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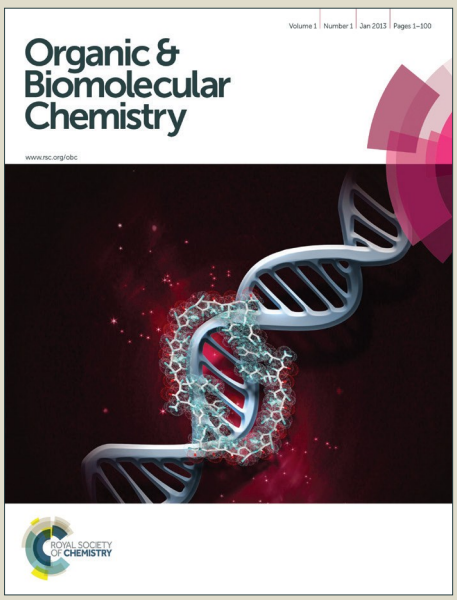

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ARTICLE

Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Access to Dihydroisoquinolinium (DHIQ) Salts

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A. Sagar,‡ Venkata Nagarjuna Babu,‡ Anand H. Shinde‡ and Duddu S. Sharada*

A reactive cyclic iminium induced one-pot Groebke-Blackburn-Bienayme (GBB) double annulation cascade (DAC) for the synthesis of skeletally diverse DHIQ salts has been described. The key features of this protocol are transition-metal and solvent-free, mild reaction conditions, robust method, one-step construction of two privileged heterocyclic rings, clean reaction profile and operational simplicity.

Introduction

The ubiquity of the isoquinoline (IQ) framework[1] in biologically active natural products, besides its applications as pharmaceuticals, functional organic materials and ligands for asymmetric catalysis have turned the attention of synthetic organic chemists in recent years. Among IQ derivatives, fused IQ salts are naturally occurring alkaloids[2] and promising lead

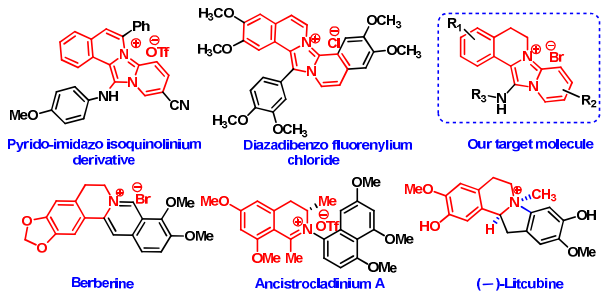
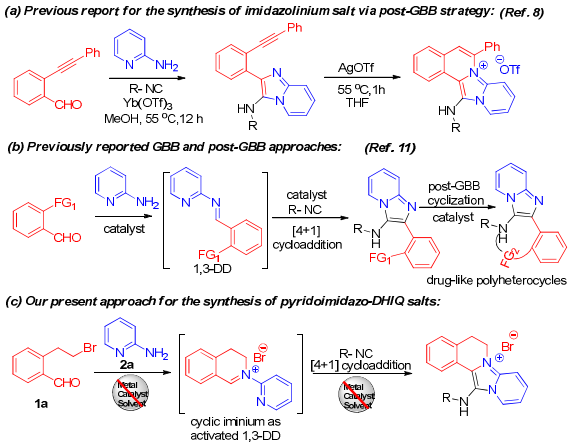


Figure 1 Representative examples of bioactive molecules and natural products.

structures in drug discovery.[3] The iminium moiety in these derivatives was found to be essential for significant biological activities.[4] Though several reports have been documented for the synthesis of these derivatives, most of the methods[5] involve starting material with preformed IQ skeleton, expensive metal catalysts, multiple steps, lack of diversity, scalability, and tedious routes to access starting material. Beside isoquinoline motif dihydroisoquinolinium (DHIQ) ion and pyrido-imidazo[5,1-*a*]isoquinolinium ion also form an important core structure[6] of natural products and pharmaceuticals (Figure 1), however, very few methods[7] have been reported for DHIQ derivatives.



Scheme 1 Various approaches to imidazopyridine based drug-like molecules *via* GBB reaction.

Recently, Shen et al. have developed an efficient approach to pyridoimidazoisoquinolinium compounds *via* $Yb(OTf)_3$ /AgOTf catalyzed one-pot synthesis (Scheme 1a).[8] However, it involves use of expensive two metal catalysts, inaccessible starting material, lack of generality and lengthy synthetic steps. Though there is a convenient approach reported for the synthesis of imidazoisoquinolinium salts, it involves preconstructed isoquinoline substrate rather than constructing the same.[9]

The versatility of 2-(2-bromoethyl)benzaldehyde (**1a**) as a promising bifunctional reactant in various organic transformations has been well documented, especially leading

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi 502285, Sangareddy, Telangana, INDIA
Phone: (040) 2301 7058; Fax: (040) 2301 6032, E-mail: sharada@iith.ac.in
† Footnotes relating to the title and/or authors should appear here.
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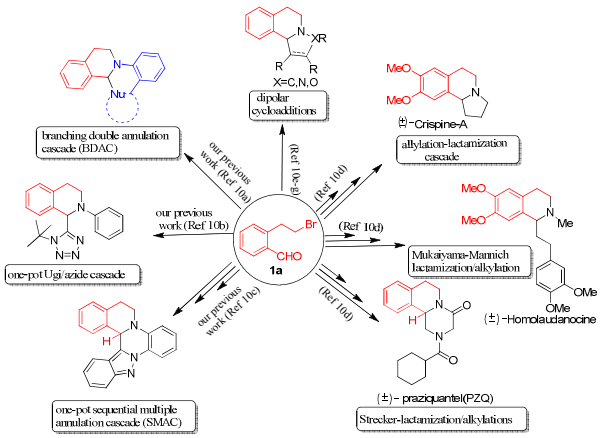
to tetrahydroisoquinoline (THIQ) motifs based natural products and their analogues (Scheme 2).[10] However, utilization of **1a** in the synthesis of fused dihydroisoquinolinium salts is not explored to date. Very recently, in our lab, we have documented some interesting cascade strategies employing **1a** for the synthesis of skeletally diverse THIQ skeletons (Scheme 2).[10a-c] Moreover, we have also reported step-economic and sustainable methods for the synthesis of imidazopyridines *via* GBB reaction.[11]

Groebke-Blackburn-Bienayme (GBB) reaction[12] is an elegant example involving [4+1] cycloaddition as a key step between activated imine i.e. 1,3-diazadiene (1,3-DD) and isocyanide resulting in drug-like imidazopyridine heterocyclic entities which are further cyclized by post-GBB modifications (Scheme 1b).[13,8] However, most of the methods were realized by either use of stoichiometric or catalytic amount of Bronsted acids or bases, Lewis acids and metal catalysts for the generation of 1,3-DD and its activation.



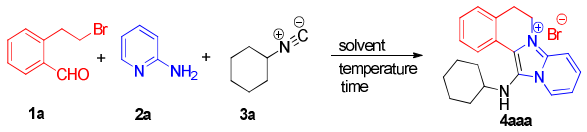
Scheme 2 Various approaches to THIQ motifs starting from 2-(2-bomoethyl) benzaldehyde.

Encouraged by our recent reports[10a-c] on employing **1a** in various organic cascade transformations, we envisioned that the bifunctional reactivity of **1a** could be tapped further (Scheme 1c). In this scenario, we conceptualized that **1a** on reaction with 2-aminopyridine **2a** would result in cyclic iminium *via* pre-GBB modification (imine formation and alkylation), which can be employed in GBB reaction as activated 1,3-DD under metal/catalyst-free conditions[14] (Scheme 1c). Herein, we disclose the cyclic iminium induced GBB double annulation cascade reaction leading to pyridoimidazo-DHIQ salts for the first time.

Results and discussion

To test the above hypothesis, a preliminary reaction of equimolar mixture of 2-(2 bromoethyl) benzaldehyde **1a**, 2-aminopyridine **2a** and cyclohexylisocyanide **3a** was performed at ambient temperature (35 °C) in methanol for 10h, which

Table 1 Double annulation cascade to pyridoimidazo-DHIQ salt **4aaa**[a,b]



entry	solvent	temp (°C)	time (h)	yield (%)
1	MeOH	rt	10	10
2	MeOH	50	20	20
3	MeOH	70	22	54
4	MeOH	90	20	64
5	EtOH	100	20	67
6	H_2O	100	20	0
7	DCE	100	23	40
8	DCM	50	14	32
9	CH_3CN	90	21	43
10	THF	90	14	35
11	1,4 dioxane	110	10	55
12	No solvent	rt	10	trace
13	No solvent	50	20	40
14	No solvent	60	2	66
15	**No solvent**	**80**	**10 min**	**91**
16	No solvent	90	10 min	70
17	No solvent	100	10 min	66

[a] Reaction conditions: **1a** (0.23 mmol), **2a** (0.23 mmol) and **3a** (0.23 mmol). [b] Yield of isolated product after column chromatography.

afforded the desired product 4aaa, albeit in low yield (Table 1, entry 1). Encouraged by this result, and to further explore, we increased the temperatures which resulted in improvement of yields up to 64% (Table 1, entries 2-4). Moreover, in protic and aprotic polar solvents, even after continuing the reaction for long hours the starting materials were not completely consumed (Table 1, entries 5-11). From the perspective of twelve principles of green chemistry,[15] solvent-free reactions have seen tremendous growth both in academia and industry.[16] Our continued interests in development of sustainable methods for synthesis of diverse heterocyclic frameworks[17,10a-c,11a,b] prompted us to perform the reaction under solvent-free conditions. Not surprisingly, higher temperatures resulted in improved yields of the products with drastic reduction in time (Table 1, entries 13-15). However, beyond 80 °C we have seen drop in the yields (Table 1, entries 16 and 17), which could be due to decomposition of reaction mixture.

With the reaction at 80 °C as optimized condition (Table 1, entry 15) for double annulation cascade (DAC) in hand we planned to evaluate the scope of our strategy. In this direction, we extended it to various aminoazines **2** and isocyanides **3**, keeping the aldehyde **1** component constant to obtain corresponding pyridoimidazoisoquinolinium derivatives (Scheme 3, **4aaa-4ace**) in good to excellent yields. The structure of **4aab** was further confirmed by single crystal X-ray crystallography as shown in Scheme 3 (see ESI). The aminoazine bearing electron withdrawing group (EWG), for example chloro substituent gave **4aha** in moderate yield (64%) compared to other aminoazines. We next investigated employing a variety of 2-(2-bromoethyl)benzaldehydes **1** and aminoazines **2** with EWG and electron donating groups (EDG),

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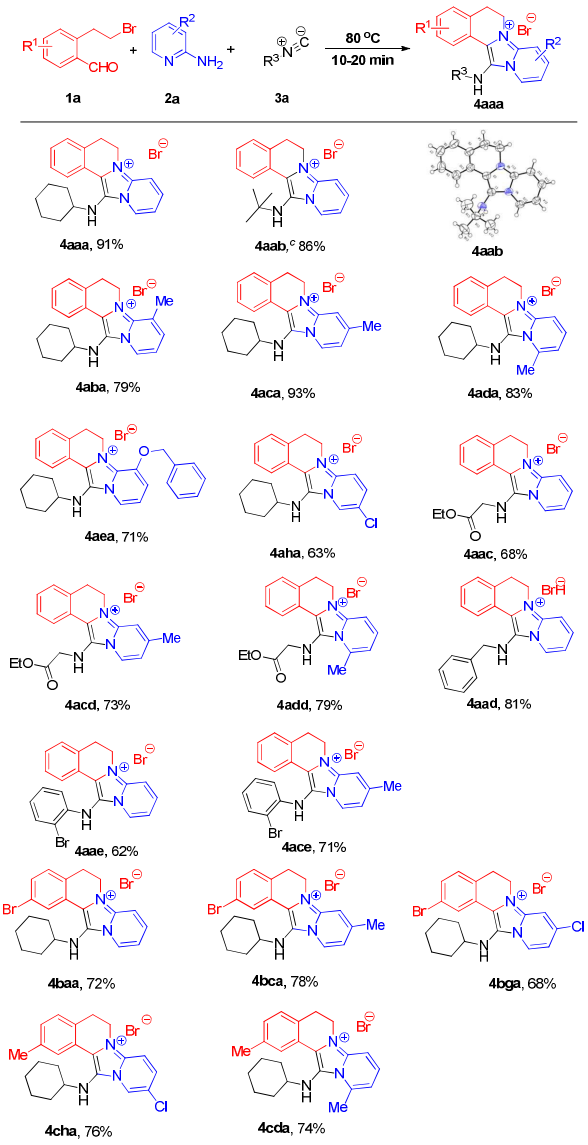
which did not show any significant difference in the outcome of the reaction. Gratifyingly, even when both aminoazines and aldehydes were employed with EWG, it resulted in good yield of the product (**4bga**, Scheme 3).

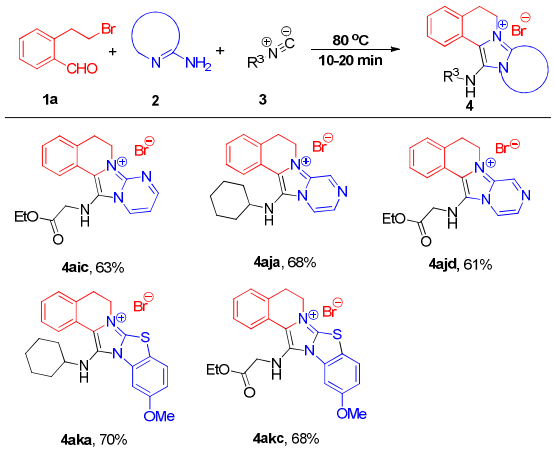
Scheme 3 Synthesis of pyridoimidazo-DHIQ scaffolds [a,b]



[a] Reactions were performed with **1** (0.23 mmol), **2** (0.23 mmol) and **3** (0.23 mmol) at 80 °C. [b] Yield of isolated product after column chromatography. [c] See ESI for X-ray crystal data.

Our pursuit for diversity oriented synthesis (DOS) impelled us to examine diversity of our present strategy. Accordingly, we probed with structurally and skeletally different aminoazines, which to our delight provided interesting and diverse tetra- and pentacyclic IQ scaffolds (Scheme 4).[18] When we have used other heterocyclic aminoazines we have not observed any detrimental effect on reaction outcome.

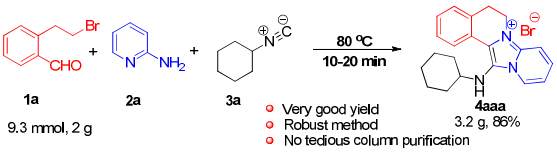
Scheme 4 Synthesis of skeletally diverse DHIQ scaffolds [a,b]



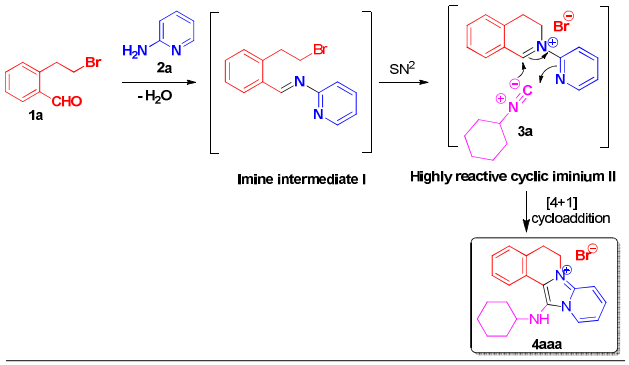
[a] Reactions were performed with **1** (0.23 mmol), **2** (0.23 mmol) and **3** (0.23 mmol) at 80 °C. [b] Yield of isolated product after column chromatography.

After having successfully developed one-pot double annulation cascade (DAC) strategy for the synthesis of diverse pyridoimidazo-DHIQ scaffolds *via* GBB reaction, we envisaged to examine the scalability of the process. Consequently, we have performed the reaction on 2 g scale and isolated the product **4aaa** as white solid in very good yield (86%) by direct filtration without the need for any tedious column purification (Scheme 5). As synthesized DHIQ compounds contain some privileged heterocyclic motifs present in drug molecules,[19] the scalability of our method should prove industrially applicable.

Scheme 5 Scalability of present DAC protocol



Scheme 6 Plausible reaction mechanism for **4aaa**



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Based on our reports,[10a-c] experimental[20] and other literatures,[4a,10d] we have proposed a plausible mechanism for the formation of pyridoimidazo-DHIQ salt **4aaa** in Scheme 6. Initially, the reaction of 2-(2-bromoethyl)benzaldehyde **1a** and 2-aminopyridine **2a** reacts to give intermediate imine **I**, which on intramolecular nucleophilic substitution will afford the highly reactive cyclic iminium **II.** Further, the cyclic iminium **II** on [4+1] cycloaddition with cyclohexylisocyanide **3a** will lead to pyridoimidazo-DHIQ bromide **4aaa**.

In summary, we have developed a mild, efficient and metal-free protocol for the synthesis of fused IQ derivatives under solvent-free conditions. We have demonstrated an unprecedented cyclic iminium induced GBB leading to construction of two privileged heterocyclic rings in one-pot. This double annulation cascade provided pyridoimidazo-DHIQs in excellent yields by easy isolation without tedious workup. In addition, readily accessible starting material, remarkably short reaction time, simplicity in operation, scope of skeletal diversity, H_2O as sole byproduct and scalability makes this approach greener, cost effective, and better alternative to existing ones. On the other hand, the scalability of the method should prove appealing for industrial applications. Further studies on biological activity of these scaffolds are currently under way in our laboratory.

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Notes

Corresponding Author

*** E-mail:** *sharada@iith.ac.in*

Author Contributions

‡ AS, VNB and AHS contributed equally.

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20 When we performed the reaction of 2-(2-bromoethyl)-benzaldehyde (1a) with aniline at 80 ^{o}C afforded the product 2-phenyl-3,4-dihydroisoquinolin-2-ium bromide salt, which was characterised by the NMR spectroscopy, thus supporting the proposed mechanism.