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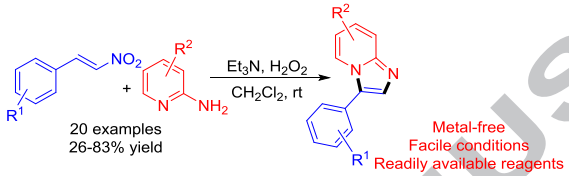

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Metal-free, base catalyzed oxidative amination and denitration reaction: regioselective synthesis of 3-arylimidazo[1,2-*a*]pyridines

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ABSTRACT

A metal-free, regioselective strategy for the synthesis of 3-arylimidazo[1,2-*a*]pyridines from β-nitrostyrenes and 2-aminopyridines using triethylamine as the catalyst and H_2O_2 (30% aq.) as the oxidant is reported. The use of an inexpensive base and facile reaction conditions make this strategy a practical alternative for the synthesis of 3-arylimidazo[1,2-*a*]pyridines.

Nitrogen-bridgehead fused heterocycles containing an imidazole ring are a common structural moiety in pharmacologically significant molecules and possess several biological activities on a wide range of targets. Among them, imidazo[1,2-*a*]pyridine is one of the most common and possesses remarkable biological properties.[1] The imidazo[1,2-*a*]pyridine moiety is found in several natural products and commercially marketed drugs such as zolpidem,[2a] olprinone,[2b] zolimidine[2c] and saripidem.[2d] Due to their biological importance, numerous synthetic approaches have been developed to gain access to substituted imidazo[1,2-*a*]pyridines.[3]

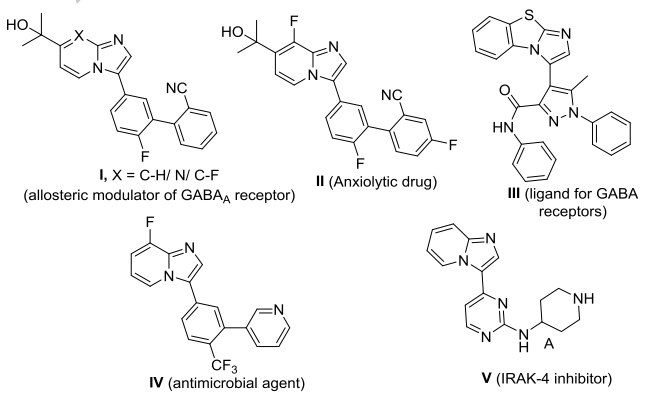


Figure 1. Structures of selected bioactive 3-arylimidazo[1,2-*a*]pyridines

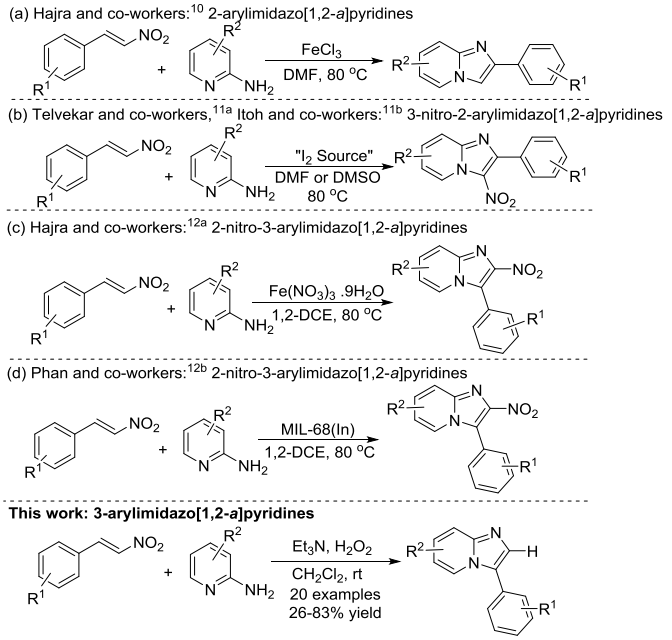
Most of these strategies focus on the synthesis of 2-aryl substituted imidazo[1,2-*a*]pyridines and approaches for the preparation of its regioisomer, i.e. 3-aryl substituted imidazo[1,2-*a*]pyridines, are rather limited.

Various transition metal-catalyzed strategies for the preparation of 3-arylimidazo[1,2-*a*]pyridines have been reported.[8] Conversely, there are few reports on the metal-free synthesis of 3-arylimidazo[1,2-*a*]pyridines.[9] However, these strategies involve either pre-functionalization of the starting materials, employ high temperatures, or require stoichiometric reagents and fluorous solvents as a reaction medium.

The oxidative amination between 2-aminopyridines and β-nitrostyrenes has proven to be an elegant strategy for the synthesis of imidazo[1,2-*a*]pyridines (Scheme 1). 2-Aminopyridine undergoes initial nucleophilic addition in two ways which controls the regioselectivity of the product: through the exocyclic amino group leading to 2-arylimidazo[1,2-*a*]pyridines (Scheme 1a),[10] and 3-nitro-2-arylimidazo[1,2-*a*]pyridines (Scheme 1b)[11] or rarely through the endocyclic pyridinium nitrogen to give 2-nitro-3-arylimidazo[1,2-*a*]pyridines (Scheme 1c, 1d).[12]

However, to the best of our knowledge, the synthesis of 2-unsubstituted-3-arylimidazo[1,2-*a*]pyridines from 2-aminopyridines with β-nitrostyrene under metal-free condition has not been reported. Recently, we reported the metal-free oxidative amidation of aldehydes with aminopyridines employing H_2O_2 (30% aq.) as the oxidant.[13] In this context, herein we present a facile metal-free, base-catalyzed construction of 3-

arylimidazo[1,2-*a*]pyridines from β-nitrostyrene and 2-aminopyridine employing H_2O_2 (30% aq.) as the oxidant.

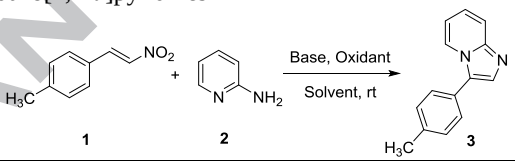


Scheme 1. Synthesis of imidazopyridines from β-nitrostyrenes and 2-aminopyridine.

In order to identify suitable reaction conditions for the preparation of 3-arylimidazo[1,2-*a*]pyridines, initial optimization studies were carried out using (*E*)-1-methyl-4-(2-nitrovinyl)benzene and 2-aminopyridine as the model substrates at room temperature (Table 1). The reaction product was compared with 2-arylimidazo[1,2-*a*]pyridines and 3-arylimidazo[1,2-*a*]pyridines from the literature in order to unambiguously confirm the formation of 3-arylimidazo[1,2-*a*]pyridines by ^{1}H and ^{13}C NMR.[9d] To begin our study, the reaction was performed in the presence of Et_3N as the base and H_2O_2 (30% aq.) as the oxidant in CH_3CN. This led to the desired product in 52% yield (Entry 1). Several polar solvents were screened and the yield was found to be highest with CH_2Cl_2 as the solvent (Entries 2-7). The yield of the desired product did not improve when the reaction was performed in non-polar solvents such as toluene, chlorobenzene and dichlorobenzene (Entries 8-10). We then shifted our focus to identifying the best oxidant for this reaction. When the reaction was performed with *tert*-butyl hydroperoxide (TBHP), the yield of the desired product decreased considerably to 42% (Entry 11) and other organic peroxides such as di-*tert*-butyl benzoyl peroxide (DTBP), dicumyl peroxide (DCP), benzoyl peroxide (BPO) or *tert*-butylperoxybenzoate (TBPB) did not afford the desired product (Entry 12). After identifying the best oxidant for this reaction, we screened various bases and it was found that organic bases worked well compared to inorganic bases and the yield was found to be optimum with Et_3N (Entries 5, 13-17). When the amount of oxidant was reduced to 2 equivalents, the product yield decreased considerably and an increase in the amount of oxidant did not increase the yield of the desired product (Entries 5, 18, 19). There was no significant increase in the yield when 0.2 equivalents of Et_3N was used (Entry 20) and under neat conditions the yield of the desired product decreased significantly (Entry 21). Thus, we arrived at the optimized reaction conditions: Et_3N (10 mol%) as the base and H_2O_2 (3.0 equiv.) as the oxidant in CH_2Cl_2 at room temperature.

With the optimized results in hand, structurally diverse β-nitrostyrenes and 2-aminopyridines were employed to investigate the scope and limitations of this base catalyzed oxidative amination (Table 2). Initially, various β-nitrostyrenes were reacted with 2-aminopyridine and the reaction was found to be tolerant of the electronic nature of the (*E*)-(2-nitrovinyl)benzenes since both electron-donating and withdrawing substituted compounds performed well, to deliver the corresponding 3-arylimidazo[1,2-*a*]pyridines in good to excellent yields (**3a–e**). However, the strongly electron withdrawing $–NO_2$ substituent in (*E*)-(2-nitrovinyl)benzene furnished the desired product in lower yield (**3f**). The steric factor had a minimal effect on this transformation, as 2-substituted (*E*)-(2-nitrovinyl)benzene gave the corresponding products in good yields (**3g–i**). In addition, with (*E*)-2-(2-nitrovinyl)naphthalene as the β-nitrostyrene variant, the corresponding product was obtained in good yield (**3j**). The expected product (**3k**) was obtained in trace amounts employing (*E*)-5-(2-nitrovinyl)benzo[*d*][1,3]dioxole as the nitroalkene variant and instead *N*-(pyridine-2-yl)benzo[*d*][1,3]dioxole-5-carboxamide was obtained. In the case of (*E*)-(2-nitroprop-1-en-1-yl) benzene, the desired product 2-methyl-3-phenylimidazo[1,2-*a*]pyridine (**3l**) was obtained along with its regioisomer, 3-methyl-2-phenylimidazo[1,2-*a*]pyridine (**3l'**) in almost equal amounts (Scheme 2).

Table 1. Optimization for the base-catalyzed construction of 3-arylimidazo[1,2-*a*]pyridines [a]



Entry	Solvent	Base	Oxidant	Yield (%)[b]
1	CH_3CN	Et_3N	H_2O_2	52
2	DMF	Et_3N	H_2O_2	45
3	H_2O	Et_3N	H_2O_2	62
4	EtOH	Et_3N	H_2O_2	23
5	DCM	Et_3N	H_2O_2	83
6	DCE	Et_3N	H_2O_2	76
7	THF	Et_3N	H_2O_2	61
8	Toluene	Et_3N	H_2O_2	46
9	PhCl	Et_3N	H_2O_2	65
10	DCB	Et_3N	H_2O_2	71
11	CH_2Cl_2	Et_3N	TBHP	42
12	CH_2Cl_2	Et_3N	Various peroxides	NR[c]
13	CH_2Cl_2	Morpholine	H_2O_2	69
14	CH_2Cl_2	Piperidine	H_2O_2	71
15	CH_2Cl_2	K_2CO_3	H_2O_2	54
16	CH_2Cl_2	Cs_2CO_3	H_2O_2	52
17	CH_2Cl_2	*t*-BuOK	H_2O_2	61
18	CH_2Cl_2	Et_3N	H_2O_2	62[d]
19	CH_2Cl_2	Et_3N	H_2O_2	79[e]
20	CH_2Cl_2	Et_3N	H_2O_2	78[f]
21	--	Et_3N	H_2O_2	34

[a] Reagents and condition: 4-methyl-β-nitrostyrene (1.2 mmol), 2-aminopyridine (1.0 mmol), base (10 mol%), oxidant (3.0 mmol), solvent (2 mL), rt.

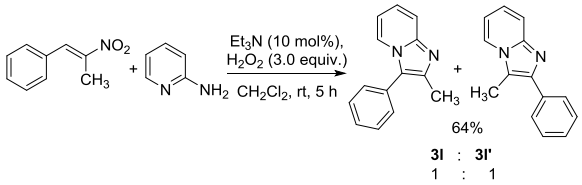
[b] Isolated yield.

[c] DTBP, DCP, BPO, TBPB.

[d] Oxidant (2.0 mmol).

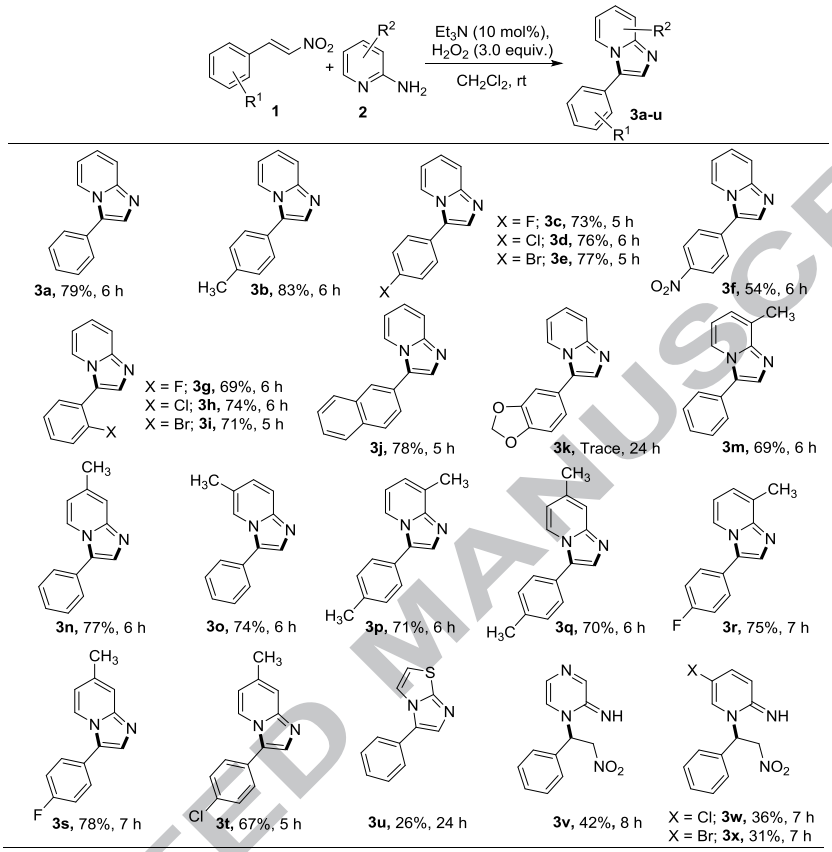
[e] Oxidant (4.0 mmol).

[f] Et_3N (20 mol%).



Scheme 2. Reaction of (*E*)-(2-nitroprop-1-en-1-yl) benzene with 2-aminopyridine.

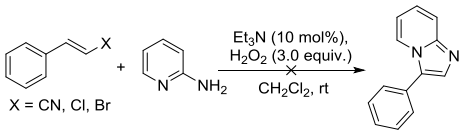
Table 2. Scope of β-nitrostyrenes and aminopyridines for the construction of 3-arylimidazo[1,2-*a*]pyridines.[a,b]



[a] Reagents and conditions: **1** (1.2 mmol), **2** (1.0 mmol), Et_3N (10 mol%), H_2O_2 (3.0 equiv.), CH_2Cl_2 (2 mL), rt.[14]

[b] Isolated yields..

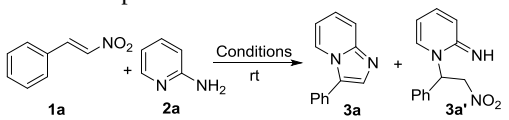
Next, we explored the scope and limitation of the process with substituted 2-aminopyridines. Methyl groups at different positions reacted well with (*E*)-(2-nitrovinyl)benzene to afford the corresponding products in good yields (**3m–o**). The scope of the reaction was further extended by varying both the substituent on the 2-aminopyridines and (*E*)-(2-nitrovinyl)benzene which gave corresponding products in good yields (**3p–t**). When 2-amino thiazole was used as the amine variant, the corresponding product was obtained in lower yield (**3u**). When the reaction was performed with 2-aminopyrazine as the amine variant, Michael adduct (**3v**) was observed along with trace amounts of the expected product. The reaction failed completely when less nucleophilic 2-aminopyridines were employed as the amine variant. When 5-chloro and 5-bromopyrin-2-amine were treated with β-nitrostyrene, only the corresponding Michael adduct was observed under the optimized reaction conditions (**3w, x**). The reaction of 5-nitropyridin-2-amine and ethyl 2-aminonicotinate with β-nitrostyrene failed to yield the corresponding 3-arylimidazo[1,2-*a*]pyridine (see ESI). When the reaction was performed with other β-substituted olefins such as cinnamonitrile, (*E*)-(2-chlorovinyl)benzene and (*E*)-(2-bromovinyl)benzene, the reaction failed completely (Scheme 3). This suggest that the highly electron withdrawing β-nitrostyrenes are ideal substrates for this oxidative cyclization.



Scheme 3. Reaction of 2-aminopyridines with β-halo and β-cyano styrenes.

In order to propose a plausible mechanism for this base-catalyzed coupling, we carried out several experiments employing (*E*)-(2-nitrovinyl)benzene and 2-aminopyridine as the model substrates (Table 3). In the absence of both base and oxidant, ~10% of Michael adduct (**3a'**) was observed (Entry 1). When the reaction was carried out only with base, Michael adduct (**3a'**) along with unreacted starting materials was observed (Entry 2). Similarly, when the reaction was carried out only with oxidant, trace amounts of the expected product was detected along with **3a'** (Entry 3). These experiments emphasize the role of the oxidant as well as the base for this oxidative amination. Under the optimized conditions, *in situ* generated Michael adduct **3a'** gave the desired 3-arylimidazo[1,2-*a*]pyridine in good yield (Entry 4). This suggests that **3a'** acts as an intermediate for this oxidative amination.

Table 3. Control experiments.[a]



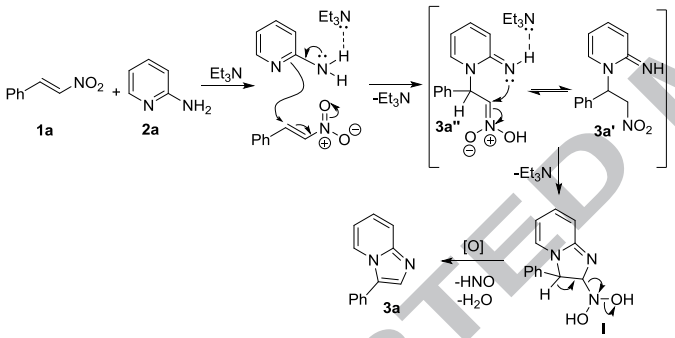
Entry	Solvent	Oxidant	Base	Yield (%)	
				3a	3a'
1	CH_2Cl_2	-	-	NR[b]	~10%
2	CH_2Cl_2	-	Et_3N	-	56
3	CH_2Cl_2	H_2O_2	-	Trace	36
4[c]	CH_2Cl_2	H_2O_2	Et_3N	73	Trace

[a] Reagents and conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), Et_3N (10 mol %), H_2O_2 (3.0 equiv.), CH_2Cl_2 (2 mL), rt.

[b] No reaction.

[c] Reaction performed with *in situ* generated Michael adduct **3a'**

Based on the above observations, we propose a mechanism as shown in Scheme 3. Initially, **1a** reacts with **2a** in the presence of base to give intermediate **3a''** through intermolecular Michael addition. The formation of tautomer **3a'** was confirmed by control experiments and was successfully isolated. Intermediate **3a''** undergoes base-catalyzed intramolecular cyclization to generate intermediate **I**, which on further oxidation, generates the final product **3a** with the removal of nitroxyl (HNO) and water.[10,15] Nitroxyl may be converted to nitrous or nitric acid under the oxidative conditions.



Scheme 2. Plausible reaction mechanism.

In conclusion, a facile protocol was developed for the regioselective synthesis of 3-arylimidazo[1,2-*a*]pyridines in the presence of an inexpensive base (Et_3N), and H_2O_2 (30% aq.) at room temperature from readily available starting materials. The scope of the reaction included several substituted β-nitrostyrenes and 2- aminopyridines to furnish a wide variety of 3-arylimidazo[1,2-*a*]pyridine in moderate to good yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.xx.xxx.

References

1. Couty, F.; Evano, G. in *Comprehensive Heterocyclic Chemistry III*, ed. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Elsevier, Oxford, 2008, vol. 11, p. 409-499; (b) Liu, J.; Chen, Q. *Huaxue Jinzhan*, **2010**, *22*, 631-638; (c) Zhou, J.; Liu, J.; Chen, Q. *Youji Huaxue*, **2009**, *29*, 1708-1718; (d) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem*. **2007**, *7*, 888-899; (e) Bartholini, G.; L. E. R. S. *Monogr, Ser*. **1993**, *8*, 1; (f) Abignente, E. *Actual. Chim. Ther*. **1991**, *18*, 193-214.
2. (a) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol*. **1990**, *46*, 61-72; (b) Harrison, T. S.; Keating, G. M. *CNS Drugs*, **2005**, *19*, 65-89; (c) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. *Cardiovasc. Drug Rev*. **2002**, *20*, 163-174; (d) Ueda, T.; Mizusgige, K.; Yukiiri, K.; Takahashi, T.; Kohno, M. *Cerebrovasc Dis*. **2003**, *16*, 396-401.
3. (a) Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem*. **2003**, *68*, 4935-4937; (b) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed*. **2010**, *49*, 2743-2746; (c) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*. **2015**, *51*, 1555-1575.
4. Humphries, A. C.; Gancia, E.; Gilligan, M. T.; Goodacre, S.; Hallett, D.; Merchant, K. J.; Thomas, S. R. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1518-1522.
5. Fradley, R. L.; Guscott, M. R.; Bull, S.; Hallett, D. J.; Goodacre, S. C.; Wafford, K. A.; Garrett, E. M.; Newman, R. J.; O'Meara, G. F.; Whiting, P. J.; Rosahl, T. W.; Dawson, G. R.; Reynolds, D. S.; Atack, J. R. J. *Psycopharm*. **2007**, *21*, 384-391.
6. Farag, A. M.; Mayhoub, A. S.; Barakat, S. E.; Bayomi, A. H. *Bioorg. Med. Chem*. **2008**, *16*, 4569-4578.
7. Buckley, G. M.; Ceska, T. A.; Fraser, J. L.; Gowers, L.; Groom, C. R.; Higueruelo, A. P.; Jenkins, K.; Mack, S. R.; Morgan, T.; Parry, D. M.; Pitt, W. R.; Rausch, O.; Richard, M. D.; Sabina, V. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 3291-3295.
8. (a) Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem*. **2000**, *65*, 6572-6575; (b) Nandi, D.; Jhou, Y.-M.; Lee, J.-Y.; Kuo, B.-C.; Liu, C.-Y.; Huang, P.-W.; Lee, H. M. *J. Org. Chem*. **2012**, *77*, 9384-9390; (c) Palani, T.; Park, K.; Kumar, M. R.; Jung, H. M.; Lee, S. *Eur. J. Org. Chem*. **2012**, 5038-5047; (d) Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett*. **2012**, *14*, 4386-4389; (e) Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett*. **2012**, *14*, 1688-1691. (f) Gao, Y.; Yin, M.; Wu, W.; Huang, H.; Jiang, H. *Adv. Synth. Catal*. **2013**, *355*, 2263-2273; (g) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*. **2015**, *51*, 1555-1575.
9. (a) Wu, Z.; Pan Y.; Zhou, X. *Synthesis*, **2011**, 2255-2260; (b) Bangade, V. M.; Reddy, B. C.; Thakur, P. B.; Babu, B. M.; Meshram, H. M. *Tetrahedron Lett*. **2013**, *54*, 4767-4771; (c) Egner, U.; Gerbling, K. P.; Hoyer, G. -A.; Krüger, G.; Wegner, P. *Pestic. Sci*. **1996**, *47*, 145-158; (d) Dixon, L. I.; Carroll, M. A.; Gregson, T. J.; Ellames, G. J.; Harrington, R. W.; Clegg, W. *Org. Biomol. Chem*. **2013**, *11*, 5877-5884; (e) S. K. Lee and J. K. Park, *J. Org. Chem*. **2015**, *80*, 3723-3729.
10. Santra, S.; Bagdi, A. K.; Majee, A.; Hajra, A. *Adv. Synth. Catal*. **2013**, *355*, 1065-1070.
11. (a) Jagadhane, P. B.; Telvekar, V. N.; *Synlett*. **2014**, *25*, 2636-2638; (b) Tachikawa, Y.; Nagasawa, Y.; Furuhashi, S.; Cui, L.; Yamaguchi, E.; Tada, N.; Miura, T.; Itoh, A. *RSC Adv*. **2015**, *5*, 9591-9593.
12. (a) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *Org. Lett*. **2014**, *16*, 4630-4633; (b) Ha, P. T. M.; Lieu, T. N.; Doan, S. H.; Phan, T. T. B.; Nguyen, T. T.; Truong, T.; Phan, N. T. S. *RSC Adv*. **2017**, *7*, 23073-23082; (c) Yadav, S.; Srivastava, M.; Rai, P.; Tripathi, B. P.; Mishra, A.; Singh, J.; Singh, J. *New J. Chem*. **2016**, *40*, 9694-9701.
13. Devi, E. S.; Alanthadka, A.; Tamilselvi, A.; Nagarajan, S.; Sridharan, V.; Maheswari, C. U. *Org. Biomol. Chem*. **2016**, *14*, 8228-8231.
14. **General procedure for the synthesis of substituted 3-arylimidazo[1,2-*a*]pyridines:** To a mixture of the β-nitrostyrene (0.195g, 1.2 mmol) and 2-aminopyridine (0.0941g, 1.0 mmol) in CH_2Cl_2 (2.0 mL), Et_3N (10 mol%) and aq. H_2O_2 (3.0 equiv.) was added and stirred at room temperature for 6 h. The reaction progress was monitored by Thin Layer Chromatography (TLC) and after reaction completion, the mixture was extracted with water. The organic layer was washed with a brine solution and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using a hexane/ethyl acetate mixture.
15. Gattu, R.; Bhattacharjee, S.; Mahato, K.; Khan, A.T. *Org. Biomol. Chem*. **2018**, *16*, 3760-3770.

- First metal free system for synthesis of 3-phenylimidazo[1,2-*a*]pyridine
- Can be performed at room temperature, unlike other reported strategies
- Inexpensive base – Et_3N and H_2O_2 (30% aq.) as oxidant were used
- Substrate scope includes substituted β-nitrostyrenes and 2-aminopyridines