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Graphical Abstract

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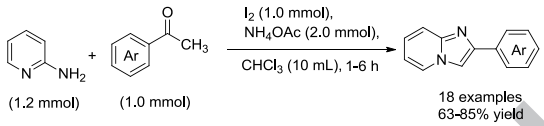

Reaction conditions

room temp.: Ar = C_6H_5, 4-MeC_6H_4, 3-$OMeC_6H_4$, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Br-4-ClC_6H_3, 2-OH-5-MeC_6H_3, 2-Cl-6-OHC_6H_3, 2-Br-6-OHC_6H_3;
Reflux: Ar = 3,4-$(OMe)_2C_6H_3$, furan-2-yl, thiophen-2-yl, 1-OH-naphthalen-2-yl, 2*H*-chromen-2-one

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Iodine-ammonium acetate promoted reaction between 2-aminopyridine and aryl methyl ketones: a novel approach towards the synthesis of 2-arylimidazo[1,2-*a*]pyridines

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ABSTRACT

I_2-NH_4OAc was found to be an efficient system for the metal-free synthesis of diversely substituted imidazo[1,2-*a*]pyridines **3a-r** from 2-aminopyridine **1** and aryl methyl ketones **2a-r** in one pot. 2-Arylimidazo[1,2-*a*]pyridines **3a-r** were obtained in good to excellent yields *via in situ* generation of an Ortoleva-King intermediate (pyridinium iodide), followed by NH_4OAc-assisted cyclization.

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Imidazo[1,2-*a*]pyridines are indispensable biologically active nitrogen containing heterocyclic scaffolds and exhibit a wide range of biological activities.[1] These are broadly investigated in materials science and organometallics.[2] Imidazo[1,2-*a*]pyridines are recognized as a 'privileged scaffold' because these have got the significant importance in pharmaceutical industry owing to their interesting biological activities such as anti-cancer,[3] anti-viral,[4] anti-inflammatory,[5] analgesic, anti-pyretic,[6] anti-ulcer[7] and anti-bacterial.[8] Prospective radio ligands for positron emission tomography (PET) for *β*-amyloid in Alzheimer's disease based on imidazo[1,2-*a*] derivatives have been widely reported.[9] They also act as GABA and benzodiazepine receptor agonists[10] and cardiotonic agents.[11] These structures are also found in clinical drugs such as alpidem,[12] zolpidem,[10] olprinone,[13] zolimidine[6] and anti-HIV drug (GSK812397),[14] etc (Figure 1). Furthermore, 2-(2-hydroxy phenyl)imidazo[1,2-*a*]pyridines exhibit excellent excited state intramolecular proton transfer (ESIPT)[15] thereby embracing significance in the field of optoelectronics. Prevalence of these skeletons in biologically active compounds continues to give chemists a momentum to develop novel methods for their synthesis.

Owing to the attractive properties of imidazo[1,2-*a*]pyridines, various methods to synthesize this core have been developed and reviewed.[16a-c] Initial coupling reaction of endocyclic nitrogen of 2-aminopyridine with various reagents such as acetophenones,[16d] *α*-haloketones,[16e] nitroalkenes,[16f] *α*-diazoketones,[16g] alkynes derivatives[16h] etc followed by cyclization *via* exocyclic amino group generates a variety of imidazo[1,2-*a*]pyridines. These reactions occur in the presence of various Bronsted or Lewis acids,[17,18] metal catalysts (Cu,[19] Fe,[20] Zn,[21]) and a carbocatalyst graphene oxide.[22] Few literature reports are available for the synthesis of 2-arylimidazo[1,2-*a*]pyridines from 2-aminopyridine and aryl methyl ketones *via in situ* generation of pyridinium iodide, first reported by Ortoleva[23] and King.[24] One of these reports has explored the I_2 catalysed Ortoleva-King reaction in combination with a strong base NaOH[25] for the intramolecular cyclization of pyridinium iodide to access *o*-hydroxy substituted 2-arylimidazo[1,2-*a*]pyridines with a limited substrate scope while the other reports make use of copper containing catalytic systems such as $CuI/In(CF_3SO_3)_3$[26] and I_2/CuO.[19d] These methods are suitable for a variety of substrates but suffer from one or more disadvantages such as high cost, long reaction time, inert and anhydrous conditions, low yields, tedious workup and product purification procedures. In view of these drawbacks and our quest to develop efficient and milder methods,[27] we contemplated the replacement of the stronger base NaOH with milder NH_4OAc in the Stasyuk's protocol.[25]

Ammonium acetate is known to be a mild base for effective Knoevenagel condensation[28] and has also been demonstrated as an important source of ammonia in the synthesis of various heterocyclic scaffolds.[29] Further, iodine-catalysed reactions are

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found to be highly efficient alternatives in C-N bond formation as compared to transition metal-catalysed reactions and therefore have attracted great interest of synthetic chemists. Iodine is inexpensive, readily available,[30] environmentally-benign as compared to transition metal catalysts[31] and operates under mild conditions.[32] Further, most iodine catalysed reactions involve domino reaction sequences[33] forming several bonds in a single operation thereby imparting molecular diversity and complexity among the compounds synthesized. Some of the well-known reactions include one-pot synthesis of 2-acylbenzothiazoles *via* iodine promoted domino oxidative cyclization,[34] one-pot synthesis of pyrrolo[1,2-*a*]quinoxaline and imidazo[1,5-*a*]quinoxaline derivatives *via* sp^3 and sp^2 C-H dehydrogenative coupling,[35] divergent synthesis of benzimidazoles, dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines,[36] oxidative esterification of *o*-alkynylaldehydes,[37] one-pot synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*] pyridines from alkylaryl ketones and 2-aminopyridines.[38]

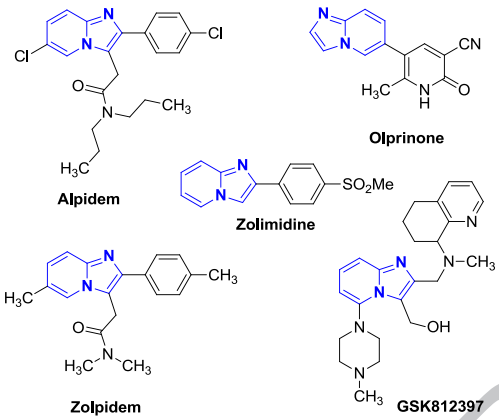
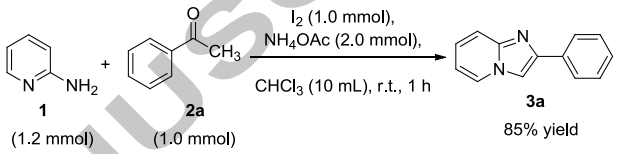


Figure 1. Bioactive drugs containing imidazo[1,2-*a*]pyridine nucleus.

One-pot reaction is much desired by the chemists because it saves time and resources by eliminating the separation processes for purification of the chemical intermediates and also improves the overall yield. We wished to develop one-pot method for the synthesis of 2-arylimidazo[1,2-*a*]pyridines by the condensation of 2-aminopyridine with various arylmethyl ketones using Ortoleva-King conditions followed by intramolecular cyclization with NH_4OAc.

The preliminary investigation was performed using 2-aminopyridine **1** and acetophenone **2a** as the model substrates. The initial reaction between 2-aminopyridine **1** (1.2 mmol), acetophenone **2a** (1.0 mmol), I_2 (1.0 mmol) and NH_4OAc (2.0 mmol) in $CHCl_3$ at room temperature for 1 h led to the formation of the desired product 2-phenylimidazo[1,2-*a*]pyridine[39] **3a** in 85% yield (Scheme 1).



Scheme 1. Synthesis of 2-phenylimidazo[1,2-*a*]pyridine **3a**

During this study, a comparison between the literature methods (entries **1-6**)[19c-d, 25,26,39,40] and present work (entries **7-10**) was made and it became evident from the Table 1 that our reaction conditions (entry **7**) were milder with better or comparable yields. Different ratios of iodine and ammonium acetate to effect this reaction (entries **7-10**) revealed the optimum requirement as the usage of 1 and 2 equivalents of I_2 and NH_4OAc with respect to ketone (entry **7**, 85% yield).

Table 1. Comparison of model reaction with literature reports.[a]

Entry	Catalyst	Ligand (10 mol%)	Additive	Solvent	Oxidant	Temp (ºC)/ Time (h)	Yield (%)[b]
1	$Cu(OAc)_2.H_2O$ (0.1 equiv)	1,10-phenanthroline	ZnI_2 (0.1 equiv)	Dichlorobenzene	O_2 (1atm)	120/24	84[39]
2	CuI (0.2 equiv)	-	-	1,4-dioxane	-	100/14	71[19c]
3[c]	CuI (0.2 equiv)	-	$BF_3.Et_2O$ (0.1 equiv)	Neat	O_2 (1atm)	40/24	70[40]
4[d]	CuI (0.05 equiv)	-	$In(CF_3SO_3)_3$ (0.01 equiv)	NMP	O_2 (1atm)	100/30	81[26]
5	Iodine (1.2 equiv)	-	aq. NaOH (45%)	-	-	100-110/	55[25]
6[e]	Iodine (1.1 equiv)	-	CuO (1.1 equiv)	MeOH	-	reflux/12	82[19d]
7	**Iodine (1.0 equiv)**	-	**NH_4OAc (2.0 equiv)**	**$CHCl_3$**	-	**r.t./1**	**85**
8	Iodine (2.0 equiv)	-	NH_4OAc (2.0 equiv)	$CHCl_3$	-	r.t./1	80
9	Iodine (1.0 equiv)	-	NH_4OAc (3.0 equiv)	$CHCl_3$	-	r.t./1	82
10	Iodine (0.5 equiv)	-	NH_4OAc (1.0 equiv)	$CHCl_3$	-	r.t./1	63

[a]Reaction Conditions: **1** (1.2 equiv), **2a** (1.0 equiv), at a given temperature and time; [b]Isolated yields; [c]**2a** (3.0 equiv) was used; [d]**2a** (2.0 equiv) was used; [e]**1** (1.0 equiv) was used.

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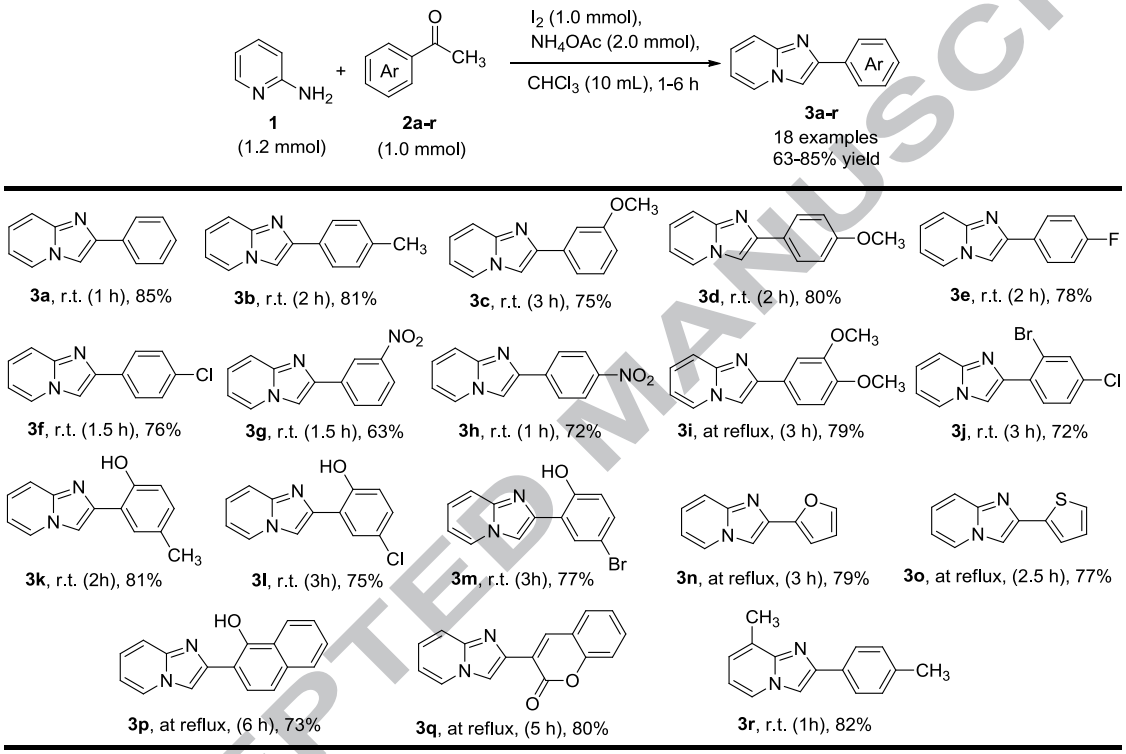
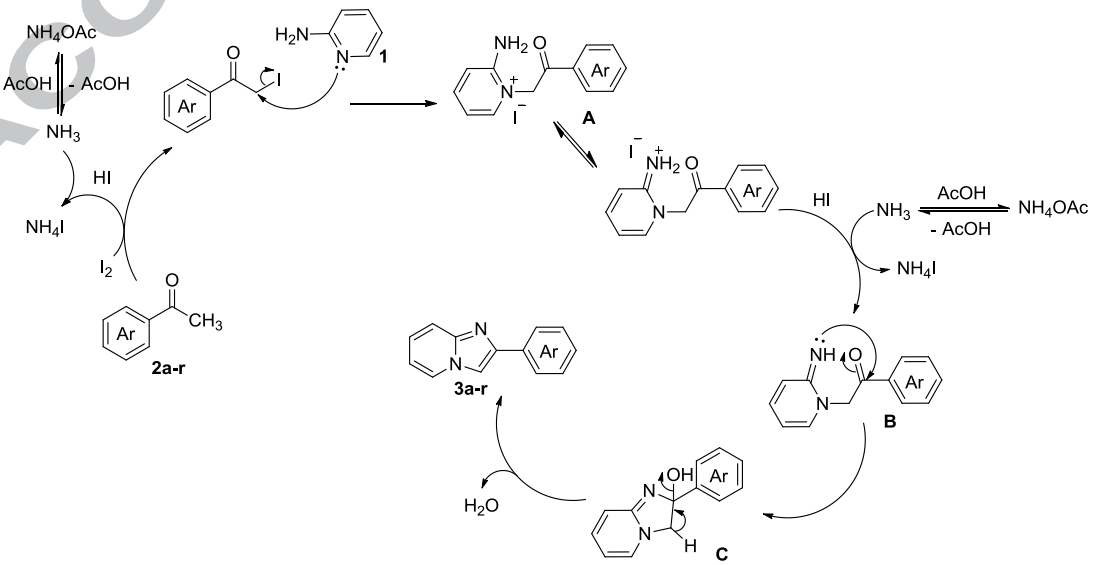
Replacement of NH_4OAc with NH_4OH, NH_4HCO_3, $NH_4H_2PO_4$, $(NH_4OOCH)_2$, $NH_4(OOCH)$, $(NH_4)_2CO_3$, NH_4Cl, NH_4NO_3, NH_4SCN, Et_3N or DMAP as well as $CHCl_3$ with CH_3CN, 1,2-DCE, DMF, EtOH, *n*-BuOH or toluene did not prove beneficial toward product yield.

Under the optimized conditions, diversely substituted aryl methyl ketones were investigated[41] and the results are summarized in Table 2. It was also noticed that for some sterically hindered and electron rich substrates (entries **2i**, **2n-q**), better yields were obtained under reflux. Aryl methyl ketones bearing electron donating (Me, OMe), electron withdrawing groups (F, Cl, NO_2) as well as disubstitution in the phenyl ring generated the corresponding 2-arylimidazo[1,2-*a*]pyridines (entries **3a-m**) in good to excellent yields (63-85%). Further, to establish the generality of the reaction, furan-2-yl/thiophen-2-yl methyl ketones were investigated and smooth formation of the corresponding furan-2-yl/thiophen-2-yl substituted imidazo[1,2-*a*]pyridines (entries **3n-o**) was observed with good yields (77-79%). The construction of imidazo[1,2-*a*]pyridines bearing bi-cyclic substitutions (entries **3p-q**) was also achieved under these optimized conditions. Interestingly, 3-acetyl-2*H*-chromen-2-one led to the formation of 3-(imidazo[1,2-*a*]pyridin-2-yl)-2*H*-chromen-2-one, a hybrid of imidazo[1,2-*a*]pyridine and coumarin (entry **3q**, 80% yield). The 2-aminopyridine with a methyl group in the 3-position smoothly underwent the reaction, and product (entry **3r**) was obtained in an appreciable 82% yield.

Table 2. I_2–NH_4OAc promoted synthesis of 2-arylimidazo[1,2-*a*]pyridines **3a-r**



In line with the mechanism proposed by Zhang *et al.*,[42] following mechanism is proposed for the synthesis of 2-arylimidazo[1,2-*a*]pyridines **3a-r** as illustrated in Scheme 2.



Scheme 2. Plausible mechanism for the formation of 2-arylimidazo[1,2-*a*]pyridines **3a-r** with I_2-NH_4OAc.

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The first step involves the reaction of pyridine endocyclic nitrogen with the α-carbon of *in situ* generated α-iodoketone leading to the formation pyridinium salt **A**. Intramolecular cyclisation of the imine **B** generated by the deprotonation of **A** gives tetrahydroimidazo[1,2-*a*]pyridin-2-ol **C**, which upon elimination of water resulted in the formation of 2-arylimidazo[1,2-*a*]pyridines **3a-r**. HI produced during the reaction is believed to be scavenged by NH_3 produced from NH_4OAc.

In summary, we have developed an efficient, metal-free synthesis of diversely substituted 2-arylimidazo[1,2-*a*]pyridines showing versatility in terms of milder reaction conditions and easy product purification avoiding the use of column chromatography.

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41 **Procedure for the synthesis of 2-arylimidazo[1,2-*a*]pyridines (3a- r):** A mixture of 2-aminopyridine **1** (1.2 mmol), aryl methyl ketone **2a-r** (1.0 mmol), I_2 (1.0 mmol) and NH_4OAc (2.0 mmol) in $CHCl_3$ (10 mL) in a 25 mL

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round-bottomed flask was stirred at room temperature until the completion of reaction (Table 2). The reaction mixture was further diluted with 20 mL of $CHCl_3$, washed with saturated solution of $Na_2S_2O_3$ (2×10 mL), water (1×10 mL), brine (1×10 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed and the residue after recrystallisation with EtOH afforded the desired 2-arylimidazo[1,2-*a*]pyridines (**3a-r**, 63-85%). For entries **2i** and **2n-q**, reaction was performed under reflux.

42 Wang, F. –J.; Xu, H.; Xin, M.; Zhang, Z. *Mol. Divers*. **2016**, *20*, 659.

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Iodine-ammonium acetate promoted reaction between 2-aminopyridine and aryl methyl ketones: a novel approach towards the synthesis of 2-arylimidazo[1,2-*a*]pyridines

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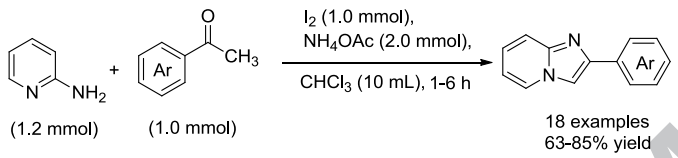
I_2-NH_4OAc was found to be an efficient system for the metal-free synthesis of diversely substituted imidazo[1,2-*a*]pyridines from 2-aminopyridine and aryl methyl ketones in one pot. 2-Arylimidazo[1,2-*a*]pyridines were obtained in good to excellent yields *via in situ* generation of an Ortoleva-King intermediate (pyridinium iodide), followed by NH_4OAc-assisted cyclization.



Reaction conditions

room temp.: Ar = C_6H_5, 4-MeC_6H_4, 3-$OMeC_6H_4$, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Br-4-ClC_6H_3, 2-OH-5-MeC_6H_3, 2-Cl-6-OHC_6H_3, 2-Br-6-OHC_6H_3;
Reflux: Ar = 3,4-$(OMe)_2C_6H_3$, furan-2-yl, thiophen-2-yl, 1-OH-naphthalen-2-yl, 2*H*-chromen-2-one

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Highlights

- An expedient, metal-free, one-pot protocol for the synthesis of diversely substituted 2-arylimidazo[1,2-*a*]pyridines
- Usage of milder reaction conditions
- Easy product isolation without column chromatography purification.
- The synthesis of novel 3-(imidazo[1,2-*a*]pyridin-2-yl)-2*H*-chromen-2-one **3q**, a hybrid of imidazo[1,2-*a*]pyridine and coumarin, has also been presented.

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