

Cite this: *RSC Adv.*, 2019, 9, 29659Facile synthesis of 3-substituted imidazo[1,2-*a*]pyridines through formimidamide chemistry†‡Rasapalli Sivappa,^{ID}*^a Vamshikrishna Reddy Sammeta,^a Yanchang Huang,^a James A. Golen^a and Sergey N. Savinov^{ID}^b

A facile entry to 3-aryl/alkenyl/alkynyl substituted imidazo[1,2-*a*]pyridines (**3a–p**, **6a–d** & **9a–9e**) has been developed from readily available benzyl/allyl/propargyl halides and 2-amino pyridines as substrates via formimidamide chemistry that is devoid of caustic or expensive reagents, such as transition metal complexes. Quantum chemical calculations performed to understand the underlying mechanism of the transformation revealed a preference for intramolecular Mannich-type addition over pericyclic 1,5-electrocyclization for the systems reported herein that enable a Baldwin allowed 5-*exo*-trig cyclization instead of a formally anti-Baldwin 5-*endo*-trig process.

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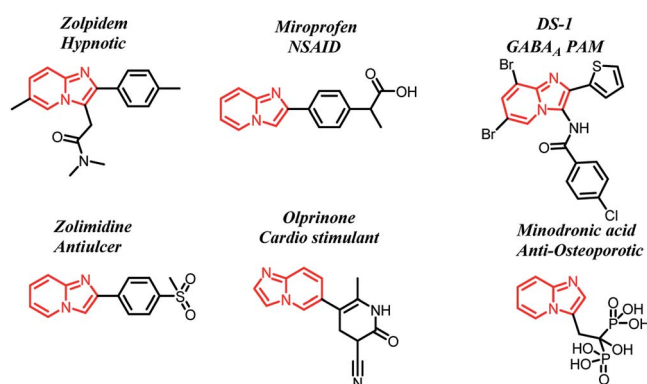
Introduction

Imidazo[1,2-*a*]pyridines, nitrogen containing fused bicyclic heterocycles, are considered to be privileged scaffolds in the field of medicinal chemistry, due to their ability to display a wide range of pharmacological activities, such as antifungal, antibacterial, antitumor, antipyretic, analgesic, antiulcer, anxiolytic, antineoplastic, cardiac stimulant and anti-osteoporotic activities.^{1–5} Zolpidem (hypnotic), miroprofen (analgesic), DS-1 (GABA_A positive allosteric modulator), zolimidine (peptic ulcer), olprinone (cardiac stimulant) and minodronic acid (anti-osteoporotic) are some of the currently marketed imidazopyridine drugs (Fig. 1).

Due to this promising potential to be a useful scaffold in drug design, continuous synthetic efforts are directed to access 2/3-substituted imidazo[1,2-*a*]pyridines in novel and facile ways. Several methods have been reported for the synthesis of substituted imidazopyridines, as shown in Scheme 1. For example, Jafarzadeh *et al.* have reported fluconazole-functionalized nanoparticle (Fe₃O₄@SiO₂-Flu) catalyzed synthesis of 3-aryl or 3-amino-imidazo[1,2-*a*]pyridines using standard α -halo ketones or aryl aldehydes and substituted isonitriles, respectively.⁶ Meshram *et al.* have reported DABCO

mediated regioselective synthesis of 3-aryl imidazopyridines using standard α -halo ketones as substrates.⁷ Enolizable aldehydes have also been utilized as substrates for the 3-substituted imidazopyridine synthesis under oxidative conditions.^{8–10} Uma Maheshwari *et al.* have reported Et₃N catalyzed oxidative amination and denitration reactions leading to 3-aryl imidazopyridines using substituted nitrostyrenes as substrates.¹¹

Kröhnke *et al.* reported synthesis of imidazopyridines using benzyl-2-iminopyridines and carboxylic anhydrides.¹² All these methods have certain advantages, as well as disadvantages, such as formation of regioisomeric mixtures, harsh and demanding conditions, need for uncommon reagents or catalysts. Inspired by the lone example reported by Würthwein *et al.*, involving base-mediated 6-electron cyclization of imino pyridinium salt to obtain 2,3-disubstituted imidazopyridine from benzyl bromide and benzaldehyde,¹³ and buoyed by our previous success in employing aminopyrimidine formimidamide chemistry,¹⁴ we became interested in extending

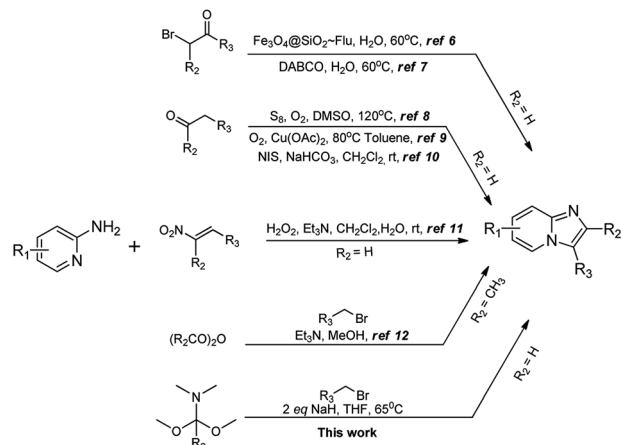
Fig. 1 Marketed imidazo[1,2-*a*]pyridine drugs.

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‡ Electronic supplementary information (ESI) available: Complete experimental procedures are provided, including copies of ¹H and ¹³C NMR spectra of all new compounds and HRMS analysis. X-ray data for **2a**, **3d**, **3i**, **8d** and **9d** is also provided. CCDC 1920094–1920096, 1922120, 1910925 and 1910928. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra05841a

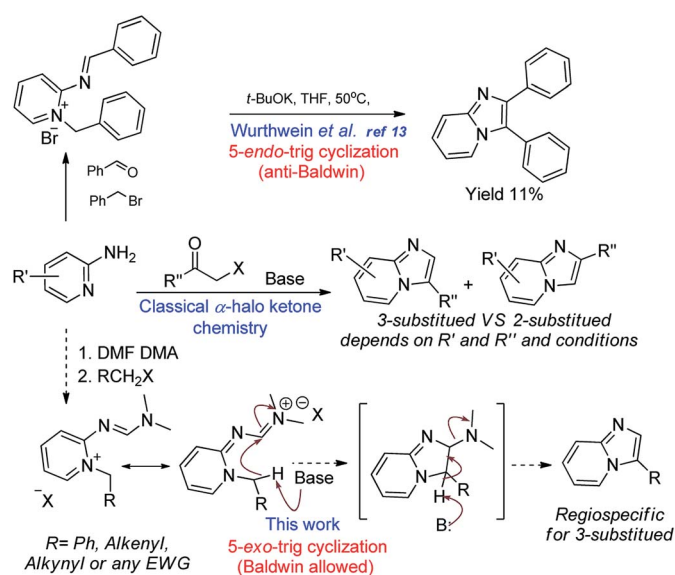


Scheme 1 Methods for the synthesis of 2/3-substituted imidazopyridines.

and furthering the scope of the later functionality to obtain 3-substituted imidazopyridines. We reasoned that activating the simple halides through formation of corresponding formimidamide-pyridinium salts and thereby incorporating an electrophilic carbon onto 2-aminopyridine would obviate the need for α -halo ketones as the corresponding 1,2-bis-electrophiles.^{15–17} In addition to the undesirable characteristics and limitations of α -halo ketones, the regioselectivity of their cyclization with 2-aminopyridines is a major concern (Scheme 2). The results of our efforts towards the same are reported herein.

Results and discussions

Our efforts commenced with the synthesis of *N,N*-dimethyl-*N*-(pyridin-2-yl)formimidamide (**1**) accessed through

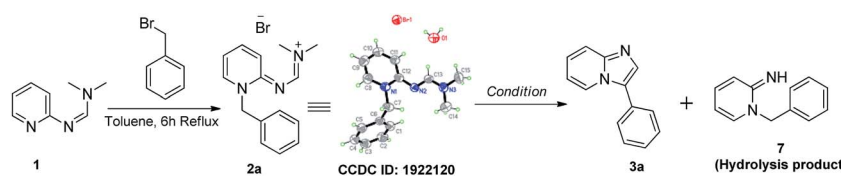


Scheme 2 Proposed chemistry for synthesis of 3-substituted imidazopyridines through formimidamide pyridinium salt to obviate the need for α -halo ketones and 5-endo-trig cyclization.

reaction between 2-aminopyridine and *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) under reflux in toluene (see Table 1).¹⁴ We initially attempted to access imidazopyridine **3a** by exposing compound **1** and benzyl bromide together to elevated temperatures (toluene/115 °C in the pressure tube), but we could only isolate the quaternary ammonium salt (**2a**). We have reasoned that the cyclization of **2a** may require the help of an acidic or basic promoter, as the attempted cyclization of **2a** even at highly elevated temperature (*i.e.*, 180 °C/DMSO) also failed to access compound **3a**. Our efforts in acid catalysis to activate the imine of formimidamide in compound **2a** using catalytic sulfuric acid or a super acid [*i.e.*, triflic acid (TfOH)] were also unsuccessful, indicating the need for a base to activate the benzylic carbon attached to the quaternary nitrogen of compound **2a** as a nucleophilic center. In the case of α -halo ketones as *N*-alkylating electrophiles, simple heating is enough to drive the cyclization as enolization and, thereby, introduction of nucleophilicity at the carbon attached to the quaternary nitrogen is facilitated by two flanking electron-withdrawing groups. In the case of benzyl halides as substrates though, the methylene carbon attached to the quaternary nitrogen is not acidic enough to drive the thermal cyclization thus demanding a base promoter. We have initially used sodium hydroxide as a base and water as a reaction medium, which failed to provide compound **3a**, but yielded rather hydrolysed product **7** (Table 1) *via* hydrolysis of the formimidamide group. The formation of such compounds accounted for the loss of the desired product in subsequent experiments, as any remaining H₂O in the reaction mixture resulted unavoidably in hydrolysis products. So, we then resorted to non-nucleophilic bases and water-free reaction conditions to suppress the same. The use of DABCO or DBU resulted in failure to generate the cyclised product **3a** though traces of hydrolysis products were still observed, along with unreacted starting material and degradation products, as the above two bases are hygroscopic and had collected H₂O upon storage. The use of potassium *t*-butoxide, however, was successful in providing compound **3a** in 16% yield which was encouraging to intensify our efforts to find a better condition. The later attempts of using one molar equivalent of sodium hydride (60% w/w in mineral oil) yielded 23% of the desired product upon reflux in THF for 0.5 h. Gratifyingly, doubling the amount of sodium hydride increased the product yield to 44%, while further attempts of increasing molar excess of NaH over the cyclization precursor had no effect on product yield. This observation suggests that proton abstraction by the base is the rate limiting and, therefore, yield-controlling step in this process. With the above conditions in hand, we have explored the scope of this reaction, using various arylmethyl halides as substrates (Scheme 3) to access compounds **3a–3p**. A closer look at the observed yields reveals that electron-withdrawing groups on the *meta* position of the benzyl substituent tend to increase the product recovery, especially for doubly substituted variants (*c.f.*, **3m**, **3n**, **3e**, **3k**, **3f**, **3h**, and **3g**).



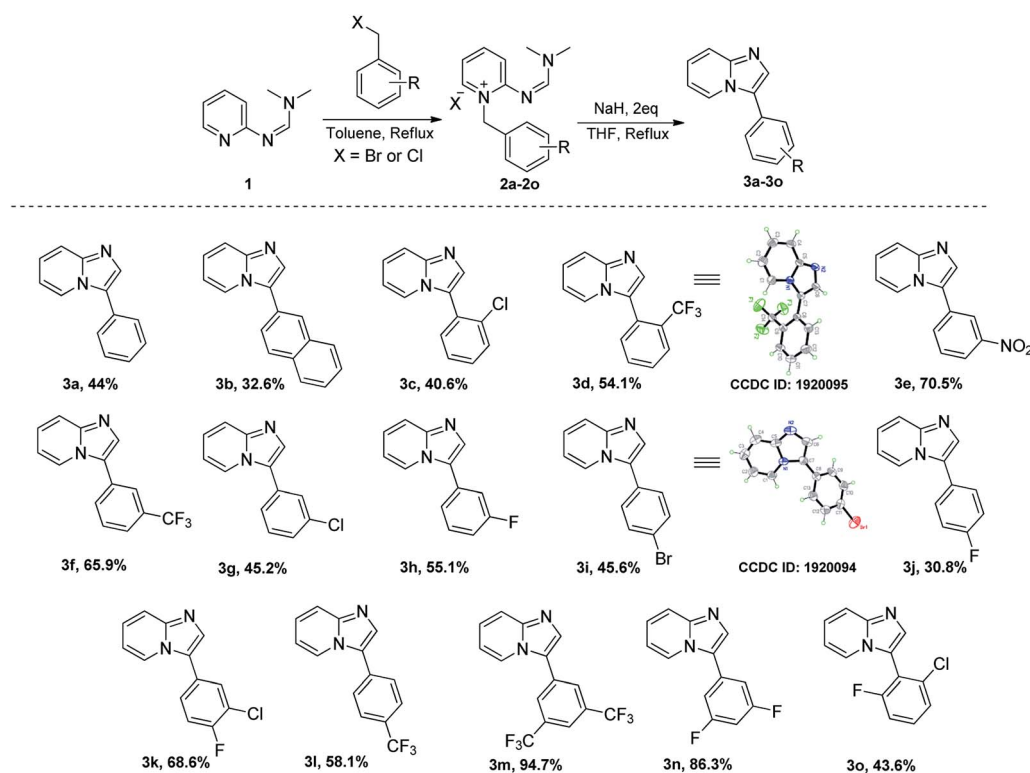
Table 1 Optimization of reaction conditions for the synthesis of 3a



Entry	Solvent	Reagent/catalyst	Equivalents	Temperature/reaction time	% isolated yield of 3a	% yield of hydrolysis product 7
1	DMSO	—	—	180 °C/6 h	Not observed	Trace
2	THF	H ₂ SO ₄	1	65 °C/12 h	Not observed	—
3	THF	Triflic acid	1	65 °C/12 h	Not observed	—
4	H ₂ O	NaOH	1	RT/30 min	Not observed	41%
5	THF	NaOH	1	RT/1 h	Not observed	35%
6	THF	DABCO	1	65 °C/12 h	Not observed	Trace
7	THF	DBU	1	65 °C/12 h	Not observed	Trace
8	THF	KOtBu	1	65 °C/2 h	16%	Trace
9	DCM	KOtBu	1	40 °C/2 h	14%	Trace
10	THF	NaH	1	65 °C/0.5 h	23%	Trace
11	THF	NaH	2	65 °C/0.5 h	44%	Trace
12	DCM	NaH	2	40 °C/0.5 h	22%	Trace
13	DMF	NaH	2	65 °C/0.5 h	20%	Trace
14	Dioxane	NaH	2	65 °C/0.5 h	11%	Trace
15	DMA	NaH	2	65 °C/0.5 h	21%	Trace

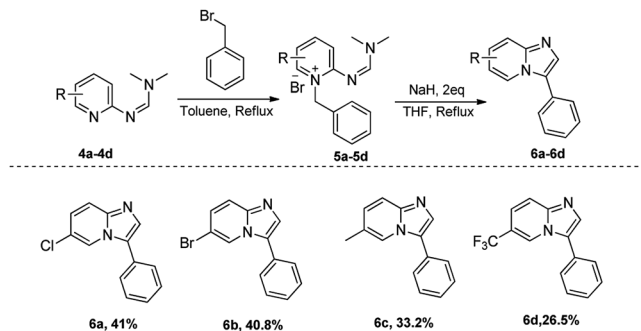
This yield trend follows closely the Hammett *meta*-effect constants,¹⁸ which correlate with both electron-withdrawing strength of substituents and acidity at the benzylic carbon, confirming the central role that the base plays in this reaction.

That is, once the pyridinium ylide is formed, the cyclization and subsequent aromatization through β -elimination of dimethylamine occurs with few (if any) interferences from unwanted side processes. In fact, the reaction can be followed visually since the

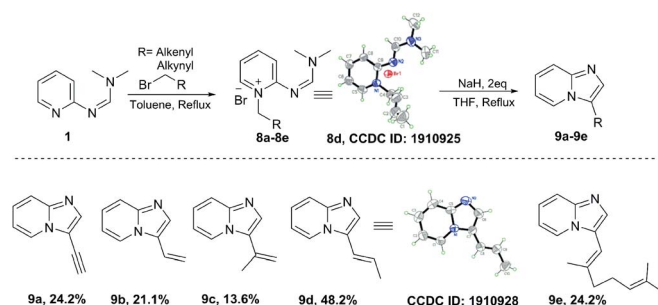


Scheme 3 Synthesis of substituted 3-aryl imidazo[1,2-a]pyridines – substrate scope.





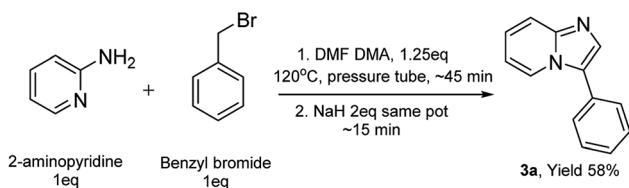
Scheme 4 Substrate scope of substituted 2-aminopyridines.



Scheme 5 Substrate scope of alkenyl/alkynyl bromides.

orange colour of the ylide solution dissipates quite rapidly. It is also quite notable that in the above reactions, no hydrolysis product was detected.

We have also explored the scopes of substituted amino pyridines as substrates (Scheme 4). While the listed yields are unoptimized, the relatively poor performance of trifluoromethyl-substituted 2-aminopyridine suggests that the nucleophilicity of the pyridine nitrogen is important for the overall reaction success. Notably, the alkylation step could be optimized further *via* solvent optimization and/or catalyst use. Finally, we have also explored the scope of allyl and propargyl bromides to access the corresponding 3-vinyl and 3-ethynyl imidazopyridines, as they provide attractive functional handles for further manipulation in organic synthesis.^{19,20} Such compounds are generally accessed through palladium-mediated coupling reactions.^{21–23} Using our formimidamide chemistry under basic conditions, we were able to access compounds **9a–9e** through transition metal-free formimidine-pyridinium route (Scheme 5), albeit in relatively low yield

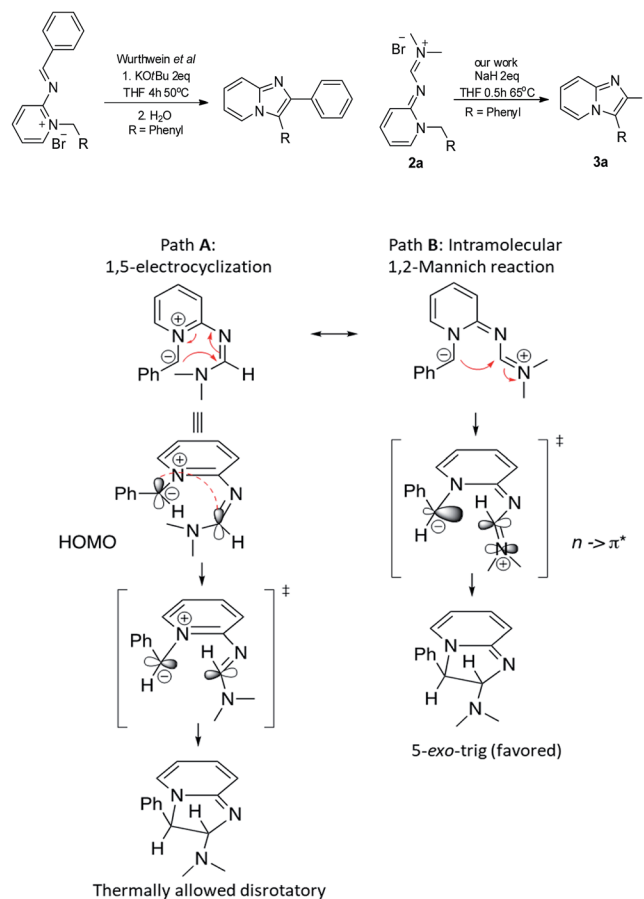
Scheme 6 One-pot synthesis of compound **3a**.

(unoptimized) due to, most likely, reduced acidity of the cyclization precursors.

The X-ray crystallography data on some of the pyridinium salts (**2a** & **2o**, see ESI†) revealed that they are hygroscopic and absorb moisture upon storage, which could negatively impact the cyclization reaction as it requires anhydrous conditions to suppress the hydrolysis product. We then thought of condensing the formation of imine, pyridinium salt, and the cyclization of the corresponding ylide to a one-pot solvent-free procedure to avoid the isolation of potentially hygroscopic pyridinium salts. Thus, we have attempted this procedure to access compound **3a** (Scheme 6) and successfully synthesized it in 58% yield, which is greater than the yield from the route shown in Scheme 3. We have also witnessed the absence of the hydrolysed product **7** in the one-pot synthesis. We are currently focusing on further optimization of this procedure and extending this to diverse substrates.

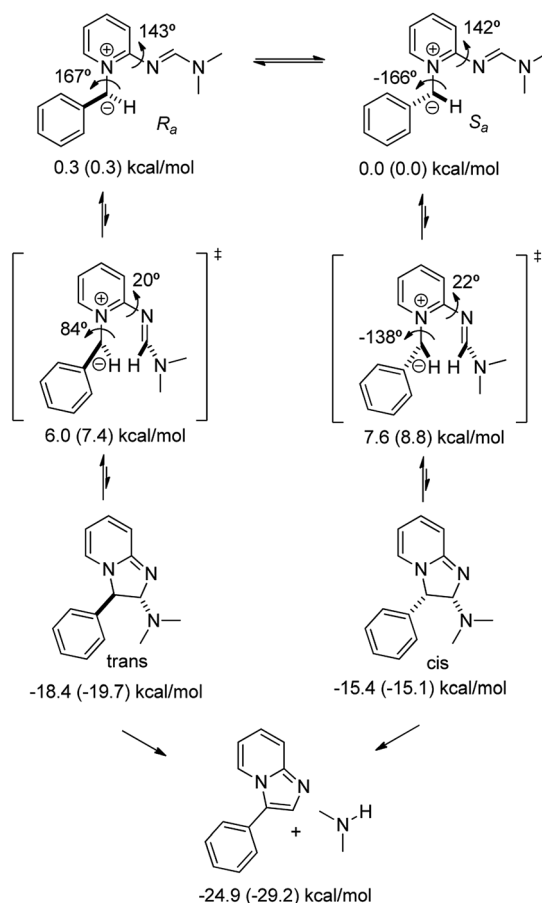
Reaction mechanism & computational studies

Previous studies by Würthwein *et al.* on a cyclization reaction of similar imino pyridinium salts, which lack the dimethylamino group, suggested that these precursors undergo an apparent base-initiated anti-Baldwin²⁴ (5-*endo*-trig) cyclization to provide imidazo[1,2-*a*]pyridines in low yields, upon 4 h exposure to KO^t-

Scheme 7 Plausible mechanistic pathways for the formation of **3a** from compound **2a**.

Bu (2 eq.) in heated THF.¹³ Quantum-chemical calculations and subsequent analysis of reaction coordinates have suggested that this sluggish anti-Baldwin reaction proceeds *via* a pericyclic 1,5-electrocyclization process, rather than an intramolecular addition. The superior yields of imidazopyridines and broader scope of our system prompted us to investigate the mechanism and the role of the dimethylamino substituent in the key cyclization step. The positioning of counter anions in the crystal structures of pyridinium salts revealed that the dimethyl amino substituent participates actively in the delocalization of positive charge throughout the trinitrogen conjugated system (**2a**, **2o** & **8d**, see ESI†), with a significant resonance contribution from the dimethylimino form. Thus, the formation of **3a** could arise from either 1,5-electrocyclization, as in the Würthwein *et al.* system, or Mannich-type intramolecular nucleophilic addition, which can now proceed *via* Baldwin-allowed 5-*exo*-trig ring closure, as shown in Scheme 7.

Geometry optimization and assessment of pK_a of benzylpyridinium salt **2a** ($pK_a \approx 27$ in DMSO), using quantum-chemical approach implemented within program Jaguar (Schrödinger, LLC), rationalized both the need for a relatively strong base, such as KOtBu (pK_a of conjugate acid ≈ 29 in DMSO)²⁵ and NaH (pK_a of conjugate acid ≥ 34),²⁶ to initiate this reaction and the observed dependence of the yield on acidity of the ylide.



Scheme 8 Minima and transition states for cyclization of ylide derived from compound **2a** to yield compound **3a**.

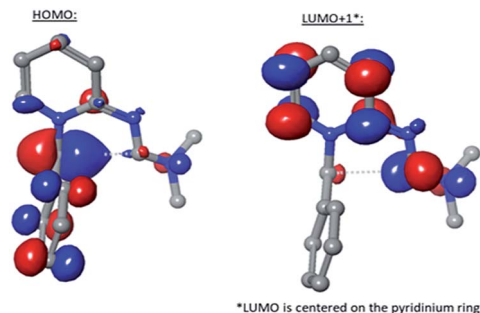


Fig. 2 FMO's of lowest energy transition state.

Search for minima and transition states (TS) for the cyclization reaction, their geometry optimizations and validation of stationary points *via* vibrational frequencies indicated that the lowest energy conformations of pyridinium ylide (R_a and S_a) have to undergo significant reorganization *via* bond rotations to bring into proximity and align the reactive centers: nucleophilic carbon of the ylide and distal electrophilic carbon of the formimidamide group (Scheme 8). The activation barriers for achieving the TS geometries (6.0 and 7.6 kcal mol⁻¹ for those leading to *trans* and *cis* products, respectively) were found to be significantly lower than those reported by Würthwein *et al.* for the dimethylamino-free imino pyridinium system (10.5 kcal mol⁻¹) at the same level of Density Functional Theory (B3LYP/6-31+G*). The less sterically congested TS leading to the *trans* product is expected to favour its formation in preference to *cis*. However, this could not be established experimentally due to facile elimination of dimethylamine with concomitant aromatization of the resulting bicycle under the reaction conditions.

The significantly reduced activation barrier resulting in improved imidazopyridine yield within the formimidamide series over the imino one raises the question of mechanistic differences in the two highly related cyclization processes. Further analysis of the frontier molecular orbitals of the formimidamide TS revealed that the highest molecular orbital coefficients at the reactive centers (ylide carbon anion and distal formimidamide carbon) reside on the highest occupied molecular orbital (HOMO) and the second lowest occupied molecular orbital (LUMO+1; LUMO is centered on pyridinium ring), respectively (Fig. 2). Notably, none of the frontier molecular orbitals extend through the 5-atom/6-electron system that would be expected for a pericyclic process (path A in Scheme 7). Both HOMO and LUMO+1, on the other hand, are fully consistent with path B mechanism, whereby the carbanion, reacts with dimethyliminium, both stabilized by extensive conjugation with adjacent groups. Thus, the dimethylamine substituent, which participates in delocalization of positive charge, as seen in the crystal structures of formimidamides (see above Scheme 5), appears to play a key role in the reaction described herein. Notably, this group converts the formally anti-Baldwin 5-*endo*-trig cyclization, forced to undergo a thermal pericyclic process, into a formally allowed 5-*exo*-trig cyclization, which yields a practical and versatile synthetic procedure for a medicinally important class of aromatic heterobicycles.



Conclusions

We have successfully developed a facile entry to 3-aryl/alkenyl/alkynyl substituted imidazo[1,2-*a*]pyridines using respective benzyl/allyl/propargyl halides and 2-amino pyridines as substrates (**3a-p** & **6a-d**) via formimidamide chemistry that is devoid of expensive or caustic reagents or transition metals. Anhydrous conditions are necessary for suppressing major side reaction and for efficient synthesis of 3-substituted imidazopyridines. We have also developed a one-pot procedure, which furnished the corresponding heterobicycle in a better yield, and are currently focussing on further optimization and scope extension. Quantum chemical analysis of the reaction mechanism revealed that dimethyliminium group, acting as an *exo* substituent in the cyclization reaction, is beneficial in reducing the activation energy by permitting a formally allowed Mannich-type reaction over Baldwin-forbidden 1,5-electrocyclization. We have also been able to access both vinyl and ethynyl substituted imidazopyridines (**9a-e**) that can, in turn, be used as starting points for further synthetic elaboration of fused heterocycles through the convenient functional handles. We have successfully expanded the repertoire of halides and 2-aminopyridines as substrates in this chemical transformation to access the imidazopyridine which otherwise was restricted to α -halo ketones. Currently, we are focusing on optimizing reaction conditions and on extending the scope of this formimidinium way of transforming a formally anti-Baldwin 5-*endo*-trig cyclization into a formally allowed 5-*exo*-trig cyclization to obtain diversely substituted fused imidazosystems through, and the results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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