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N-heterocyclic carbene-mediated formal [3+3] annulation of isatin-derived α, β-unsaturated acids: Access to functionalized 3,4′-spirooxindole δ-lactones

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ABSTRACT

An *in situ* activation of isatin-derived α,β-unsaturated acids **2** for the generation of isatin-derived α,β-unsaturated acyl azoliums **II** was described. The acyl azoliums **II** were successfully applied to undergo a formal [3 + 3] annulation with 1,3-dicarbonyl compounds to access functionalized 3,4′-spirooxindole δ-lactones **4**. A scale-up synthesis and an enantioselective variant of this protocol were also investigated. The stable and easily prepared acids **2** may be further utilized as promising versatile electrophilic 1,3-synthons for divergent synthesis of spirooxindoles.

1. Introduction

Spirooxindoles represent privileged scaffolds with prevalence in numerous natural products and pharmacologically relevant drugs.[1] As an important subtype of spirooxindoles, 3,4′-spirooxindole δ-lactone is found as the core structure of many alkaloids and synthetic compounds with promising pharmaceutical activities (Fig. 1).[2] However, the architecture of this framework remains a challenging endeavor for organic chemists and limited synthetic approaches have been documented.[3] Therefore, the development of simple and versatile substrates and synthetic methods for the efficent construction of 3,4′-spirooxindole δ-lactone skeleton is practically important.

Over the past few decades, *N*-heterocyclic carbenes have emerged as unique and efficient organocatalysts to enable various unconventional chemical transformations *via* diverse reactive intermediates.[4] Among these intermediates, α,β-unsaturated acyl azoliums **I** commonly generated from ynals,[5] enals,[5f,6] 2-haloenals,[7] α,β-unsaturated esters[8] or acyl fluorides[9] have been used as novel and versatile electrophilic 1,3-synthons for the synthesis of numerous heterocyclic compounds. Recently, Ye and his coworkers[10] pioneered an alternative pathway to generate α,β-unsaturated acyl azoliums **I** *via* an *in situ* activation of carboxylic acids[11] that are easily available and more stable (Scheme 1a). In recently years, our group has been engaged in developing organocatalytic novel synthetic methods to access diverse heterocyclic compounds especially spirooxindoles.[4l,5b,5f,6i,7f,12] With the aim of discovering novel and versatile substrates and methodologies for divergent synthesis of skeletally diverse spirooxindoles, we previously achieved the application of isatin-derived α-bromoenals **1** as precursors to generate isatin-derived α,β-unsaturated acyl azoliums **II** for the synthesis of 3,4′-spirooxindole δ-lactones **4** (Scheme

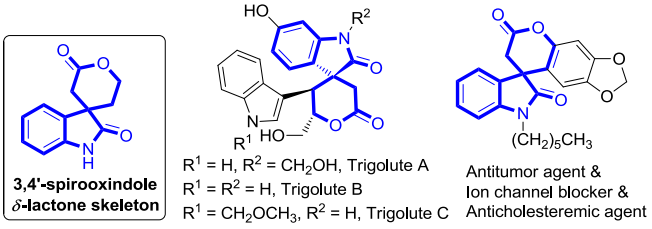

Fig. 1. Representative natural products or pharmaceuticals with 3,4′-spirooxindole δ-lactone skeleton.

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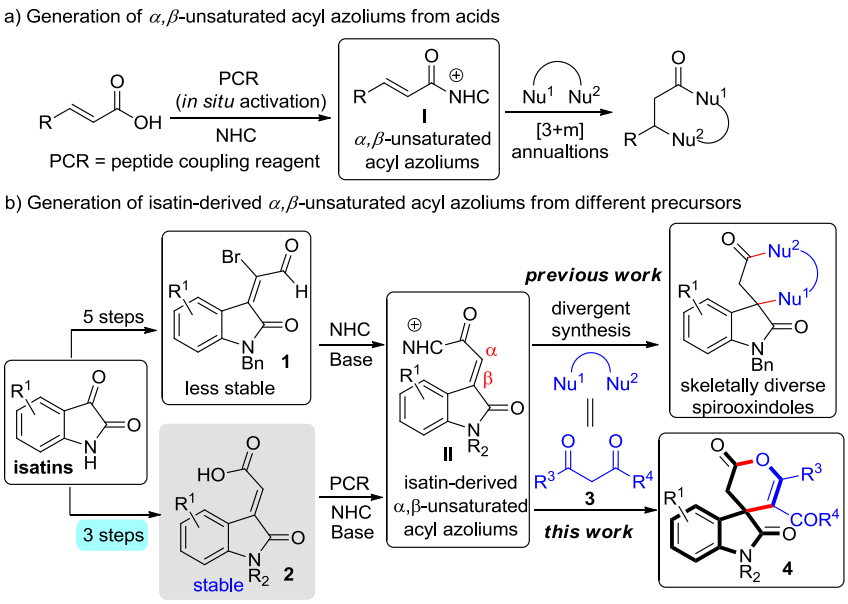


Scheme 1. Generation of α, β-unsaturated acyl azoliums from different precursors.

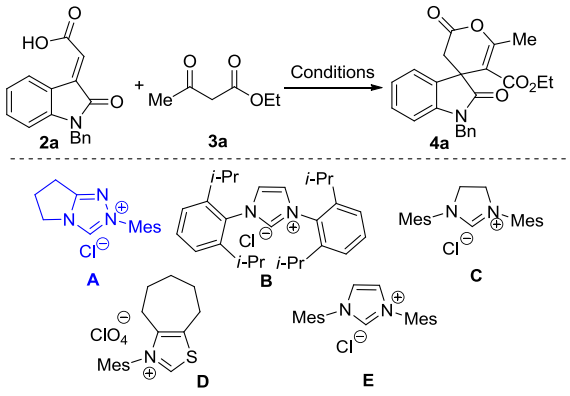
1b).[12d] Although isatin-derived α-bromoenals **1** proved to be more stable and easier to handle than isatin-derived enals which were used as substrates in NHC-catalyzed annulations by Zhong[6h] and Enders,[13] we reasoned that isatin-derived α,β-unsaturated acids **2** could be alternative or even better precursors as they are much more stable than the corresponding α-bromoenals **1** and are easier to prepare from the substituted isatins. To test the reactivity of isatin-derived α,β-unsaturated acids **2** and building upon our previous findings, we herein report an NHC-catalyzed formal [3 + 3] annulation of isatin-derived α,β-unsaturated acids **2** with 1,3-dicarbonyl compounds for the synthesis of 3,4′-spirooxindole δ-lactones **4** *via* an *in situ* activation strategy.

2. Results and discussion

We initiate the study by selecting acid **2a** and ethyl acetoacetate **3a** as the model substrates to examine the efficiency of several peptide coupling reagents (PCRs) under the catalysis of **A** in DCM at room temperature (Table 1, entries 1–3). Gratifyingly, HATU was found to be the optimal PCR which promoted the reaction to afford the desired product **4a** in 65% yield (entry 3). We then focused on screening of diverse carbene precursors **B**-**E** to enhance the reaction yield but none of these catalysts were found to be better than catalyst **A** (entries 4–6). Unfortunately, further examination of various bases and solvents did not give positive results (entries 7–13). Lewis acids like LiCl and $Sc(OTf)_3$ also failed to improve the reaction yield (entries 14 and 15). Therefore, the conditions shown in entry 3 was established as the optimal one for further scope exploration. It is noteworthy that the reaction is moisture sensitive, so 4 Å MS was used to absorb trace amount of water in the reaction system.

With the optimized reaction conditions, we moved on to explore the scope of this reaction initially by variation of *N*-substituents of acids **2** (Table 2). *N*-Substituents of the acids have great impact on the reaction (entries 1–4). If the nitrogen of the acids was substituted with electron-donating groups such as Bn, Me and allyl, the reaction afforded the desired products in moderate yields (entries 1–3). However, *N*-Ac-substituted acid **2d** was not applicable to this protocol (entry 4). Therefore, we used *N*-Bn-substituted acid **2a** as the model substrate for further exploration of

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	PCR	Base	Solvent	Additive	Yield (%)[b]
1	**A**	CDI	Cs_2CO_3	DCM	None	trace
2	**A**	BOP	Cs_2CO_3	DCM	None	49
3	***A***	***HATU***	***Cs_2CO_3***	***DCM***	***None***	***65***
4	**B/C**	HATU	Cs_2CO_3	DCM	None	0
5	**D**	HATU	Cs_2CO_3	DCM	None	31
6	**E**	HATU	Cs_2CO_3	DCM	None	35
7	**A**	HATU	K_2CO_3	DCM	None	40
8	**A**	HATU	DIPEA	DCM	None	16
9	**A**	HATU	K_3PO_4	DCM	None	26
10	**A**	HATU	Cs_2CO_3	THF	None	trace
11	**A**	HATU	Cs_2CO_3	PhMe	None	trace
12	**A**	HATU	Cs_2CO_3	DCE	None	32
13	**A**	HATU	Cs_2CO_3	$CHCl_3$	None	51
14	**A**	HATU	Cs_2CO_3	DCM	LiCl[c]	39
15	**A**	HATU	Cs_2CO_3	DCM	$Sc(OTf)_3$[d]	32

Bold-italics are used to highlight that this is the optimal reaction condition.
[a] Unless otherwise noted, all reactions were performed on a 0.2 mmol scale with 1.0 equiv of **2a**, 2.0 equiv of **3a**, 20 mol% of a carbene precursor, 1.5 equiv of a PCR, 2.5 equiv of a base and 200 mg of 4 Å MS in an anhydrous solvent (3 mL) at rt for 24 h under N_2.
[b] Isolated yields based on **2a**.
[c] 1.1 equiv of LiCl was used.
[d] 20 mol% of $Sc(OTf)_3$ was used. Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine.