important motifs imidazo[1,2–a]pyridines, and 3–sulfenylimidazo[1,2–a]pyridines via one-pot multi–component reactions (MCR). Diversity in small heterocyclic molecular synthesis has been demonstrated with tolerance of broad range of functional groups establishing the generality of the reaction and as well as demonstrating preparation of libraries of potential pharmacophores. The reactions are believed to proceed via selective and tandem reactions in the presence of GO and NaI (as the additive), and the catalyst GO was found to be easily recoverable and recyclable with appreciable conversions.

Introduction:

Imidazo[1,2–a]pyridines represent an important *N*–bridged and fused bicyclic scaffolds finding versatile applications in pharmaceuticals and organic functional materials.[1] The heterocyclic motif occurs in various clinical drugs including alpidem, necopidem, zolpidem, saripidem, olprinone, miroprofen, zolimidine and anti–HIV drugs GSK812397, a few representative examples are shown in Fig. 1.[2] Its anticancer,[3a] antiviral,[3b-c] antimicrobial,[3d] anti–rhinoviral,[3e-f] antiulcer[3g] activities are responsible for its wide applications in medicinal chemistry. This moiety has also been used in material sciences.[4] Further functionalized *N*–bridged fused bicyclic imidazo[1,2–a]pyridines, such as 3–sulfenylimidazo[1,2–a]pyridines, (Figure 1) are also of considerable therapeutic value against a variety of diseases and do find broad spectrum uses in pharmaceutical industries.[5]

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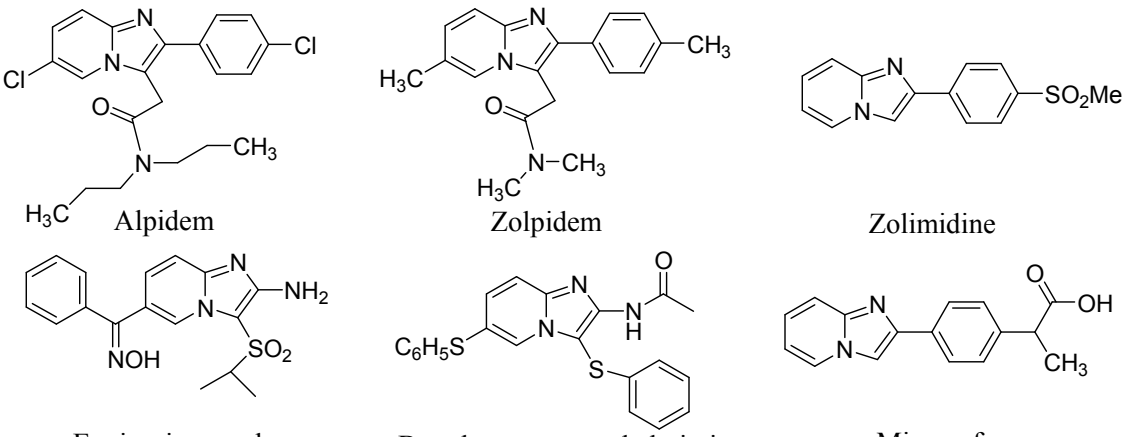

Fig. 1 Representative examples of imidazo[1,2–a]pyridine–based drugs.

In spite of enormous applications, most of the imidazo[1,2–a]pyridine derivatives are not commercially available and hence its synthesis from easily available substances has remained in the focus of synthetic organic and pharmaceutical chemists. Most synthetic procedures involve the reaction of 2-aminopyridine with a variety of chemicals like acetophenones, α-haloketones, α-diazoketones, α-tosyloxyketones, nitroalkenes, suitably substituted alkyne derivatives etc.[6] The reactions are usually done through condensation, tandem reactions or in a multi-component approach in the presence of Brønsted or Lewis acids or other metal catalysts. For example, protic acid,[7a,b] Lewis acids[7c-e] or metal catalysts like Cu(I) salts,[7f-h] Cu(I)/Cu(II),[7i,j] Cu(I)/Zn(II),[7k] Cu(II)/Fe(III)[7l] systems have been employed for the synthesis of imidazo[1,2–a]pyridine derivatives.

Among several approaches, $CeCl_3.7H_2O$/NaI–catalyzed multicomponent tandem procedure,[7c] has emerged possibly as a powerful methodology. However, modern green practices demand for eco-friendly procedures without metal toxicity, contamination with the product and final disposal. As such, the need for metal–free, non–toxic and easily available or prepared catalysts are attractive targets for green and sustainable synthesis. In this perspective, carbon materials like GO has emerged as an efficient and promising carbocatalyst.[8] Large surface area, bio–compatibility, inertness, and outstanding electronic, optical, thermal & mechanical properties make GO as an versatile material, which is obtained from low–cost and easily available starting materials.[9] The presence of multiple functionalities such as epoxide, hydroxyl and carboxyl groups (Fig. 2) account for its acidic nature (pH 4.5 at 0.1 mg/mL),[10] and strong oxidizing property.[11] Harnessing these unique qualities over the last few years, GO has been finely exploited as a metal-free and robust carbocatalyst in various synthetic processes like hydration of alkyne,[12] selective oxidation of

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thiols and sulphides,[11c] oxidation of olefins to diones, methyl benzenes to aldehydes, diarylmethanes to ketones,[11d] oxidative coupling of amines to imines,[11e] Friedel–Craft addition of indole to α, β–unsaturated ketones etc.[11f] From our laboratory, we successfully developed controlled use of this carbocatalyst in one–pot sequential dehydration–hydrothiolation of *sec*–aryl alcohols,[13a] as well as chemoselective thioacetalization of aryl aldehydes.[13b]

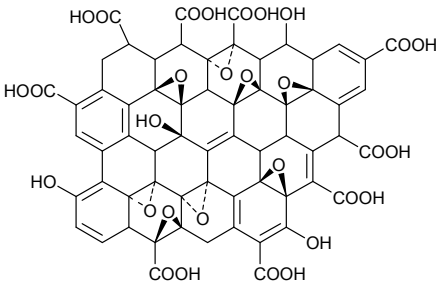

Fig.2 Schematic presentation of graphene oxide (GO)

Considering the vast applicability of GO as the carbocatalyst in C–H oxidation, C–C and C–heteroatom bond-forming reactions,[13f,14] and our previous findings on one-pot diverse reactions to prepare complex molecules,[13a] we wanted to explore further GO–catalyzed synthesis of complex heterocycles of biological relevance. We describe herein highly selective metal-free synthetic protocol for imidazo[1,2–a]pyridines from the reaction of 2–aminopyridine and acetophenone, and an efficient one-pot MCR procedure using aryl/alkyl thiol as the third component leading to the synthesis of 3–sulfenylimidazo[1,2–a]pyridines in the presence of a catalytic combination of GO and NaI.

Results and discussion:

Direct reaction of 2–aminopyridine (**1**) and acetophenone (**2**) can produce a number of possible products like 3–(1–phenylethane)–2–phenyl (**3**), 3–(1–phenylethene)–2–phenyl (**4**) and 2–phenyl (**5**) substituted imidazo[1,2–a] compounds and 4–methyl–2,4–diphenyl–4*H*–pyrido[1,2–a]pyrimidine (**6**), either via ketimine intermediate or via Ortoleva-King type reaction intermediate (Scheme 1).[7a] Among metal-free catalytic conditions, Kurteva et al demonstrated *p*TSA–catalyzed selective formation of **3** from a mixture of 2–aminopyridine (**1**) and acetophenone (**2**) at 210 ^{o}C.[7b] Hitherto, there are no metal-free conditions developed that can furnish selectively a single product other than **3**.

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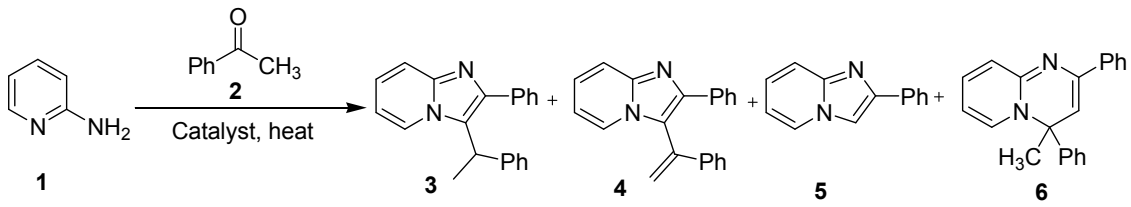

Scheme 1. Possibility of formation of different products from 2-aminopyridine and acetophenone

As GO has been shown to act as an efficient carbocatalyst for both oxidation and acid–catalyzed reactions,[11-13] we presume that the use of GO in this reaction might play an active role. We thus conducted experiments taking equimolar quantities of 2–aminopyridine and acetophenone in the presence of catalytic amounts of GO under varying reaction conditions. The results are presented in Table 1. Initial attempt of heating a mixture of reactants **1** (1 mmol) and **2** (1 mmol), the catalyst GO (100 mg) in acetonitrile (1 mL) at 80 ^{o}C did not afford any product (entry 1). However, the same reaction in the presence of an additive (NaI, 10 mol%) did produce a single product **5** in good yield (82%, entry 2). It is interesting to observe that other possible products **3**, **4** & **6** (Scheme 1) were not formed and the compound **5** was obtained as the sole product (HPLC analysis of the reaction mixture before purification). Being encouraged by this finding, we tried to optimize other facets of the reaction. For example, varying the quantity of GO, it was found that 50 mg of GO is the minimal requirement to obtain >80% isolated yield of **5** (entries 3, 4). Reactions performed in different solvents such ethanol or water were not productive either (entries 6, 7), but the same reaction carried out in toluene afforded the single product **5** in excellent yield (entries 8, 9). As seen from the results, the additive NaI does have a significant role in the catalytic process, and possibly in the selective formation of **5**. Decreasing its quantity below 10 mol% afforded the product **5** either in low yields or not formed at all (entries 5, 10 and 1). In the absence of GO, lowering of temperature or carrying out the reactions under N_2 resulted in rather poor yields of the desired product (entries 10-12). Use of other alkali metal salts such as KI or KBr acted less efficiently as compared to NaI (entries 13, 14). Thus the optimized condition established at our hand is as in entry 8, with the combination of GO (50 mg mmol^{-1}) and the additive, especially NaI (10 mol%), in solvent toluene, can produce selectively the product **5** in excellent yield. When we scaled up the reaction up to 3-5 mmols of the starting compounds in the presence of GO (50-100 mg), appreciable conversions (67-88%) were achieved (entries 15-17). This signifies that proportionate increase in the quantity of the

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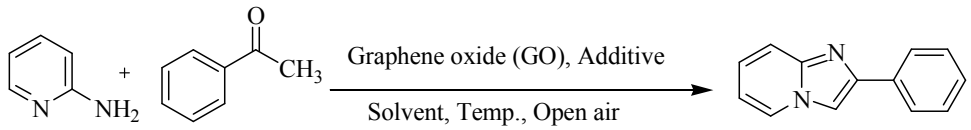
catalyst (50 mg of GO $mmol^{-1}$) is not an essential factor. Among the solvents tried for the reaction, non-polar toluene performed best, polar aprotic solvent like acetonitrile can also perform the reaction, but protic and polar solvents like ethanol or water were not suitable for this conversion. Among other greener solvents,[15] the reaction works as well in ethyl acetate (entry 18).

Table 1: Optimization of the reaction conditions[a]



1 **2** **5**

Entry	GO (mg)	Additive (Salt/mol%)	Solvent	Temp. (°C)	Time (h)	**5** (Yield %)[b]
1	100	Nil	CH_3CN	80	8	No product
2	100	NaI/10	CH_3CN	80	8	82
3	50	NaI/10	CH_3CN	80	14	81
4	30	NaI/10	CH_3CN	80	20	20
5	50	NaI/5	CH_3CN	80	24	65
6	50	NaI/10	EtOH	80	24	40
7	50	NaI/10	H_2O	80	24	No product
8	**50**	**NaI/10**	**toluene**	**80**	**6**	**92**
9	50	NaI/20	toluene	80	6	92
10	50	NaI/10	toluene	60	15	55
11	Nil	NaI/10	toluene	80	24	No product
12[c]	50	NaI/10	toluene	80	24	trace
13	50	KI/10	toluene	80	15	57
14	50	KBr/10	toluene	80	15	34
15[d]	50	NaI/10	toluene	80	8	67
16[e]	100	NaI/10	toluene	80	8	88
17[f]	**100**	**NaI/10**	**toluene**	**80**	**8**	**81**
18	50	NaI/10	ethyl acetate	reflux	12	84
19	50	NaI/10	2-propanol	80	15	48

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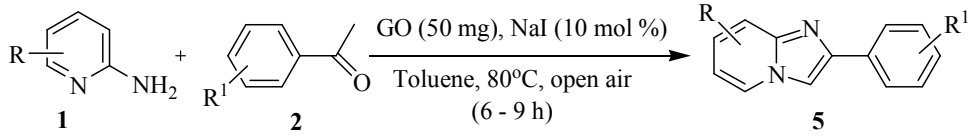
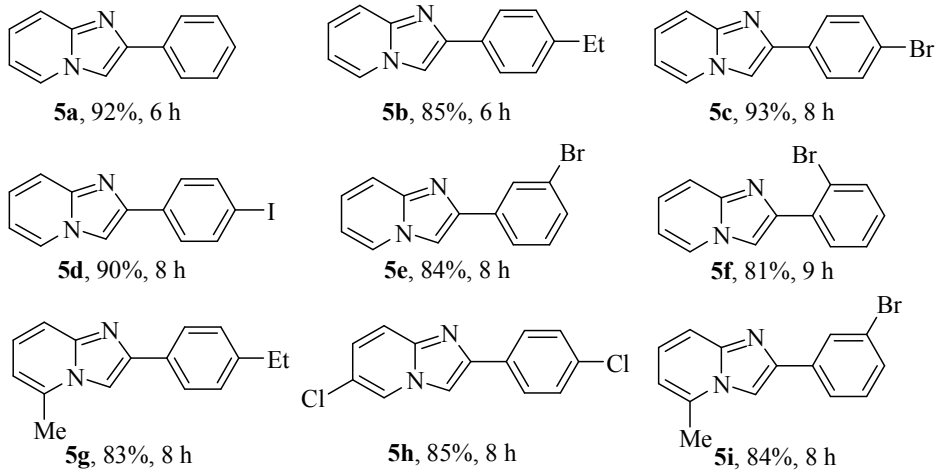
[a] General reaction conditions: Mixture of 2–aminopyridine (1 mmol), acetophenone (1 mmol), GO and NaI in solvent (1 mL) was stirred with a magnetic spin bar at temperatures/times. [b] Yield represents pure product isolated after purification. [c] Reaction was carried out under N_2 blanket. [d] Reaction was carried out with 3 mmol of **1** & **2**. [e] Reaction was performed in 3 mmol scale. [f] Reaction was performed in 5 mmol scale.

Next, the scope of this selective one–pot condensation–cyclization reaction was examined employing the optimized condition and the results are summarized in Table 2. It can be seen that diverse functional groups attached with the aromatic moiety of both reaction partners did not have significant influence in the course of the reaction and in all cases the desired imidazo[1,2–a]pyridine derivatives were obtained as the sole product and in good to excellent yields. We studied with amino pyridines substituted with $–CH_3$ and –Cl, while the acetophenones bearing $–C_2H_5$, –Cl, –Br or –I afforded the corresponding product in a highly selective manner (Table 2, compounds **5a–i**). All reactions were carried out under open air and at 80 ^oC.

Table 2: Reaction of different 2–aminopyridines with different acetophenones to synthesise imidazo[1,2–a]pyridines.[a,b]





5a, 92%, 6 h; **5b**, 85%, 6 h; **5c**, 93%, 8 h; **5d**, 90%, 8 h; **5e**, 84%, 8 h; **5f**, 81%, 9 h; **5g**, 83%, 8 h; **5h**, 85%, 8 h; **5i**, 84%, 8 h

[a] A mixture of **1** (1 mmol), **2** (1 mmol), **GO** (50 mg), **NaI** (10 mol%) in toluene (1 mL) was stirred at 80 ^oC in open air. [b] Yield represents pure product isolated by column chromatography.

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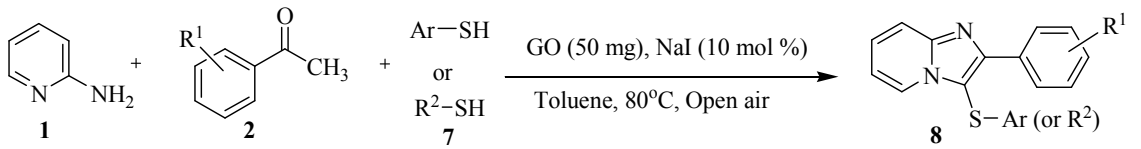
The electrophilic addition to imidazo[1,2–a]pyridine ring system is ought to be facile and likely to take place at C-3 position. Since thiol addition would lead to important pharmacophores,[16,7c] we performed a three–component reaction involving 2–aminopyridine, acetophenone and benzenethiol in the presence of GO and NaI. Indeed the thiophenol is suitably reactive to add to imidazo[1,2–a]pyridine in a selective manner yielding the 2–phenyl–3–(phenylthio)*H*–imidazo[1,2–a]pyridine (**8a**) in 84% isolated yield. Based on this observation, we performed the GO/NaI–catalyzed MCR of broad range of functionalized aminopyridines, acetophenones and arylthiols to generate a library of potential heterocyclic scaffolds, 3–sulfenylimidazo[1,2–a]pyridines (**8**). In general, the reaction occurred fairly smoothly producing the corresponding 3–sulfenylimidazo[1,2–a]pyridine derivatives in 70–89% isolated yields. Critically, a marginal effect of the presence of *ortho*-substitutent in thiophenol has been observed affording slightly lower yields of **8e**, **8f**, **8l**, **8q**), possibly due to steric encumbrance. However, there was no significant electronic effect of the substitutents present in either benzenethiol or acetophenone observed. Aliphatic thiol also worked efficiently to afford the corresponding heterocyclic scaffold (**8r**). In general, the present MCR procedure using the catalytic combination of GO and NaI was found to be effective with diverse functional groups, as listed in the Table 3.

Table 3: Preparation of library of 3–sulfenylimidazo[1,2–a]pyridines from multi–component reaction of 2–aminopyridines, acetophenone and thiol under the optimized reaction condition.[a,b]



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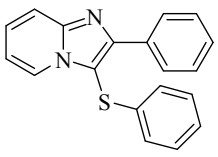
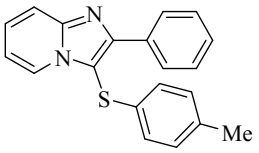
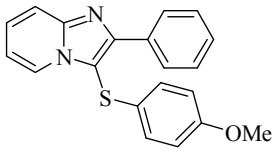
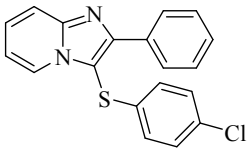
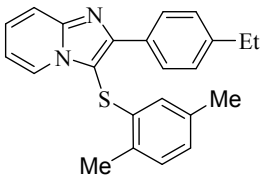
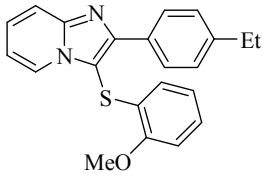

8a, 84%, 12 h

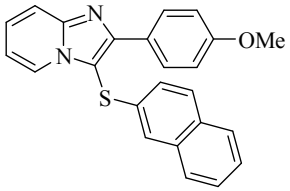

8b, 86%, 10 h

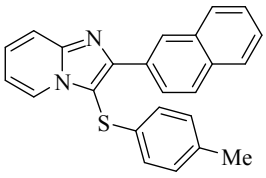

8c, 89%, 10 h

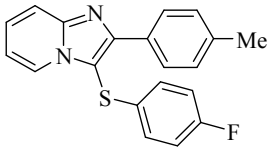

8d, 81%, 12 h

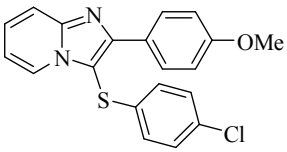

8e, 80%, 13 h

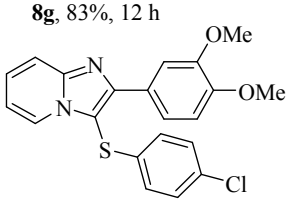

8f, 81%, 12 h

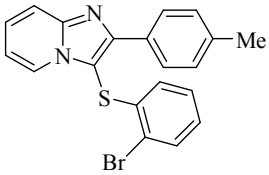

8g, 83%, 12 h

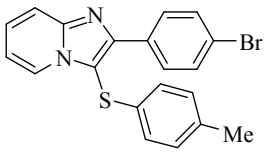

8h, 79%, 14 h

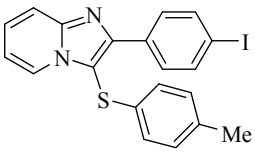

8i, 84%, 12 h

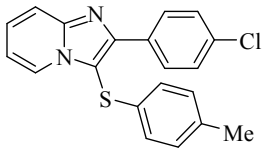

8j, 82%, 14 h

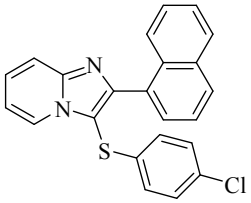

8k, 87%, 12 h

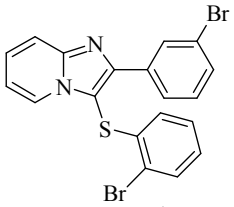

8l, 73%, 14 h

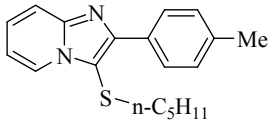

8m, 80%, 14 h


8n, 76%, 14 h


8o, 74%, 14 h


8p, 77%, 12 h


8q, 73%, 14 h


8r, 70%, 15 h

[a] A mixture of **1** (1 mmol), **2** (1 mmol), **GO** (50 mg), **7** (1.2 mmol), NaI (10 mol%) in toluene (1 mL) was stirred at 80 °C in open air. [b] Yield represents isolated product by column chromatography.

Catalytic performance is often measured by its life-cycle. After recovering the GO from the first batch of reaction by simple filtration, it was washed successively with ethyl acetate, water and acetone and finally dried under vacuum. The recovered free-flowing GO black powder was reused along with fresh NaI for three consecutive batches under similar reaction conditions giving nearly same yield in each batch (Table 4, 84–80%). In order to see any changes of the catalyst, we compared the FT–IR spectra of GO before and after use, and found no significant changes in characteristic absorption bands (Figure 3). The absorption bands for various functional groups of graphene oxide remain unchanged during the course of

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the reaction. Isolation of the product in comparable yield in each run suggest the active sites of the surface of GO remain unaffected.

Table 4: Recyclability of GO in three–component tandem reaction of 2–aminopyridine, acetophenone and thiophenol.[a]

Entry	Yield (%) [b]
1st run	84
2nd run	83
3rd run	84
4th run	80

[a] 2–aminopyridine (1 mmol), acetophenone (1 mmol), thiophenol (1.2 mmol), GO (50 mg), NaI (10 mol%) in toluene was stirred at 80°C. [b] Yield represents isolated pure product.

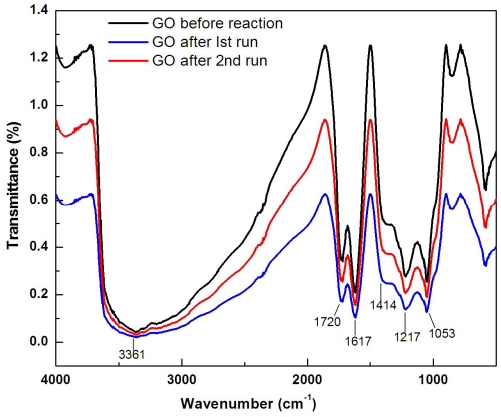

Fig. 4 Comparative FT-IR spectra of GO before use (black), after 1st (blue) and 2nd run (red).

Previous mechanistic considerations suggest for two possible mechanistic pathways, viz. via ketimine or Ortoleva–King type intermediate.[7a,b] Since the reaction condition results in the formation of the bicyclic imidazo[1,2–a]pyridine **5** selectively, the reaction might proceed via Ortoleva–King type intermediate and possibly not through the formation of ketimine. Control experiments in the absence of GO (Table 1, entry 11) and under N_2 (Table 1, entry 12), afforded no product or trace conversion respectively signifying that the oxidation of iodide to iodine is likely to be possible in the presence of GO under aerobic condition. Based on our experimental observations, we propose that initially NaI is oxidized under aerobic condition to I_2 in the presence of GO and then acetophenone is iodinated to phenacyl iodide **9** (Scheme 2). Liberation of I_2 vapour is realized on mixing of GO with NaI in a blank test and without the presence of either of the components, the reaction is unsuccessful. Subsequently,

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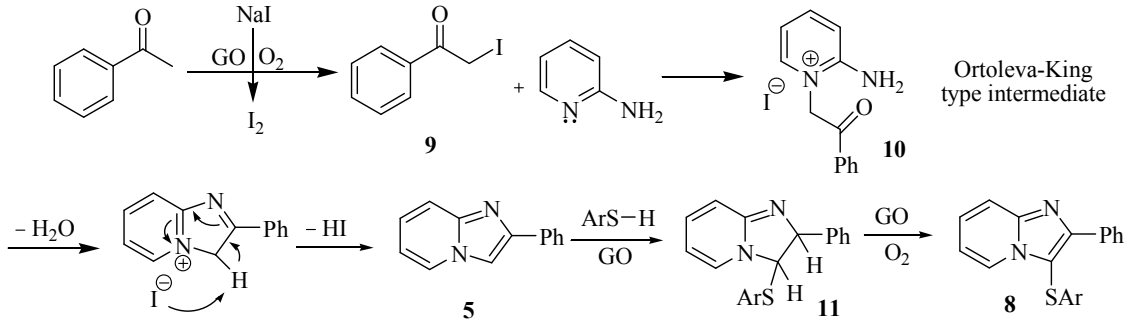
phenacyl iodide **9** is attacked by the lone–pair pyridine nitrogen electrons to form the Ortoleva–King type intermediate **10**, which is eventually on dehydration afforded bicyclic imidazo[1,2–a]pyridine **5**. In the presence of thiol, compound **5** presumably undergoes hydrothiolation entirely in anti–Markovnikov fashion **11**, which is then oxidized to the desired 3–sulfenylimidazo[1,2–a]pyridines (Scheme 2). While GO has been shown to catalyze oxidation under aerobic condition, the active sites of the GO surface consisting of carboxylic acids may also help in acid–catalyzed reactions. In the present study, presumably the primary role of GO is to promote the oxidation of NaI to I_2 as well as that of the hydrothiolated intermediate **11** efficiently, resulting in the formation of 3–sulfenylimidazo[1,2–a]pyridines **8**.



Scheme 2 Proposed mechanism for the formation of 3–sulfenylimidazopyridine via Ortoleva–King type intermediate.

Conclusion:

In summary, we have demonstrated that catalytic amounts of graphene oxide in combination with NaI can efficiently perform the reaction of 2–aminopyridine and acetophenone leading to the selective formation of important pharmacophore imidazo[1,2–a]pyridine. The same catalytic system can further carry out one–pot multi-component reactions, established with the formation of another class of important scaffolds 3–thiophenyl imidazo[1,2–a]pyridine. Both reactions are highly selective, metal-free, tolerant with diverse functional groups, and the carbocatalyst can be recovered and reused. The GO–catalyzed multi–component tandem reactions and application to important pharmaceutically active scaffolds are hitherto unknown and reported for the first time. Further applications of this sustainable and easily available carbonaceous material are expected to come out in the synthesis of diverse complex molecules of importance in pharmaceutical chemistry and material sciences.

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Experimental section:

All chemicals were purchased from commercial suppliers (Sigma–Aldrich) and used without further purification. NMR spectra were recorded on Varian AV–300 spectrometer using $CDCl_3$ solvent. Chemical shifts (δ) are reported in ppm and referenced to TMS for ^1H NMR and residual solvent signals for ^{13}C NMR as internal standard. Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, qnt = quintet, m = multiplet. Melting points were determined by heating in open capillary tube.

Preparation of Graphene Oxide (GO):

GO was prepared according to the modified Hummer's method,[9c,17] and our previously reported conditions (see ESI, S1).[13a]

General procedure for the synthesis of imidazo[1,2–a]pyridines (Table 2, 5a–5i):

To a solution of 2–aminopyridine (1 mmol), acetophenone (1 mmol) in toluene (1 mL) was added GO (50 mg) followed by NaI (15 mg, 10 mol%). The reaction mixture was then stirred using a small spin bar at 80^{o}C under an open air for the time indicated in Table 2. After completion of the reaction (monitored by tlc), the catalyst was filtered off, washed with ethyl acetate (3 x 3 mL) and the combined organic layer was washed with H_2O, dried (anhy. Na_2SO_4) and concentrated under vacuum. The residue was purified by passing through a short path of silica gel and elution with 9:1 light petroleum/ethyl acetate to afford the desired imidazo[1,2–a]pyridine (**5a**–**5i**). All products were characterized by ^1H– & ^{13}C–NMR spectral data and comparison with their melting points with the literature value, wherever reported (see ESI, S2).

General procedure for the multi–component synthesis of 3–sulfenylimidazo[1,2–a]pyridines (Table 3, 8a–8i):

To a solution of 2–aminopyridine (1 mmol), acetophenone (1 mmol) and thiol (1.2 mmol) in toluene (1 mL), were added GO (50 mg), and NaI (15 mg, 10 mol%). The reaction mixture was stirred with magnetic spin bar at 80^{o}C for the time indicated in Table 3. After completion of the reaction (monitored by tlc), the catalyst was filtered off and the catalyst washed with ethyl acetate (3 x 3 mL) and the combined filtrate was washed with H_2O and then dried (anhy. Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography over silica gel and elution with light petroleum/ethyl acetate (19:1 – 9:1) to obtain the desired 3–sulfenylimidazo[1,2–a]pyridine (Table 3, **8a – 8i**) in pure form.

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All products were characterized by ^{1}H–& ^{13}C–NMR spectral data and comparison of melting points with their literature values, wherever reported (see ESI, S2).

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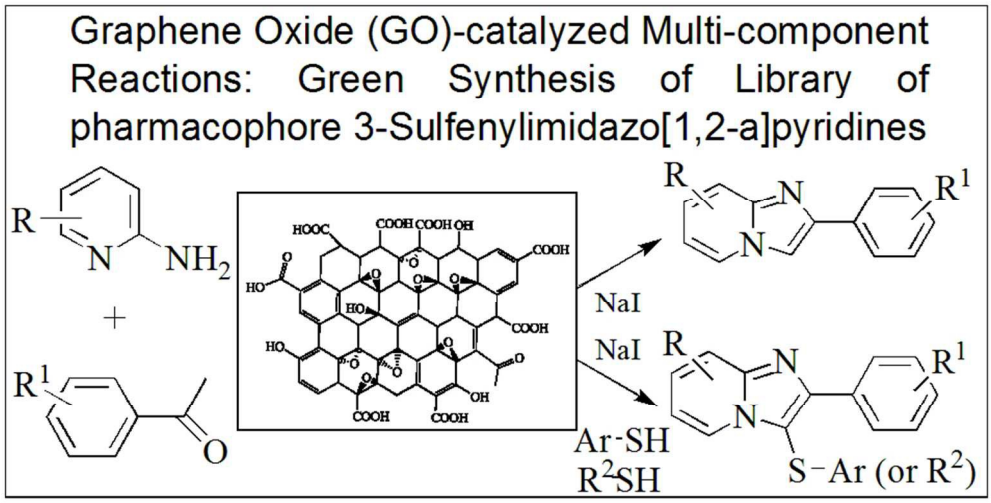

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