Chapter 3

Iodine-mediated Synthesis of 2-Carbonylimidazo[1,2-*a*]pyridines *via* Intramolecular Cyclization of *N*-Propargyl Pyridinium Salts

3.1 INTRODUCTION

Imidazo[1,2-*a*]pyridine, 10π e^- containing a bicyclic hetero-aromatic compound is a fused heterocycle which is the combination of an electron-deficient pyridine and imidazole by overlapping of two C-N bonds from each ring. These structural motifs have been recognized as a privileged scaffold due to the existence in several natural products and pharmacologically relevant structures with a wide range of biological activities. The importance of these scaffolds is evident by its presence as core structure in commercially available drugs such as Zolimidine (treatment of peptic ulcers), Zolpidem (treatment of insomnia and certain brain disorders), Olprinone (cardiotonic agent), Alpidem, Necopidem and Saripidem (anxiolytics), Olprinone (cardiotonic agent), Miroprofen (analgesic) ans Minodronic acid (treatment of osteoporosis) (**Figure 3.1**).[1] Apart from biological significance, imidazo[1,2-*a*]pyridine exhibits profound applications in the field of material science,[2] optoelectronics[3] and agrochemistry.[4]

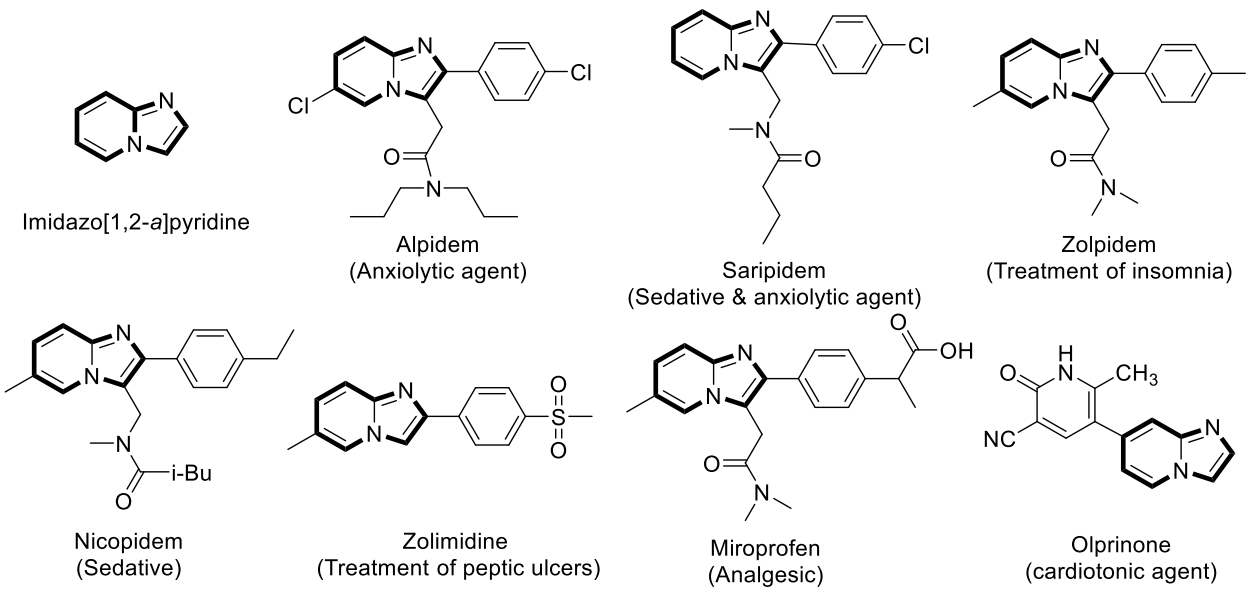
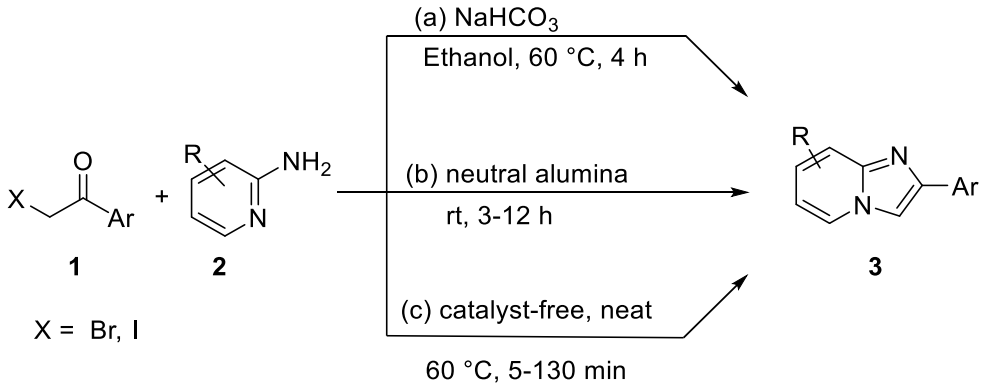


Figure 3.1 Representative structure of marketed drugs having imidazo[1,2-*a*]pyridine

During the last decade, much research effort has been devoted to methodology development for the construction and functionalization of the imidazo[1,2-*a*]pyridines.[5-6] Developing strategies for the synthesis of imidazo[1,2-*a*]pyridine derivatives through transition-metal catalysis remained as one of the central topics in modern organic chemistry. However, transition metal-free approaches have always been an attractive conceptual alternative in organic transformation.

3.1.1 Transition Metal-free Synthesis of Imidazo[1,2-*a*]pyridines

The conventional method to access imidazo[1,2-*a*]pyridine (**3**) scaffolds are the base-mediated condensation of *α*-haloketones (**1**) with 2-aminopyridines (**2**) (**Scheme 3.1**(**a**)).[7] Over the years, new advances have been made to improve the synthesis of **3** by using newer techniques. Sahu *et al.* redefined the traditional synthesis by using alumina as a solid surface to construct imidazo[1,2-*a*]pyridines (**3**) at room temperature (**Scheme 3.1**(**b**)).[8] A few interesting reports were evolved as a clean method deprived of a catalyst and a solvent for the synthesis of imidazo[1,2-*a*]pyridine (**Scheme 3.1**(**c**)).[9-10]



Scheme 3.1 Imidazo[1,2-*a*]pyridine derivatives from *α*–haloketones

The transition metal-free reactions have been subdivided into two types of approaches which depends upon the nature of the starting materials used.

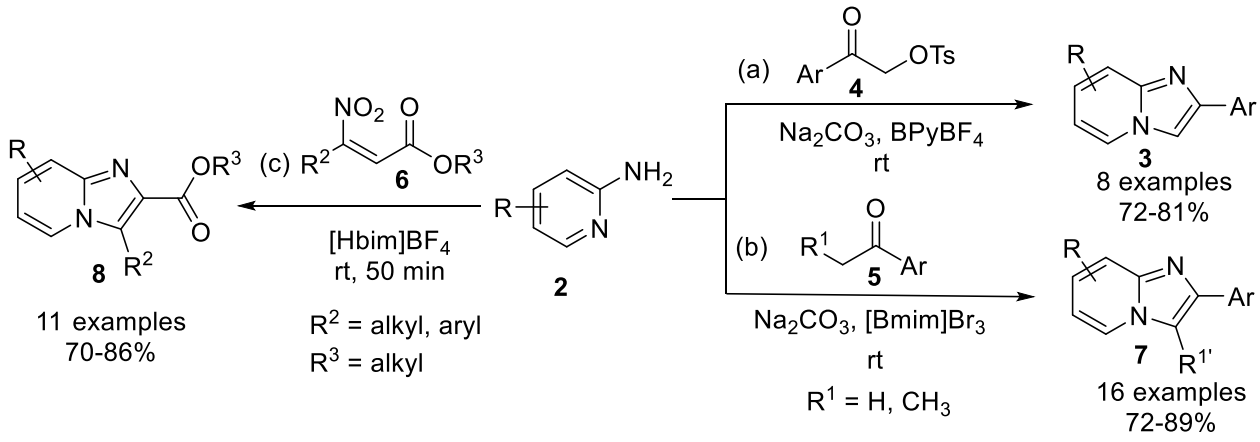
3.1.1.1 Intermolecular Cyclization Reaction: When two or more starting materials are reacted to obtain product molecule under different reaction conditions. In this type of reaction, the one molecule is obtained at the expense of two molecules, thus these are entropically disfavored.

3.1.1.2 Intramolecular Cyclization Reaction: When a single multi-functionalized starting material is used under various reaction condition to obtain the desired molecule. These types of reactions are entropically favored than the previous type.

3.1.1.1 Intermolecular Cyclization Reactions

Chen *et al.* reported the condensation of 2-aminopyridine (**2**) and α-tosyloxyacetophenone (**4**) using the ionic liquid *n*-butylpyridinium tetrafluoroborate ($BPyBF_4$) as a greener solvent. The rate

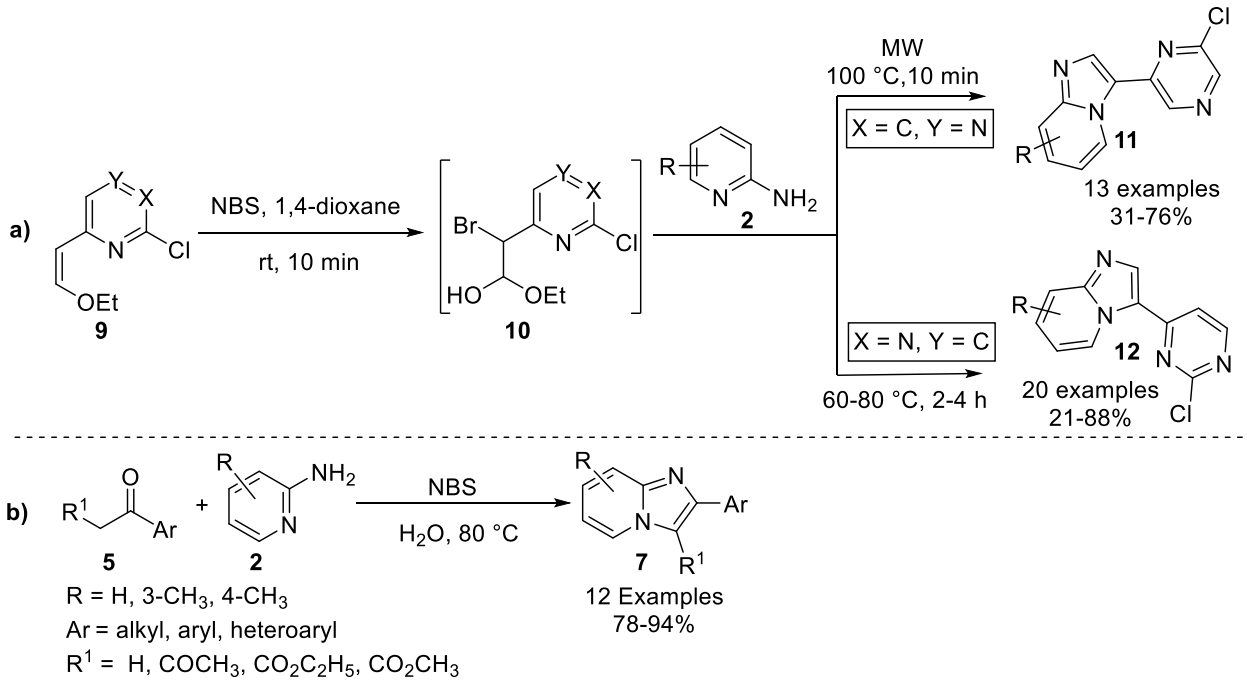
enhancement, improved yields of products and recyclability of the solvent were salient features of the method (**Scheme 3.2a**).[11] Zhang and co-workers synthesized 2,3-disubstituted imidazo[1,2-*a*]pyridine (**7**) using base-mediated condensation reaction of aryl ketones (**5**) and 2-aminopyridine (**2**) in presence of [Bmim]Br_3. It was believed that [Bmim]Br_3 played a dual role as solvent as well as a reagent which assisted in *in situ* activations of aryl ketones. The devoid of toxic solvent or catalyst, lachrymatory phenacyl bromides, and a high yield of products under environmentally benign conditions were noted advantages of the protocol (**Scheme 3.2b**).[12] Meshram *et al.* disclosed a useful method for the synthesis of 2-carboxylated imidazo[1,2-*a*]pyridines (**8**) by the reaction of 2-aminopyridines (**2**) and *β*−nitro acrylates (**7**) in the ionic liquid, [Hbim]BF_4 at room temperature. The catalyst and solvent-free approach along with excellent yields of imidazo[1,2-*a*]pyridines were the advantages of the procedure (**Scheme 3.2c**).[13] Baltork and co-workers developed an efficient method for synthesis of imidazo[1,2-*a*]pyridines (**3**) from the reaction of 2-aminopyridine (**2**) and phenacyl bromide (**1**) using ionic liquid-supported nano-silica as an efficient and reusable catalyst.[14] Our group has reported solvent and base-free synthesis of imidazo[1,2-*a*]pyridines (**3**) *via* ionic liquid phase synthesis utilizing ionic liquid-supported acetophenone and 2-aminopyridine (**2**) under a heating condition. The ionic liquid-supported acetophenone was synthesised by using the reaction of acetophenone and ionic liquid-supported hypervalent iodine in acetonitrile. The method was also extended to synthesize 2-aminothiazoles.[15]



Scheme 3.2 Imidazo[1,2-*a*]pyridine from 2-aminopyridines

Ducray and co-workers reported the preparation of 3-(2-chloropyrimidin-4-yl)imidazo[1,2-*a*]pyridines (**11**) *via N*-bromosuccinimide (NBS)-promoted reaction of 2-aminopyridines (**2**) and

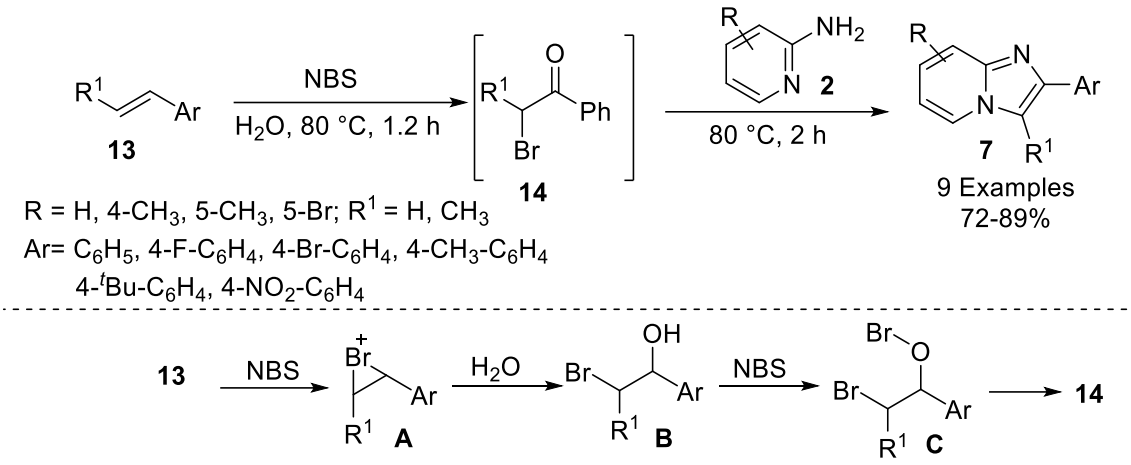
vinyl ether of 2-chloropyrimidines (**9**) which were synthesized through phosphine-free Heck reaction. The protocol was also utilized for the synthesis of pyrazolo[1,5-*a*]pyridines.[16] The similar synthetic concept was applied by Collins *et al.* to synthesize 3-pyrazinylimidazo[1,2-*a*]pyridines starting from pyrazine analogues by performing the reaction under microwave irradiation (**Scheme 3.3a**).[17] Telvekar *et al.* reported the metal-free approach to synthesize 2,3-disubstituted imidazo[1,2-*a*]pyridines (**7**) from the condensation of 2-aminopyridines (**2**) with activated ketones (**5**) in presence of TBHP using water as a solvent. The key step in the reaction involved the generation of *in situ* α-brominated intermediates of ketones which in turn reacted with 2-aminopyridine to give pyridinium ylide which subsequently cyclized and aromatized to corresponding imidazo[1,2-*a*]pyridine. The method was also extended towards the synthesis of imidazo[1,2-*a*]pyrimidines and imidazo[2,1-*b*]thiazole. The high yields of products, aqueous reaction condition, and operational simplicity were the merits of the method (**Scheme 3.3b**).[18]



Scheme 3.3 *N*-bromosuccinimide (NBS)-promoted synthesis of imidazo[1,2-*a*]pyridines

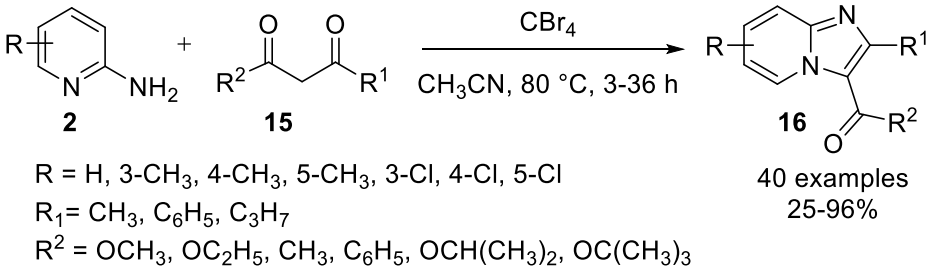
Kshirsagar and co-workers demonstrated the one-pot, two-step reaction using styrene (**13**) as one of the precursors in the synthesis of imidazo[1,2-*a*]pyridines (**7**) *via* NBS-promoted aqueous phase reaction. The reaction proceeded by the NBS/H_2O-mediated formation of bromohydrin (**B**) followed by NBS-promoted oxidation of a secondary benzylic alcohol for the *in situ* formation of

phenacyl bromide (**14**). Finally, the condensation of **14** with 2-aminopyridine (**2**) delivered the desired product imidazo[1,2-*a*]pyridine. The dual role played by NBS as oxidant and bromine source and aqueous phase reaction were highlights of the method (**Scheme 3.4**).[19]



Scheme 3.4 Imidazo[1,2-*a*]pyridines from styrene

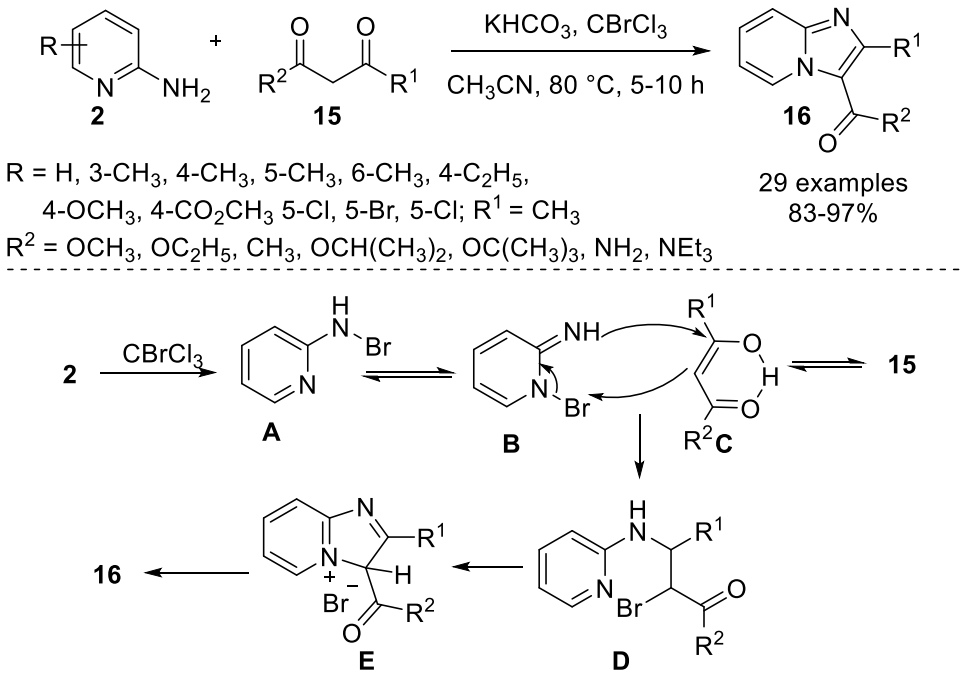
Huo *et al.* reported the synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates (**16**) *via* carbon tetrabromide-mediated oxidative C–N bond formation of 2-aminopyridines (**2**) with β-keto esters or 1,3 diones (**15**). The CBr_4-promoted bromination of **15** followed by nucleophilic substitution with 2-aminopyridines (**2**) furnished the **16**. The method was also applied to access imidazo[1,2-*a*]pyrimidines from the reaction of 2-aminopyrimidines with corresponding β-keto esters or 1,3-diones (**Scheme 3.5**).[20]



Scheme 3.5 CBr_4-promoted synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates (**16**)

Jaenicke and Chuah group also developed a distinctive method for synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates derivatives (**16**) using condensation reaction of 2-aminopyridines (**2**) with 1,3-diketones (**15**) in presence of $CBrCl_3$ and 2-aminopyridine (**2**) system. The uniqueness of

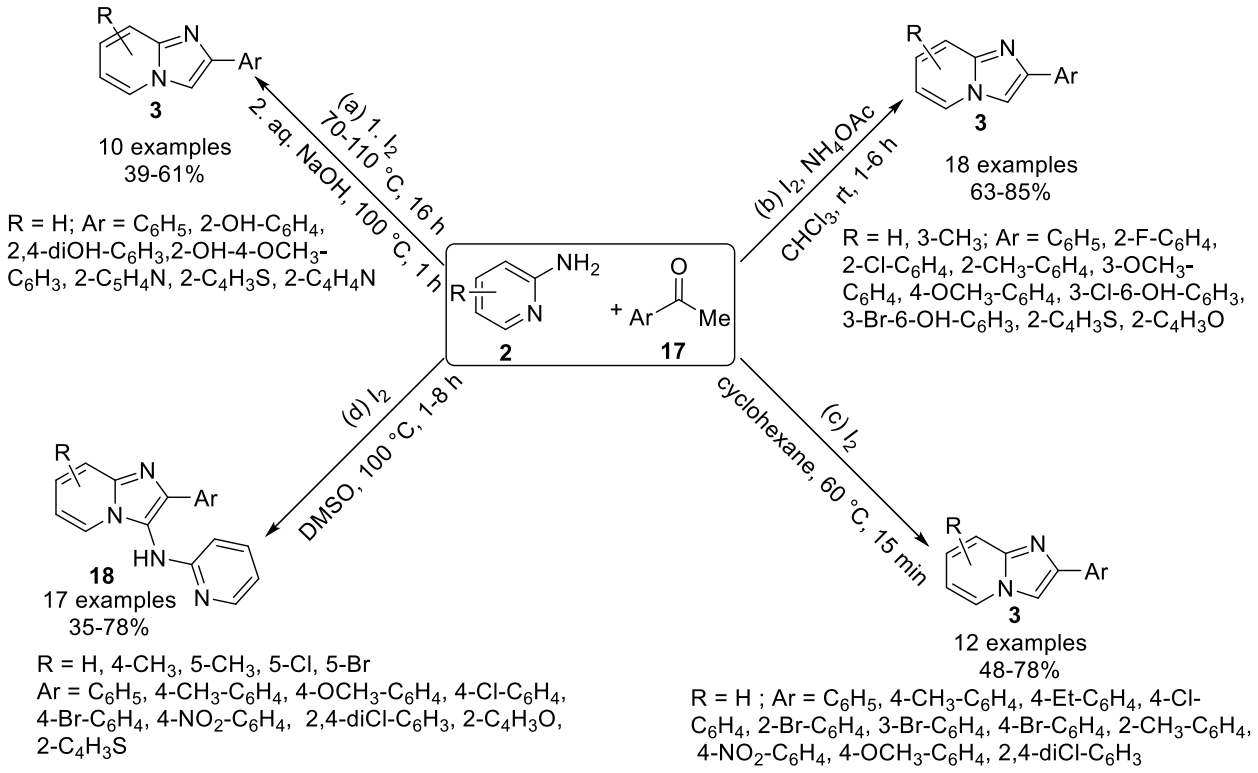
the method was the use of 2-aminopyridine (**2**) as a substrate as well as a shuttle for bromine transfer from $CBrCl_3$ to the α-carbon of the 1,3-dicarbonyl (**15**) compounds. The reaction proceeded with initial formation of *N*-bromopyridin-2-amine (**A**) by the radical reaction of **2** and $CBrCl_3$ which simultaneously underwent addition reaction with 1,3-diketone (**14**) to produce a bromo-hemiaminal intermediate (**D**). The dehydration of **D** followed by intramolecular cyclization produced the final product **16** (**Scheme 3.6**).[21]



Scheme 3.6 Imidazo[1,2-*a*]pyridine-3-carboxylates (**16**) from 2-aminopyridine (**2**) as a bromine shuttle

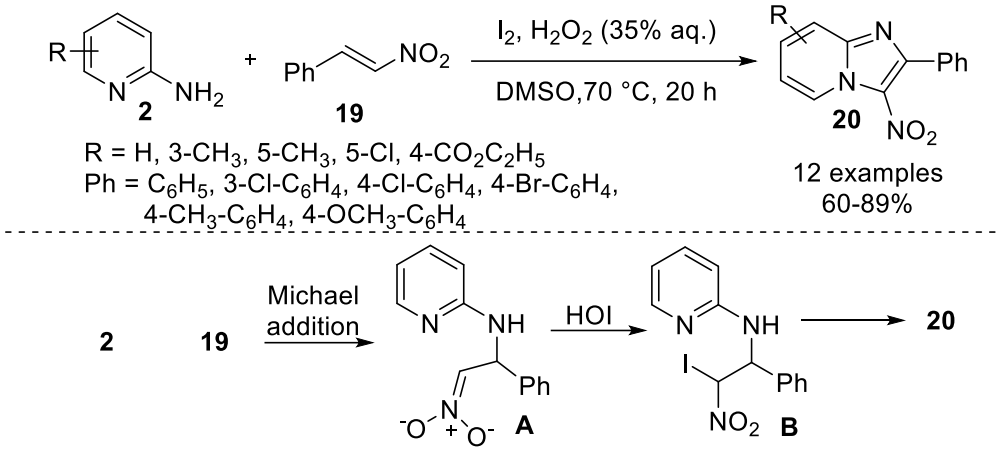
Stasyuk *et al.* described the Ortoleva–King-type reaction to deliver 2-arylimidazo[1,2-*a*]pyridine (**3**) from aryl methyl ketones (**17**) and 2-aminopyridines (**2**) using iodine. The reaction proceeded *via* formation of α-iodo ketone which reacted with pyridine to furnish pyridinium salt followed by base-mediated intramolecular ring-closure to deliver the final product. The various functional groups such as OH, $N(CH_3)_2$, Br and OCH_3 were compatible with the method. The products containing a 2-(2-hydroxyphenyl) substituent showed excited-state intramolecular proton transfer (ESIPT) in nonpolar and polar-aprotic solvents (**Scheme 3.7(a)**).[22] Kapoor and co-workers reported the condensation reaction of 2-aminopyridine (**2**) and aryl methyl ketones (**17**) in iodine/ammonium acetate system to access 2-aryimidazo[1,2-*a*]pyridine (**3**). While iodine helped

in generating *in situ* α-iodo ketone, ammonium acetate was scavenger for hydrogen iodide released in reaction (**Scheme 3.7**(**b**)).[23] Very recently, Das and group described the iodine-catalyzed synthesis of 2-arylimidazo[1,2-*a*]pyridine (**3**) in cyclohexane (**Scheme 3.72**(**c**)).[24] Wu *et al.* reported the synthesis of 2-aryl-3-(2-pyridylamino)imidazo[1,2-*a*]pyridines (**18**) by iodine-promoted reaction of aryl methyl ketones (**17**) and 2-aminopyridines (**2**). The method allowed the synthesis of 3-[(heteroaryl)amino]imidazo[1,2-*a*]pyridine distinctively without using metal, base, or ligand (**Scheme 3.7**(**d**)).[25]



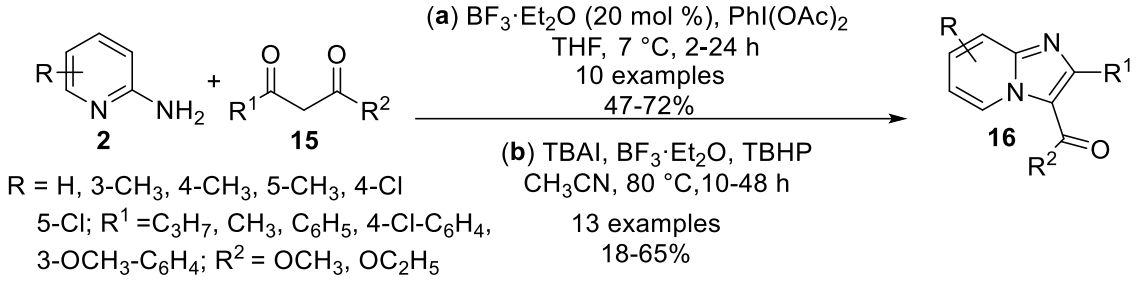
Scheme 3.7 Iodine-promoted reaction of ketones and 2-aminopyridine

Itoh and co-workers enabled an access to 2-nitro-2-alkylimidazo[1,2-*a*]pyridines (**20**) by the reaction of nitroolefines (**19**) and 2-aminopyridines (**2**) in the presence of a catalytic amount of iodine and hydrogen peroxide. It was proposed that Michael addition of 2-aminopyridine (**2**) and nitroalkene (**19**) gave adduct (**A**) which on iodination afforded **B**. Subsequently, intramolecular nucleophilic substitution and oxidation produced **20** (**Scheme 3.8**).[26]



Scheme 3.8 Imidazo[1,2-*a*]pyridine from condensation of nitroolefin (**19**) and 2-aminopyridines

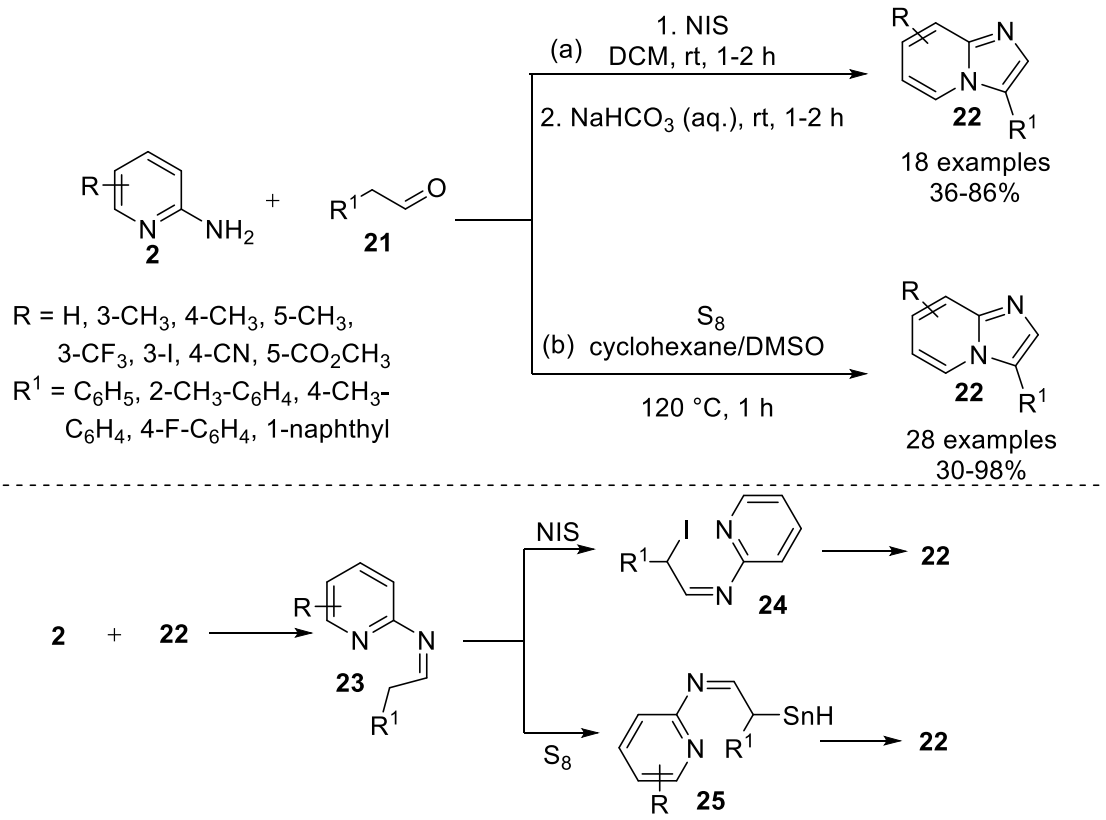
Imidazo[1,2-*a*]pyridine-3-carboxylates (**16**) have been prepared by iodine reagents such as (diacetoxyiodo)benzene (PIDA) as well as tertiary butyl iodide (TBAI)-mediated oxidative coupling between 2-aminopyridines (**2**) and 1,3-dicarbonyl (**15**) compounds respectively. Yu and co-workers reported that the reaction of 1,3-dicarbonyls (**15**) with $PhI(OAc)_2$ generated an intermediate which on reaction with pyridinium endocyclic nitrogen followed by intramolecular condensation and subsequent aromatization yielded the desired imidazo[1,2-*a*]pyridines (**16**) (**Scheme 3.9** (**a**)).[27] Later, the group disclosed synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates (**16**) using TBAI as an iodine catalyst in combination with TBHP as terminal oxidant. It was assumed that the TBHP oxidized TBAI to active hyper-valent iodine reagent which interacted with the *β*-keto esters (**15**) in same modus as in previous report (**Scheme 3.9** (**b**)).[28]



Scheme 3.9 Synthesis of imidazo[1,2-*a*]pyridine-3-carboxylates

Park *et al.* explored *N*-iodosuccinimide (NIS)-mediated one-pot, two-step method for synthesis of 3-alkylated imidazo[1,2-*a*]pyridine (**22**) by reaction of 2-aminopyridine (**2**) and 2-arylacetaldehydes (**21**). It was proposed that the simple mixing of 2-aminopyridine (**2**), 2-

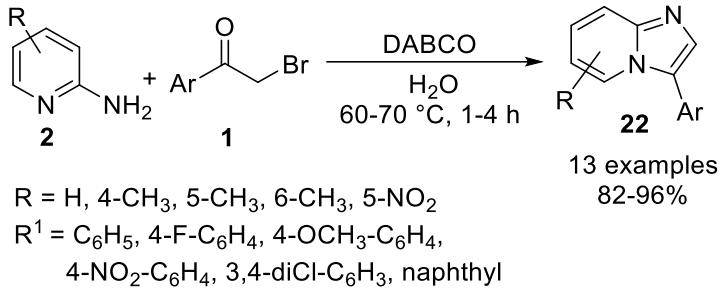
phenylacetaldehyde (**21**) in presence of NIS produced iodo-hemiaminal intermediate (**24**) which readily cyclized by treatment with a saturated aqueous solution of $NaHCO_3$. The transition metal-free method provided the desired products rapidly from readily available starting materials (**Scheme 3.10** (**a**)).[29] Recently, the research group of Deng and Huang revealed elemental sulfur (S_8)-mediated oxidative annulation of 2-aminopyridines and aldehydes in an effort to synthesize 3-alkylated imidazo[1,2-*a*]pyridine (**22**) under metal and base-free approach. The oxidative process was expected to proceed *via* formation of enamine intermediate (**23**) which subsequently converted to poly-sulfur intermediate (**25**) from interaction with elemental sulfur through Willgerodt–Kindler type oxidation. Finally, intramolecular cyclization followed by deprotonation furnished the desired product (**Scheme 3.10** (**b**)).[30]



Scheme 3.10 (**a**) *N*-iodosuccinimide (NIS)-mediated synthesis of 3-arylimidazo[1,2-*a*]pyridine; (**b**) Sulfur-promoted synthesis of 3-aryl/alkylimidazo[1,2-*a*]pyridine

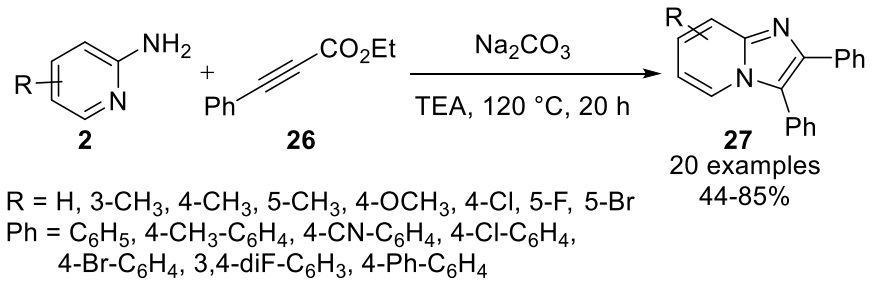
To assemble imidazo[1,2-*a*]pyridine in atom economic and environmental benign process, the base-mediated reaction of readily available starting materials is interesting protocol. Meshram and

co-workers accessed 3-arylimidazo[1,2-*a*]pyridines (**22**) by the 1,4-diazabicyclo[2.2.2]octane (DABCO)-mediated condensation reaction of phenacyl halides (**1**) and 2-aminopyridines (**2**). This was one of the first example demonstrating the base-mediated synthesis of 3-arylimidazo[1,2-*a*]pyridines (**22**) instead of their 2-aryl counterparts (**3**) (**Scheme 3.11**).[31]



Scheme 3.11 DABCO-promoted synthesis of 3-arylimidazo[1,2-*a*]pyridine

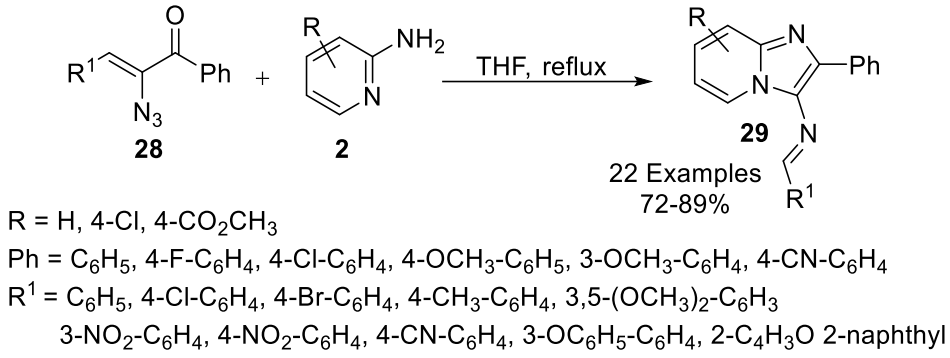
Chen and Wang group delivered 2,3-diphenyl imidazo[1,2-*a*]pyridine (**27**) from base-mediated intermolecular cyclization of 2-aminopyridines (**2**) with alkynes (**26**). It was proposed that the Michael addition of two molecules of alkynes with 2-aminopyridine formed an intermediate which underwent [2+2] cycloaddition reaction followed by ring opening to furnish 2,3-diphenylimidazo[1,2-*a*]pyridine (**27**) (**Scheme 3.12**). The highlight of the protocol was the cleavage of a C–C bond and the formation of a new C(sp^2) – C(sp^2) bond under transition metal-free conditions.[32]



Scheme 3.12 Synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridine

Maurya and co-workers devised a novel strategy for the synthesis of 3-imine substituted imidazo[1,2-*a*]pyridines (**29**) *via* efficient catalyst/metal-free unprecedented annulations of α-keto vinyl azides (**28**) and 2-aminopyridines (**2**) (**Scheme 3.13**). The reaction involved tandem formation of three new C–N bonds with the release of H_2O and N_2 as the only side-products

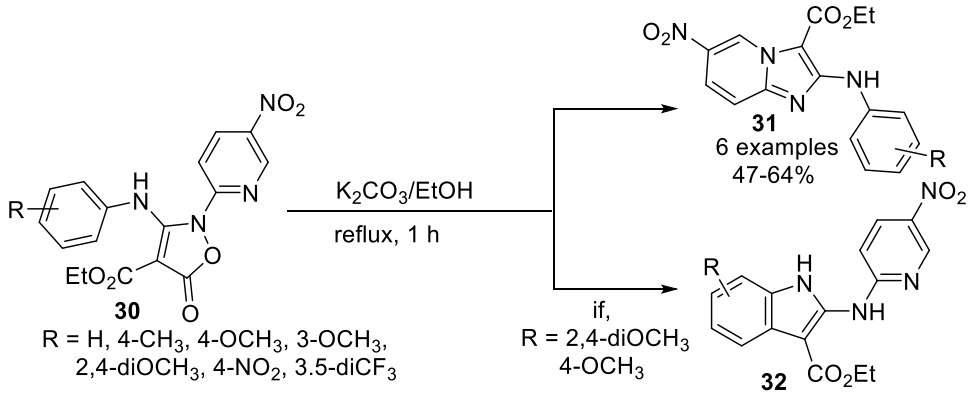
through condensation, cyclization, and ring opening reaction. The advantage of the reaction was being atom-economical with omission of column chromatography procedure and high purity of the desired products.[33]



Scheme 3.13 Synthesis of 3-imine substituted imidazo[1,2-*a*]pyridines

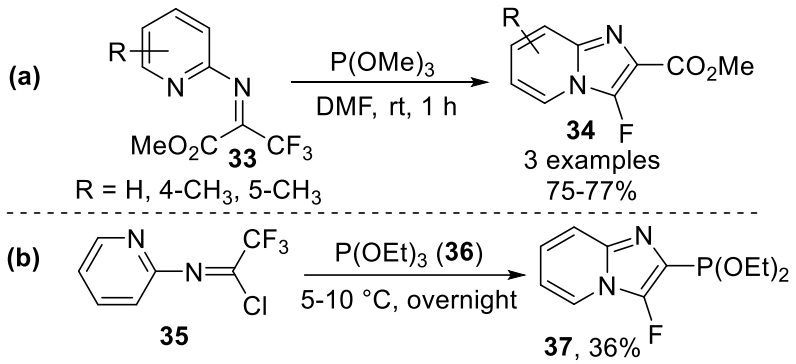
3.1.1.2 Intramolecular Cyclization Reactions

Prager and co-workers disclosed K_2CO_3-promoted ring opening rearrangement reaction of 2-aryl-3-arylaminoisoxazol-5(2*H*)-ones (**30**) to imidazo[1,2-*a*]pyridines (**31**) along with indole (**32**) as a side product. The outcome of cyclization was highly influenced by the substituents on aryl ring. For example, the aryl ring substituted with electron rich group like 4-methoxy and 2,4- dimethoxy yielded indole derivative in high yields (**Scheme 3.14**).[34] In the same year, Khalafy *et al.* also reported the triethylamine catalyzed rearrangement of 2-(5-nitropyrid-2-yl)-3-(4-aryl)aminoisoxazol-5(2*H*)-ones for the production of imidazo[1,2-*a*]pyridine and indoles.[35]



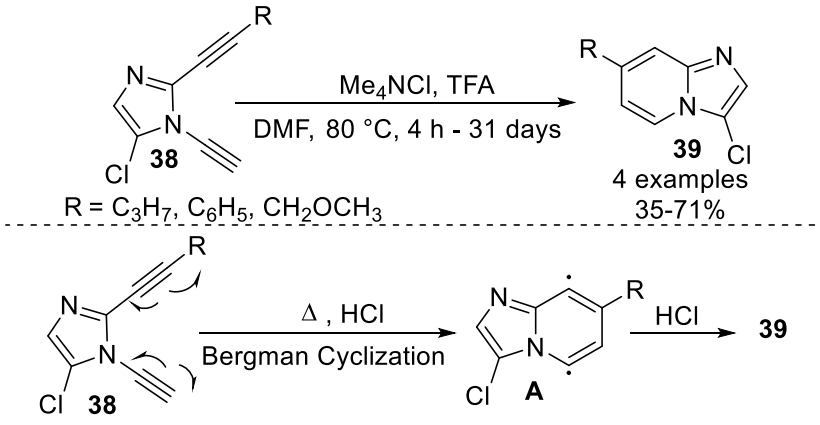
Scheme 3.14 Base-mediated rearrangement of 2-aryl-3-arylaminoisoxazol-5(2*H*)-ones

Sokolov *et al.* reported reaction of methyl (E)-3,3,3-trifluoro-2-(pyridin-2-ylimino)propanoate (**33**) with trimethylphosphite to synthesize methyl 3-fluoro imidazo[1,2-*a*]pyridine-2-carboxylates (**34**) through defluorination of trifluoromethyl group and intramolecular ring closure (**Scheme 3.15(a)**).[36] Later, Aksinenko *et al.* synthesized one example of 3-fluoro-2-(diethoxyphosphoryl)imidazo[1,2-*a*]pyridine (**37**) through a one-pot reaction of *N*-(pyridin-2-yl)-2,2,2-trifluoroacetimidoyl chloride (**35**) with triethylphosphite (**36**) (**Scheme 3.15 (b)**).[37]



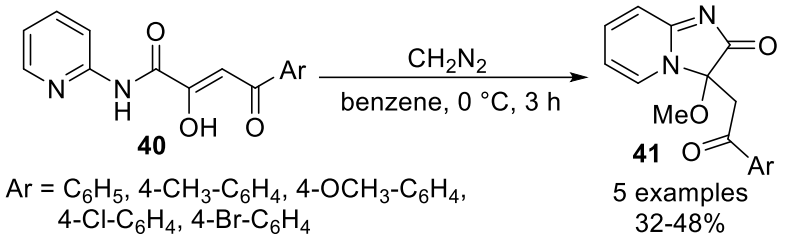
Scheme 3.15 Trialkylphosphite-promoted synthesis of imidazo[1,2-*a*]pyridine

Kerwin and Nadipuram revealed the intramolecular cascade thermal cyclization of dialkynylimidazoles (**38**) in the presence of chlorinated solvents in an effort to synthesize imidazo[1,2-*a*]pyridines (**39**). It was proposed that the interaction of Me_4NCl and TFA produced *in situ* HCl which allowed the aza-Bergman type cyclisation of **38** leading to the formation of diradical intermediate (**A**). Finally, the protonation of (**A**) furnished desired product **39** (**Scheme 3.16**).[38]



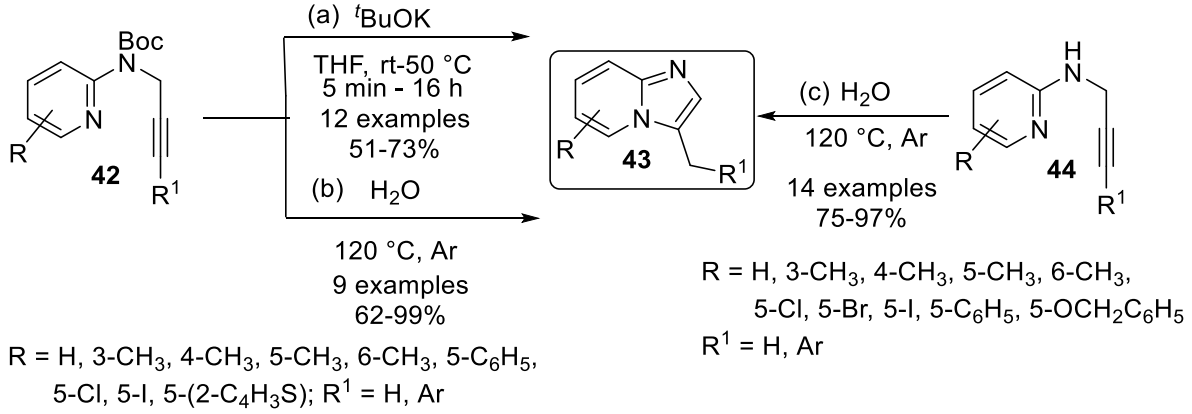
Scheme 3.16 Synthesis of imidazo[1,2-*a*]pyridines *via* aza-Bergman cyclization

An interesting report published by Zalesov and co-workers documented the synthesis of imidazo[1,2-*a*]pyridine analogues (**41**) through the intramolecular cyclisation reaction of *N*-(2-pyridyl)-amides of *Z*-4-aryl-2-hydroxy-4-oxobut-2-enoic acids (**40)** with diazomethane (**Scheme 3.17**).[39]



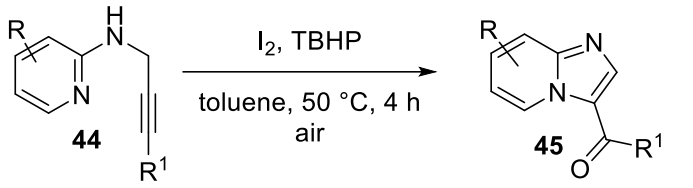
Scheme 3.17 Diazomethane-mediated intramolecular cyclisation reaction of *N*-(2-pyridyl)-amide

Savic and co-workers described the conversion of Boc-protected *N*-propargyl-2-aminopyridines (**42**) to 3-alkylimidazo[1,2-*a*]pyridines (**43**) by base-promoted intramolecular cyclisation. The reaction proceeded through intramolecular hydroamination pathway (**Scheme 3.18a**).[40] Later Adimurthy *et al.* improved the same reaction by performing water-promoted intramolecular hydroamination of (**42**) to obtain higher yields of 3-alkyl/benzylimidazo[1,2-*a*]pyridines (**43**). The reaction of the substrates with electron releasing groups on pyridine ring yielded a pure product which does not require column chromatography purification (**Scheme 3.18b**).[41] The group also explored the intramolecular hydroamination reaction of unprotected *N*-propargyl-2-aminopyridines (**44**) promoted by water. The substrates with electron-releasing groups on pyridine ring delivered almost quantitative yields of the corresponding (**43**) (**Scheme 3.18c**).[42]



Scheme 3.18 Intramolecular hydroamination approach for 3-alkylimidazo[1,2-*a*]pyridines

Recently, Huang and He group synthesized 3-acylated imidazo[1,2-*a*]pyridines (**45**) using iodine-catalysed intramolecular dehydrogenative amino-oxygenation of *N*-propargyl-2-aminopyridines (**44**) in presence of TBHP as an oxidant. The method was also applied to synthesize 4 examples of acylated indolizines using ethyl-2-(pyridin-2-yl)pent-4-ynoate derivatives as substrate. The significant features of the protocol were the use of iodine as catalyst and TBHP as an oxidant leading to the construction of diverse examples of acylated imidazo[1,2-*a*]pyridine and indolizines in good to excellent yields (**Scheme 3.19**). [43]



R = H, 4-CH_3, 5-CH_3, 4-OCH_3, 5-Br, 4-CO_2CH_3
R^1 = CH_3, 3-C_5H_4N, C_6H_5, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 4-C_6H_5-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 3,5-diCH_3-C_6H_3

Scheme 3.19 Synthesis of 3-acylated imidazo[1,2-*a*]pyridine *via* intramolecular aminooxygenation reaction

3.1.2 Formylation of Imidazo[1,2-*a*]pyridine

As evident from **Figure 3.2**, the biological activities of imidazo[1,2-*a*]pyridine chiefly reliant on the functionality at C-3 and C-2 positions. In this regard, the C-3 functionalization of imidazo[1,2-*a*]pyridines has gained wide interest [44-48] however there is dearth in the exploration of C-2 functionalization of imidazo[1,2-*a*]pyridines.[49] Among numerous functional group incorporation, the formylation of imidazo[1,2-*a*]pyridines has gained meticulous interest due to their important application in further functionalization and construction of numerous drug related molecules.

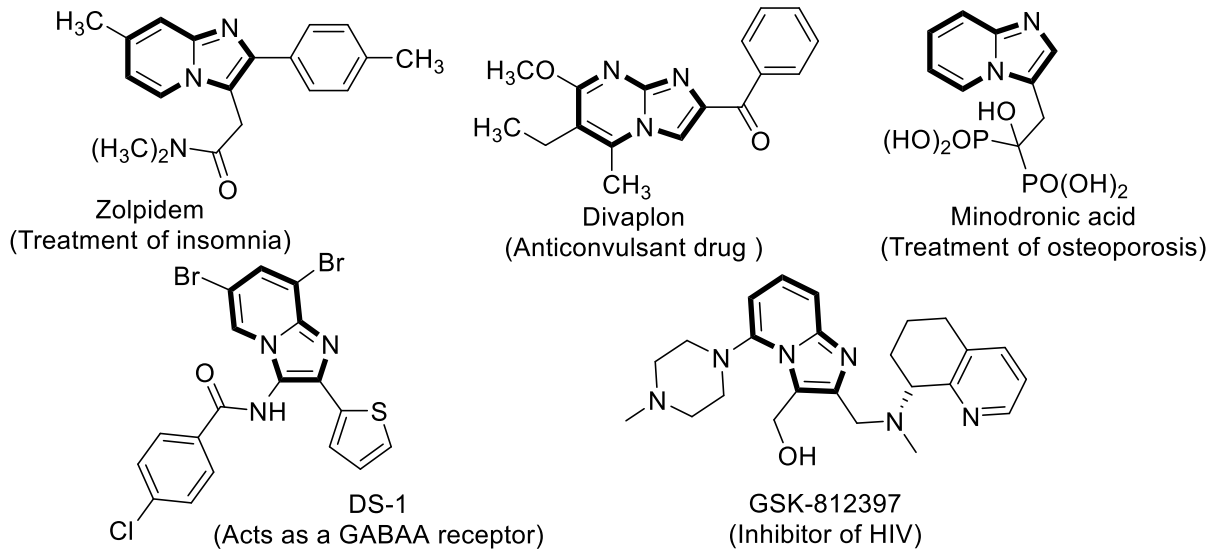
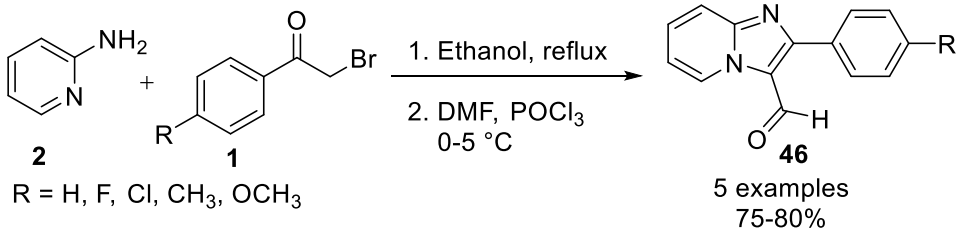


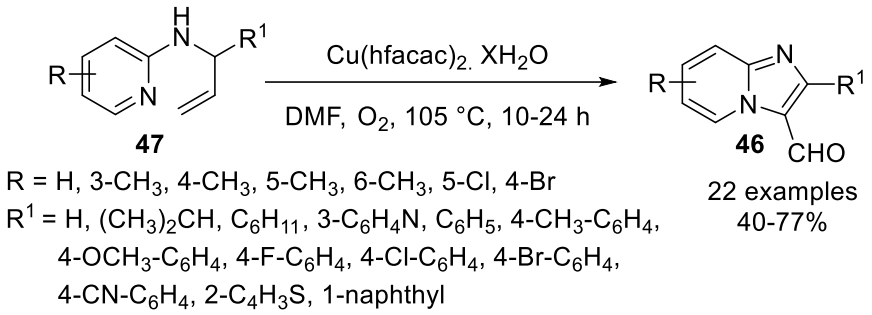
Figure 3.2 C-2 and C-3 functionalized medicinally important imidazo[1,2-*a*]pyridines

Vilsmeier–Haack formylation is a traditional method for the introduction of formyl functional group in heterocycles[50] and recently Kamal and group utilized this traditional method to report two step procedure for C-3 formylation of imidazo[1,2-*a*]pyridine by condensation reaction of 2-aminopyridine (**2**) with phenacyl bromide derivatives (**1**) followed by Vilsmeier–Haack formylation. The formylated products (**46**) were further utilized to synthesize complex heterocyclic molecules (**Scheme 3.20**).[51]



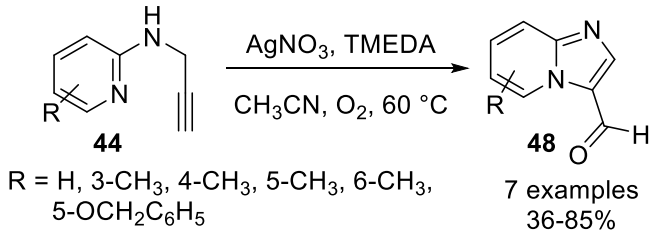
Scheme 3.20 Vilsmeier–Haack formylation of imidazo[1,2-*a*]pyridine

The traditional formylation reaction required harsh reagents and reaction conditions. In this anticipation, Zhu *et al.* developed copper-catalyzed intramolecular dehydrogenative amino-oxygenation (IDA) process to produce imidazo[1,2-*a*]pyridine-3-carbaldehydes (**46**) from *N*-(1-phenylallyl)-2-aminopyrines (**47**) using molecular oxygen as the terminal oxidant. The involvement of single electron transfer (SET) mechanism assisted by copper and oxygen was proposed (**Scheme 3.21**).[52]



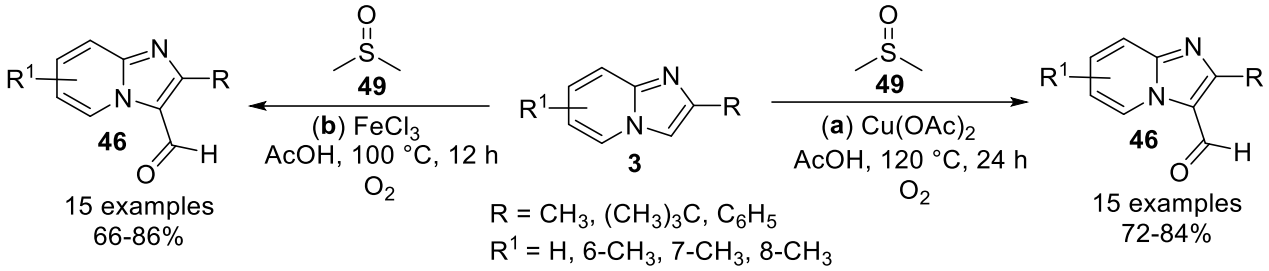
Scheme 3.21 Copper-catalyzed IDA reaction to access imidazo[1,2-a]pyridine-3-carbaldehydes

Adimurthy and coworkers explored Ag-catalyzed intramolecular amino-oxygenation reaction of *N*-propargyl-2-aminopyridines (**44**) to synthesize C-3 formylated imidazo[1,2-*a*]pyridines (**48**), employing molecular oxygen as terminal oxidant. It was believed that the intramolecular hydroamination reaction followed by silver and oxygen-promoted oxidation of intermediate afforded the desired product (**Scheme 3.22**).[42]



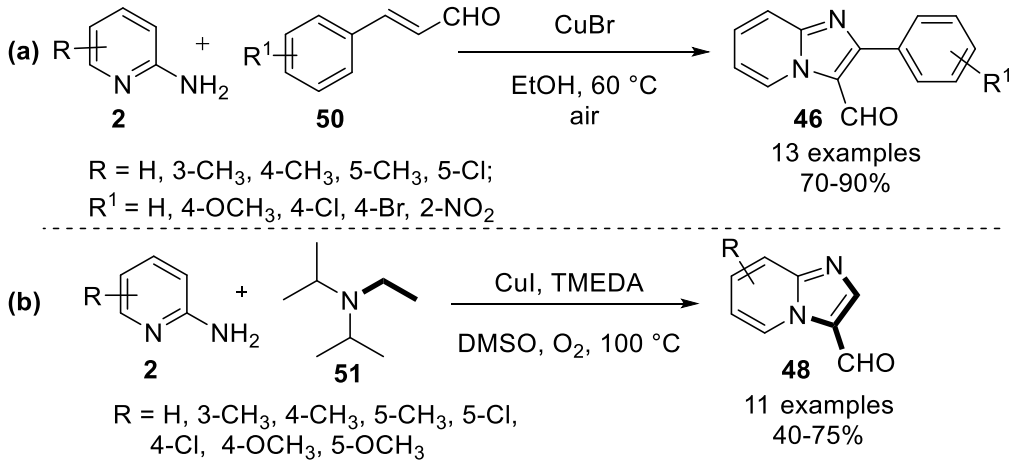
Scheme 3.22 Silver-catalyzed amino-oxygenation of *N*-propargyl-2-aminopyridines

Cao and group developed an elegant method involving Cu-catalyzed C-3 formylation of imidazo[1,2-*a*]pyridines (**3**), utilizing dimethyl sulfoxide (**49**) as one carbon source as well as a solvent in presence of molecular oxygen as the terminal oxidant (**Scheme 3.23**(**a**)).[53] The reaction was believed to proceed *via* single electron transfer (SET) radical pathway. Subsequently, Liu and coworkers reported the same product using dimethyl sulfoxide (**49**) as the carbon source under Fe(III)-catalyzed reaction of imidazo[1,2-*a*]pyridines (**3**). They also proposed the involvement of a single electron transfer (SET) oxidation process with the aid of ferric chloride and molecular oxygen (**Scheme 3.23**(**b**)).[54]



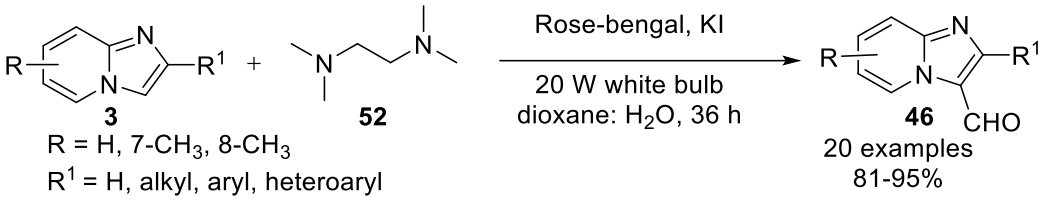
Scheme 3.23 C-3 formylation of imidazo[1,2-*a*]pyridines by employing DMSO as a carbon source

Bharate *et al.* devised a method to access 3-formyl-2-phenyl-imidazo[1,2-*a*]pyridines (**46**) *via* copper-catalyzed aerobic oxidative coupling of 2-aminopyridines (**2**) with cinnamaldehydes (**50**). The reaction steps included the formation of Michael adduct which followed aerobic oxidative cyclisation assisted by copper catalyst (**Scheme 3.24**(**a**)).[55] Song and co-workers efficiently synthesized 3-formyl imidazo[1,2-*a*]pyridine (**48**) under Cu-catalyzed aerobic oxidative reaction and by utilizing tertiary ethyl amines (**51**) as carbon sources. The reaction involved copper-catalyzed activation of 2 molecules of **51** in which simultaneous selective cleavage of C−C bond and C−N bond of ethyl group with molecular oxygen as terminal oxidant led to *in situ* formations of acrylaldehyde as active intermediate. The active intermediate then underwent oxidative coupling with 2-aminopyridine (**2**) to produce formylated product (**48**) (**Scheme 3.24**(**a**)).[56]



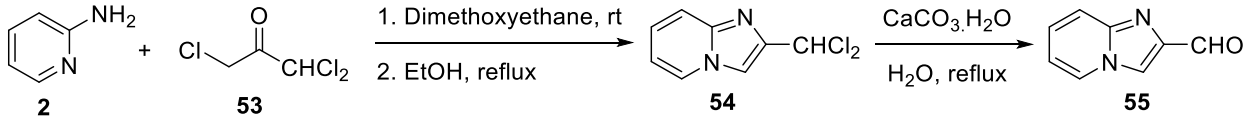
Scheme 3.24 Cu-catalysed aerobic oxidative coupling reaction of (**a**) 2-aminopyridine and cinnamaldehyde; (**b**) 2-aminopyridine and tertiary ethyl amine, for the synthesis of 3-formylated imidazo[1,2-*a*]pyridines

Recently, Hajra and co-workers reported metal-free and visible-light-mediated 3-formylation of imidazo[1,2-*a*]pyridine (**3**) employing tetramethylethylenediamine (**52**) as a one carbon source and rose bengal as a photosensitizer under ambient air condition. The reaction follwed a radical pathway initiated by rose bengal and air as an oxidant (**Scheme 3.25**).[57]



Scheme 3.25 Visible light-promoted synthesis of of 3-formylated imidazo[1,2-*a*]pyridine

On the other hand, scarce reports are available for development of 2-formylimidazo[1,2-*a*]pyridine derivatives. One of the traditional two step method involving condensation of 2-aminopyridine (**2**) with an excess of 1,1,3-trichloroacetone (**53**) followed by hydrolysis is commonly utilized for the synthesis of 2-formylimidazo[1,2-*a*]pyridine derivative (**55**).[58]



Scheme 3.26 Traditional method of 2-formylimidazo[1,2-*a*]pyridine synthesis

The lack of synthetic reports in this direction strongly necessitates the development of new methodology for C-2 formylation of imidazo[1,2-*a*]pyridine.

As earlier described in chapter 1 (**Section 1.3.3**), pyridinium salts play a pivotal role in the design and synthesis of imidazo[1,2-*a*]pyridines under transition metal-catalysed and transition metal-free conditions. Inspired by the valuable chemistry of pyridinum salts, in this chapter, we aimed to synthesize 2-carbonylimidazo[1,2-*a*]pyridines *via* iodine-mediated intramolecular cyclization of *N*-propargyl pyridinium bromide.

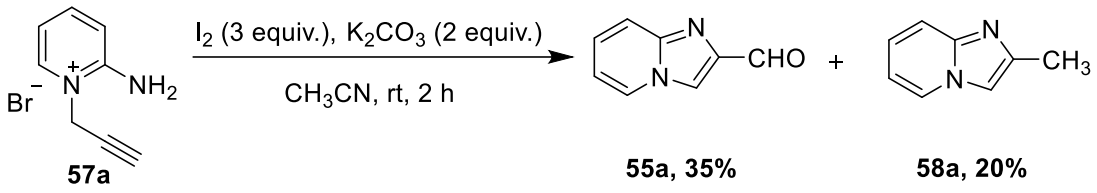
3.2 RESULTS AND DISCUSSION

Encouraged by numerous reports concerning iodine-promoted iodocyclization of tethered heteroatom-containing alkynyl systems resulting into heterocyclic compounds,[59-62] we sought to

investigate intramolecular iodocyclization of 2-amino-1-(prop-2-ynyl)pyridinium bromide (**57a**) prepared from the quaternization reaction of 2-aminopyridine derivatives (**2**) and propargyl bromides (**56**).

3.2.1 Optimization of Reaction Conditions

Our initial investigation commenced with the intramolecular iodocyclisation of 2-amino-1-(prop-2-ynyl)pyridinium bromide (**57a**) using I_2 (3 equiv.) and K_2CO_3 (2 equiv.) at room temperature in acetonitrile. The reaction produced two products, 2-formylimidazo[1,2-*a*]pyridine (**55a**) and 2-methylimidazo[1,2-*a*]pyridine (**58a**) in 35% and 20% yields, respectively (**Table 3.1,** entry 1**)** (**Scheme 3.27**).



Scheme 3.27 Intramolecular iodocyclisation of 2-amino-1-(prop-2-ynyl)pyridinium bromide

Structures of both the products **55a** and **58a** were ascertained by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry analysis. The appearance of a strong peak at 1690 cm^{-1} along with peaks at 2916 and 2962 cm^{-1} in the IR spectrum of **55a** indicated the presence of aldehyde group. In the ^{1}H NMR of **55a**, two singlets appeared at δ 10.18 and 8.18 ppm for aldehydic and C-3 protons, respectively along with peak for other four protons (**Figure 3.3**). Finally, the appearance of a peak at δ 188.04 ppm in the ^{13}C NMR spectrum indicated the presence of carbonyl carbon in structure (**Figure 3.4**) and a peak in the HRMS at *m/z* 147.0559 corresponding to molecular formula $C_8H_7N_2O$ $[M+H]^+$ ion confirmed the structure of **55a**.

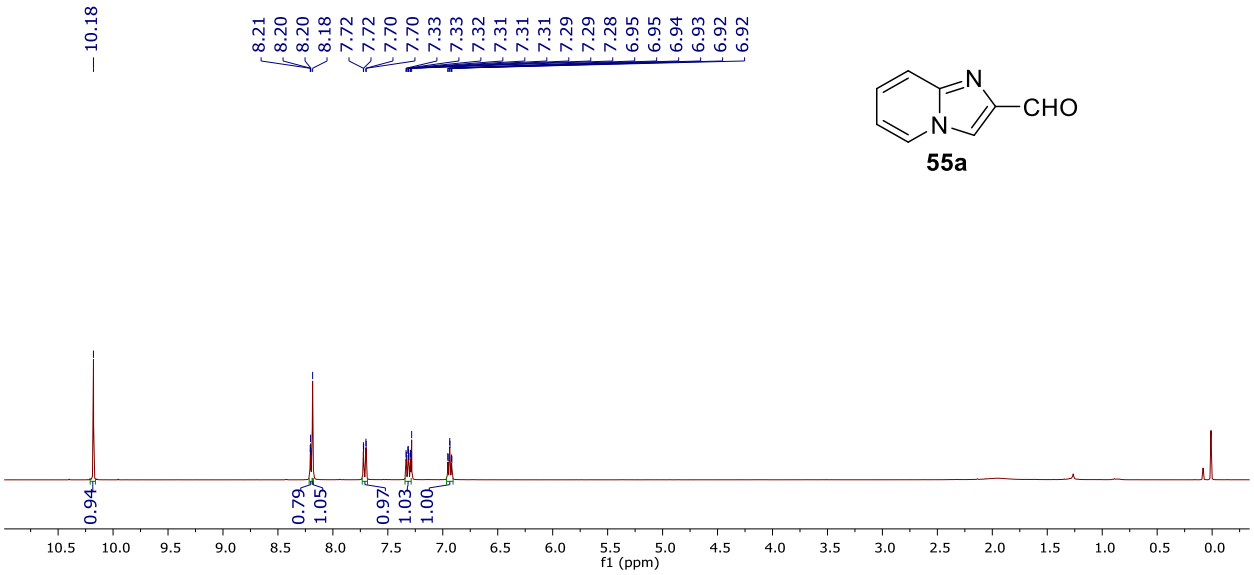


Figure 3.3 ^{1}H NMR spectrum of **55a**

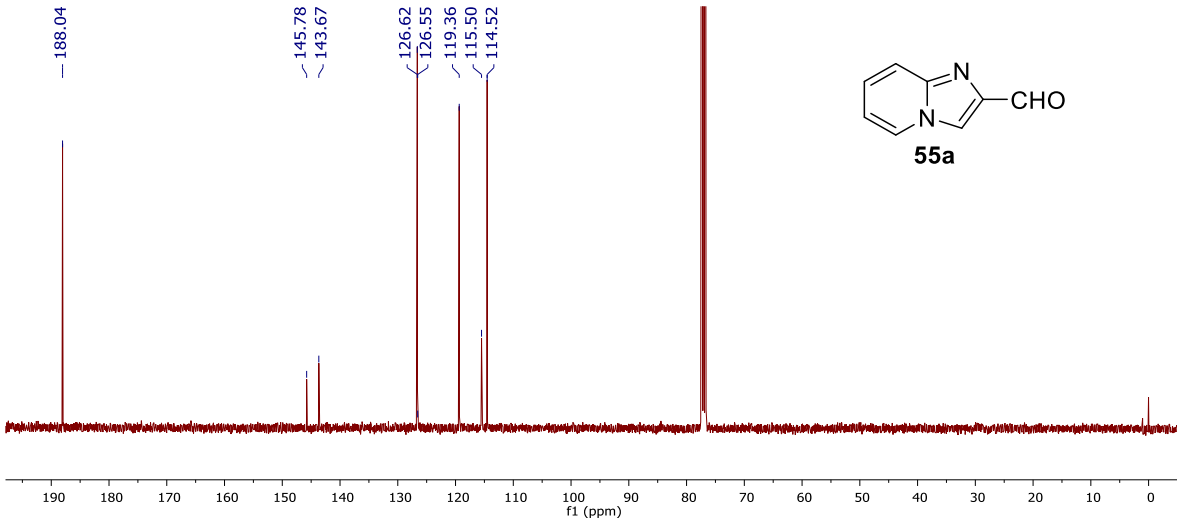


Figure 3.4 ^{13}C NMR spectrum of **55a**

Similarly, in the ^{1}H NMR of **58a,** two singlets appeared at δ 2.45 and 7.32 ppm for CH_3 and C-3 protons, respectively along with peak for other aromatic protons. A peak for methyl carbon was observed at δ 34.1 ppm in ^{13}C NMR spectrum and HMRS analysis showed a peak at *m/z* 133.0763 corresponding to molecular formula $C_8H_9N_2$ $[M+H]^+$ ion confirmed the structure of **58a**.

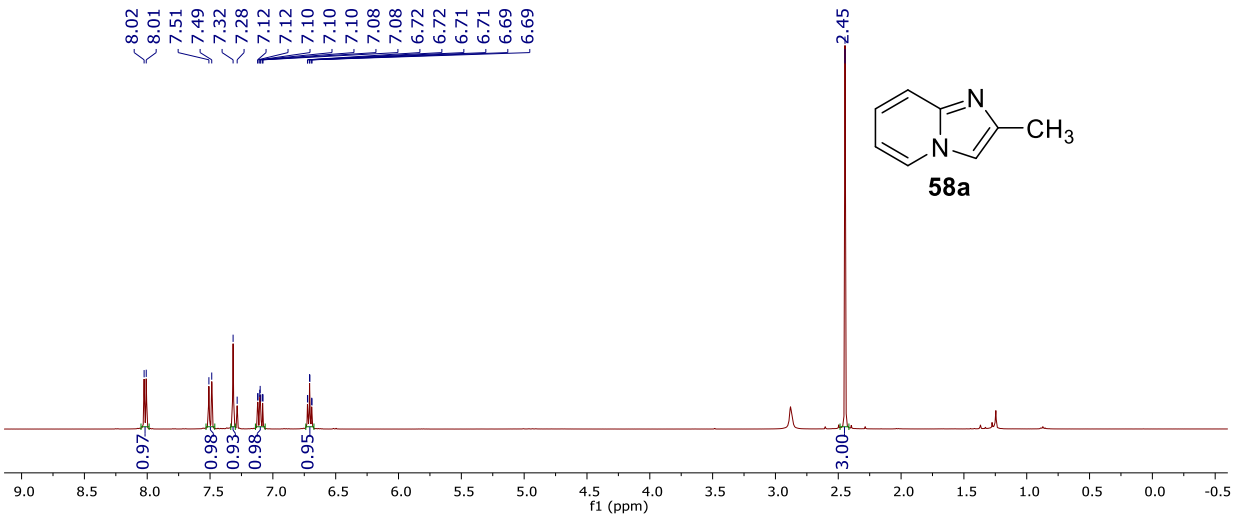


Figure 3.5 ^{1}H NMR spectrum of **58a**

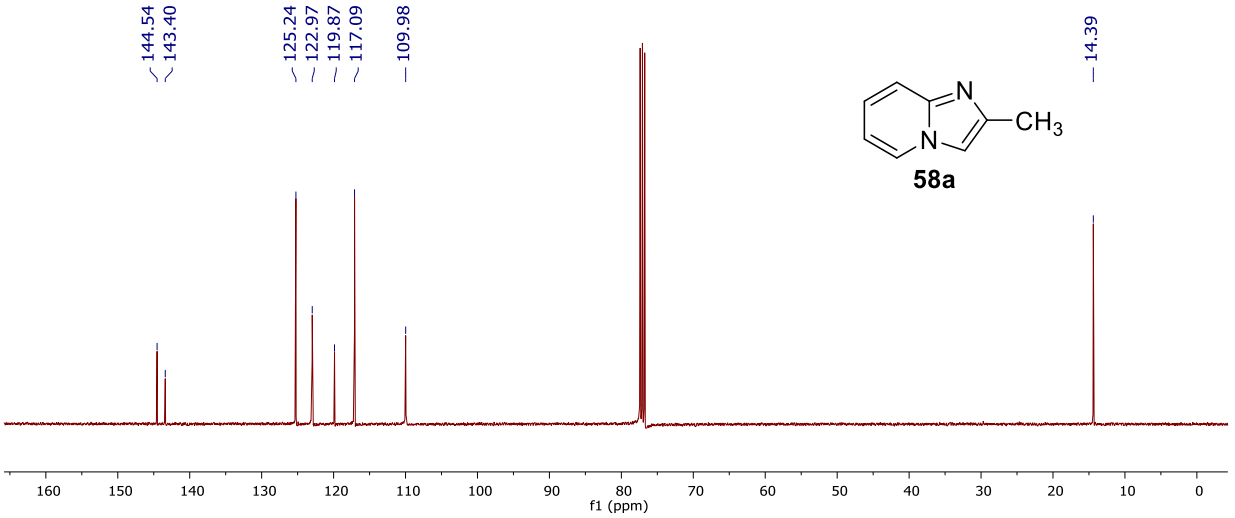
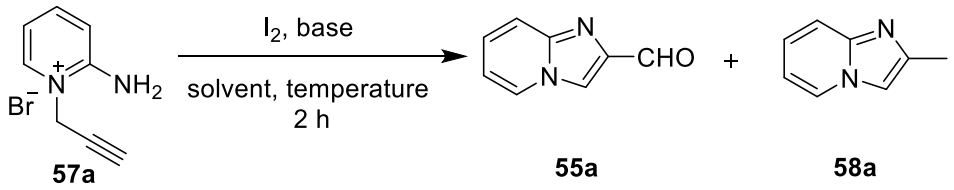


Figure 3.6 ^{13}C NMR spectrum of **58a**

In the quest to find optimized reaction conditions for the synthesis of 2-formylimidazo[1,2-*a*]pyridine **55a** through intramolecular iodocyclization, we performed several experiments by varying the amount of I_2, different bases, solvents and reaction temperature. The results of these reaction condition optimization experiments are shown in **Table 3.1**. Increasing temperature of the model reaction from room temperature to 80 °C resulted in increased yield (45%) of **55a (Table 3.1,** entry 2**)**. In the absence of base, neither **55a** nor **58a** was formed, signifying the essentiality of the base for this transformation (**Table 3.1,** entry 3). However, in the absence of iodine, **58a**

was obtained in 58% yield. Consequently, screening of various bases such as K_2CO_3, NaOH (2N and 4N), KOH (2N), triethylamine and K_3PO_4 revealed that best yield of **55a** was obtained with 2N NaOH (**Table 3.1,** entries 5-9). It was also worth mentioning that organic base triethylamine was highly detrimental for this reaction (**Table 3.1,** entry 7) whereas, use of 4N NaOH resulted in the selective formation of **58a** in 75% (**Table 3.1,** entry 6). In the next step, screening of different solvents such as THF, toluene, dioxane, and H_2O was carried out (**Table 3.1,** entries 4 and 10-13). The best yield of **55a** (55%) was obtained in dioxane whereas **58a** was a major product with 45% yield in water. The yield of **55a** increased slightly on increasing the reaction temperature to 100 ^{O}C but decreased significantly on decreasing the reaction temperature to 60 °C (**Table 3.1,** entries 14-15). This variation in yield of **55a** and **58a** with a change in temperature indicated that **55a** is formed in a major amount at a higher temperature, whereas **58a** is formed in a major amount at a lower temperature. Decreasing the concentration of NaOH to 1N improved the yield of **55a** to 62% with a trace amount of **58a** (**Table 3.1,** entry 16). Finally, using 2 equivalents of iodine along with 1N NaOH in dioxane was found to be the best condition to give **55a** in 78% yield (**Table 3.1,** entry 17).

Table 3.1 Optimization of reaction conditions for the synthesis of **55a**.[a]



S No.	Base	Solvent	Temp. (^{o}C)	% Yield[b]	
				55a	**58a**
1	K_2CO_3	CH_3CN	RT	35	20
2	K_2CO_3	CH_3CN	80	45	10
3	-	CH_3CN	80	-	-
4[c]	K_2CO_3	CH_3CN	80	-	58
5	2N NaOH	CH_3CN	80	50	15
6	4N NaOH	CH_3CN	80	Trace	75

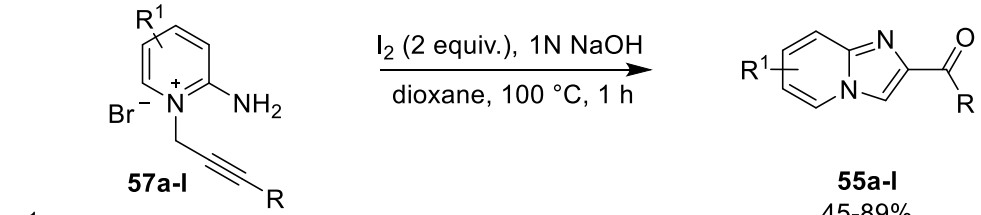
7	NEt_3	CH_3CN	80	-	-
8	K_3PO_4	CH_3CN	80	25	40
9	2N KOH	CH_3CN	80	28	20
10	2N NaOH	THF	50	Trace	25
11	2N NaOH	Toluene	80	20	15
12	2N NaOH	H_2O	100	Trace	45
13	2N NaOH	Dioxane	80	55	15
14	2N NaOH	Dioxane	100	57	10
15	2N NaOH	Dioxane	60	45	18
16	1N NaOH	Dioxane	100	62	Trace
17[d]	**1N NaOH**	**Dioxane**	**100**	**78**	**Trace**

[a]Reaction condition: **57a** (1 mmol), iodine (3 equiv.), base (2 equiv.), solvent (10 mL), 2 h; [b]Isolated yield; [c]In the absence of iodine; [d]Iodine (2 equiv.), 1 h.

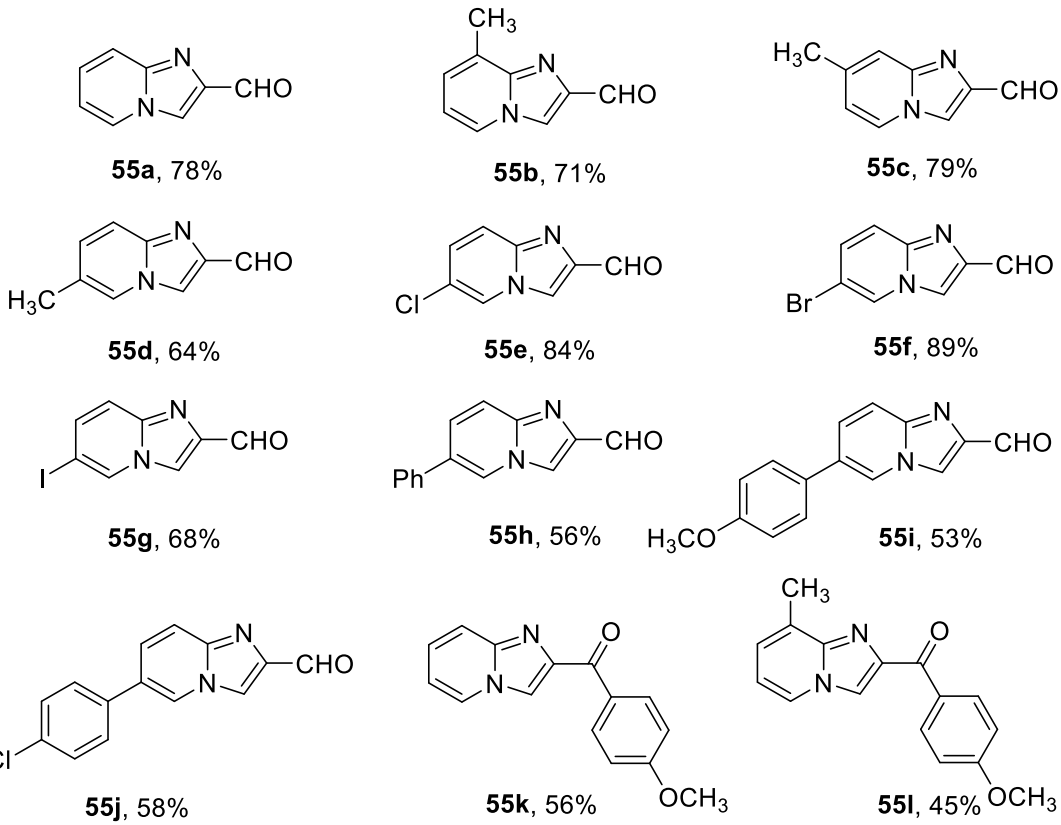
3.2.2 Synthesis of 2-carbonylated Imidazo[1,2-*a*]pyridines

After having the optimized reaction conditions in hand (**Table 3.1,** entry 17), the generality of the process was investigated by employing variously substituted pyridinium bromides (**57a-l**) to give substituted 2-carbonylimidazo[1,2-a]pyridines (**55a-l**) (**Table 3.2**). Initially, 2-amino-1-(prop-2-ynyl)pyridinium having methyl substitution at various positions was studied (**Table 3.2, 55a-55e**). Among the studied salts, 2-amino-4-methyl-1-(prop-2-ynyl)pyridinium bromide furnished 2-formyl product in good yields i.e 78% (**Table 3.2, 55b-55d**). Next, 2-amino-1-(prop-2-ynyl)pyridinium bromide bearing halogen substitutions at C5 were screened (**Table 3.2, 55e-55g**). Gratifyingly, bromo-substituted salt afforded excellent yield (89%) of product (**Table 3.2, 55g**). The reaction of 5-phenyl substituted pyridinium bromide also resulted in moderate yields of the desired product (**Table 3.2, 55h-2j**). Interestingly, the reaction of 2-amino-1-(prop-2-ynyl)pyridinium bromide bearing terminal phenyl group resulted in 2-aroylimidazo[1,2-*a*]pyridine. (**Table 3.2, 55k-55l**).

Table 3.2 Substrate scope for the synthesis of 2-carbonylimidazo[1,2-*a*]pyridine[a,b]



R^1= H, 3-CH_3, 4-CH_3, 5-CH_3, 5-C_6H_5
5-(4-OCH_3-C_6H_5), 5-Cl, 5-Br, 5-I
R= H, 4-OCH_3-C_6H_5



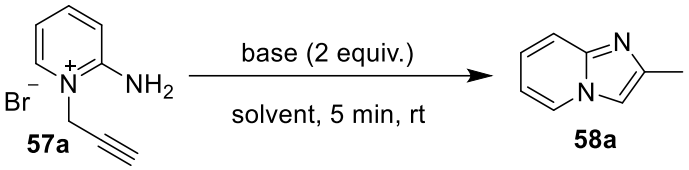
[a]Reaction condition: **57a** (1 mmol), iodine (2 equiv.), 1 N NaOH, dioxane (10 mL), 100 °C, 1 h; [b]Isolated yield

3.2.3 Synthesis of 2-Methylimidazo[1,2-*a*]pyridines

During optimization of reaction for **55a**, the base mediated hydroamination of 2-amino-1-(prop-2-ynyl)pyridinium bromide (**57a**) leading to the formation of **58a** in 75% yields prompted us to look into this cyclization (**Table 3.1,** entry 6). Inspired from this outcome, we next moved our attention towards the synthesis of 2-methylimidazo[1,2-*a*]pyridine derivatives (**58**) from 2-amino-1-(prop-

2-ynyl)pyridinium bromides (**57**). In order to improve the yield of **58a**, we further optimized the reaction condition, the findings of which are summarized in **Table 3.3.** Initially, the reaction was performed in water without a base to observe the unreacted starting material. Next reaction was performed by adding K_2CO_3 in reaction, to observe 93% yields of **58a** (**Table 3.3,** entry 2). Among other bases (K_2CO_3, Na_2CO_3, KOH, NaOH, NEt_3) screened, 2N NaOH was found to be effective (**Table 3.3,** entry 4). Next, the effect of solvents was studied by varying different solvents such as DCM, methanol, THF and acetonitrile to observe that none of those in comparison to H_2O produced a better yield of **58a**.

Table 3.3. Optimization of Reaction Conditions for the base-mediated Synthesis of **58a.**[a]



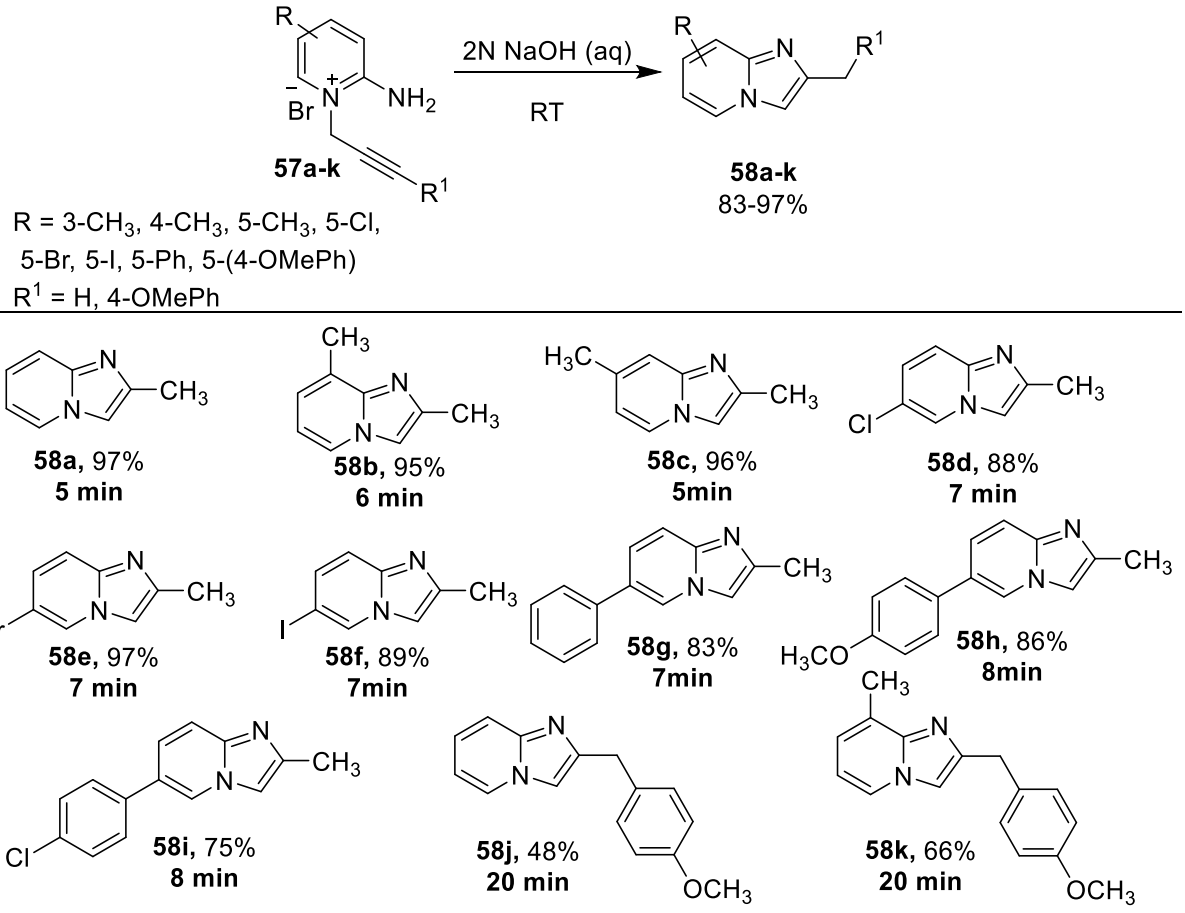
S. No.	Base	Solvent	%Yield[b] of **58a**
1.	-	H_2O	NR
2.	K_2CO_3	H_2O	93
3.	Na_2CO_3	H_2O	81
4.	**2N NaOH**	**H_2O**	**97**
5.	2N KOH	H_2O	95
6.	NEt_3	H_2O	Trace
7.	2N NaOH	DCM	86
8.	2N NaOH	CH_3OH	77
9.	2N NaOH	CH_3CN	83
10.	2N NaOH	Toluene	56

[a]Reaction condition: **57a** (1 mmol), base (2 equiv.), solvent (5 mL), 5 min; [b]Isolated yield

The results are summarized in **Table 3.4**. In the beginning, methyl substituted 2-amino-1-(prop-2-ynyl)pyridinium bromide at different positions were examined, and the corresponding 2-methylimidazo[1,2-*a*]pyridines formed in excellent yield (**Table 3.4, 58b-58d**). When C-5 halogen

substituted 2-amino-1-(prop-2-ynyl)pyridinium bromide were used, the reaction smoothly occurred to afford corresponding products in high yields (**Table 3.4, 58e-58g**). Similarly, the reaction of 5-phenyl-2-aminopyridinium bromide proceeded smoothly under the condition to give the desired product in good yields (**Table 3.4, 58h-58i**). Interestingly, the reaction of 2-amino-1-(prop-2-ynyl)pyridinium bromide bearing terminal phenyl group resulted to 2-benzylimidazo[1,2-*a*]pyridine in moderate yields by taking longer reaction time (**Table 3.4, 58j & 58k**). Unfortunately, during the preparation of this manuscript Nguyen *et al.* reported exactly the same strategy to access identical molecules.[63]

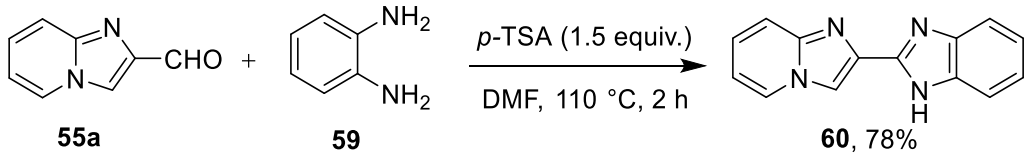
Table 3.4 Scope of base-promoted synthesis of 2-methylimidazo[1,2-*a*]pyridines[a,b] (**58a**)



[a]Reaction condition: **57a** (1 mmol), 2N NaOH (2 equiv.), H_2O (5 mL), 5 min; [b]Isolated yields

3.2.4 Synthetic Application

We took advantage of the presence of formyl group at the C-2 position of imidazo[1,2-*a*]pyridine **55a** to implement an additional reaction which aimed at providing straight-forward access to additionally functionalized imidazo[1,2-*a*]pyridine. Thus, 2-(imidazo[1,2-*a*]pyridin-2-yl)-1*H*-benzo[*d*]imidazole (**60**) was prepared in 78% yield by reacting **55a** with *o*-phenylenediamine (**59**) in the presence of *p*-TsOH (**Scheme 3.28**).

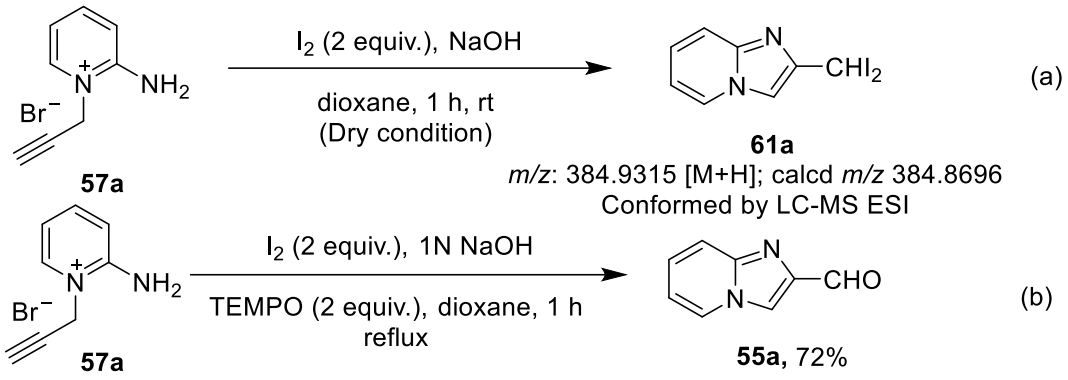


55a **59** **60**, 78%

Scheme 3.28 Synthesis of 2-(imidazo[1,2-*a*]pyridin-2-yl)-1*H*-benzo[*d*]imidazole

3.2.5 Control Experiments

Next, we performed a set of control experiments to get an insight into the reaction mechanism for the synthesis of **55a**. Formation of 2-(diiodomethyl)imidazo[1,2-*a*]pyridine (**61a**) as an intermediate was presumed by LC-MS analysis of the reaction of **57a** with iodine and base (powdered NaOH 2 equiv.) at room temperature (**Scheme 2.29**(**a**)). However, we were not able to isolate 2-(diiodomethyl)imidazo[1,2-*a*]pyridine (**61a**) as it converted to 2-formylimdazo[1,2-*a*]pyridine (**2a**) during work-up procedure. The reaction of **57a** under a standardized condition in the presence of TEMPO produced **55a** in 72% yield, indicating that the reaction does not involve radical mechanism (**Scheme 2.29**(**b**)). We also applied different iodine-based reagents in the model reaction, use of *N*-iodosuccinimide (NIS) led to the formation of **55a** in 32% yield along with some unidentified products, whereas, **58a** was formed in 35% yield by using tetrabutylammonium iodine (TBAI). No product formation was observed on using iodobenzene diacetate.



Scheme 3.29 Control experiments

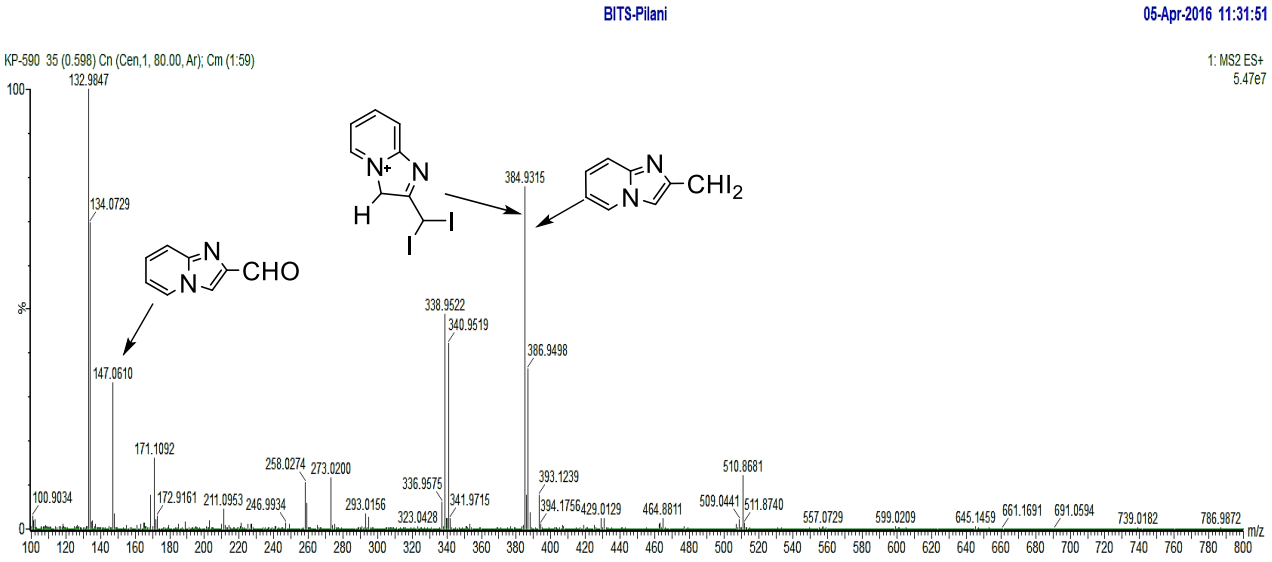
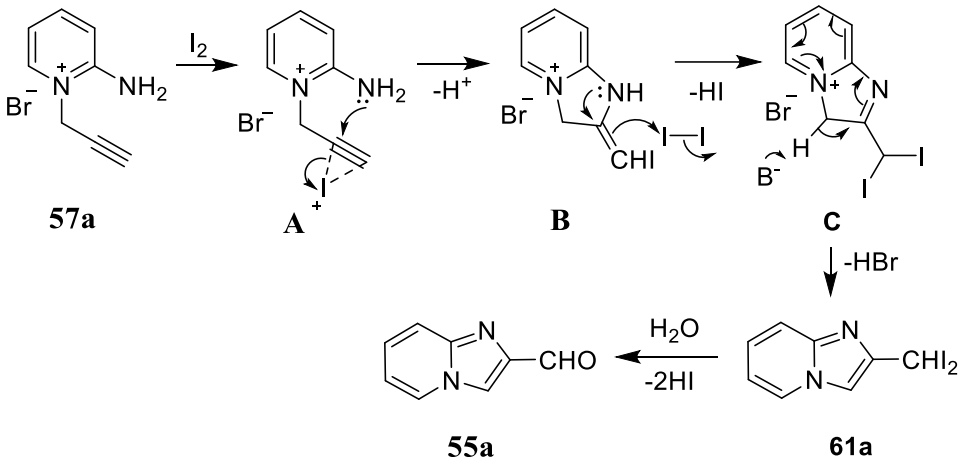


Figure 3.7 Representative **ESI**-mass spectrum of the reaction mixture

3.2.6 Plausible Mechanism

Based on reports on iodine mediated hydrative cyclization[64-65] and results of control experiments, a tentative mechanism for the reaction is proposed by taking a synthesis of **55a** as an example (**Scheme 3.30**). Initially, an iodonium ion **A** is formed by the reaction of **57** with iodine which on 5-*exo*-*dig* type iodocyclization results in the formation of vinyl iodide intermediate **B**. Attack of another iodine molecule on **B** leads to geminal diiodide salt **C**. The loss of HBr from geminal diiodide salt **C** furnishes 2-(diiodomethyl)imidazo[1,2-*a*]pyridine (**D**). The formation of intermediate **65a** was confirmed by the presence of a peak at *m/z* 384.8693 in the LC-MS-ESI

mass spectrum of the reaction mixture after 1h (**Figure 3.7**). Finally, hydrolysis of intermediate **61a** results in the formation of **55a**.



Scheme 3.30 Proposed mechanism

3.3 CONCLUSIONS

In summary, we have developed an efficient and transition metal-free approach for the easy access of 2-carbonylimidazo[1,2-*a*]pyridines from 2-aminopyridinium bromides *via* iodine-mediated intramolecular cyclization. The method provided different substituted 2-carbonylimidazo[1,2-*a*]pyridines in good to excellent yields (45-89%). The protocol is environmentally benign and considered to be attractive for the synthesis of 2-carbonylimidazo[1,2-*a*]pyridines which are potentially active pharmacophores in the synthesis of relevant medicinally important drugs.

3.4 EXPERIMENTAL SECTION

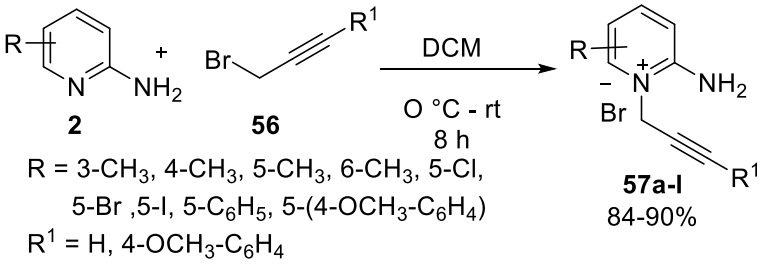
3.4.1 Materials and Methods

The nuclear magnetic resonance spectra were recorded on Bruker AV 400 spectrometer in $CDCl_3$ and DMSO-d_6. The chemical shifts were expressed in parts per million (ppm) and coupling constants (*J*) in hertz (Hz). The IR spectra were recorded on ABB Bomen MB 3000 FTIR spectrophotometer. The progress of the reaction was determined on thin-layer chromatography (TLC) performed on Merck-precoated silica gel 60-F_{254} plates. Melting points were determined on the open capillary tube on MPA-120G EZ-Melt automated melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were carried out using a quadrupole time of-

flight (Q-TOF) mass spectrometer (Applied Biosystem). LCMS mass spectra were recorded on a Waters™ system equipped with a Waters™ 3100 mass detector. 2-Aminopryidines, propargyl bromide, and other reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified.

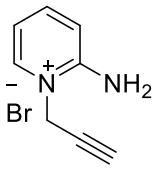
3.4.2 General Procedure for Synthesis of 2-Amino-1-(prop-2-ynyl)pyridinium Bromide (57)

A solution of 2-aminopyridine (0.500 g, 5 mmol) in DCM was cooled at 0 °C and propargyl bromide (80% in toluene, 0.900 mL, 6 mmol) was added slowly with stirring. The resulting reaction mixture was stirred at room temperature for 8 h. The precipitate formed was filtered off from DCM to afford the solid mass, washed with diethyl ether (2 × 10 mL). The pure 2-amino-*N*-propargylpyridinium bromide (**57a**) was obtained in 90% yield.



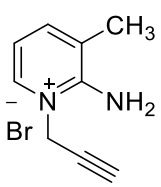
Scheme 3.29: Synthesis of 2-amino-1-(prop-2-ynyl)pyridinium bromide derivatives

2-Amino-1-(prop-2-ynyl)pyridinium bromide (57a).



Off-White solid (1.065 g, 90%); MP 169 – 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 2H, NH_2), 8.21 (d, J = 6.0 Hz, 1H, C6-H), 8.00 – 7.86 (m, 1H, C4-H), 7.18 (d, J = 8.6 Hz, 1H, C3-H), 6.95 (td, J = 6.9, 1.1 Hz, 1H, C5-H), 5.13 (d, J = 2.4 Hz, 2H, CH2), 3.84 (t, J = 2.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.08, 143.20, 139.45, 115.44, 113.59, 80.05, 75.65, 43.41; FT-IR ν_{max} (neat) 771, 1660, 2114, 3202, 3271; HRMS (ESI, *m/z*) calcd for $C_8H_9N_2^+$ [M-Br]$^+$: 133.0760, found: 133.0785.

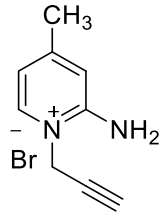
2-Amino-3-methyl-1-(prop-2-ynyl)pyridinium bromide (57b).



Off-White solid (0.924 g, 88%) MP 192 – 195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 2H, NH_2), 8.13 (d, J = 6.5 Hz, 1H, C6-H), 7.83 (d, J = 7.1 Hz, 1H, C4-H), 6.93 (t, J = 6.9 Hz, 1H, C5-H), 5.20 (d, J = 2.1 Hz, 2H, CH_2), 3.83 (s, 1H, CH), 2.25 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.18, 142.09, 137.47,

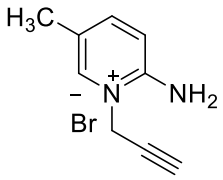
124.13, 113.32, 79.99, 75.87, 44.00, 17.87; FT-IR ν_{max} (neat) 710, 1651, 2122, 3256, 3286; HRMS (ESI, *m/z*) calcd for $C_9H_{11}N_2^+$ $[M\text{-}Br]^+$: 147.0917, found: 147.0925.

2-Amino-4-methyl-1-(prop-2-ynyl)pyridinium bromide (57c).



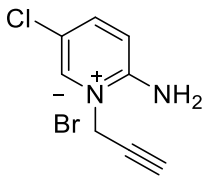
Cream colored solid (0.931 g, 89%); MP 180 – 181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 2H, NH2), 8.09 (d, J = 6.9 Hz, 1H, C6-H), 6.94 (s, 1H, C3-H), 6.82 (dd, J = 6.9, 1.6 Hz, 1H, C5-H), 5.10 (d, J = 2.3 Hz, 2H, CH_2), 3.81 (t, J = 2.3 Hz, 1H, CH), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.38, 153.58, 138.69, 115.68, 113.65, 79.79, 75.85, 42.88, 21.52; FT-IR ν_{max} (neat) 910, 1674, 2114, 3174, 3272; HRMS (ESI, *m/z*) calcd for $C_9H_{11}N_2^+$ $[M\text{-}Br]^+$: 147.0917, found: 147.0930.

2-Amino-5-methyl-1-(prop-2-ynyl)pyridinium bromide (57d).



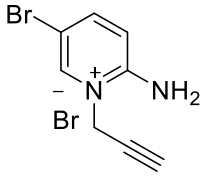
Yellow colored solid (0.931 g, 89%); MP 175 – 177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2H, NH_2), 8.02 (s, 1H, C6-H), 7.81 (d, J = 8.8 Hz, 1H, C4-H), 7.08 (d, J = 8.9 Hz, 1H, C3-H), 5.04 (s, 2H, CH_2), 3.37 (s, 1H, CH), 2.17 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.6, 145.3, 136.9, 122.9, 115.2, 79.8, 75.8, 43.2, 16.8; FT-IR ν_{max} (neat) 910, 1659, 2114, 3171, 3271; HRMS (ESI, *m/z*) calcd for $C_9H_{11}N_2^+$ $[M\text{-}Br]^+$: 147.0917, found: 147.0933.

2-Amino-5-chloro-1-(prop-2-ynyl)pyridinium bromide (57e).



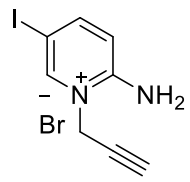
Off-White solid, (0.839 g, 87%); MP 178 – 179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 2H, NH_2), 8.53 (s, 1H, C6-H), 8.02 (d, J = 9.1 Hz, 1H, C4-H), 7.20 (d, J = 9.3 Hz, 1H, C3-H), 5.08 (s, 2H, CH_2), 3.86 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.1, 143.3, 137.1, 118.6, 117.0, 80.2, 75.2, 43.7; FT-IR ν_{max} (neat) 825, 1659, 2122, 3155, 3217; HRMS (ESI, *m/z*) calcd for $C_8H_8ClN_2^+$ $[M\text{-}Br]^+$: 167.0371, found: 167.0392.

2-Amino-5-bromo-1-(prop-2-ynyl)pyridinium bromide (57f).



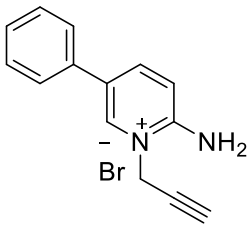
White solid (0.759 g, 90%); MP 176 – 177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 2H, NH_2), 8.55 (d, J = 2.0 Hz, 1H, C6-H), 8.06 (dd, J = 9.5, 2.2 Hz, 1H, C4-H), 7.11 (d, J = 9.5 Hz, 1H, C3-H), 5.05 (d, J = 2.4 Hz, 2H, CH_2), 3.84 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 150.2, 143.9, 121.8, 109.8, 85.0, 80.0, 48.3; FT-IR ν_{max} (neat) 872, 1669, 2122, 3178, 3217; HRMS (ESI, *m/z*) calcd for $C_8H_8BrN_2^+$ $[M\text{-}Br]^+$: 210.9865, found: 210.9842.

2-Amino-5-iodo-1-(prop-2-ynyl)pyridinium bromide (57g).



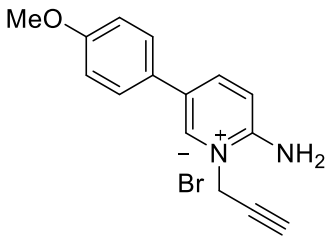
White solid (0.685 g, 89%); MP 164 – 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 2H, NH_2), 8.52 (s, 1H, C6-H), 8.11 (s, 1H, C4-H), 6.99 (s, 1H, C3-H), 5.04 (s, 2H, CH_2), 3.83 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 150.2, 143.9, 121.8, 109.8, 85.0, 80.0, 48.3; FT-IR ν_{max} (neat) 872, 1651, 2129, 3217, 3271; HRMS (ESI, *m/z*) calcd for $C_8H_8IN_2^+$ $[M–Br]^+$: 258.9727, found: 258.9730.

2-Amino-5-phenyl-1-(prop-2-ynyl)pyridinium bromide (57h).



White solid (0.756 g, 89%); MP 164 – 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 2H, NH_2), 8.63 (d, J = 1.8 Hz, 1H, C6-H), 8.34 (dd, J = 9.3, 1.9 Hz, 1H, C4-H), 7.68 (d, J = 7.3 Hz, 2H, C3`-H & C5`-H), 7.53 (t, J = 7.5 Hz, 2H, C2`-H & C6`-H), 7.44 (t, J = 7.3 Hz, 1H, C4`-H), 7.23 (d, J = 9.3 Hz, 1H, C3-H), 5.18 (d, J = 2.2 Hz, 2H, CH_2), 3.84 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.1, 141.9, 136.7, 134.2, 129.7, 129.0, 126.4, 125.85, 115.8, 79.8, 75.7, 43.7; FT-IR ν_{max} (neat) 895, 1659, 2122, 3209, 3279; HRMS (ESI, *m/z*) calcd for $C_{14}H_{13}N_2^+$ $[M–Br]^+$: 209.1073, found: 209.1059.

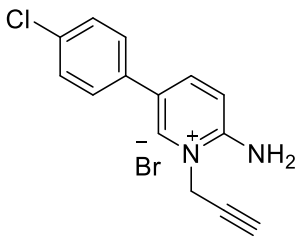
2-Amino-5-(4-methoxyphenyl)-1-(prop-2-ynyl)pyridinium bromide (57i).



White solid (0.677 g, 85%) MP 210 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 2H, NH_2), 8.57 (s, 1H, C6-H), 8.30 (d, J = 9.0 Hz, 1H, C4-H), 7.63 (d, J = 8.4 Hz, 2H, C3`-H & C5`-H), 7.23 (d, J = 9.2 Hz, 1H, C3-H), 7.07 (d, J = 8.4 Hz, 2H, C2`-H & C6`-H), 5.19 (s, 2H, CH_2), 3.83 (s, 1H, CH), 3.80 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz,

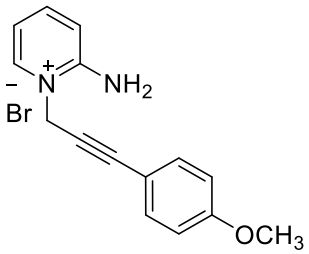
DMSO-d_6) δ 160.0, 152.7, 141.7, 135.7, 127.7, 126.5, 125.7, 115.7, 115.1, 79.8, 75.8, 55.8, 43.6; FT-IR ν_{max} (neat) 825, 1659, 2122, 3209, 3217; HRMS (ESI, *m/z*) calcd for $C_{15}H_{15}N_2O^+$ $[M–Br]^+$: 239.1179, found: 239.1182.

2-Amino-5-(4-chlorophenyl)-1-(prop-2-ynyl)pyridinium bromide (57j).



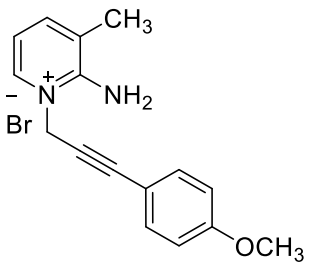
Cream solid (0.665 g, 84%); MP 210 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 2H, NH_2), 8.66 (s, 1H, C6-H), 8.33 (d, *J* = 9.1 Hz, 1H, C4-H), 7.72 (d, *J* = 8.0 Hz, 2H, C3`-H & C5`-H), 7.60 (d, *J* = 7.9 Hz, 2H, C2`-H & C6`-H), 7.22 (d, *J* = 9.1 Hz, 1H, C3-H), 5.16 (s, 2H, CH_2), 3.84 (s, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.1, 141.7, 137.0, 133.8, 133.2, 129.7, 128.2, 124.5, 115.9, 79.8, 75.7, 43.7; FT-IR ν_{max} (neat) 895, 1659, 2122, 3209, 3279; HRMS (ESI, *m/z*) calcd for $C_{14}H_{12}ClN_2$ $[M–Br]^+$: 243.0684, found: 243.0692.

2-Amino-1-(3-(4-methoxyphenyl)prop-2-ynyl)pyridinium bromide (57k).



White solid (1.463 g, 86%); MP 210 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 2H, NH_2), 8.26 (d, *J* = 6.2 Hz, 1H, C6-H), 7.98 – 7.85 (m, 1H, C4-H), 7.44 (d, *J* = 8.8 Hz, 2H, C2`-H & C6`-H), 7.14 (d, *J* = 8.8 Hz, 1H, C3-H), 6.98 (d, *J* = 8.8 Hz, 2H, C3`-H & C5`-H), 6.96 (bs, 1H, C5-H), 5.30 (s, 2H, CH_2), 3.78 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 158.8, 147.9, 144.2, 138.6, 120.2, 119.6, 118.3, 117.8, 92.8, 84.3, 60.5, 48.9; FT-IR ν_{max} (neat) 895, 1659, 2119, 3209, 3279; HRMS (ESI, *m/z*) calcd for $C_{15}H_{15}N_2O^+$ $[M–Br]^+$: 239.1179, found: 239.1194.

2-Amino-1-(3-(4-methoxyphenyl)prop-2-ynyl)-3-methylpyridinium bromide (57l).



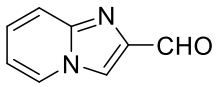
Brown liquid (1.310 g, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H, NH_2), 8.20 (d, *J* = 6.6 Hz, 1H, C6-H), 7.84 (d, *J* = 7.0 Hz, 1H, C4-H), 7.44 (d, *J* = 8.6 Hz, 2H, C2`-H & C6`-H), 6.97 (d, *J* = 8.5 Hz, 2H, C3`-H & C5`-H), 6.93 (d, *J* = 7.0 Hz, 1H, C5-H), 5.40 (s, 2H, CH_2), 3.78 (s, 3H, O-CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 153.2, 142.0, 137.4, 133.8, 124.1, 114.9, 113.3, 113.1, 87.9, 79.8,

55.8, 44.8, 17.8; FT-IR ν_{max} (neat) 895, 1659, 2119, 3209, 3279; HRMS (ESI, *m/z*) calcd for $C_{16}H_{17}N_2O^+$ $[M–Br]^+$: 253.1335, found: 253.1351.

3.4.3 General Procedure for Synthesis of Imidazo[1,2-*a*]pyridine-2-carbaldehyde (55) from 2-Amino-1-(prop-2-ynyl)pyridinium Bromide (57)

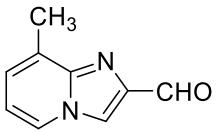
2-Amino-1-(prop-2-ynyl)pyridinium bromide (**57a**) (0.100 g, 0.46 mmol), 1N NaOH (aq.) (2.0 equiv.), iodine (0.240 g, 0.92 mmol) and dioxane (10 mL) were mixed in a clean oven dried 25 mL round bottom flask. The resulting reaction mixture was heated at 100 °C with stirring for 1 h. Progress of the reaction was monitored by TLC and reaction mixture was cooled to room temperature after 1h. After cooling, the reaction mass was quenched with aqueous solution of sodium thiosulphate pentahydrate (20 mL) and extracted by ethyl acetate (2 × 20 mL). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (30-35%) as eluent to give pure **55a** in 78% yield.

Imidazo[1,2-a]pyridine-2-carbaldehyde (55a).



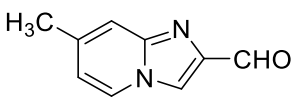
White solid (0.050 g, 74%); MP 100 – 101 °C (lit. 99 – 101 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H, CHO), 8.22 – 8.19 (m, 1H, C5-H), 8.18 (s, 1H, C3-H), 7.71 (dd, J = 9.3, 0.8 Hz, 1H, C8-H), 7.31 (ddd, J = 9.2, 6.7, 1.2 Hz, 1H, C7-H), 6.94 (td, J = 6.8, 0.9 Hz, 1H, C6-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 145.7, 143.6, 126.6, 119.3, 115.5, 114.5; FT-IR ν_{max} (neat) 756, 1257, 1690, 2800, 2916, 2962; HRMS (ESI, *m/z*) calcd for $C_8H_7N_2O^+$ $[M+H]^+$: 147.0553, found: 147.0559.

8-Methylimidazo[1,2-a]pyridine-2-carbaldehyde (55b).



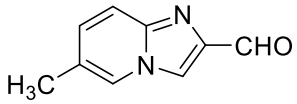
Off-white solid (0.050 g, 71%); MP 124 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H, CHO), 8.18 (s, 1H, C3-H), 8.06 (d, J = 6.8 Hz, 1H, C5-H), 7.10 (d, J = 6.8 Hz, 1H, C7-H), 6.84 (t, J = 6.8 Hz, 1H, C6-H), 2.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 146.5, 143.2, 129.4, 125.0, 124.3, 116.1, 114.5, 17.1; FT-IR ν_{max} (neat) 756, 1350, 1697, 2831, 2916, 2955; HRMS (ESI, *m/z*) calcd for $C_9H_9N_2O^+$ $[M+H]^+$: 161.0709, found: 161.0712.

7-Methylimidazo[1,2-a]pyridine-2-carbaldehyde (55c).



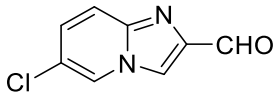
White solid (0.054 g, 78%); MP 122 – 124 ^{O}C (lit. 124 – 125 °C); 1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 8.11 (d, J = 0.6 Hz, 1H, C3-H), 8.07 (d, J = 7.0 Hz, 1H, C5-H), 7.45 (s, 1H, C8-H), 6.77 (dd, J = 7.0, 1.5 Hz, 1H, C6-H), 2.45 (d, J = 1.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 146.2, 143.5, 137.8, 125.6, 117.3, 117.2, 115.2, 21.5; FT-IR ν_{max} (neat) 802, 1250, 1690, 2839, 2916, 2955; HRMS (ESI, *m/z*) calcd for $C_9H_9N_2O^+$ $[M+H]^+$: 161.0709, found: 161.0720.

6-Methylimidazo[1,2-a]pyridine-2-carbaldehyde (55d).



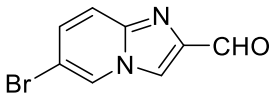
Off white solid (0.045 g, 64%); MP 126 – 127 °C (lit. 125 – 127 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 8.10 (s, 1H, C3-H), 7.97 (d, J = 1.2 Hz, 1H, C5-H), 7.61 (d, J = 9.4 Hz, 1H, C8-H), 7.16 (dd, J = 9.4, 1.6 Hz, 1H, C7-H), 2.37 (d, J = 1.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 144.8, 143.5, 130.0, 124.4, 123.9, 118.5, 115.1, 18.2; FT-IR ν_{max} (neat) 810, 1265, 1690, 2816, 2854, 2924; HRMS (ESI, *m/z*) calcd for $C_9H_9N_2O^+$ $[M+H]^+$: 161.0709, found: 161.0722.

6-Chloroimidazo[1,2-a]pyridine-2-carbaldehyde (55e).



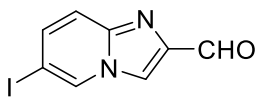
White solid (0.061 g, 84%); MP 185 – 187 °C (lit. 186 – 187 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H, CHO), 8.26 (d, J = 1.0 Hz, 1H, C3-H), 8.15 (s, 1H, C5-H), 7.67 (d, J = 9.7 Hz, 1H, C8-H), 7.28 (dd, J = 8.2, 1.5 Hz, 1H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 144.3, 144.0, 128.3, 124.3, 122.9, 119.7, 115.5; FT-IR ν_{max} (neat) 818, 1172, 1690, 2839, 2924, 3009; HRMS (ESI, *m/z*) calcd for $C_8H_6ClN_2O^+$ $[M+H]^+$: 181.0163, found: 181.0169.

6-Bromoimidazo[1,2-a]pyridine-2-carbaldehyde (55f).



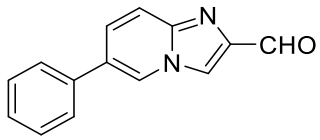
White solid (0.068 g, 89%); MP 205 – 206 °C (lit. 207 – 208 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, CHO), 8.37 (dd, J = 1.7, 0.8 Hz, 1H, C5-H), 8.14 (s, 1H, C3-H), 7.63 (d, J = 9.7 Hz, 1H, C8-H), 7.38 (dd, J = 9.7, 1.8 Hz, 1H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 144.1, 130.4, 126.5, 119.9, 115.1, 109.4; FT-IR ν_{max} (neat) 810, 1257, 1690, 2847, 2924, 2955; HRMS (ESI, *m/z*) calcd for $C_8H_6BrN_2O^+$ $[M+H]^+$: 224.9658, found: 224.9664.

6-Iodoimidazo[1,2-a]pyridine-2-carbaldehyde (55g).



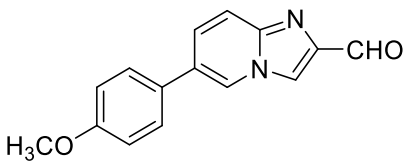
White solid (0.035 g, 44%); MP 209 – 210 °C (lit. 210 – 211 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H, CHO), 8.48 (s, 1H, C5-H), 8.11 (s, 1H, C3-H), 7.50 (s, 1H, C8-H), 7.48 (d, J = 1.5 Hz, 1H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 139.0, 129.9, 126.6, 115.4, 109.8, 73.1; FT-IR ν_{max} (neat) 810, 1257, 1690, 2847, 2924, 2955; HRMS (ESI, *m/z*) calcd for $C_8H_6IN_2O^+$ $[M+H]^+$: 272.9519, found: 272.9522.

6-Phenylimidazo[1,2-a]pyridine-2-carbaldehyde (55h).



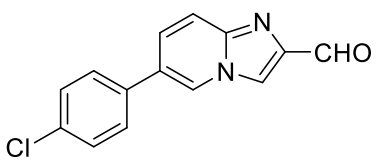
Brown liquid (0.035 g, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, CHO), 8.35 (s, 1H, C5-H), 8.24 (s, 1H, C3-H), 7.78 (d, J = 9.5 Hz, 1H, C8-H), 7.60 (d, J = 7.2 Hz, 3H, C3`-H, C4`-H & C5`-H), 7.53 (t, $J$ = 7.4 Hz, 2H, C2`-H & C6`-H), 7.49 – 7.43 (m, 1H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 145.0, 144.0, 136.3, 129.3, 129.0, 128.5, 127.7, 126.9, 123.5, 119.1, 115.7; FT-IR ν_{max} (neat) 764, 1265, 1659, 2870, 2939, 3101; HRMS (ESI, *m/z*) calcd for $C_{14}H_{11}N_2O^+$ $[M+H]^+$: 223.0866, found: 223.0870.

6-(4-methoxyphenyl)imidazo[1,2-a]pyridine-2-carbaldehyde (55i).



Sticky solid (0.033 g, 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H, CHO), 8.28 (s, 1H, C5-H), 8.21 (s, 1H, C3-H), 7.75 (d, J = 9.4 Hz, 1H, C8-H), 7.55 (dd, J = 9.5, 1.6 Hz, 1H, C7-H), 7.52 (d, J = 8.6 Hz, 2H, C2`-H & C6`-H), 7.04 (d, J = 8.7 Hz, 2H, C3`-H & C5`-H), 3.89 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 159.9, 144.9, 143.9, 128.6, 128.1, 127.7, 122.7, 118.9, 115.7, 114.7, 55.4; FT-IR ν_{max} (neat) 802, 1257, 1690, 2831, 2924, 2962; HRMS (ESI, *m/z*) calcd for $C_{15}H_{13}N_2O_2^+$[M+H]$^+$: 253.0972, found: 253.0979.

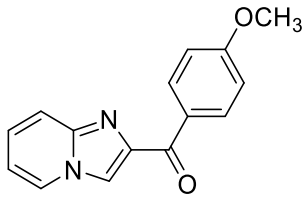
6-(4-chlorophenyl)imidazo[1,2-a]pyridine-2-carbaldehyde (55j).



Pink solid (0.040 g, 51%); MP 205 – 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, CHO), 8.34 (s, 1H, C5-H), 8.23 (s, 1H, C3-H), 7.79 (d, J = 9.5 Hz, 1H, C8-H), 7.54 (d, J = 9.3 Hz, 1H), 7.51 (d, J = 5.5 Hz, 2H, C2`-H & C6`-H), 7.49 (d, J = 8.6 Hz, 2H, C3`-H & C5`-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 145.0, 144.2, 134.8, 134.7, 129.5, 128.2, 127.9,

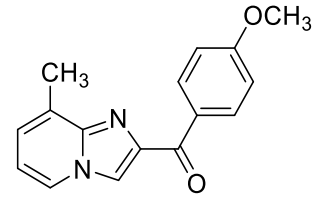
127.3, 123.5, 119.3, 115.7; FT-IR ν_{max} (neat) 895, 1265, 1659, 2870, 2939, 3101; HRMS (ESI, *m/z*) calcd for $C_{14}H_{10}ClN_2O^+$ $[M+H]^+$: 257.0476, found: 257.0479.

Imidazo[1,2-a]pyridin-2-yl(4-methoxyphenyl)methanone (55k).



Off white solid (0.038 g, 48%) MP 118 – 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 6.8 Hz, 1H, C5-H), 8.22 (s, 1H, C3-H), 7.91 (d, J = 8.7 Hz, 2H, C2`-H & C6`-H), 7.80 (d, J = 8.9 Hz, 1H, C8-H), 7.58 – 7.48 (m, 1H, C7-H), 7.14 (t, J = 6.7 Hz, 1H, C6-H), 7.04 (d, J = 8.7 Hz, 2H, C3`-H & C5`-H), 3.92 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 162.9, 148.9, 144.8, 131.8, 131.0, 129.1, 128.8, 123.5, 117.7, 114.9, 113.9, 55.5; FT-IR ν_{max} (neat) 895, 1257, 1612, 2970, 3101; HRMS (ESI, *m/z*) calcd for $C_{15}H_{13}N_2O_2^+$ $[M+H]^+$: 253.0972, found: 253.0978.

(4-Methoxyphenyl)(8-methylimidazo[1,2-a]pyridin-2-yl)methanone (55l).

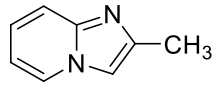


Cream solid, (0.028 g, 35%); MP 139 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H, C3-H), 9.53 (d, J = 6.7 Hz, 1H, C5-H), 7.81 (d, J = 8.7 Hz, 2H, C2`-H & C6`-H), 7.39 (d, J = 7.0 Hz, 1H, C7-H), 7.08 (d, J = 8.7 Hz, 2H, C3`-H & C5`-H), 7.06 – 7.01 (m, 1H, C6-H), 3.91 (s, 3H, O-CH_3), 2.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 179.5, 160.9, 157.8, 131.2, 129.4, 127.3, 126.5, 125.0, 120.9, 115.1, 114.3, 55.4, 17.0; FT-IR ν_{max} (neat) 795, 1257, 1643, 2962; HRMS (ESI, *m/z*) calcd for $C_{16}H_{15}N_2O_2^+$ $[M+H]^+$: 267.1128, found: 267.1133.

3.4.4 Representative Procedure for The Synthesis of 2-Alkylimidazo[1,2-*a*]pyridines (58)

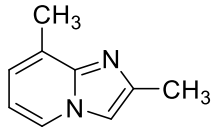
2-Amino-1-(prop-2-ynyl)pyridinium bromide (**57a**) (0.100 g, 0.46 mmol), 2N NaOH (aq.) (2.0 equiv.), water (5 mL) were mixed in a clean 25 mL round bottom flask. The resulting reaction mixture was stirring for 5 minutes at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction the product was extracted by ethyl acetate (20 mL × 2). The combined organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure to give pure **58a** in 97% yield.

2-Methylimidazo[1,2-a]pyridine (58a).



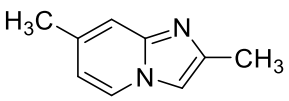
Brown viscous liquid, Yield 97%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.8 Hz, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.32 (s, 1H), 7.15 – 7.05 (m, 1H), 6.71 (td, J = 6.7, 0.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 143.0, 125.1, 124.2, 116.6, 111.9, 109.4, 14.1.

2,8-Dimethylimidazo[1,2-a]pyridine (58b).



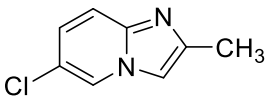
Brown viscous liquid, Yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 6.7 Hz, 1H), 7.32 (s, 1H), 6.94 – 6.88 (m, 1H), 6.63 (t, J = 6.8 Hz, 1H), 2.59 (s, 3H), 2.47 (d, J = 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.5, 126.5, 123.0, 122.8, 111.7, 109.9, 17.1, 14.4.

2,7-Dimethylimidazo[1,2-a]pyridine (58c).



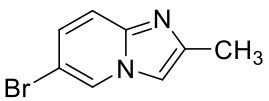
Brown viscous liquid, Yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 6.8 Hz, 1H), 7.24 (s, 1H), 7.23 (s, 1H), 6.54 (d, J = 6.6 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.9, 134.7, 124.3, 115.2, 114.3, 108.7, 21.2, 14.3.

6-Chloro-2-methylimidazo[1,2-a]pyridine (58e).



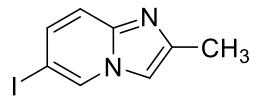
Brown viscous liquid, Yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 1.2 Hz, 1H), 7.45 (d, J = 9.5 Hz, 1H), 7.32 (s, 1H), 7.08 (dd, J = 9.5, 2.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 143.4, 125.2, 122.9, 119.8, 117.0, 109.9, 14.3.

6-Bromo-2-methylimidazo[1,2-a]pyridine (58f).



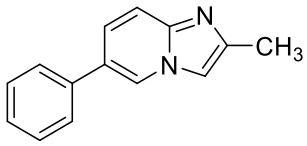
Brown viscous liquid, Yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.1 Hz, 1H), 7.39 (d, J = 9.5 Hz, 1H), 7.30 (s, 1H), 7.16 (dd, J = 9.5, 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.4, 127.2, 125.1, 117.3, 109.7, 106.2, 14.3.

6-Iodo-2-methylimidazo[1,2-a]pyridine (58g).



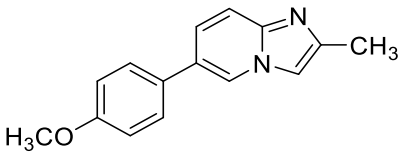
Brown viscous liquid, Yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.30 (m, 1H), 7.33 (d, J = 9.3 Hz, 1H), 7.30 (s, 1H), 7.29 (d, J = 6.5 Hz, 1H), 2.46 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.6, 131.8, 130.0, 117.9, 109.3, 74.3, 14.3.

2-Methyl-6-phenylimidazo[1,2-a]pyridine (58h).



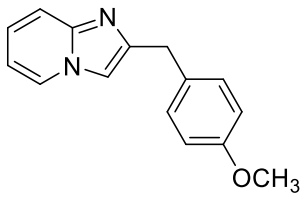
Brown viscous liquid, Yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 0.8 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 2.2 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.43 – 7.37 (m, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.9, 137.4, 129.0, 127.7, 126.8, 126.3, 124.7, 122.5, 116.6, 109.9, 14.4.

6-(4-Methoxyphenyl)-2-methylimidazo[1,2-a]pyridine (58i).



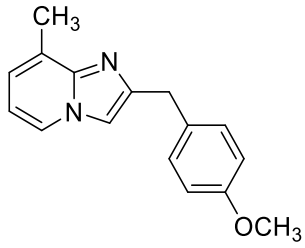
Brown viscous liquid, Yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.37 (s, 2H), 7.00 (d, J = 7.6 Hz, 2H), 3.87 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 144.1, 143.6, 129.8, 127.9, 126.0, 124.8, 121.8, 116.4, 114.4, 109.8, 55.4, 14.3.

2-(4-Methoxybenzyl)imidazo[1,2-a]pyridine (58j).



Brown viscous liquid, Yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 6.7 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 31.8 Hz, 2H), 7.15 – 7.08 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.72 (t, J = 6.6 Hz, 1H), 4.11 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 147.8, 145.2, 131.7, 129.9, 125.4, 124.1, 117.1, 113.9, 111.8, 109.7, 55.2, 34.8.

2-(4-Methoxybenzyl)-8-methylimidazo[1,2-a]pyridine (58k).

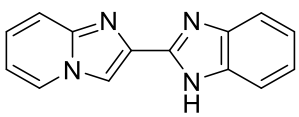


Brown viscous liquid, Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 5.9 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.23 (s, 1H), 7.05 (s, 1H), 6.84 (d, J = 7.3 Hz, 2H), 6.50 (d, J = 5.5 Hz, 1H), 4.05 (s, 2H), 3.77 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 147.3, 145.6, 135.0, 131.8, 129.9, 124.6, 115.4, 114.4, 113.8, 109.0, 55.2, 34.7, 21.3.

3.4.5 Experimental Procedure for Synthesis of 60

An oven dried 10 mL round bottom flask was charged with **55a** (0.5 mmol), *o*-phenylenediamine (**66**) (0.5 mmol), DMF (2 mL) and *p*-TsOH (0.75 mmol). The reaction mixture was heated and stirred at 110 °C for 8 h. The reaction mixture was cooled, neutralized with aqueous Na_2CO_3 (10 mL) and product was extracted into ethyl acetate (2 ×10 mL). The organic phase was dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure on a rotatory evaporator. The crude product was purified by column chromatography over silica gel using hexane: ethyl acetate (0-30%, *v/v*) to afford pure **60** in 78% yield.

2-(Imidazo[1,2-a]pyridin-2-yl)-1H-benzo[d]imidazole (60).



Yellow solid, Yield 78%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H, NH), 8.66 (d, J = 6.7 Hz, 1H, C5-H), 8.59 (s, 1H, C3-H), 7.66 (d, J = 9.1 Hz, 1H, C8-H), 7.59 – 7.48 (m, 2H, C4`-H & C7`-H), 7.40 – 7.31 (m, 1H, C7-H), 7.23 – 7.14 (m, 2H, C5`-H & C6`-H), 7.01 (t, J = 6.6 Hz, 1H, C6-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.0, 145.2, 137.0, 127.8, 126.3, 122.9, 122.0, 118.8, 117.2, 113.4, 112.6; HRMS (ESI *m/z*) calcd for $C_{14}H_{11}N_4^+$ $[M+H]^+$: 235.0978, found: 235.0985.

3.5 REFERENCES

[1] L. S. K. Tara, *Current Topics in Medicinal Chemistry* **2016**, *16*, 3274-3302.

[2] M. Yadav, D. Behera, S. Kumar, *Surface and Interface Analysis* **2014**, *46*, 640-652.

[3] Y. Shigemitsu, T. Mutai, H. Houjou, K. Araki, *The Journal of Physical Chemistry A* **2012**, *116*, 12041-12048.

[4] Y. Ishida, K. Ohta, S. Itoh, T. Nakahama, H. Miki, H. Yoshikawa, *Journal of Pesticide Science* **1993**, *18*, 175-182.

[5] K. Pericherla, P. Kaswan, K. Pandey, A. Kumar, *Synthesis* **2015**, *47*, 887-912.

[6] J. Koubachi, S. El Kazzouli, M. Bousmina, G. Guillaumet, *European Journal of Organic Chemistry* **2014**, *2014*, 5119-5138.

[7] A. E. Tschitschibabin, *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1925**, *58*, 1704-1706.

[8] S. Ponnala, S. T. V. S. Kiran Kumar, B. A. Bhat, D. Prasad Sahu, *Synthetic Communications* **2005**, *35*, 901-906.

[9] D.-J. Zhu, J.-X. Chen, M.-C. Liu, J.-C. Ding, H.-Y. Wu, *Journal of the Brazilian Chemical Society* **2009**, *20*, 482-487.

[10] D. L. Kong, X. H. Wang, Z. F. Shi, M. S. Wu, Q. Lin, X. Wang, *Journal of Chemical Research* **2016**, 529-531.

[11] Y.-Y. Xie, Z.-C. Chen, Q.-G. Zheng, *Synthesis* **2002**, *2002*, 1505-1508.

[12] Z.-G. Le, Z.-B. Xie, J.-P. Xu, *Molecules* **2012**, *17*, 13368-13375.

[13] B. M. Babu, G. S. Kumar, P. B. Thakur, V. M. Bangade, H. Meshram, *Tetrahedron Letters* **2014**, *55*, 3473-3477.

[14] M. Soltani, I. Mohammadpoor-Baltork, A. R. Khosropour, M. Moghadam, S. Tangestaninejad, V. Mirkhani, *Journal of the Iranian Chemical Society* **2015**, *12*, 1369-1380.

[15] S. Choudhary, M. K. Muthyala, A. Kumar, *RSC Advances* **2014**, *4*, 47368-47372.

[16] R. Ducray, P. Boutron, M. Didelot, H. Germain, F. Lach, M. Lamorlette, A. Legriffon, M. Maudet, M. Ménard, G. Pasquet, F. Renaud, I. Simpson, G. L. Young, *Tetrahedron Letters* **2010**, *51*, 4755-4758.

[17] M. R. Collins, Q. Huang, M. A. Ornelas, S. A. Scales, *Tetrahedron Letters* **2010**, *51*, 3528-3530.

[18] S. B. Bhagat, V. N. Telvekar, *Tetrahedron Letters* **2017**, *58*, 3662-3666.

[19] M. H. Shinde, U. A. Kshirsagar, *Green Chemistry* **2016**, *18*, 1455-1458.

[20] C. Huo, J. Tang, H. Xie, Y. Wang, J. Dong, *Organic Letters* **2016**, *18*, 1016-1019.

[21] R. I. Iskandar, N. Kian-Hong, C. Gaik-Khuan, J. Stephan, *Advanced Synthesis & Catalysis* **2016**, *358*, 364-369.

[22] A. J. Stasyuk, M. Banasiewicz, M. K. Cyrański, D. T. Gryko, *The Journal of Organic Chemistry* **2012**, *77*, 5552-5558.

[23] D. Kour, R. Khajuria, K. K. Kapoor, *Tetrahedron Letters* **2016**, *57*, 4464-4467.

[24] P. Ghosh, B. Ganguly, B. Kar, S. Dwivedi, S. Das, *Synthetic Communications* **2018**, *48*, 1076-1084.

[25] Z. Fei, Y.-P. Zhu, M.-C. Liu, F.-C. Jia, A.-X. Wu, *Tetrahedron Letters* **2013**, *54*, 1222-1226.

[26] Y. Tachikawa, Y. Nagasawa, S. Furuhashi, L. Cui, E. Yamaguchi, N. Tada, T. Miura, A. Itoh, *RSC Advances* **2015**, *5*, 9591-9593.

[27] X. Wang, L. Ma, W. Yu, *Synthesis* **2011**, 2445-2453.

[28] L. Ma, X. Wang, W. Yu, B. Han, *Chemical Communications* **2011**, *47*, 11333-11335.

[29] S. K. Lee, J. K. Park, *The Journal of Organic Chemistry* **2015**, *80*, 3723-3729.

[30] J. Tan, P. Ni, H. Huang, G.-J. Deng, *Organic & Biomolecular Chemistry* **2018**, *16*, 4227-4230.

[31] V. M. Bangade, B. C. Reddy, P. B. Thakur, B. M. Babu, H. Meshram, *Tetrahedron Letters* **2013**, *54*, 4767-4771.

[32] Z. Chen, Y. Wen, G. Luo, M. Ye, Q. Wang, *RSC Advances* **2016**, *6*, 86464-86467.

[33] P. R. Adiyala, G. S. Mani, J. B. Nanubolu, K. C. Shekar, R. A. Maurya, *Organic Letters* **2015**, *17*, 4308-4311.

[34] D. Jeffery, R. H. Prager, D. Turner, M. Dreimanis, *Tetrahedron* **2002**, *58*, 9965-9972.

[35] J. Khalafy, D. Setamdideh, K. Dilmaghani, *Molecules* **2002**, *7*, 907-916.

[36] V. B. Sokolov, A. Y. Aksinenko, I. V. Martynov, *Russian Chemical Bulletin* **2005**, *54*, 470-471.

[37] A. Y. Aksinenko, T. V. Goreva, T. A. Epishina, V. B. Sokolov, *Journal of Fluorine Chemistry* **2012**, *137*, 105-107.

[38] A. K. Nadipuram, S. M. Kerwin, *Tetrahedron* **2006**, *62*, 3798-3808.

[39] Z. G. Aliev, L. O. Atovmyan, S. S. Kataev, V. V. Zalesov, *Chemistry of Heterocyclic Compounds* **2007**, *43*, 377-381.

[40] S. Husinec, R. Markovic, M. Petkovic, V. Nasufovic, V. Savic, *Organic Letters* **2011**, *13*, 2286-2289.

[41] D. Chandra Mohan, N. B. Sarang, S. Adimurthy, *Tetrahedron Letters* **2013**, *54*, 6077-6080.

[42] D. Chandra Mohan, S. Nageswara Rao, S. Adimurthy, *The Journal of Organic Chemistry* **2013**, *78*, 1266-1272.

[43] Y. He, W. Yin, J. Wang, J. Huang, X. Pang, C. Gan, F. Yang, C. Huang, *Organic Chemistry Frontiers* **2018**, *5*, 1772-1776.

[44] D. Yang, K. Yan, W. Wei, Y. Liu, M. Zhang, C. Zhao, L. Tian, H. Wang, *Synthesis* **2016**, *48*, 122-130.

[45] D. Yang, K. Yan, W. Wei, G. Li, S. Lu, C. Zhao, L. Tian, H. Wang, *The Journal of Organic Chemistry* **2015**, *80*, 11073-11079.

[46] H. Cao, L. Chen, J. Liu, H. Cai, H. Deng, G. Chen, C. Yan, Y. Chen, *RSC Advances* **2015**, *5*, 22356-22360.

[47] P. Liu, Y. Gao, W. Gu, Z. Shen, P. Sun, *The Journal of Organic Chemistry* **2015**, *80*, 11559-11565.

[48] K. Monir, A. K. Bagdi, M. Ghosh, A. Hajra, *The Journal of Organic Chemistry* **2015**, *80*, 1332-1337.

[49] D. Kour, A. Gupta, K. K. Kapoor, V. K. Gupta, Rajnikant, D. Singh, P. Das, *Organic & Biomolecular Chemistry* **2018**, *16*, 1330-1336.

[50] A. Vilsmeier, A. Haack, *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1927**, *60*, 119-122.

[51] A. Kamal, V. S. Reddy, S. Karnewar, S. S. Chourasiya, A. B. Shaik, G. B. Kumar, C. Kishor, M. K. Reddy, M. P. Narasimha Rao, A. Nagabhushana, K. V. S. Ramakrishna, A. Addlagatta, S. Kotamraju, *ChemMedChem* **2013**, *8*, 2015-2025.

[52] H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang, Q. Zhu, *Angewandte Chemie International Edition* **2011**, *50*, 5678-5681.

[53] H. Cao, S. Lei, N. Li, L. Chen, J. Liu, H. Cai, S. Qiu, J. Tan, *Chemical Communications* **2015**, *51*, 1823-1825.

[54] S. Xiang, H. Chen, Q. Liu, *Tetrahedron Letters* **2016**, *57*, 3870-3872.

[55] J. B. Bharate, S. Abbat, P. V. Bharatam, R. A. Vishwakarma, S. B. Bharate, *Organic & Biomolecular Chemistry* **2015**, *13*, 7790-7794.

[56] C. Rao, S. Mai, Q. Song, *Organic Letters* **2017**, *19*, 4726-4729.

[57] G. Kibriya, A. K. Bagdi, A. Hajra, *Organic & Biomolecular Chemistry* **2018**, *16*, 3473-3478.

[58] S. Dalapati, B. K. Paul, S. Jana, N. Guchhait, *Sensors and Actuators B: Chemical* **2011**, *157*, 615-620.

[59] B. Gabriele, R. Mancuso, G. Salerno, R. C. Larock, *The Journal of Organic Chemistry* **2012**, *77*, 7640-7645.

[60] A.-Y. Peng, Y.-X. Ding, *Organic Letters* **2004**, *6*, 1119-1121.

[61] A. K. Verma, V. Rustagi, T. Aggarwal, A. P. Singh, *The Journal of Organic Chemistry* **2010**, *75*, 7691-7703.

[62] G. Bartolo, M. Raffaella, C. L. Richard, *Current Organic Chemistry* **2014**, *18*, 341-358.

[63] M. R. Chapman, M. H. T. Kwan, G. E. King, B. A. Kyffin, A. J. Blacker, C. E. Willans, B. N. Nguyen, *Green Chemistry* **2016**, *18*, 4623-4627.

[64] I. Kim, S. G. Kim, J. Y. Kim, G. H. Lee, *Tetrahedron Letters* **2007**, *48*, 8976-8981.

[65] H. Batchu, S. Batra, *Tetrahedron Letters* **2014**, *55*, 6236-6239.