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A facile synthesis of tetrahydroimidazo[1,2-*a*]pyridines and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines through NHC-catalyzed cascade annulations†

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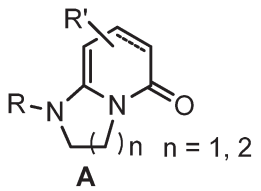
A new efficient approach for the synthesis of tetrahydroimidazo[1,2-*a*]pyridines and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines with biological significance was successfully developed through a NHC-catalyzed cascade C–C bond and C–N bond formation process. This new alternative approach for the assembly of these multi-functionalized nitrogen bridgehead-fused heterocycles features mild conditions, moderate to high yields and operational simplicity.

The imidazo-fused bridgehead-nitrogen scaffold is an important structural motif in pharmacological molecules displaying a wide range of bioactivities like antimicrobial,[1] anti-rhinoviral[2] and anticoccidial[3] activities. Therefore, the fabrication of these nitrogen bridgehead-fused heterocycles incorporating an imidazole ring has attracted considerable attention during recent decades.[4]

As an important type of imidazo-fused bridgehead-nitrogen heterocycle, bicyclic pyridone motifs **A** (Fig. 1) and their substituted variants (n = 1, 2) have been reported as the basis for analgesics, anti-inflammatory agents and inhibitors of pilus assembly in uropathogenic *Escherichiacoli* (so-called pilicides).[5] The bicyclic pyridone framework can be constructed *via* three approaches: the cyclocondensation of ketenaminals,[6] the addition of diamines to cyanobutenoic esters[7] and the addition of diamines to 1-halo or methylthiopyridones.[8] However, considering the biological significance and synthetic efficiency of these scaffolds, it is still highly desirable to develop new strategies to install them rapidly.

Because of the conjugation effect of the electron-donating amino groups and the electron-withdrawing aroyl substituent, the electron density on the α-carbon is enhanced leading to higher nucleophilicity than that of nitrogen. Therefore, heterocyclic ketene aminals (HKAs) **B** (Fig. 2) have been successfully used as powerful and versatile bisnucleophiles to manufacture a wide variety of *N*-bridgehead-fused heterocycles in the past few decades. Previous studies delineated the successful synthesis of bicyclic pyridones **A** through the reaction of HKAs with a number of biselectrophilic reagents, including α,β-unsaturated carboxylic acid derivatives,[4c,6b,6c] Meldrum's acid and aryl aldehydes,[9] itaconic anhydride,[10] propiolic acid ester[11] and allenic esters.[12] In general, all of these methods involving C–N bond-formation rely on activated carboxylate derivatives as coupling partners. Although much progress has been achieved, the preparation of some of these specific carboxylate derivatives remains difficult and, to date, the use of activated carboxylate derivatives is to some extent limited. Herein, this motivated us to develop a new, effectively catalytic, method to meet the increasing scientific demands.

Due to the unique inversion of the classical reactivity (Umpolung) in organic synthesis, the direct *in situ* activation of aldehydes by *N*-heterocyclic carbenes (NHCs) have drawn considerable attention from organic chemists.[13] Umpolung of aldehydes to acyl nucleophiles ($a^1 \rightarrow d^1$ umpolung, $a^3 \rightarrow d^3$ umpolung) has become an intense topic of current research.[14] Recently, according to the present state of NHC organocatalysis, another field of NHC-catalyzed redox reactions to yield acyl azolium has experienced tremendous growth in this



A

Fig. 1 Bicyclic pyridone motifs **A**.

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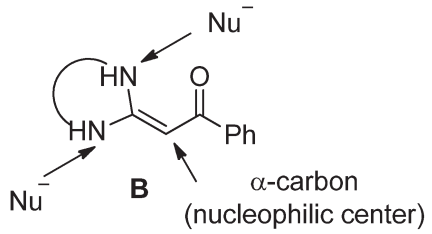


Fig. 2 Heterocyclic ketene aminals (HKAs) **B**.

area.[15] In this field the acyl azolium has been exploited as a novel synthon in new reactions to give a variety of highly functionalized products from simple starting materials. Furthermore, several literature works showed NHC-catalyzed reactions could generate α,β-unsaturated acyl azolium **C** as biselectrophiles from readily available starting material including alkynyl aldehydes,[15a,15e,15f] α,β-unsaturated aldehydes[15a,15c] and α-bromoenal[15b,15d] *via* internal or external redox processes. Moreover, α,β-unsaturated acid fluorides could also be transformed into **C** in the presence of a NHC (Fig. 3).[15g]

Since HKAs are highly reactive bisnucleophiles, we hypothesized that they would react with 1,3-biselectrophilic α,β-unsaturated acyl azolium efficiently to give bicyclic pyridones through C–C bond and C–N bond formations. To continue our work on the NHC-catalyzed cascade synthesis of heterocycles,[15b,16] we herein wish to describe a new NHC-catalyzed C–C bond and C–N bond formation strategy for assembling the scaffold of imidazo(pyrido)[1,2-*a*]pyridine and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridine *via* the reactions of HKAs with bromoenals.

Initially, several readily available NHC precursors were tested as a model reaction, in which α-bromocinnamic aldehyde **1a**, 2-(imidazolidin-2-ylidene)-1-phenylethanone **2a** and imidazolium salt **4d** were found to be the most efficient combination affording a promising 45% yield of the desired product **3a** at 60 °C in THF (Table 1, entry 4). We then examined the reaction using acetonitrile, methylene dichloride (DCM), tetrahydrofuran (THF), and toluene as solvents. Among the solvents tested, toluene was found to be preferable for the reaction giving 55% yield (Table 1, entry 8). Several

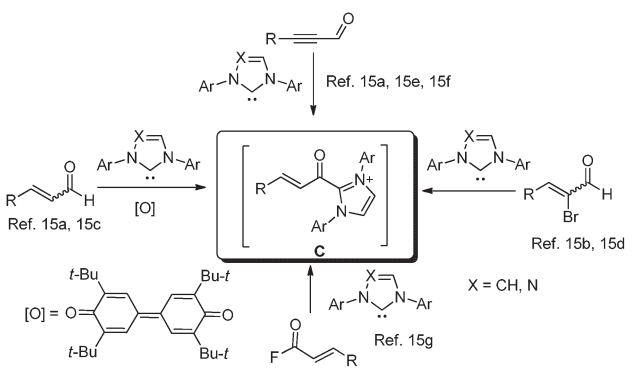
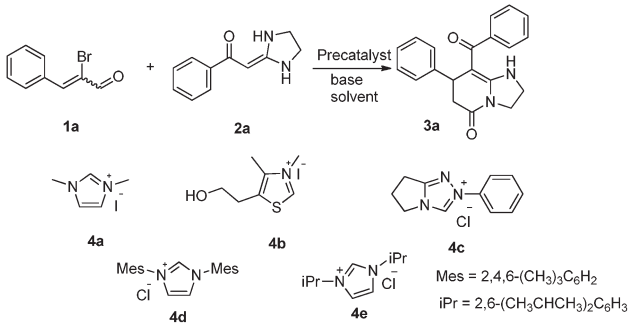


Fig. 3 Reported methods for generating α,β-unsaturated acyl azolium.

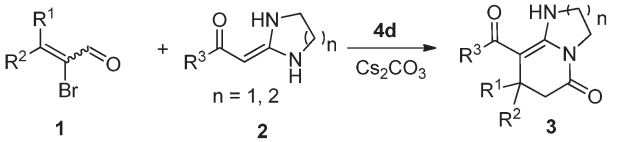
Table 1 Optimization of the reaction conditions



Entry	Precat. [a]	**1a** (mol%)	Solvent	Base (mol%)	*T* (°C)	Yield (%)[b]
1	**4a**	100	THF	K_2CO_3 (110)	60	ND
2	**4b**	100	THF	K_2CO_3 (110)	60	ND
3	**4c**	100	THF	K_2CO_3 (110)	60	ND
4	**4d**	100	THF	K_2CO_3 (110)	60	45
5	**4e**	100	THF	K_2CO_3 (110)	60	40
6	**4d**	100	DCM	K_2CO_3 (110)	60	ND
7	**4d**	100	CH_3CN	K_2CO_3 (110)	60	ND
8	**4d**	100	Toluene	K_2CO_3 (110)	60	55
9	**4d**	100	Toluene	NEt_3 (110)	60	50
10	**4d**	100	Toluene	*t*-BuOK (110)	60	43
11	**4d**	100	Toluene	Cs_2CO_3 (110)	60	60
12	**4d**	100	Toluene	DBU (110)	60	35
13	**4d**	100	Toluene	Cs_2CO_3 (110)	50	55
14	**4d**	100	Toluene	Cs_2CO_3 (110)	65	65
15	**4d**	100	Toluene	Cs_2CO_3 (110)	70	60
16	**4d**	100	Toluene	Cs_2CO_3 (110)	80	57
17	**4d**	150	Toluene	Cs_2CO_3 (160)	65	70
18	**4d**	200	Toluene	Cs_2CO_3 (210)	65	71
19	—	150	Toluene	Cs_2CO_3 (160)	65	ND

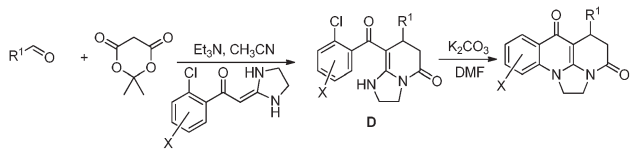
[a] Precatalyst (10 mol%). [b] Isolated yields.

Table 2 Substrate scope for the synthesis of tetrahydroimidazo[1,2-*a*]pyridines



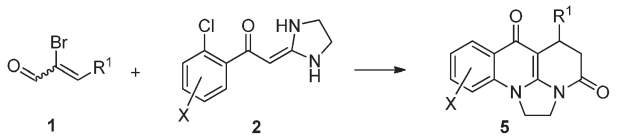
Entry	R^1	R^2	R^3	*n*	Product[a]	Yield (%)[b]
1	C_6H_5	H	C_6H_5	1	**3a**	71
2	4-ClC_6H_4	H	2,4-$Cl_2C_6H_3$	1	**3b**	75
3	C_6H_5	H	C_6H_5	2	**3c**	73
4	4-ClC_6H_4	H	C_6H_5	1	**3d**	72
5	C_6H_5	H	2,4-$Cl_2C_6H_3$	1	**3e**	72
6	3-ClC_6H_4	H	2,4-$Cl_2C_6H_3$	1	**3f**	74
7	4-ClC_6H_4	H	2,5-$Cl_2C_6H_3$	1	**3g**	70
8	C_6H_5	H	2-ClC_6H_4	1	**3h**	71
9	C_6H_5	H	4-BrC_6H_4	1	**3i**	75
10	4-$CH_3OC_6H_4$	H	2,4-$Cl_2C_6H_3$	1	**3j**	72
11	CH_3	H	C_6H_5	1	**3k**	60
12	CH_3	CH_3	C_6H_5	1	**3l**	50

[a] Products **3a–3k** were obtained using α-bromoenal (1.5 mmol), HKA (1.0 mmol), catalyst **4d** (34 mg) and Cs_2CO_3 (520 mg) in toluene (7 mL). Product **3l** was synthesised using α-bromoenal (2 mmol), HKA (1.0 mmol), catalyst **4d** (34 mg) and triethylamine (112 mg) in toluene (7 mL). [b] Isolated yields.



Scheme 1 The cascade synthesis of tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines.

Table 3 One-pot synthesis of tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines from a variety of α-bromoenals and HKAs

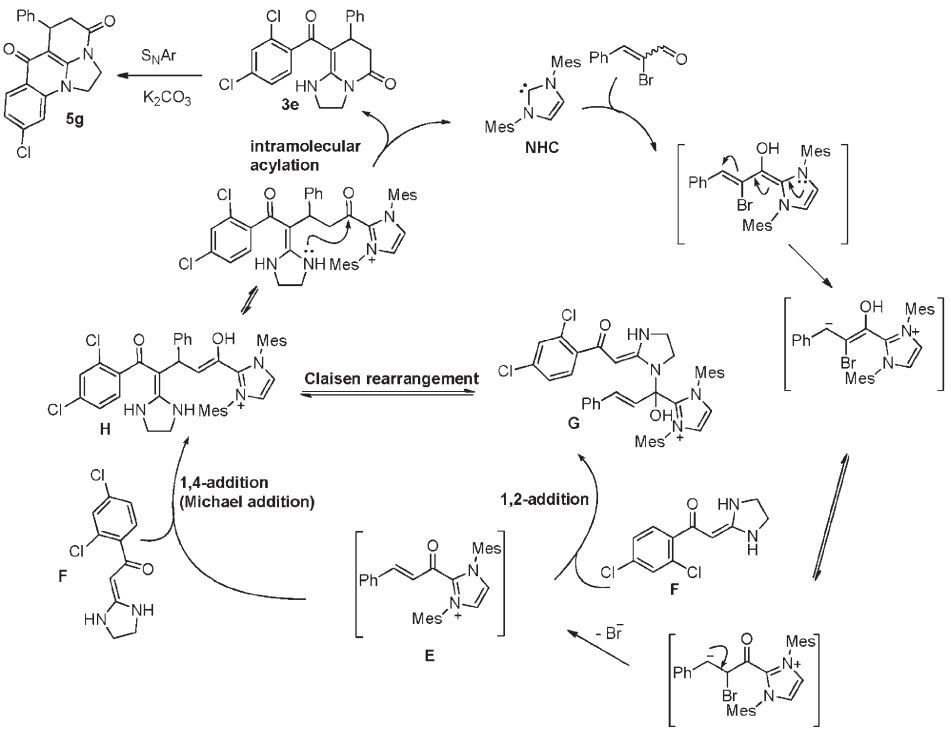


Entry	X	R^1	Product	Yield (%)[a]
1	5-Cl	4-$CH_3OC_6H_4$	**5a**	65
2	4-Cl	4-$CH_3OC_6H_4$	**5b**	60
3	5-Cl	3-$CH_3OC_6H_4$	**5c**	64
4	5-Cl	3-ClC_6H_4	**5d**	65
5	4-Cl	3-ClC_6H_4	**5e**	63
6	4-Cl	4-ClC_6H_4	**5f**	60
7	4-Cl	C_6H_5	**5g**	62

[a] Total isolated yields.

typical bases including K_2CO_3, Cs_2CO_3, DBU, NEt_3 and *t*-BuOK were tested for this reaction. As Table 1 showed, Cs_2CO_3 was found to be the best among the bases tested (Table 1, entry 11). Temperature screening revealed that 65 °C was the optimal reaction temperature. It was worth noting that the use of 1.5 equiv. of **1a** resulted in the best yield after examination. To validate the catalysis of NHC in this reaction, a further blank experiment was processed in the absence of the precatalyst **4d**, but none of the desired product was obtained.

Encouraged by these results, we then focused on the substrate scope of this catalytic method for the synthesis of tetrahydroimidazo[1,2-*a*]pyridines. Firstly, we studied the reaction using a series of HKAs (Table 2). It was noticeable that varying the ring size of the cycles in the heterocyclic ketene aminals (five-membered HKAs or six-membered HKAs) had no obvious effect on yield. Furthermore, a variety substituents on the phenyl rings of the HKAs were well tolerated in the reaction. Additionally, it was found that α-bromoenals bearing electron-rich or electron-deficient phenyl groups could participate in the reaction and afford the desired products in favorable yields. Interestingly, we discovered that simple 2-bromobut-2-enal could also participate in this reaction giving 60% yield. On the basis of the previous results, 2-bromo-3-methylbut-2-enal was used in this reaction. Excitingly, we successfully obtained the product in 50% yield. Although the yield was not satisfying, it provided a promising avenue for the enantioselective assembly of this framework containing a quaternary carbon catalyzed by chiral NHCs.[20a]



Scheme 2 Proposed mechanism (*e.g.*, product **5g**).

Recently, Li *et al.*[17] reported that the condensation of an aldehyde, Meldrum's acid and a functionalized HKA could give rise to an imidazo(pyrido)[1,2-*a*]pyridine intermediate **D** bearing a highly polarized push-pull interaction C–C double bond and a Cl atom as a leaving group. The subsequent intramolecular cyclization readily provided fused heterocycles *via* an S_NAr process (Scheme 1).[17] To further expand the applications and scope of the above-mentioned NHC-catalyzed cascade cyclization, the following S_NAr reaction was explored (Table 3). After consumption of the HKAs with a chlorine atom at the *ortho*-position with respect to the carbonyl group, the solvent was replaced with DMF and the reaction mixture was kept at 100 °C, yielding tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8]naphthyridines **5** in a smooth one-pot process.[20b]

On the basis of all the above results, two reasonable pathways were proposed to account for the cyclization as illustrated in Scheme 2.[12,15c,15f,15g,17–19] Both pathways involved in the formation of **E** at the beginning. On the one hand, **H** was proposed as an intermediate derived from the Claisen rearrangement of **G**, which was generated by the 1,2-addition of **E** to **F**.[15c,15f,19] On the other hand, the reaction between **E** and **F** could lead to the formation of **H** directly, through a 1,4-addition. The following intramolecular acylation could then liberate the NHC catalyst and generate **3e**.[15g,18,19] Finally, an intramolecular S_NAr reaction displacing the *o*-chlorine of the aryl group due to attack of the NH group gave the ultimate product **5g**.[12,17]

Conclusions

In conclusion, we have developed a new NHC-catalyzed domino procedure as an alternative method for the synthesis of bicyclic pyridones with different substituted patterns and tetrahydrobenzo[*b*]imidazo[3,2,1-*ij*][1,8]naphthyridines in a one-pot process starting from a variety of HKAs and α-bromoenals. A wide range of potential biologically active nitrogen bridgehead-fused heterocycles for biomedical screening have been synthesized successfully.

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20 (*a*) General procedure for the synthesis of **3**: Into an oven-dried 25 mL vial were weighed precatalyst **4d** (34 mg) and Cs_2CO_3 (520 mg). Toluene (7 mL) was added and the resulting mixture was stirred at 25 °C for 5 min followed by the addition of the α-bromo-α,β-unsaturated aldehyde (1.5 mmol) and HKA **2** (1 mmol), after which the reaction mixture was stirred for about 7 min. The reaction system was kept at 65 °C with stirring until completion (monitored by TLC). After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, mixture of ethyl acetate/petroleum ether, 3 : 1, v/v); (*b*) General procedure for the synthesis of **5**: Into an oven-dried 25 mL vial were weighed catalyst **4d** (34 mg) and Cs_2CO_3 (520 mg). Toluene (7 mL) was added and the resulting mixture was stirred at 25 °C for 5 min followed by the addition of the α-bromo-α,β-unsaturated aldehyde (1.5 mmol) and HKA **2** (1 mmol), after which the reaction mixture was stirred for about 7 min. The reaction system was kept at 65 °C with stirring until completion (monitored by TLC). After the removal of the solvent under reduced pressure, K_2CO_3 (138 mg, 1.0 mmol) and DMF (9 mL) were added and the mixture was heated to 100 °C. After the completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. 50 mL of water was added to precipitate the product, which was then filtered and washed with a small amount of ethanol to give the pure product **5**.