# CHAPTER II

## Graphene oxide (GO)-catalyzed selective synthesis of Imidazo[1,2-a]pyridines and further one-pot three-component reaction to 3-Sulfenylimidazo[1,2-a]pyridines

## II.A. Introduction

An important pharmacophore, imidazopyridine consists of imidazole moiety and pyridine ring fused together. It is widely distributed in number of biologically active compounds.[1] Among various imidazopyridine derivatives (Figure II.A.1), the imidazo[1,2–a]pyridine in particular is of huge importance.

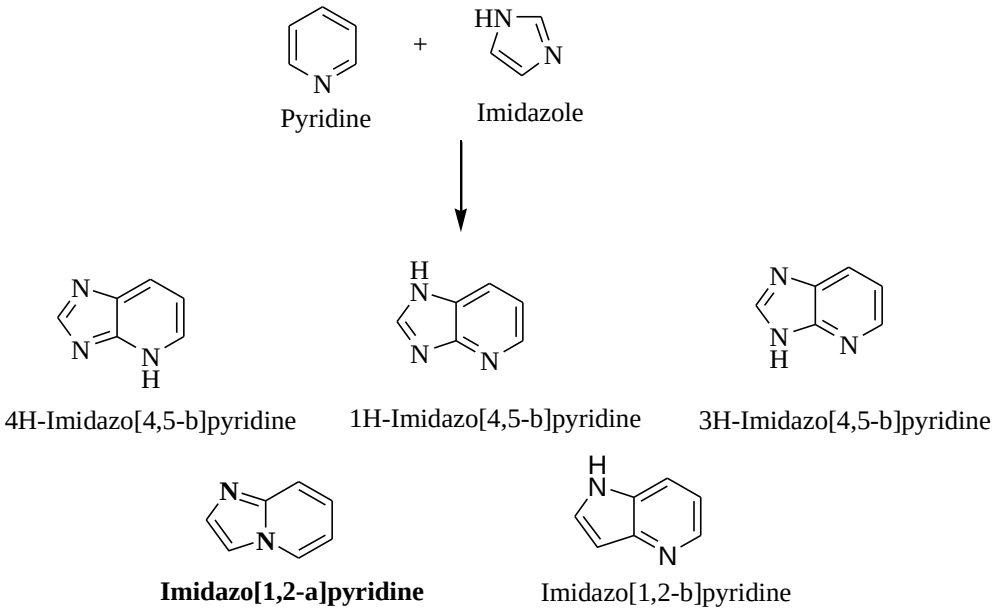



**Figure II.A.1.** Different types of imidazopyridine derivatives

The structural moiety of imidazo[1,2-a]pyridine represents an important *N*–bridged and fused bicyclic scaffolds with versatile applications in pharmaceuticals and organic functional materials.[1a,2] It occurs in various clinical drugs including alpidem, necopidem, zolpidem, saripidem, olprinone, miroprofen, zolimidine and GSK812397, a few representative examples are shown in Figure II.A.2,[3] due to their wide range of biological activities such as hypotensive,[4a] antifungal,[4b] bradycardic,[4c] antiasthmatic,[4d] cytoprotective,[4e] antibacterial,[4f] antitumor,[4g] analgesic,[4h] antiinflammatory,[4i] antipyretic,[4j] antileukemia,[4k] and anxioselective[4l] activities. Among these drugs alpidem, necopidem and saripidem are used as anxiolytic agent,[5,6] zolpidem is used in the treatment of insomnia,[5] whereas olprinone and zolimidine are used for the treatment of acute heart failure,[7] and peptic ulcer,[8] respectively. In addition, imidazo[1,2-a]pyridine derivatives are also used in calcium channel blocking agents,[9] and as HIF-1$\alpha$-prolyl hydroxylase inhibitors.[10] Imidazo[1,2–a]pyridine based optically active GSK812397 and rifaximin drug are used for the treatment of HIV infection,[11] and antibiotic agents,[12] respectively. Again this moiety can inhibit the formation of $\beta$-amyloid.[13] It can act as agonist for GABA and benzodiazepine receptor and also as a cardiotonic agent.[14-16]

Moreover its anticancer,[17a] antiviral,[17b,c] antimicrobial,[17d] anti–rhinoviral,[17e,f] antiulcer,[17g] activities have opened a new era in medicinal chemistry. Because of their structural characters derivatives of imidazo[1,2–a]pyridine moiety are also used in bioimaging probes and molecular sensors for molecular recognition.[18] The pharmacological profiles are shown to be strongly dependent on the nature of substituents at 2- and 3- positions; for example

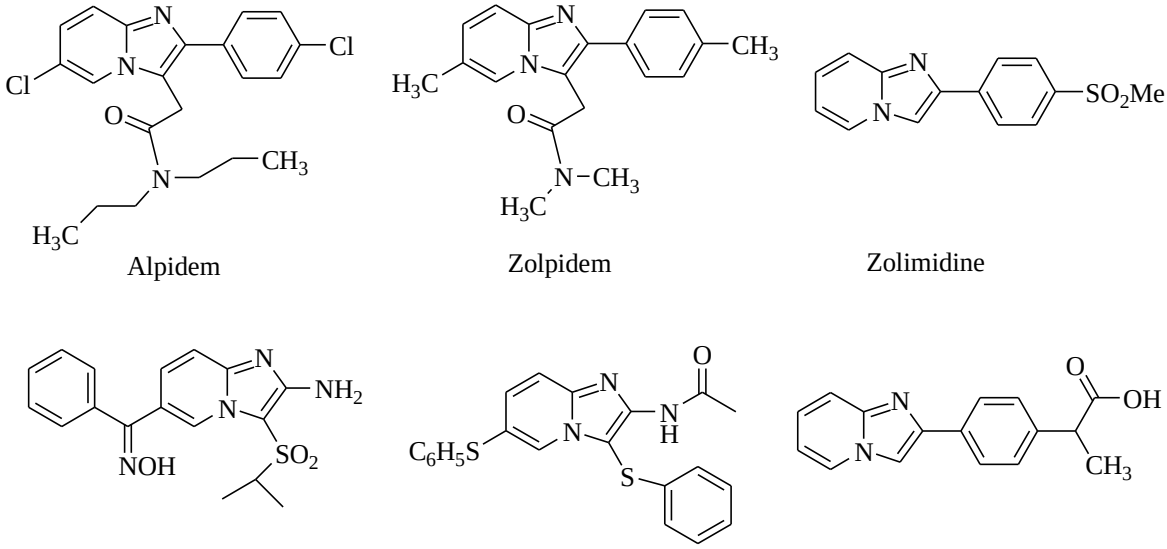



**Figure II.A.2.** Representative examples of imidazo[1,2–a]pyridine-based drugs

imidazo[1,2–a]pyridine moiety bearing the 2-hydroxyphenyl substituent at the 2-position exhibits exited state intra-molecular proton transfer,[19] in the field of optoelectronics. Further functionalized *N*–bridged fused bicyclic imidazo[1,2–a]pyridines, such as 3–sulfenylimidazo[1,2–a]pyridines, (Figure II.A.2) are also of considerable therapeutic value against a variety of diseases and do find broad spectrum uses in pharmaceutical industries.[20] Some abnormal *N*-heterocyclic carbenes are also prepared from imidazo[1,2–a]pyridines.[21,22] This moiety has also been used in material sciences.[23]

## II.B. Background and objectives

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. Accordingly, there is continuous effort towards the development of new methodology for the synthesis of imidazo[1,2-a]pyridine derivatives with a variety of substituents at the 2- and 3-positions. A short review based on the synthetic strategies of imidazo[1,2-a]pyridines described in this context is represented in figure II.A.3. 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.[24] The reactions are usually done through condensation, tandem reactions or in a multicomponent approach in the presence of Brønsted or Lewis acids or other metal catalysts. For example, protic acid,[25a,b] Lewis acids,[25c-e] or metal catalysts like Cu(I) salts,[25f-h] Cu(I)/Cu(II),[25i,j] Cu(I)/Zn(II),[25k] Cu(II)/Fe(III),[25l] Cu(I),[25m] systems have been employed for the synthesis of imidazo[1,2–a]pyridine derivatives. A traditional approach for the synthesis of imidazo[1,2–a]pyridines has been developed by the condensation reaction of 2-aminopyridine either with acetophenones or α-haloketones or α-diazoketones or *α*-tosyloxyketones respectively whereas Cu(I)-catalyzed tandem coupling reaction between nitroolefin and 2-aminopyridine towards the synthesis of this novel scaffolds has been also placed in organic synthetic chemistry.

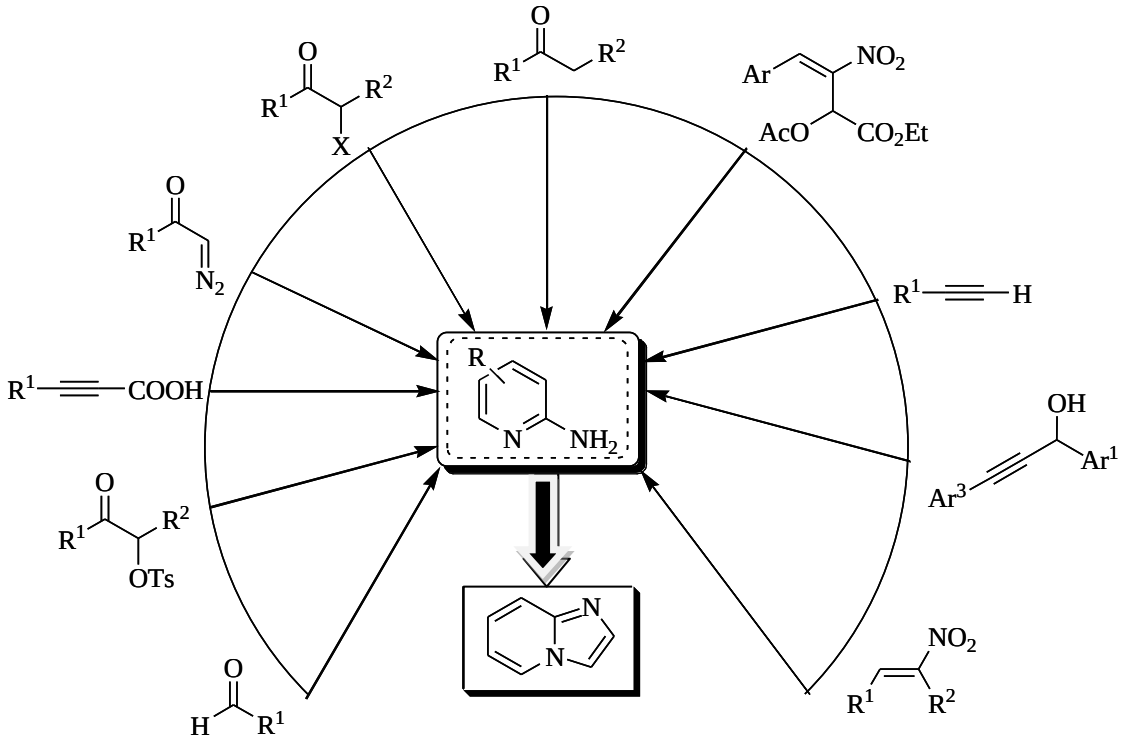
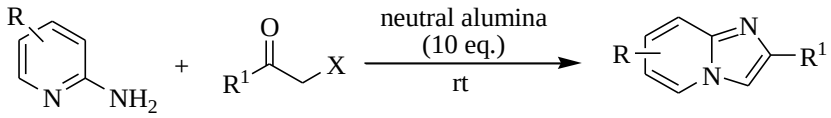



**Figure II.B.3.** Schematic representation of the synthesis of imidazo[1,2–a]pyridines from variety of starting materials with 2-aminopyridine

For the synthesis of *N*–bridged fused bicyclic heterocycles like imidazo[1,2–a]pyridines, the one–pot multicomponent tandem oxidative C–H activation reaction is also considered as highly efficient, atom economical.[26] This reaction offers the possibility to inhibit pre–

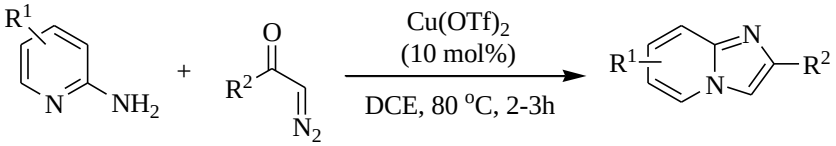
functionalization of the reactants before coupling,[27] which is one of the advantages of MCRs over the traditional step-wise synthesis.

Sahu et al. followed the traditional approach towards the synthesis of imidazo[1,2-a]pyridines via the condensation reaction of $\alpha$-haloketones,[28] with 2-aminopyridines using neutral alumina at room temperature.



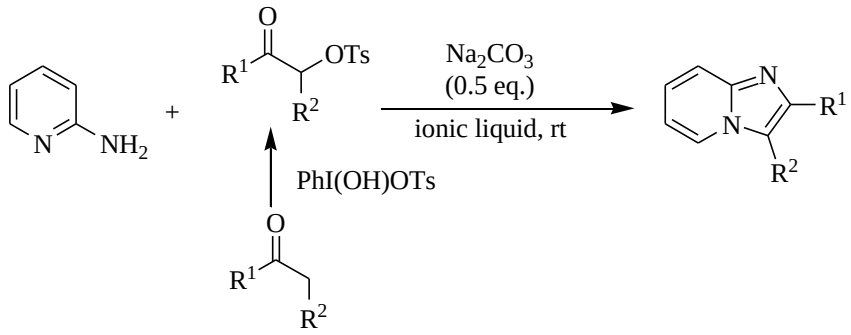

**Scheme II.B.1.** Neutral alumina-mediated condensation reaction of $\alpha$-haloketones with 2-aminopyridines

$Cu(OTf)_2$-catalyzed,[29] a selective procedure was developed from the reaction of $\alpha$-diazoketones and 2-aminopyridines via the imine formation followed by nitrogen insertion.



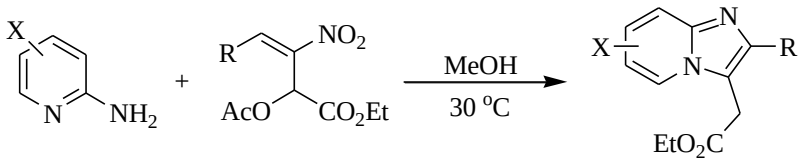

**Scheme II.B.2.** $Cu(OTf)_2$-catalyzed condensation reaction of $\alpha$-diazoketones with 2-aminopyridines

Another process involved the condensation reaction of $\alpha$-tosyloxyketones,[30] with 2-aminopyridine in ionic liquid at room temperature to afford the imidazo[1,2-a]pyridine derivatives. A straight forward synthetic route can be from ketone via in situ generation of the $\alpha$-tosyloxyketones when used PhI(OH)OTs.



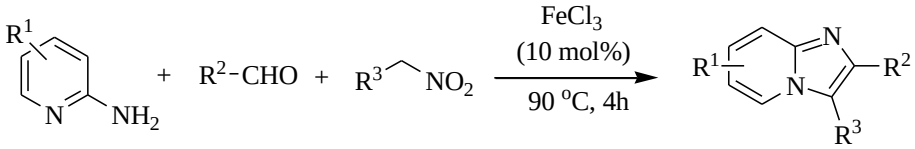

**Scheme II.B.3.** Condensation reaction of $\alpha$-tosyloxyketones with 2-aminopyridines to the synthesis of imidazo[1,2-a]pyridine derivatives

Namboothiri et al. synthesized,[31] functionalized imidazo[1,2-a]pyridines performing a reagent-free tandem reaction on the Morita-Baylis-Hillman (MBH) acetates of nitroalkenes and 2-aminopyridines at room temperature in methanol.



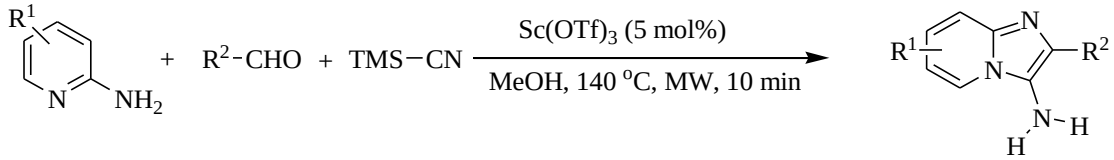

**Scheme II.B.4.** Tandem reaction on the Morita-Baylis-Hillman (MBH) acetates of nitroalkenes and 2-aminopyridines

A one-pot multicomponent cross-coupling strategy was utilized by Huang et al.,[25e] using $FeCl_3$ as catalyst for the synthesis of imidazo[1,2-a]pyridines.



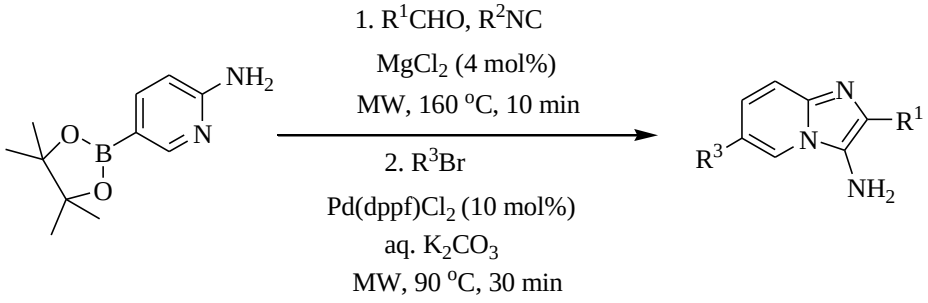

**Scheme II.B.5.** $FeCl_3$-catalyzed one-pot multicomponent synthesis of imidazo[1,2-a]pyridines

Again scandium triflate-catalyzed,[32] another multicomponent approach towards 3-aminoimidazo[1,2-a]pyridines by the reaction of 2-aminopyridine, aldehyde and trimethylsilylcyanide (TMSCN) in methanol was developed by Hulme et al. under microwave irradiation.




**Scheme II.B.6.** Scandium triflate-catalyzed multicomponent reaction of 2-aminopyridine, aldehyde and trimethylsilylcyanide (TMSCN)

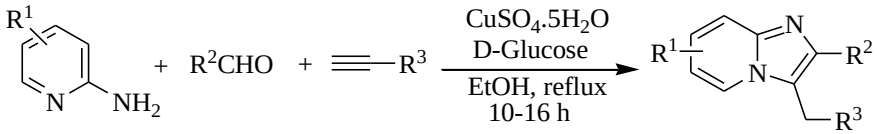
Various 2,6-disubstituted-3-amino-imidazo[1,2-a]pyridines were synthesized by DiMauro et al.,[33] under microwave irradiation via one-pot cyclization followed by Pd-catalyzed Suzuki coupling reaction.




**Scheme II.B.7.** Pd-catalyzed Suzuki coupling reaction of 2,6-disubstituted-3-amino-imidazo[1,2-a]pyridines

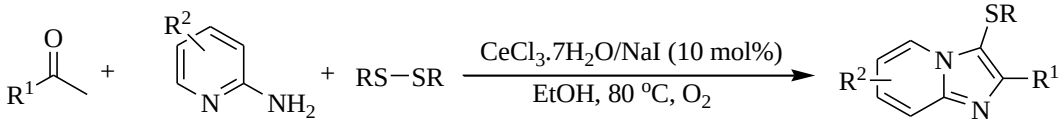
An efficient and environmentally benign process has been developed by Guchhait et al.,[25j] where partial reduction of $CuSO_4$ by glucose in ethanol under open air generated Cu(I)-Cu(II)

system to catalyze multicomponent cascade reaction of heterocyclic amidine with aldehyde and alkynecarboxylic acid followed by cyclization producing N-fused imidazoles.



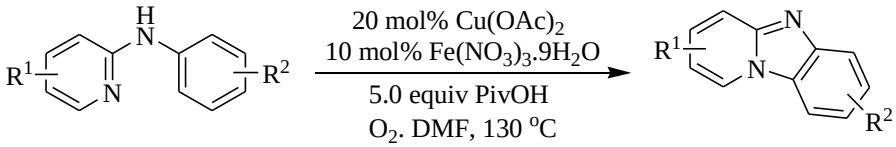

**Scheme II.B.8.** Cu(I)-Cu(II) system in multi-component cascade reaction

A very new convenint and novel tandem synthetic route has been developed by Wei et al. towards 3-sulfenylimidazo[1,2-a]pyridine.[25c] It was an aerobic multicomponent synthesis from ketones, 2-aminopyridines and disulfides catalyzed by $CeCl_3.7H_2O$/NaI. The process involved imidazo[1,2-a]pyridine formation followed by Friedel-Crafts sulfenylation in one-pot under mild conditions.



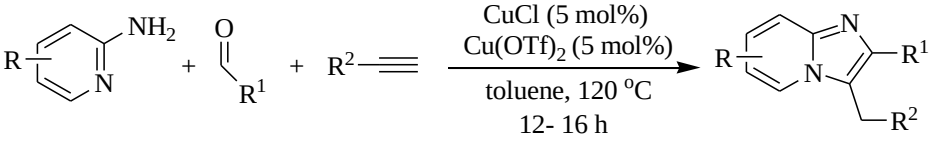

**Scheme II.B.9.** $CeCl_3.7H_2O$/NaI-promoted multi-component synthesis of 3-sulfenylimidazo[1,2-a]pyridines

Zhang and Zhu et al. synthesized pyrido[1,2-*a*]benzimidazoles through direct intra-molecular aromatic C–H amination of *N*-aryl-2-aminopyridines, cocatalyzed by $Cu(OAc)_2$ and $Fe(NO_3)_3.9H_2O$ in DMF under $O_2$ atmosphere.[25l] Fe(III) is believed to facilitate the formation of more electrophilic Cu(III) species, which accounts for the electrophilic aromatic substitution ($S_EAr$) pathway. Dioxygen acts as the terminal oxidant here.



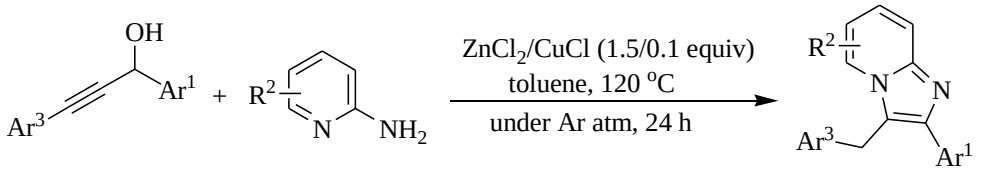

**Scheme II.B.10.** Synthesis of pyrido[1,2-*a*]benzimidazoles cocatalyzed by $Cu(OAc)_2$ and $Fe(NO_3)_3.9H_2O$

Chernyak & Gevorgyan developed copper-catalyzed three-component coupling (TCC) reaction,[34a] of 2-aminopyridines with aryl aldehydes and alkynes towards one-pot synthesis of alpidem and zolpidem via the formation of imidazo[1,2-a]pyridines.



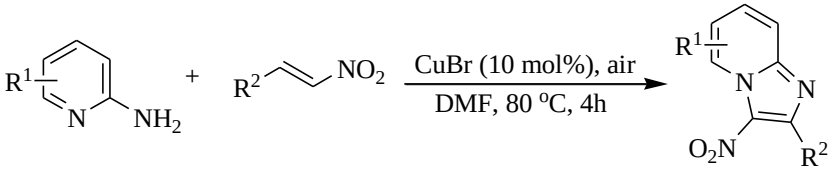

**Scheme II.B.11.** Copper catalyzed one-pot synthesis of imidazo[1,2-a]pyridines derivatives

Another similar route has been developed by Lei and Lin et al. to imidazo[1,2-a]pyridines through tandem amination of aryl propargylic alcohols with 2-aminopyridines followed by intra-molecular cycloisomerization,[25k] using $ZnCl_2$/CuCl system.



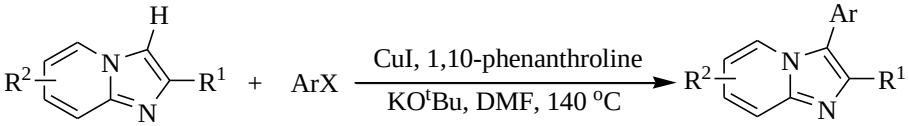

**Scheme II.B.12.** $ZnCl_2$/CuCl-catalyzed tandem amination of aryl propargylic alcohols with 2-aminopyridines

Yan and Huang et al. have introduced another one-pot synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines and nitro olefins catalysed by Cu(I) using air as oxidising agent.[34b]



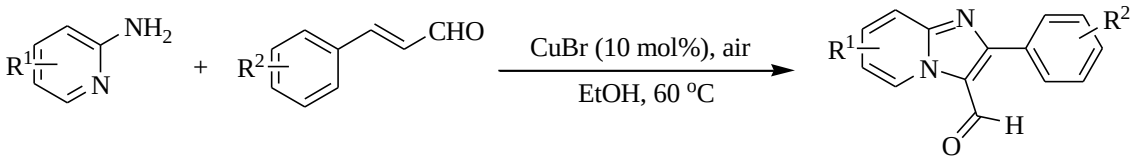

**Scheme II.B.13.** One-pot synthesis of imidazo[1,2-a]pyridines using CuBr

Cu(I)-catalyzed first C-3 arylation of substituted imidazo[1,2-a]pyridine to construct various functionalized imidazo[1,2-a]pyridine core was developed by Cao and Jiang et al.[34c] Variety of aryl eletrophiles like bromides, iodides and triflates can well tolerate the reaction condition.

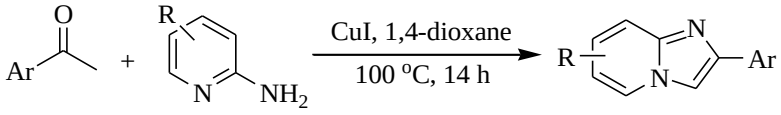



**Scheme II.B.14.** Cu(I) catalyzed arylation of substituted imidazo[1,2-a]pyridine

CuBr-promoted aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes has been developed by Vishwakarma and Bharate et al.[25m]

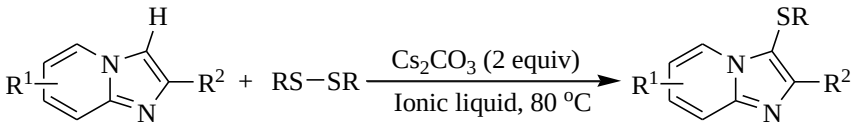



Variety of imidazo[1,2-a]pyridines were prepared from acetophenones and 2-aminopyridines by Kumar et al.,[25h] via copper-catalyzed imine formation followed by intra-molecular aerobic oxidative C-H bond amination/cyclization.



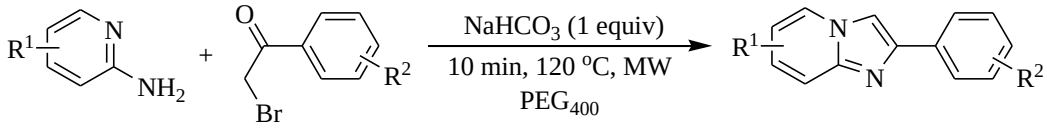

**Scheme II.B.15.** CuI-catalyzed intramolecular aerobic oxidative C-H bond amination/cyclization

Very recently an environment-friendly protocol has been introduced by Zhang et al.,[26b] to synthesize 3-sulfenylimidazo[1,2-a]pyridine via $Cs_2CO_3$-promoted sulfenylation of imidazo[1,2-a]pyridines in ionic liquids free from transition metals and volatile organic solvents.



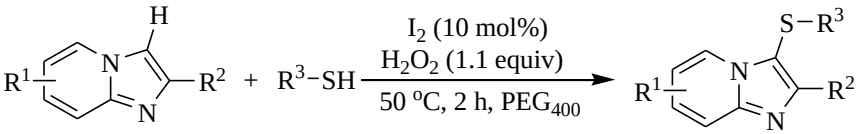

**Scheme II.B.16.** $Cs_2CO_3$/IL-promoted sulfenylation of imidazo[1,2-a]pyridines

Another recent work by Raboin et al. utilized $PEG_{400}$ as a suitable medium for the one-pot condensation and Pd-catalyzed C−H arylation of various 2-amino pyridines with $\alpha$-bromo ketones towards a straightforward synthetic route for 2,3-diarylimidazo[1,2-a]pyridines.[26e]




**Scheme II.B.17.** Pd salt-catalyzed synthesis of 2,3-diarylimidazo[1,2-a]pyridines

Again Hiebel et al.,[26f] introduced a metal-free regioselective sulfenylation of imidazo[1,2-a]pyridines catalyzed by iodine in $PEG_{400}$ medium using hydrogen peroxide as oxidizing agent.




**Scheme II.B.18.** Regioselective sulfenylation of imidazo[1,2-a]pyridines using iodine

Among several approaches, $CeCl_3.7H_2O$/NaI–catalyzed multicomponent tandem procedure,[25c] 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.[35] Large surface area, bio–compatibility, inertness, and outstanding electronic, optical, thermal & mechanical properties make GO as a versatile material, which is obtained

from low–cost and easily available starting materials.[36] The presence of multiple functionalities such as epoxide, hydroxyl and carboxyl groups (Figure II.A.4) account for its acidic nature (pH 4.5 at 0.1 mg/mL),[37] and strong oxidizing property.[38] 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,[39] selective oxidation of thiols and sulphides,[38c] oxidation of olefins to diones, methyl benzenes to aldehydes, diarylmethanes to ketones,[38d] oxidative coupling of amines to imines,[38e] Friedel–Craft addition of indole to *α*, *β*–unsaturated ketones etc.[38f] From our laboratory, we have successfully developed controlled use of this carbocatalyst in one–pot sequential dehydration–hydrothiolation of *sec*–aryl alcohols,[40a] as well as chemoselective thioacetalization of aryl aldehydes.[40b]

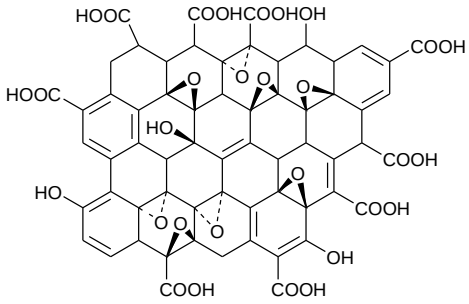
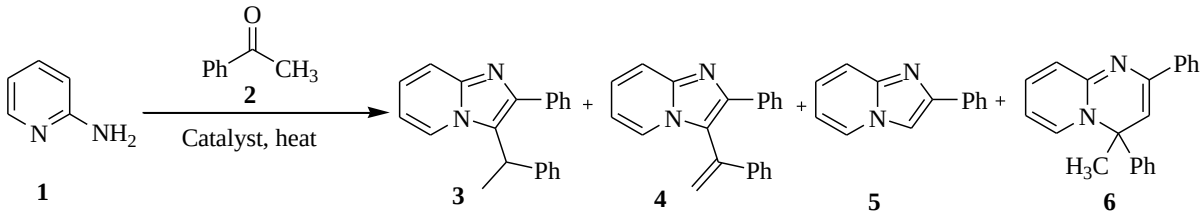



**Figure II.A.4.** Schematic presentation of graphene oxide (GO)

Considering the vast applicability of GO as the carbocatalyst in C–H oxidation, C–C and C–heteroatom bond-forming reactions,[38f,39] and our previous findings on one-pot diverse reactions to prepare complex molecules,[40a] we wanted to explore further GO–catalyzed synthesis of complex heterocycles of biological relevance. We have developed 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.

## II.C. 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 II.C.19).[25a]



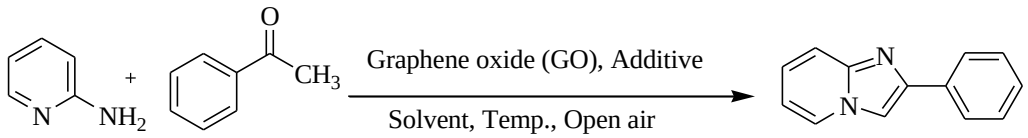

**Scheme II.C.19.** Possibility of formation of different products from 2-aminopyridine and acetophenone

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.[25b] Hitherto, there are no metal-free conditions developed that can furnish selectively a single product other than **3**.

Generally imidazo[1,2-a]pyridine synthesis has been carried out by metal catalyst basically utilizing their lewis acid character. Since various problems are associated with the metal catalysts like toxicity, disposal problem, high cost etc. these have to be replaced by environtmentally benign, low cost, recyclable catalyst. As GO has been shown to act as an efficient carbocatalyst for both oxidation and acid– catalyzed reactions,[38-40] 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 II.C.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 II.C.12) 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 (Table II.C.1). 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 as 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 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,[41] the reaction works as well in ethyl acetate (entry 18).

**Table II.C.1. Optimization of the reaction conditions[a]**



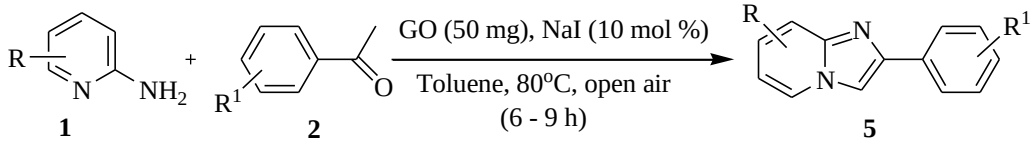

**1** **2** **5**

| 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 |

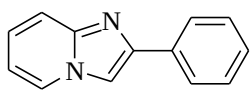
| | | | | | | |
|---|---|---|---|---|---|---|
| 12[c] | 50 | NaI/10 | toluene | 80 | 24 | trace |
| 13 | 50 | KI/10 | toluene | 80 | 15 | 57 |
| 14 | 50 | KBr/10 | toluene | 80 | 15 | 34 |
| 15[d] | 50 | NaI/10 | toluene | 80 | 8 | 67 |
| 16[e] | 100 | NaI/10 | toluene | 80 | 8 | 88 |
| **17[f]** | **100** | **NaI/10** | **toluene** | **80** | **8** | **81** |
| 18 | 50 | NaI/10 | ethyl acetate | reflux | 12 | 84 |
| 19 | 50 | NaI/10 | 2-propanol | 80 | 15 | 48 |

[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.

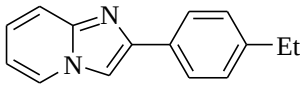
**Table II.C.2. Reaction of different 2–aminopyridines with different acetophenones to synthesize imidazo[1,2–a]pyridines[a,b]**



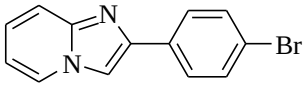

**1** **2** **5**



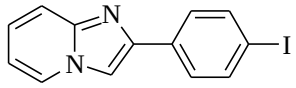
**5a**, 92%, 6 h



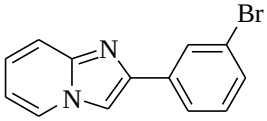

**5b**, 85%, 6 h



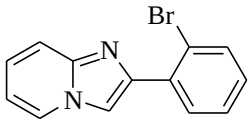

**5c**, 93%, 8 h



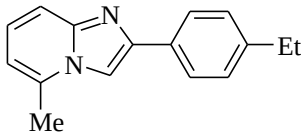

**5d**, 90%, 8 h



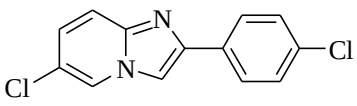

**5e**, 84%, 8 h



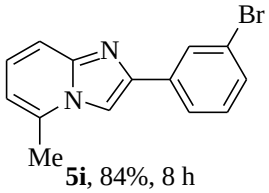

**5f**, 81%, 9 h




**5g**, 83%, 8 h




**5h**, 85%, 8 h

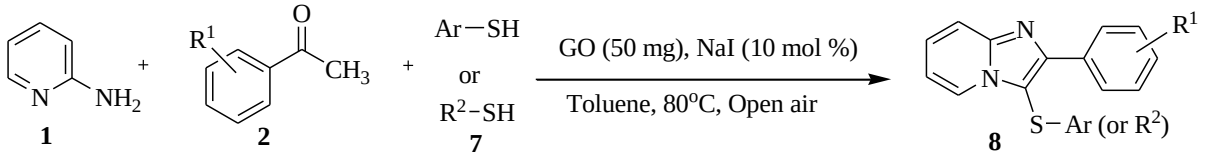



**5i**, 84%, 8 h

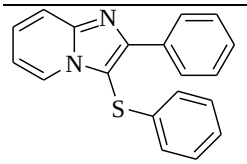
[a] A mixture of **1** (1 mmol), **2** (1 mmol), **GO** (50 mg), **NaI** (10 mol%) in toluene (1 mL) was stirred at 80 °C in open air. [b] Yield represents pure product isolated by column chromatography.

Next, the scope of this selective one-pot condensation-cyclization reaction was examined employing the optimized condition and the results are summarized in Table II.C.2. It can be

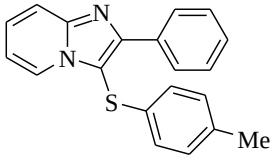
**Table II.C.3. Preparation of library of 3–sulfenylimidazo[1,2–a]pyridines from multi–component reaction of 2–aminopyridines, acetophenone and thiol under the optimized reaction condition[a,b]**



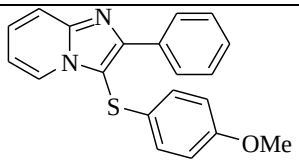

**1** **2** **7** **8**



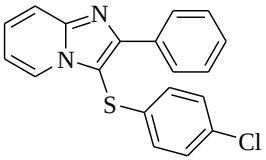
**8a**, 84%, 12 h



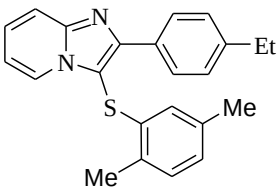
**8b**, 86%, 10 h



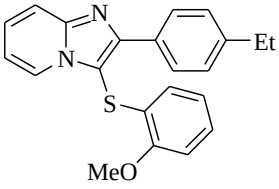
**8c**, 89%, 10 h



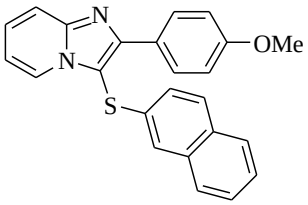
**8d**, 81%, 12 h



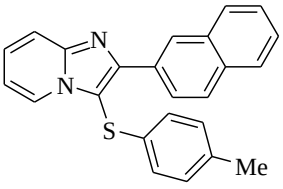
**8e**, 80%, 13 h



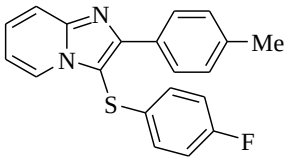
**8f**, 81%, 12 h



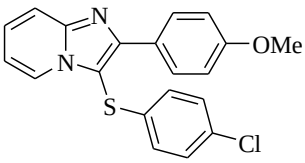
**8g**, 83%, 12 h



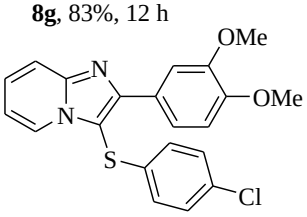
**8h**, 79%, 14 h



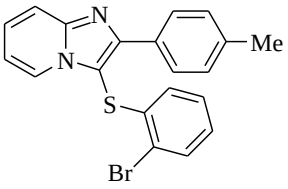
**8i**, 84%, 12 h



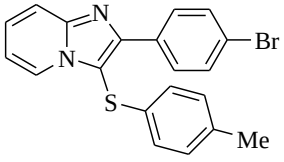
**8j**, 82%, 14 h



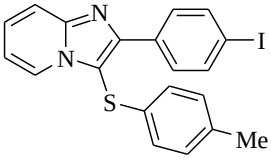
**8k**, 87%, 12 h



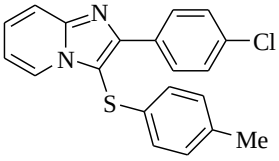
**8l**, 73%, 14 h



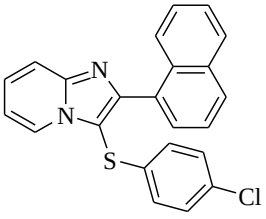
**8m**, 80%, 14 h



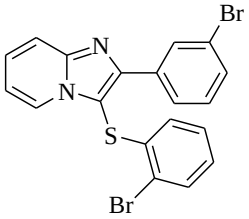
**8n**, 76%, 14 h



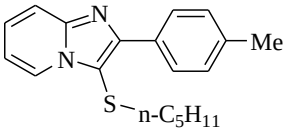
**8o**, 74%, 14 h



**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.

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 in good to excellent yields. We studied with amino pyridines substituted with 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 II.C.2, compounds **5a–i**). All reactions were carried out under open air and at 80 $^oC$. Since electrophilic addition to imidazo[1,2–a]pyridine ring system is ought to be facile and likely to take place at C-3 position, 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 and efficient manner yielding the 2–phenyl–3–(phenylthio)*H*–imidazo[1,2–a]pyridine (**8a**) in 84% isolated yield. It was observed that the use of thiophenol in slightly excess (in 1: 1: 1.2 ratios) can afford the desired product in better 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**). The results are presented in Table II.C.3. 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, (**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. We tested one example using aliphatic thiol, which also worked expectedly yielding corresponding *S*–alkyl derivative of the heterocyclic scaffold but relatively in lower yield. This however may be attributed to the reactivity difference between

**Table II.C.4. Recyclability of GO in three-component tandem reaction of 2–aminopyridine, acetophenone and phenylthiol[a]**

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

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

aromatic and aliphatic thiols. In general, this procedure came up to the expectation with diverse functional groups like –Me, –Et, –OMe, and halogens (–F, –Cl, –Br, –I) etc., paving the way for generation of library of compounds as well as for further functionalization in the presence of catalytic combination of GO and NaI. 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.

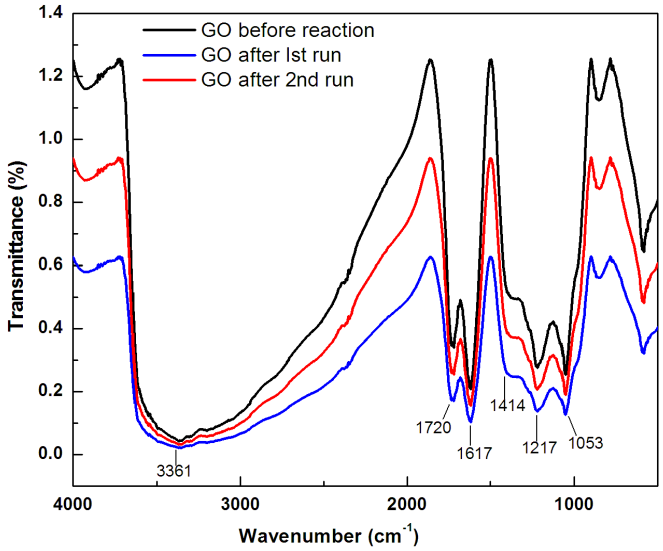
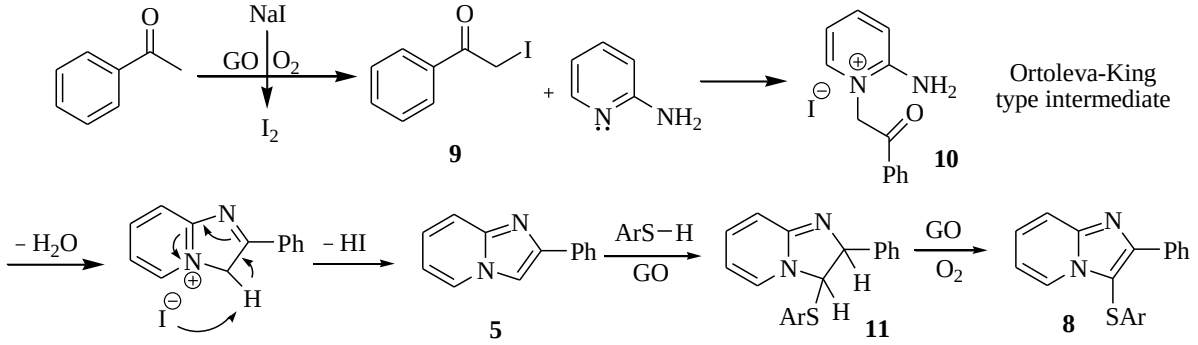



**Figure II.C.5.** Comparative FT-IR spectra of GO before use (black), after 1st (blue) and 2nd run (red)

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 II.C.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 II.C.5). The absorption bands for various functional groups of graphene oxide remain unchanged during the course of the reaction. Isolation of the product in comparable yield in each run suggests that the active sites of the surface of GO remain unaffected.

Previous mechanistic considerations suggest for two possible mechanistic pathways, viz. via ketimine or Ortoleva–King type intermediate.[25a,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 II.C.1, entry 11) and under $N_2$ (table II.C.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 20). 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, 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




**Scheme II.C.20.** Proposed mechanism for the formation of 3–sulfenylimidazopyridine via Ortoleva–King type intermediate

to the desired 3–sulfenylimidazo[1,2–a]pyridines (scheme II.C.20). 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**.

## II.D. 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. The major important facet of this reaction, which makes it unique, is the utilization of green carbocatalyst GO instead of traditional metal catalysts keeping the whole process environment friendly. As a result, further applications of this sustainable and easily available carbonaceous material would be expected to come out in green synthesis of diverse complex molecules of importance in pharmaceutical chemistry and material sciences.

## II.E. Experimental section:

### II.E.1. General information

All chemicals were purchased from commercial suppliers (Sigma–Aldrich) and used without further purification. For column chromatography: silica (60-200 μm) (SRL, India), and for tlc, Merck plates coated with silica gel 60, $F_{254}$ were used. FT-IR spectra were recorded in FT-IR-8300 SHIMADZU spectrophotometer using Nujol mulling for liquid compounds and KBr pellets for solid compounds. NMR spectra were recorded on Bruker AV–300 spectrometer, operating respectively at 300MHz & 75MHz 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. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm). Melting points were determined by heating in open capillary tube. High resolution Mass Spectra (HRMS) were performed in Micromass Q-TOF Spectrometer under ESI (positive mode) by the services at the Indian Association for the Cultivation of Science, Kolkata. Single crystal X-ray structure determinations were done in Bruker Nonius Smart Apex II Diffractometer from IIT, Guwahati.

### II.E.2. Preparation of graphene oxide (GO)

GO was prepared according to the modified Hummer's method,[43a,b] and our previously reported conditions.[40a]

To an ice-cold concentrated sulfuric acid (46 mL) was slowly added 0.1 g of sodium nitrate

portion-wise and then graphite powder (2 g) with vigorous magnetic stirring. After the complete addition of graphite powder, potassium permanganate (6 g) was added to the reaction mixture very slowly, maintaining the temperature within 0–5 $^{o}$C to avoid any possible explosion. The mixture was allowed to stir at room temperature for 6 h forming a thick paste. It was diluted with distilled water (92 mL) under stirred condition. The temperature of the solution was then raised to about 90 $^{o}$C and the mixture was allowed to stir for another 30 min. Finally, water (280 mL) was added followed by slow addition of $H_2O_2$ (30%, 3 mL). The colour of the solution gradually changes from dark brown to yellowish brown. The overall solution was exfoliated under sonication for about 30 min followed by centrifuged at 15000 rpm to collect the solid mass at the bottom. This process was continued for several times until the pH of the supernatant aqueous part becomes neutral (using pH paper). Finally, the brown mass was collected and dried at 60 $^{o}$C under vacuum to obtain solid graphene oxide (GO). A comparable literature data,[43c] were obtained when characterized by FT-IR spectroscopy: $\nu_{max}$(KBr): 3359, 1719, 1618, 1411, 1218, 1052 $cm^{-1}$.

**II.E.3. 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 $^{1}$H– & $^{13}$C–NMR spectral data and comparison with their melting points with the literature value, wherever reported.

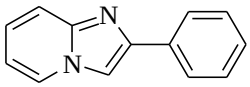
**II.E.4. General procedure for the multi–component synthesis of 3–sulfenylimidazo[1,2–a]pyridines (Table 3, 8a–8r):**

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 – 8r**) in pure form. All products were characterized by $^1$H–& $^{13}$C–NMR spectral data and comparison of melting points with their literature values, wherever reported.

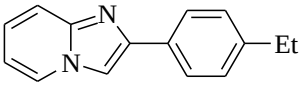
**II.E.5. Spectral data**:

**Table 2:**



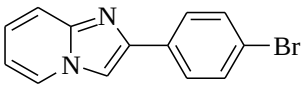
**5a**

**2-Phenyl*H*-imidazo[1,2-*a*]pyridine (5a)**: Pale yellow solid, mp 134-136 $^o$C (lit.,[44] 135 $^o$C). $^1$H NMR (300 MHz, $CDCl_3$), δ: 6.60 (t, *J* = 6.6 Hz, 1H), 7.02-7.07 (m, 1H), 7.26-7.31 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 1H), 7.89-7.93 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 107.9, 112.0, 117.0, 124.4, 125.3, 125.7, 127.6, 128.4, 133.5, 145.3.



**5b**

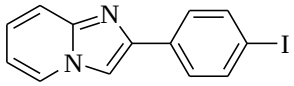
**2-(4-Ethylphenyl)*H*-imidazo[1,2-*a*]pyridine (5b)**: Brown solid, mp 115-117 $^o$C. $^1$H NMR (300 MHz, $CDCl_3$), δ: 1.25 (t, J = 7.5 Hz, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 6.64 (t, *J* = 6.6 Hz, 1H), 7.06-7.07 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.70 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.94-7.97 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 15.5, 28.7, 107.8, 112.2, 117.2, 124.5, 125.6, 126.0, 128.2, 131.1, 144.1, 145.5, 145.8; HRMS (ESI) calcd for $C_{15}H_{14}KN_2$ 261.0794; found 261.0778.



**5c**

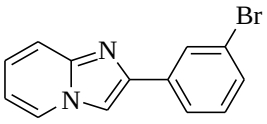
**2-(4-Bromophenyl)*H*-imidazo[1,2-*a*]pyridine (5c)**: Pale yellow solid, mp 215-217 $^o$C (lit.,[45] 216 $^o$C). $^1$H NMR (300 MHz, $CDCl_3$), δ: 6.75-6.80 (m, 1H), 7.15-7.20 (m, 1H), 7.52-7.64 (m,

3H), 7.78-7.82 (m, 3H), 8.07-8.09 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 108.2, 112.7, 117.4, 121.9, 125.1, 125.6, 127.5, 131.8, 132.5, 144.4, 145.5.



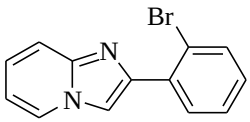

**5d**

**2-(4-Iodophenyl)*H*-imidazo[1,2-*a*]pyridine (5d)**: White solid, mp 225-227 $^{o}$C (lit.,[46] 227 $^{o}$C). $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.75-6.80 (m, 1H), 7.14-7.20 (m, 1H), 7.60-7.85 (m, 6H), 8.08-8.10 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 93.4, 108.3, 112.6, 117.6, 124.9, 125.6, 127.8, 133.3, 137.8, 144.7, 145.7.



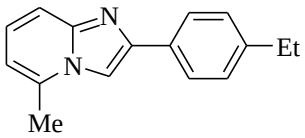

**5e**

**2-(3-Bromophenyl)*H*-imidazo[1,2-*a*]pyridine (5e):** Pale yellow solid, mp 135-137 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.70-6.75 (m, 1H), 7.11-7.16 (m, 1H), 7.22-7.28 (m, 1H), 7.39-7.43 (m, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.76-7.83 (m, 2H), 8.02-8.10 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 108.4, 112.6, 117.3, 122.8, 124.4, 124.9, 125.6, 128.8, 130.1, 130.6, 135.7, 143.9, 145.5.



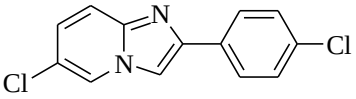

**5f**

**2-(2-Bromophenyl)*H*-imidazo[1,2-*a*]pyridine (5f)**: Pale yellow liquid. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.77-6.80 (m, 1H), 7.15-7.20 (m, 2H), 7.39-7.44 (m, 1H), 7.63-7.68 (m, 2H), 8.13-8.16 (m, 2H), 8.27 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 112.0, 112.6, 117.6, 121.5, 124.9, 125.8, 127.6, 128.9, 131.7, 133.7, 134.3, 143.1, 144.5.



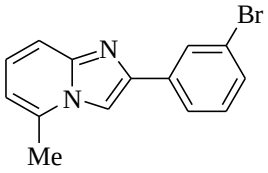

**5g**

**2-(4-Ethylphenyl)-5-methyl*H*-imidazo[1,2-*a*]pyridine (5g)**: Brown liquid. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 1.27 (t, *J* = 7.5 Hz, 3H), 2.59 (s, 3H), 2.69 (q, *J* = 7.5 Hz, 2H), 6.58-6.60 (m, 1H), 7.10-7.15 (m, 1H), 7.26-7.28 (m, 2H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.69 (s, 1H), 7.89-7.92 (m, 2H) .$^{13}$C NMR (75 MHz, $CDCl_3$), δ: 15.4, 18.7, 28.7, 104.9, 111.5, 114.8, 124.7, 126.1, 128.2, 131.3, 134.3, 144.1, 145.9, 146.1; HRMS (ESI) calcd for $C_{16}H_{16}KN_2$ 275.0951; found 275.0963.




**5h**

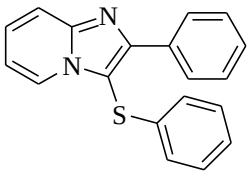
**6-Chloro-2-(4-chlorophenyl)*H*-imidazo[1,2-*a*]pyridine (5h)**: Pale yellow solid, mp 204-206 $^{o}$C (lit.,[47] 209 $^{o}$C). $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 7.13-7.17 (m, 1H), 7.37-7.41 (m, 2H), 7.57 (d, *J* = 9.6 Hz, 1H), 7.78 (s, 1H), 7.82-7.86 (m, 2H), 8.14 (s, 1H).$^{13}$C NMR (75 MHz, $CDCl_3$), δ: 108.5, 117.7, 120.9, 123.4, 126.5, 127.3, 129.0, 131.6, 134.1, 143.9, 145.5.




**5i**

**2-(3-Bromophenyl)-5-methyl*H*-imidazo[1,2-*a*]pyridine (5i)**: Pale yellow solid, mp 106-108 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 2.49 (s, 3H), 6.61-6.63 (m, 1H), 7.13-7.18 (m, 1H), 7.26-7.31 (m, 1H), 7.42-7.45 (m, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.71 (s, 1H), 7.88-7.91 (m, 1H), 8.13-8.15 (m, 1H).$^{13}$C NMR (75 MHz, $CDCl_3$), δ: 18.7, 105.7, 111.8, 115.0, 122.9, 124.6, 125.2, 129.0, 130.2, 130.7, 134.5, 136.1, 144.2, 146.2.

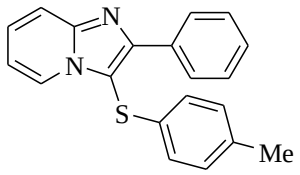
**Table 3:**




**8a**

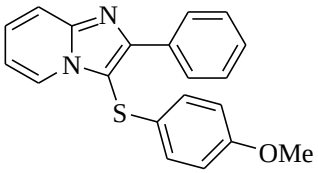
**2-Phenyl-3-(phenylthio)*H*-imidazo[1,2-*a*]pyridine (8a):** Pale yellow solid, mp 106-108 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.81-6.86 (m, 1H), 6.97-7.09 (m, 2H), 7.11-7.25 (m, 3H), 7.28-7.46 (m, 4H), 7.73 (d, *J* = 9.0 Hz, 1H), 8.19-8.27 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$),

δ: 106.4, 113.1, 117.6, 124.5, 125.6, 126.1, 126.7, 128.4, 128.5, 128.6, 129.5, 133.3, 135.2, 147.1, 151.4.



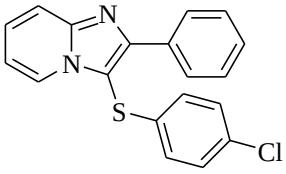

**8b**

**3-(*p*-Tolylthio)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (8b):** Pale yellow solid, mp 141-143 $^{o}$C (lit.,[48] 142-143 $^{o}$C). $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 2.22 (s, 3H), 6.78-7.00 (m, 5H), 7.23-7.44 (m, 4H), 7.70 (d, *J* = 9.0 Hz, 1H), 8.20-8.25 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 20.8, 106.8, 112.9, 117.5, 124.4, 125.7, 126.5, 128.3, 128.5, 130.1, 131.4, 133.3, 135.9, 146.9, 151.0.



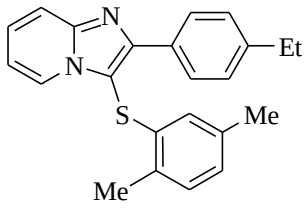

**8c**

**3-(4-Methoxyphenylthio)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (8c):** Pale yellow solid, mp 124-126 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 3.67 (s, 3H), 6.71-6.75 (m, 2H), 8.82-6.85 (m, 1H), 6.96-6.99 (m, 2H), 7.25-7.31 (m, 1H), 7.36-7.47 (m, 3H), 7.70 (d, *J* = 9.3 Hz, 1H), 8.24-8.30 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 55.2, 107.8, 112.9, 115.1, 117.5, 124.4, 125.4, 126.4, 128.0, 128.3, 128.4, 128.5, 133.4, 146.7, 150.7, 158.5.



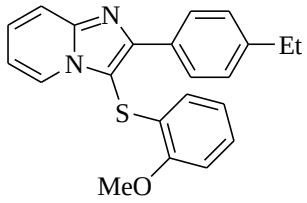

**5d**

**3-(4-Chlorophenylthio)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (8d):** Pale yellow solid, mp 161-163 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.86-6.93 (m, 3H), 7.16-7.47 (m, 6H), 7.74 (d, *J* = 9.0 Hz, 1H), 8.16-8.24 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 105.8, 113.3, 117.8, 124.3, 126.8, 126.9, 128.3, 128.5, 128.8, 129.6, 132.1, 133.1, 133.7, 147.2, 151.5.



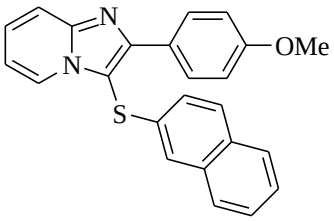

**5e**

**3-(2,5-Dimethylphenylthio)-2-(4-ethylphenyl)*H*-imidazo[1,2-*a*]pyridine (8e):** Pale yellow solid, mp 131-133 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 1.22 (t, *J* = 7.5 Hz, 3H), 1.97 (s, 3H), 2.44 (s, 3H), 2.64 (q, *J* = 7.5 Hz, 2H), 6.24 (s, 1H), 6.71-6.81 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.20-7.26 (m, 3H), 7.70 (d, *J* = 9.0 Hz, 1H), 8.12-8.14 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 15.5, 19.4, 21.1, 28.8, 105.4, 112.9, 117.5, 124.5, 124.6, 126.5, 126.6, 128.0, 128.4, 130.6, 130.9, 131.9, 133.8, 136.7, 144.8, 147.2, 151.8; HRMS (ESI) calcd for $C_{23}H_{22}KN_2S$ 397.1141; found 397.1154.




**5f**

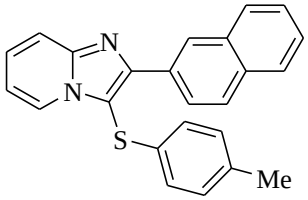
**3-(2-Methoxyphenylthio)-2-(4-ethylphenyl)*H*-imidazo[1,2-*a*]pyridine (8f):** Brown solid, mp 146-148 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 1.24 (t, *J* = 7.5 Hz, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 3.92 (s, 3H), 6.37-6.40 (m, 1H), 6.66-6.67 (m, 1H), 6.82-6.89 (m, 2H), 6.09-6.10 (m, 1H), 7.24-7.33 (m, 3H), 7.73 (d, *J* = 9.0 Hz, 1H), 8.11-8.25 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 15.4, 28.7, 55.8, 104.9, 110.8, 112.8, 117.4, 121.5, 123.3, 124.7, 125.5, 126.5, 126.8, 127.9, 128.3, 130.7, 144.7, 147.1, 151.7, 156.1.




**8g**

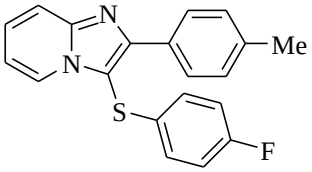
**2-(4-Methoxyphenyl)-3-(naphthalen-3-ylthio)*H*-imidazo[1,2-*a*]pyridine (8g):** Pale yellow liquid. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.79-7.84 (m, 1H), 6.94-6.97 (m, 2H), 7.14-7.18 (m, 1H), 7.29-7.40 (m, 4H), 7.55-7.58 (m, 1H), 7.68-7.77 (m, 3H), 8.18-8.28 (m, 3H). $^{13}$C NMR

(75 MHz, $CDCl_3$), δ: 55.2, 105.2, 113.1, 113.9, 117.3, 123.3, 123.8, 124.4, 125.6, 125.7, 126.7, 126.8, 126.9, 127.7, 129.2, 129.7, 131.7, 132.6, 133.8, 146.9, 151.2, 160.1.



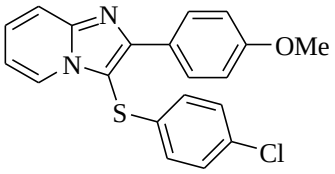

**8h**

**3-(*p*-tolylthio)-2-(naphthalen-3-yl)*H*-imidazo[1,2-*a*]pyridine (8h):** Pale yellow solid, mp 134-136 ºC. $^1$H NMR (300 MHz, $CDCl_3$), δ: 6.80-6.85 (m, 1H), 6.96-7.04 (m, 4H), 7.27-7.33 (m, 1H), 7.46-7.51 (m, 2H), 7.76-7.95 (m, 4H), 8.30-8.32 (m, 1H), 8.45-8.48 (m, 1H), 8.80-8.81 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 20.7, 107.5, 112.9, 117.4, 124.4, 125.8, 125.9, 125.95, 125.98, 126.0, 126.2, 126.5, 127.5, 127.7, 128.6, 130.1, 130.8, 131.4, 133.3, 136.0, 146.9, 150.8.




**8i**

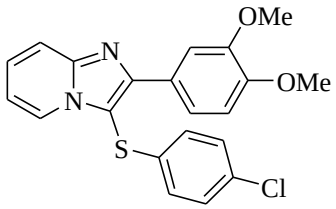
**3-(4-Fluorophenylthio)-2-*p*-tolylH-imidazo[1,2-*a*]pyridine (8i):** Pale yellow liquid. $^1$H NMR (300 MHz, $CDCl_3$), δ: 3.38 (s, 3H), 6.81-6.87 (m, 1H), 6.89-6.92 (m, 2H), 6.95-7.00 (m, 2H), 7.25-7.33 (m, 3H), 7.71 (d, *J* = 9.0 Hz, 1H), 8.13-8.15 (m, 2H), 8.23-8.26 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 21.4, 106.3, 113.1, 116.4, 116.7, 117.6, 124.3, 126.7, 127.6, 127.7, 128.2, 129.2, 130.2, 130.3, 130.4, 138.6, 147.0, 151.4, 159.9, 163.1.




**8j**

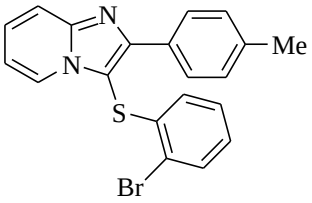
**3-(4-Chlorophenylthio)-2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridine (8j):** Pale yellow solid, mp 143-145 ºC. $^1$H NMR (300 MHz, $CDCl_3$), δ: 3.81 (s, 3H), 6.81-6.98 (m, 5H), 7.12-7.16 (m, 2H), 7.27-7.33 (m, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 8.14-8.21 (m, 3H). $^{13}$C NMR (75

MHz, $CDCl_3$), δ: 55.1, 104.6, 112.9, 113.8, 117.3, 124.1, 125.6, 126.6, 126.7, 129.4, 129.5, 131.8, 133.8, 147.0, 151.3, 160.0.



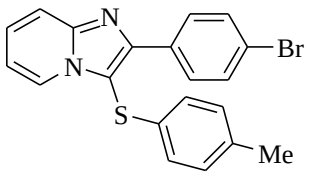

**8k**

**3-(4-Chlorophenylthio)-2-(3,4-dimethoxyphenyl)*H*-imidazo[1,2-*a*]pyridine (8k):** Pale yellow solid, mp 156-158 °C. $^1$H NMR (300 MHz, $CDCl_3$), δ: 3.89 (s, 3H), 3.90 (s, 3H), 6.85-6.94 (m, 4H), 7.15-7.18 (m, 2H), 7.28-7.36 (m, 1H), 7.70-7.82 (m, 3H), 8.24-8.26 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 55.8, 104.9, 111.0, 111.4, 113.0, 117.4, 120.9, 124.1, 125.9, 126.6, 126.7, 129.5, 132.0, 133.9, 147.0, 148.8, 149.6, 151.3.




**8l**

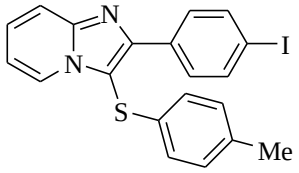
**3-(2-Bromophenylthio)-2-*p*-tolylH-imidazo[1,2-*a*]pyridine (8l):** White solid, mp 159-161 °C. $^1$H NMR (300 MHz, $CDCl_3$), δ: 2.34 (s, 3H), 6.33-6.36 (m, 1H), 6.80-6.83 (m, 1H), 6.93-6.96 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.27-7.32 (m, 1H), 7.51-7.54 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 6.9 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 21.4, 105.0, 113.2, 117.6, 120.4, 124.4, 125.6, 126.9, 127.0, 128.2, 129.2, 130.2, 133.3, 136.4, 138.7, 147.4, 152.1.




**8m**

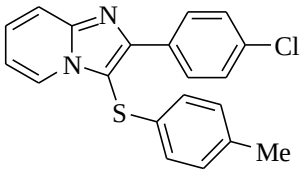
**3-(*p*-tolylthio)-2-(4-bromophenyl)*H*-imidazo[1,2-*a*]pyridine (8m):** White solid, mp 147-149 °C. $^1$H NMR (300 MHz, $CDCl_3$), δ: 2.24 (s, 3H), 6.82-6.89 (m, 3H), 6.99-7.01 (m, 2H), 7.25-7.34 (m, 1H), 7.53-7.56 (m, 2H), 7.70 (d, *J* = 9.0 Hz, 1H), 8.10-8.15 (m, 2H), 8.26 (d, *J*

= 6.9 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 20.8, 107.1, 113.1, 117.5, 122.8, 124.4, 125.8, 126.8, 129.8, 130.2, 131.0, 131.5, 132.3, 136.2, 146.9, 149.7.



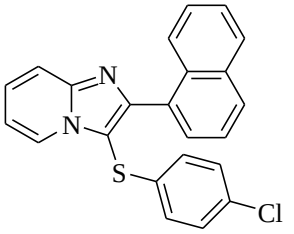

**8n**

**3-(*p*-tolylthio)-2-(4-iodophenyl)*H*-imidazo[1,2-*a*]pyridine (8n):** Pale yellow solid, mp 134-136 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 2.24 (s, 3H), 6.82-6.89 (m, 3H), 6.99-7.02 (m, 2H), 7.25-7.34 (m, 1H), 7.69-7.76 (m, 3H), 7.97-8.00 (m, 2H), 8.24-8.27 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 20.8, 94.8, 107.2, 113.2, 117.5, 124.4, 125.8, 126.8, 129.9, 130.2, 131.0, 132.8, 136.2, 137.5, 146.8, 149.7.




**8o**

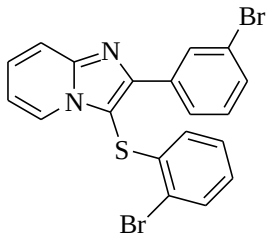
**3-(*p*-tolylthio)-2-(4-chlorophenyl)*H*-imidazo[1,2-*a*]pyridine (8o):** Pale yellow solid, mp 133-135 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 2.25 (s, 3H), 6.84-6.90 (m, 3H), 7.01 (d, $J$ = 8.1 Hz, 2H), 7.30-7.41 (m, 3H), 7.70-7.74 (m, 1H), 8.18-8.20 (m, 2H), 8.26-8.29 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 20.8, 107.1, 113.2, 117.5, 124.5, 125.8, 126.9, 128.6, 129.5, 130.2, 131.0, 131.7, 134.5, 136.2, 146.8, 149.6.




**8p**

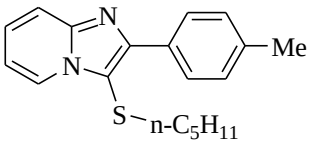
**3-(4-Chlorothio)-2-(naphthalen-1-yl)*H*-imidazo[1,2-*a*]pyridine (8p):** White solid, mp 208-210 $^{o}$C. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.82-6.95 (m, 3H), 7.10-7.14 (m, 2H), 7.36-7.60 (m, 5H), 7.80-7.92 (m, 3H), 8.17-8.17 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 108.7, 113.4,

117.9, 124.5, 124.9, 125.8, 126.1, 126.4, 126.8, 127.1, 128.2, 128.7, 129.2, 129.4, 130.4, 131.9, 132.2, 133.7, 133.8, 147.0, 152.7.




**8q**

**3-(2-Bromophenylthio)-2-(2-bromophenyl)*H*-imidazo[1,2-*a*]pyridine (8q):** White solid, mp 185-187 ºC. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 6.31-6.34 (m, 1H), 6.85-6.99 (m, 3H), 7.23-7.56 (m, 4H), 7.74 (d, *J* = 9.0 Hz, 1H), 8.09-8.20 (m, 2H), 8.36-8.37 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 106.1, 113.5, 117.7, 120.5, 122.6, 124.4, 125.5, 126.6, 127.1, 127.2, 128.1, 129.8, 131.1, 131.5, 133.3, 135.0, 135.8, 147.2, 150.0.




**8r**

**3-(Pentylthio)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine (8r):** Pale yellow liquid. $^{1}$H NMR (300 MHz, $CDCl_3$), δ: 0.77 (t, *J* = 6.9 Hz, 3H), 1.10-1.28 (m, 4H), 1.42 (qnt, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 6.9 Hz, 1H), 7.22-7.29 (m, 3H), 7.65 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 2H), 8.46-8.49 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$), δ: 13.7, 21.2, 22.0, 29.0, 30.6, 35.6, 109.9, 112.4, 117.3, 124.2, 125.7, 128.1, 128.9, 130.9, 137.9, 146.1, 149.4; HRMS (ESI) calcd for $C_{19}H_{22}KN_2S$ 349.1141; found 349.1136.

## II.F. References:

References for chapter II are given in Bibliography section (page 134–138).