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Synthesis of Dihydropyridinone-Fused Indoles and α-Carbolines via N-Heterocyclic Carbene-Catalyzed [3 + 3] Annulation of Indolin-2-imines and Bromoenals

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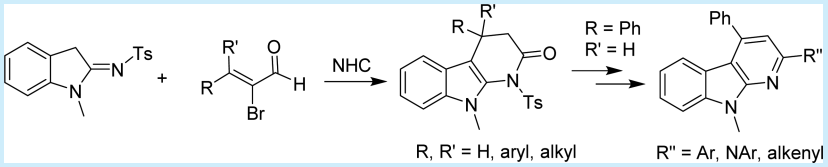
Supporting Information



ABSTRACT: The N-heterocyclic carbene catalyzed [3 + 3] annulation of indolin-2-imines and bromoenals was developed to give dihydropyridinone-fused indoles in good to high yields, which were transformed to α-carbolines with different 2-subsituents by a process of dehydrogenation, tosylation, and palladium catalyzed C−C or C−N coupling reaction.

Construction of heterocycles combining two biologically attractive motifs is highly desired in drug discovery.[1] α-Carbolines (pyrido[2,3-*b*]indoles), combining indole[2] and pyridine,[3] are known to exhibit an array of biological activities,[4] such as grossularine-1 and grossularine-2 as anticancer compounds,[4a−c] mescengricin as the inhibitor of L-glutamate excitotoxicity in neurons,[4d] and isoxazolo[5′,4′:5,6]pyrido[2,3-*b*]indoles as a new kind of anticancer lead (Figure 1).[4e] Many strategies have been developed for the synthesis of α-carbolines, including Graebe Ullmann reactions,[5] Diels−Alder reaction,[6] Vilsmeier−Haack reaction,[7] palladium-catalyzed C−C coupling[8] and C−N-coupling reactions,[9] and the 6π-electrocyclization of indole-3-alkenyl oximes.[10] In those methods, functional groups at the 2-position, which is crucial to many naturally occurring α-carbolines, had to be introduced in advance.

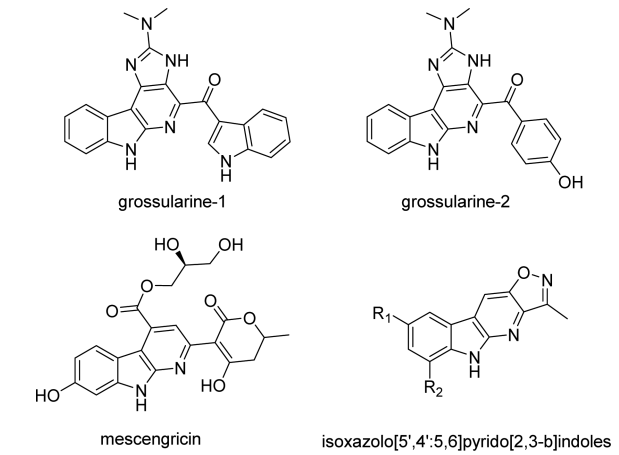


Figure 1. Bioactive α-carbolines.

In the past decades, N-heterocyclic carbene (NHC) catalyzed annulation reactions emerged as a powerful tool for the synthesis of various heterocycles.[11] The NHC-catalyzed generation of α,β-unsaturated acyl azolium and its [3 + 3] annulation with imines afforded dihydropyridinones,[12] which is a key motif for many bioactive compounds.[13] In this letter, we report the NHC-catalyzed [3 + 3] annulation of indolin-2-imines with bromoenals to give dihydropyridinones-fused indoles, which could be transformed to carbolines with different 2-subsituents via later modification.

Initially, the model reaction of indolin-2-imines **1a** with bromoenal **2a** was carried out under NHC catalysis (Table 1). We were encouraged to find that the reaction gave the desired cycloadduct **3aa** in 27% yield in the presence of 10 mol % thiazolium NHC precursor **A** and 1.2 equiv of potassium acetate as the base (entry 1). A series of NHC precursors **A**−**G** were then tested for their ability to catalyze the reaction (entries 2−7). While low yields were observed for thioazlium NHC precursors **A** and **B** (entries 1−2), no or only trace of cycloadduct **3aa** was detected for imidazolium NHC precursors **C** and **D**, respectively (entries 3−4). The yields were improved dramatically when triazolium salt NHC precursors **E**−**G** were used (entries 5−7). Several other organic and inorganic bases were screened but did not perform as well as potassium acetate (entries 8−11). Besides

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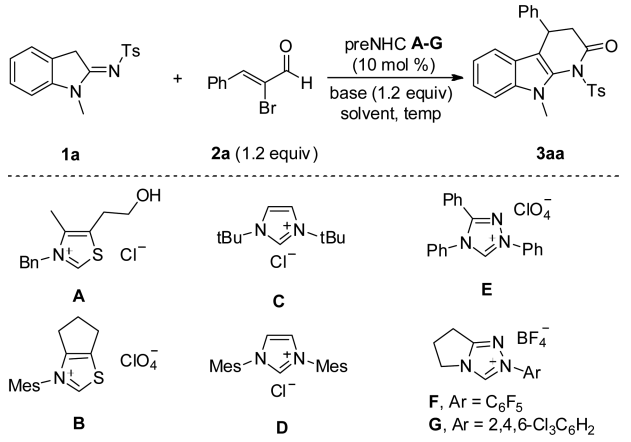
Table 1. Optimization of Reaction Conditions[a]



entry	pre-NHC	base	solvent	temp	yield (%)[b]
1	**A**	KOAc	THF	rt	27
2	**B**	KOAc	THF	rt	13
3	**C**	KOAc	THF	rt	NR
4	**D**	KOAc	THF	rt	trace
5	**E**	KOAc	THF	rt	68
6	**F**	KOAc	THF	rt	57
7	**G**	KOAc	THF	rt	68
8	**G**	DBU	THF	rt	27
9	**G**	DIPEA	THF	rt	32
10	**G**	K_2CO_3	THF	rt	18
11	**G**	$KHCO_3$	THF	rt	15
12	**G**	KOAc	ether	rt	66
13	**G**	KOAc	1,4-dioxane	rt	66
14	**G**	KOAc	THF	40 °C	99

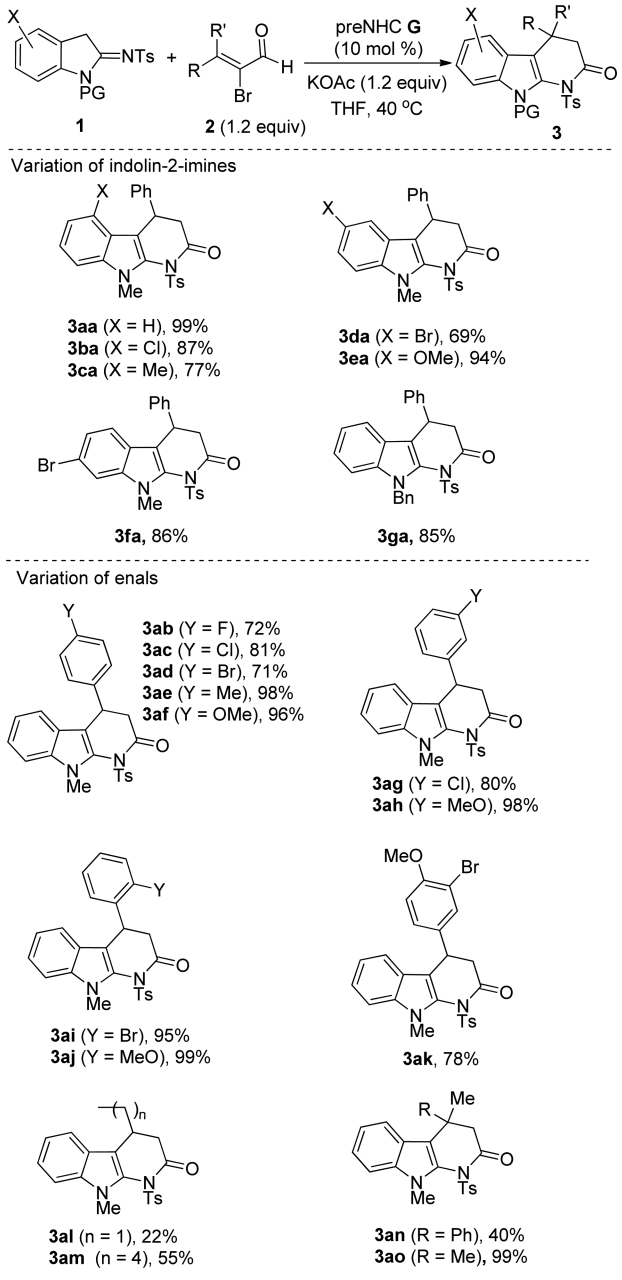
[a]General conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), cat. **A**–**G** (10 mol %), base (1.2 equiv), solvent (2 mL). [b]Isolated yield. NR = no reaction.

THF, the reaction proceeded smoothly in ether and 1,4-dioxane (entries 12–13). Finally, the yield was increased to 99% when the reaction was carried out at 40 °C (entry 14).

With the optimized conditions in hand, a variety of substituted indolin-2-imines and bromoenals were then explored (Scheme 1). It was found that both indolin-2-imines with substituents at the 4-/5-position of electron-withdrawing groups (X = 4-Cl, 5-Br) and electron-donating groups (X = 4-Me, 5-MeO) gave the products (**3ba**–**3ea**) in good to high yields. Substitution at 6-position (X = 6-Br) also resulted in good yield (**3fa**). Furthermore, an *N*-benzyl indolin-2-imine worked just as well as the *N*-methylsubstrates, giving cycloadduct **3ga** in 85% yield.

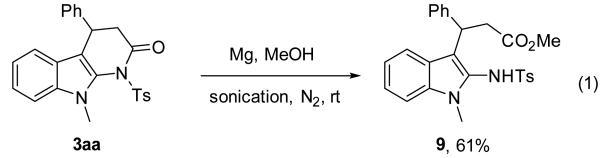
Both β-aryl-α-bromoenals with electron-withdrawing group (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4) and with electron-donating group (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$) worked well, although the later ones afforded better yields (**3ab**–**3ac** vs **3ae**–**3af**). All the reactions of arylbromoenals with *meta*-substituents (Ar = 3-ClC_6H_4, 3-$MeOC_6H_4$), with *ortho*-substituents (Ar = 2-BrC_6H_4, 2-$MeOC_6H_4$) and with disubstituents (Ar = 3-Br-4-$MeOC_6H_3$) went smoothly to give the cycloadducts (**3ag**–**3ak**) in high yields. Notably, the reaction of aliphatic α-bromoenal (R = *n*-C_2H_5, *n*-C_5H_{11}) gave the desired product (**3al**–**3am**) in low and moderate yield, respectively. In addition, β,β-disubstituted bromoenals could also participate in the reaction to give the cycloadducts **3an** and **3ao** with a quaternary carbon in moderate to high yields.

Scheme 1. Reaction Scope



The synthesis of α-carbolines from cycloadduct **3aa** was then investigated (Scheme 2). The dehydrogenation of **3aa** with Pd/C gave indole-fused pyridinone,[14] which was tosylated to afford compound **5**.[15] The palladium-catalyzed coupling reaction of heteroaryl tosylate **5** with aniline, phenylboronic acid, and alkene gave the corresponding α-carbolines **6**–**8** with 2-amino, 2-phenyl, and alkenyl substituent, respectively.[16]

In addition, the dihydropyridinone is hydrolyzed with methanol could be ring-opened to give the 2-amino-3-substituted indole **9** in 61% yield (eq 1).



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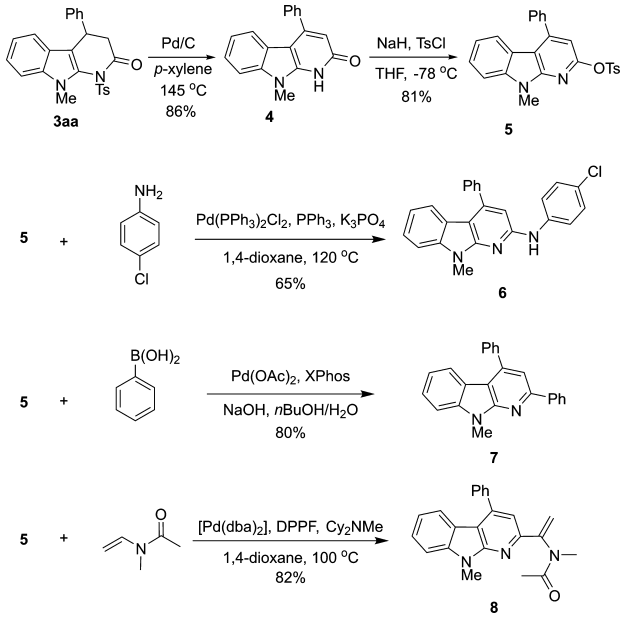
Scheme 2. Synthesis of α-Carbolines



The structure of cycloadduct **3da** was established by the X-ray analysis of its single crystal (Figure 2).

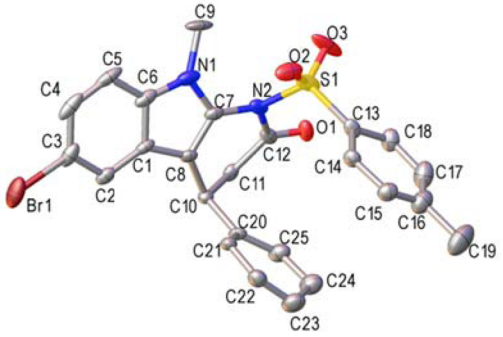


Figure 2. X-ray structure of **3da**.

A plausible catalytic cycle for the reaction was depicted in Figure 3. As previously reported,[12a] the key intermediate α,β-unsaturated acyl azolium **I** is generated by nucleophilic addition of NHC catalyst to bromoenal followed by elimination of bromide. The addition of enamine anion **1′**, generated from indoline-2-imines in the presence of base, to α,β-unsaturated acyl azolium intermediate **I** gives adduct **II**, which is transformed to enamine anion **III** via proton transfer. Subsequent lactamization yields the final [3 + 3] annulation product **3** and regenerates NHC catalyst.

In conclusion, the N-heterocyclic carbene-catalyzed [3 + 3] annulation of indolin-2-imines and bromoenals was developed to give dihydropyridinone-fused indoles in good to high yields. The cycloadduct could be transformed to α-carbolines with different 2-substituents by dehydrogenation, tosylation, and palladium-catalyzed coupling reactions. Further development of NHC-catalyzed [3 + 3] annulation reactions is underway in our laboratory.

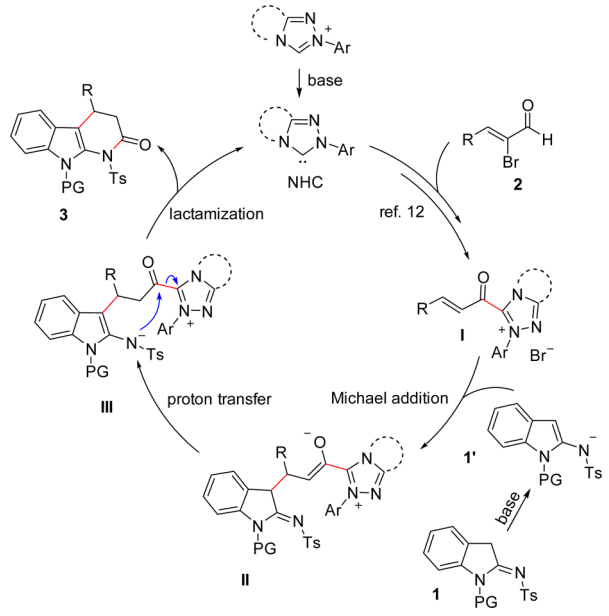


Figure 3. Plausible catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00820.

Experimental details and NMR spectra for obtained compounds (PDF)

X-ray data for **3da** (CIF)

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Notes

The authors declare no competing financial interest.

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