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TFA-catalysed tandem double cyclisation: A one-pot, metal-free routes for novel indolo-imidazo[1,2-a]pyridine derivatives

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Abstract: A transition-metal free, one-pot tandem synthetic routes for novel indole and imidazo[1,2-a]pyridine derivative hybrids have been established. An efficient three-component reaction was designed with incorporation of two sequential Groebke–Blackburn–Bienayme (GBB) and cyclization reaction in one-pot under mild acidic condition. The salient feature of this protocol is atom economy, good yield and operational simplicity. A molecular prospective library of **32** compounds was synthesized by utilizing the various substituted aryl aldehydes and 2-aminopyridine.

Keywords: tandem double cyclisation, one-pot, metal-free, indoloimidazo[1,2-a]pyridines

Introduction

Heterocyclic architectures are the promising scaffolds in various bioactive natural products including marketed pharmaceuticals, agrochemicals, dyes, and many other application-oriented materials.[1] Over the past decade, there has been growing interest in the synthesis and studies of properties of heteroaromatic compounds specially the construction of fused N-heterocyclic scaffolds due to their presence in drugs and functional materials.[2] Among them, imidazopyridine and related diversity has been reported for a wide range of biological profiles including diabetes, cancers, microbial infection etc and thus imidazo[1,2]pyridine is often considered a privileged scaffold that can be combined with other fragments and lead to complex polyheterocyclic molecules which can serve as novel therapeutics in drug discovery studies.[3] During the past few years, hybrid drugs have generated much attention. The objective of developing new potent small molecules is to furnish new therapeutic heterocyclic hybrid molecules where two or more bioactive heterocyclic scaffolds are embedded in a single molecule to exert multiple or combined biological activities.[4,5,6] Kamal et al. have reported the synthesis of imidazopyridine-oxindole and pyrazole-oxindole conjugates which exhibit excellent antiproliferative activity.[7,8] The

Im us small-molecule drug discovery programs.[9,10,11] Recent studies from many groups have shown the presence of these scaffolds in the therapeutics of many of the most common diseases, including diabetes, cancers, microbial infection etc. **Fig.1** shows some examples of compounds containing either imidazo[1,2]pyridine or indole as their basic core structure; these compounds have been reported to exhibit a wide range of physical, chemical and biological properties.

Several synthetic approaches to access functionalized imidazo[1,2]pyridine derivatives have been widely reported by using condensation, tandem reaction, multicomponent strategy, intramolecular C–H amination, oxidative coupling.[12] In contrast, the synthesis of indole has been reported by using metal-free C−H amination,[13] coupling/cyclization under aerobic conditions,[14] from 2-aminobenzyl phosphonium salts,[15] synthesis from anilines and ketones,[16] ruthenium catalyzed heterocyclizations[17]. But, there are no literature precedents for the synthesis of their hybrid imidazo[1,2]pyridine-indole frameworks. In recent years, multicomponent reactions (MCRs) followed by post synthetic transformations have emerged as the most powerful approaches for diversity-oriented synthesis of polyheterocyclic scaffolds having novel biological properties. Multicomponent reactions (MCRs) provide the tandem performance of multiple reactions in one pot, high atom, structural and bond-forming economy, convergent synthesis, and the probability of furnishing maximum chemical diversity elements in one chemical reaction.[18] Recently, people are exploring a Ugi-variant Groebke–Blackburn–Bienayme (GBB)[19] tandem reactions to further extend the structural diversity of Ugi products. The GBB reaction is a three component processes (3 CR) which involve an aldehyde, an amine and an isocyanide and delivers libraries of bioactive compounds in a highly effective fashion. These types of tandem reactions are highly efficient and atom-economical as isolation of intermediates is not required. It is interesting to note that only simple isocyanides have been successfully employed as starting materials for GBB reactions, whereas the reactivity of convertible isocyanides remain largely unexplored. Encouraged by the skeletal diversity of N-rich heterocyclic compounds, we report our efforts toward the synthesis of novel indolo-imidazo[1,2-a]pyridine analogues in one pot *via* double cyclisation approach. To the best of our knowledge, this is first report to synthesize novel indolo-imidazo[1,2-a]pyridine analogues by utilising GBB-3CR followed by cyclisation under acidic medium.

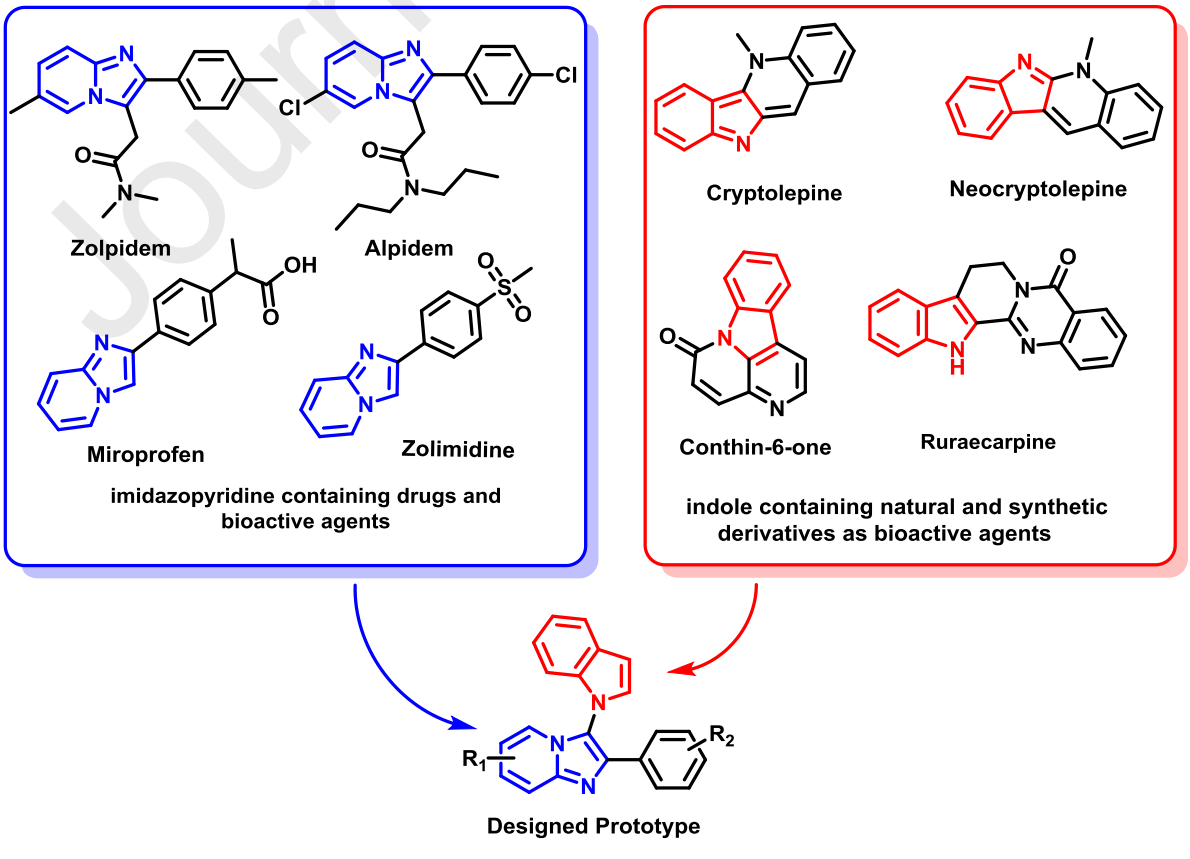
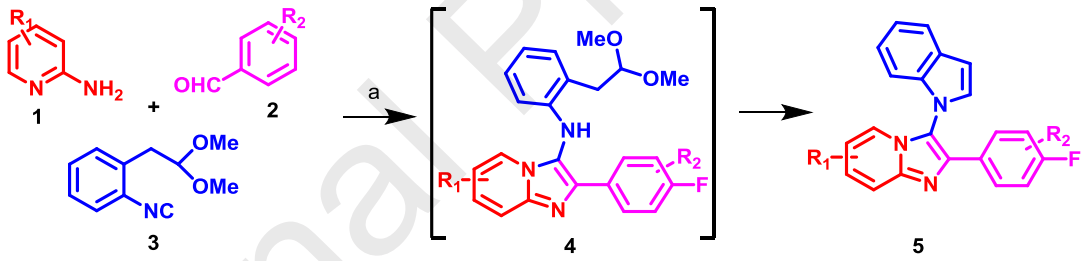


Fig. 1 Imidazo[1,2]pyridine and indole containing some drugs and bio-active agents and designed indolo-imidazopyridine hybrid prototype.

Results and Discussion

The synthesis was started from the commercially available substituted aromatic aldehydes, substituted 2-amino pyridine and isocyanide. The beauty of our reaction is diverse use of convertible isocyanide. A new and promising convertible isocyanide, 1-isocyano2-(2,2-dimethoxyethyl)-benzene (**3**) has been introduced, by the Wessjohann and Kobayashi groups.[20,21,22,23,24] It is stable, easily accessible, versatile, and reacts specifically, as proven elegantly in the total synthesis of (-)-Dysibetaine.[25] Earlier people have used this type of convertible isocyanide in Ugi MCR.[26] In our work, we first time introduced this novel convertible isocyanide also called indole–isonitrile (**3**) in GBB MCR to synthesize the designed 3-(1H-indol-1-yl)-2-phenylimidazo [1,2-a]pyridine derivatives because this isocyanide is capable of being further deprotected and eventually cyclized to deliver the intended scaffolds.



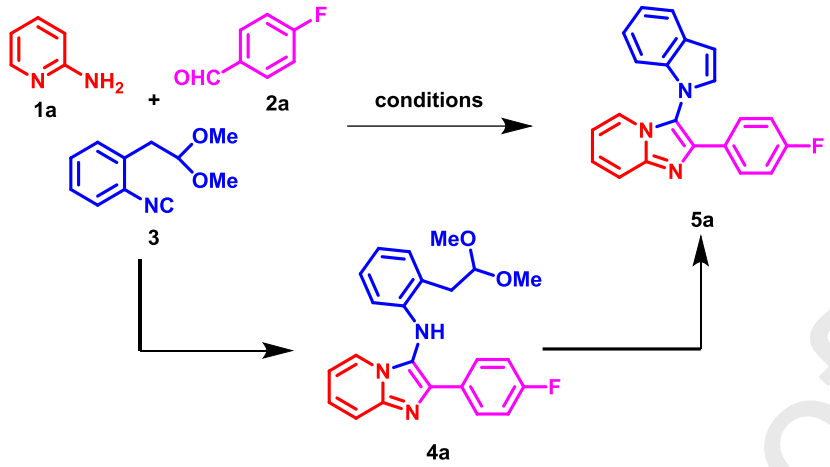
5a, R_1= H, R_2= 4-F
5b, R_1= H, R_2= 3-F
5c, R_1= H, R_2= 2-F
5d, R_1= H, R_2= 4-CF_3
5e, R_1= H, R_2= 3-CF_3
5f, R_1= H, R_2= 4-OCF_3
5g, R_1= H, R_2= 4-$OCHF_2$
5h, R_1= H, R_2= 3,5-bis(CF_3)
5i, R_1= H, R_2= 4-phenyl
5j, R_1= H, R_2= 2-Br
5k, R_1= H, R_2= 2-OMe
5l, R_1= H, R_2= 3-OMe
5m, R_1=H, R_2= 3-Cl
5n, R_1= H, R_2= 4-OH
5o, R_1= H, R_2= 2-F, 4-OMe
5p, R_1= H, R_2= 4-OC_2H_5

5q, R_1= H, R_2= 4-SCH_3
5r, R_1= H, R_2= 4-NO_2
5s, R_1= H, R_2= 2,4-bis(F)
5t, R_1= H, R_2= 2-Cl, 4-NO_2
5a', R_1= 5-Cl, R_2= 4-CF_3
5b', R_1= 5-Cl, R_2= 4-OCF_3
5c', R_1= 5-Cl, R_2= 4-F
5d', R_1= 5-Cl, R_2= 4-CN
5e', R_1= 5-Cl, R_2= $OCHF_2$
5f', R_1= 5-Cl, R_2= NO_2
5a'', R_1= 4-CH_3, R_2= 4-CF_3
5b'', R_1= 4-CH_3, R_2= 4-F
5c'', R_1= 4-CH_3, R_2= 4-NO_2
5d'', R_1= 4-CH_3, R_2= OCF_3
5e'', R_1= 4-CH_3, R_2= $OCHF_2$
5f'', R_1= 4-CH_3, R_2= CN

Scheme-1: (a) TFA (20 mol%), 1,4-dioxane, 110 °C, 2-3 h, 60-70% yield.

bromo, trifluoromethane etc at the *para* position based on their role in introducing metabolic stability in molecules in medicinal chemistry. The synthesis was achieved by utilizing the Groebke, Blackburn, Bienayme multicomponent technique which involved the reaction of 2-aminopyridines, substituted benzaldehydes and isocyanides in the presence of acid. In a typical simple reaction condition, 2-aminopyridine, substituted benzaldehyde and isocyanide in 1,4-dioxane in a *via*l was treated with 20 mol% TFA under argon flush and sealed with a teflon cap and was allowed to stir at 110 °C for 2 h. After completion of the reaction, solvent was evaporated and standard workup was done. Purification by column chomatography over silica gel delivered the final compounds in good to excellent yields. To optimize the conditions, the reaction was initially done with 2-aminopyridine **1a**, 4-fluorobenzaldehyde **2a** and isocyanide **3** in 1,4-dioxane at 110 °C for 8 h in the absence of any catalyst. In this case, the desired product was not observed and the reaction was stopped at the intermediate stage (**Table 1, entry 1**) which was isolated and later reacted with acid to furnish the desired product **5a**. Encouraged by the preliminary result, we thought of directly synthesizing the final product **5a** in one pot without isolating the intermediate **4a**. So, various reaction conditions were investigated and the results are summarized in **Table 1**.

Table 1. Optimization of reaction conditions[a]



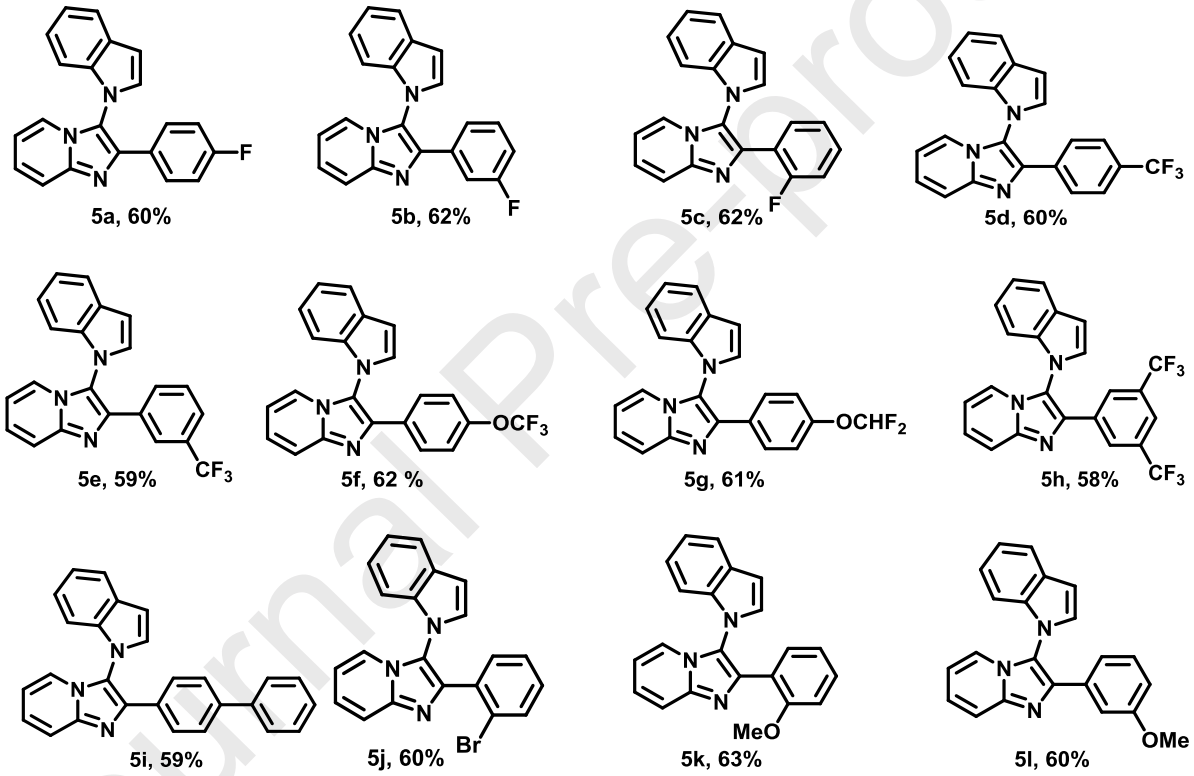
Entry	Acid	Solvent	Temp. (°C)	Time (h)	Yield % (4a)[b]	Yield % (5a)[b]
1	-	1,4-dioxane	110	8	70	-
2	$ZnCl_2$ (20 mol%)	1,4-dioxane	110	4	60	10
3	$Sc(OTf)_3$ (5 mol%)	MeOH:DCM	RT	24	50	8
4	AcOH (200 mol%)	MeOH	60	24	60	15
5	4N HCl (dioxane 20 mol%)	1,4-dioxane	RT	12	60	5
6	4N HCl (dioxane 20 mol%)	1,4-dioxane	110	4	40	40
7	TFA (20 mol %)	1,4-dioxane	RT	12	70	10
8	TFA (20 mol %)	1,4-dioxane	110	2	-	70
9	TFA (20 mol %)	EtOH	75	24	50	20
10	TFA (40 mol %)	EtOH	75	24	30	45
11	TFA (20 mol %)	MeOH	60	24	50	20
12	TFA (40 mol %)	MeOH	60	24	30	40

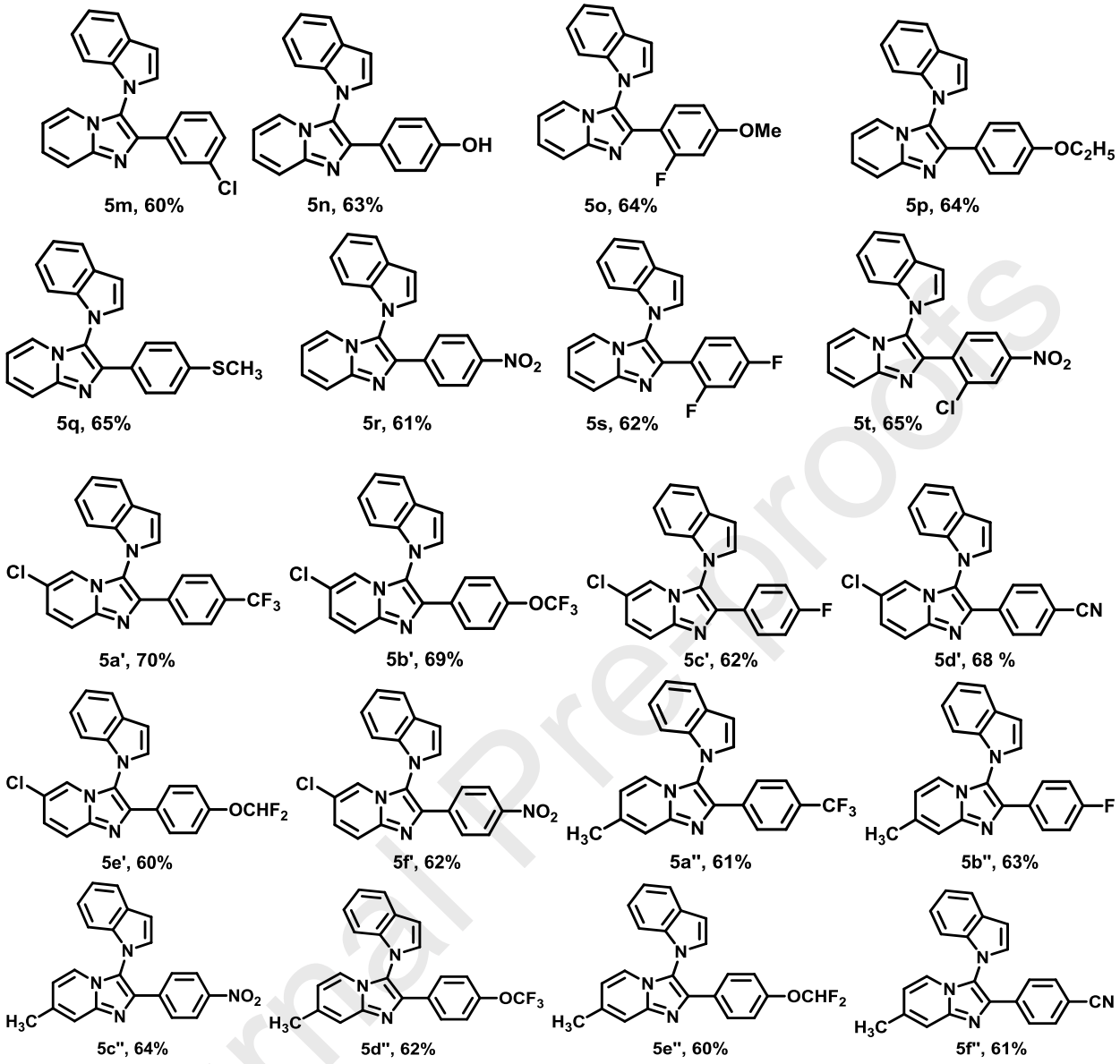
[a]Reaction conditions: 1a (0.6 mmol), 2a (0.6 mmol), 3a (0.6 mmol), catalyst, solvent (2 ml, sealed tube) according to the described conditions. The *vial* was flushed with argon and sealed with a teflon cap and was allowed to stir for required time. [b]Isolated Yields.

The results revealed that the nature of acid had a significant effect on the outcome of the reaction. In the absence of acid, only intermediate **4a** was obtained (**Table 1, entry 1**). The employment of Lewis acids was less effective and only trace amount of the target product was formed (**Table 1, entries 2−3**). Among various Brønsted acids, TFA gave the best result with 70% yield (**Table 1, entries 4−12**). After screening different amount of TFA with various solvents, we found that 20 mol% of TFA in 1,4-dioxane was the most suitable (**Table 1, entries 7-12**). Varying the reaction temperature from room temperature to 110 °C indicated that 110 °C was optimal for this reaction (**Table 1, entries 7, 8**). We further investigated the influence of solvents, namely, MeOH, EtOH, but the yield of the desired product was not improved (**Table 1, entries 9-12**). Finally, the optimal conditions were determined as **1a** (1 equiv), **2a** (1 equiv), **3** (1

equiv) and TFA (20 mol%) in 1,4-dioxane at 110 °C for 2 h (**Table 1, entry 8**). With the optimized reaction conditions in hand, the scope to generate various functionalized 3-(1H-indol-1-yl)-2-phenylimidazo [1,2-a]pyridine derivatives was explored. As shown in **Table 2**, various starting materials were successfully transformed into corresponding products *via* double cyclisation in one step in 60-70% yields with only one purification, indicating wide functional group tolerability with either electron donating or electron withdrawing substituents. The present protocol is broadly applicable and accommodates a variety of substitution patterns. A small library of **32** derivatives was prepared using the optimized synthetic protocol.

Table 2. Substrate scope





Based on our experimental results and literature reports, we proposed a possible mechanism for the formation of 3-(1H-indol-1-yl)-2-phenylimidazo [1,2-a]pyridine as shown in **Figure 2**. Firstly, the imine intermediate was generated by the reaction of amino-pyridine (**1**) with benzaldehyde (**2**), which after formal [4+1] cycloaddition reaction with isocyanide (**3**) forms cyclic intermediate **C** which subsequently forms an oxonium ion because of the acidic conditions employed. The intermediate **C** was then undergoes [1,3-H] shift to afford the intermediate **D** which has one nucleophilic center and can attack to the positive carbon and provides the cyclized intermediate **E**. The intermediate **E** afforded the desired product **5** in good yield with removal of methanol.

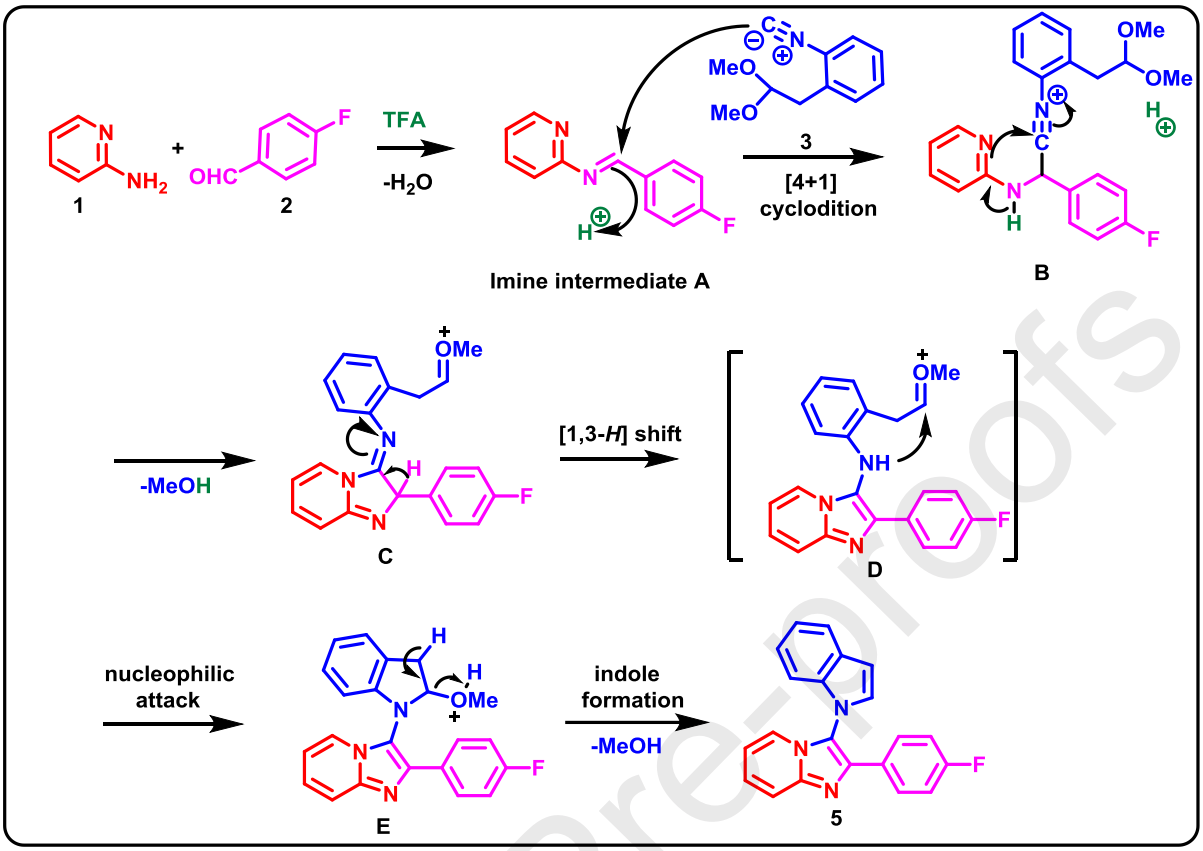


Figure 2: Plausible reaction mechanism or the synthesis of 3-(1H-indol-1-yl)-2-phenylimidazo [1,2-a]pyridine.

Conclusion

In this work, we introduced the convertible isocyanide (**3**) in GBB thee component reactions which furnished a library of biologically valuable poly-heterocyclic compounds using one-pot, tandem GBBR/post cyclisation protocol. To our knowledge, this is the first report for the construction of indolo-imidazopyridine hybrids. This methodology is highly efficient and straight forward towards the preparation of diverse indolo-imidazopyridine analogues. The salient feature of our protocol is high atom-economy, operational simplicity, easy work-up, and easily available precursors. These indolo-imidazopyridine hybrids are expected to possess enhanced biological activity as two pharmacophores are embedded in a single molecule. Synthesis of chemical library based on this pharmacophore as possible *Mycobacterial Tuberculosis ATP* synthase inhibitor is currently underway.

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Supporting Information

Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra of the synthesized compounds.

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- **Highlights**
  Transition-metal free
- One-pot tandem synthetic routes
- Atom economy, good yield and operational simplicity.