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Hydride transfer initiated ring expansion of pyrrolidines toward highly functionalized tetrahydro-1-benzazepines†

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A novel hydride transfer initiated ring expansion of 4-pyrrolidinyl isatins to synthesize tetrahydro-1-benzazepines has been developed. This methodology represents an atom- and step-economical protocol to assemble seven-membered polycyclic amines from pyrrolidine derivatives in one step.

Highly functionalized seven-membered nitrogen-containing heterocycles are privileged motifs in a wide range of natural products[1] and pharmaceutically important agents.[2] Among these families, 1-benzazepine derivatives are conspicuous members due to their extensive application in many medicinal molecules, such as tolvaptan (vasopressin receptor antagonist),[2e] zilpaterol (beef improvement agent),[2f] benazepril (angiotensin-converting-enzyme inhibitor),[2g] fedovapagon (antidiuretic),[2h] and mianserin and mirtazapine (antidepressants)[2i] (Fig. 1). Therefore, the development of synthetic methodologies to access structurally diverse 1-benzazepine derivatives is of great significance. However, this issue remains a daunting challenge in organic synthesis because of the unfavorable transannular interactions, entropic penalties and angle strains.[3] Recently, a couple of protocols have been reported to assemble 1-benzazepine analogues, such as Mannich-type reaction,[4a,b] Friedel–Crafts-type annulation,[4c–e] [1,5]-hydride shift/7-endo cyclization[4f,g] and oxidative cross-coupling reaction.[4h] Nevertheless, these direct annulation strategies commonly rely on linear synthetic precursors, suffering from slow cyclization kinetics.[5] Furthermore, the necessity of highly engineered starting materials decrease the efficiency and practicality of these synthetic methods. As a consequence, the exploration of new efficient methodologies to construct 1-benzazepine derivatives is still in great demand.

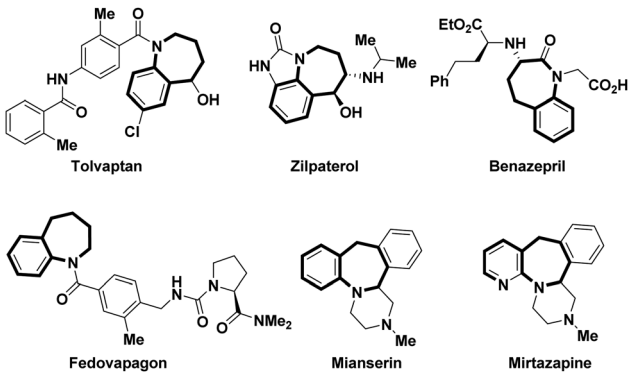

Fig. 1 Representative pharmaceuticals containing 1-benzazepine skeletons.

The ring expansion of cyclic compounds provides one of the most powerful tools to construct seven-membered azacycles. During the past few years, several ring expansion approaches have been developed, with three-,[6] four-[7] and six-membered[8] heterocycles as starting materials (Scheme 1a). Meanwhile, so far, ring expansion starting from five-membered pyrrolidines to access tetrahydro-1-benzazepines has never been realized, despite the fact that pyrrolidines are widely present in plenty of natural alkaloids and drugs.[9] To the best of our knowledge, the ring expansion of pyrrolidines still poses formidable challenges since these transformations are thermodynamically unfavourable processes.[10] Remarkably, although the ring expansion of five-membered pyrrolidines has enabled the straightforward construction of six-, eight- and nine-membered rings,[11] there is no report dealing with the synthesis of seven-membered tetrahydro-1-benzazepines. To address these challenges and as our continuing interest in establishing one-step assembly of molecular complexity,[12] herein, we report the first ring expansion of a five-membered nitrogen-containing ring to a seven-membered

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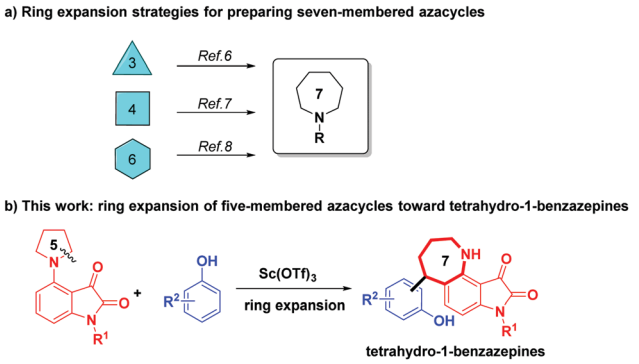
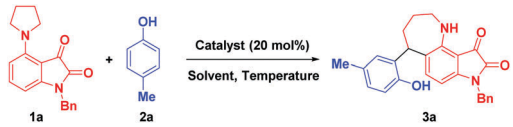


Scheme 1 Ring expansion strategies toward seven-membered azacycles.

heterocycles, providing an efficient synthesis of highly functionalized tetrahydro-1-benzazepines from pyrrolidines (Scheme 1b).

The initial attempt began with the reaction between 1-benzyl-4-pyrrolidinyl isatin **1a** and *p*-cresol **2a** in DCE at 120 °C with methanesulfonic acid (MsOH) as a catalyst. Surprisingly, the ring expansion product **3a** was isolated in 13% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 2). Other Brønsted acids such as trifluoromethanesulfonic acid (TfOH), bis(trifluoromethanesulfonyl)amide (Tf_2NH) and (−)-10-camphorsulfonic acid ((−)-CSA) led to inferior results (Table 1, entries 2–4). Subsequently, various Lewis acids were examined and it was found that $Sc(OTf)_3$ showed the best efficiency, delivering **3a** in 40% yield (Table 1, entries 5–9). Further screening the solvents and temperature indicated that DCE

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	MsOH	DCE	120	13
2	TfOH	DCE	120	10
3	Tf_2NH	DCE	120	n.r
4	(−)-CSA	DCE	120	n.r.
5	$ZnCl_2$	DCE	120	Trace
6	$Sc(OTf)_3$	DCE	120	40
7	$Sm(OTf)_3$	DCE	120	25
8	$Y(OTf)_3$	DCE	120	30
9	$Gd(OTf)_3$	DCE	120	38
10	$Sc(OTf)_3$	DCE	100	59
11	$Sc(OTf)_3$	DCE	80	50
12	$Sc(OTf)_3$	Toluene	100	30
13	$Sc(OTf)_3$	DCM	100	26
14	$Sc(OTf)_3$	$CHCl_3$	100	18
15	$Sc(OTf)_3$	MeCN	100	n.r.
16	$Sc(OTf)_3$	THF	100	n.r.
17	$Sc(OTf)_3$	HFIP	100	n.r.
18[c]	$Sc(OTf)_3$	DCE	100	<8
19[d]	$Sc(OTf)_3$	DCE	100	38

[a] Reaction conditions: a solution of **1a** (0.1 mmol), catalyst (0.02 mmol), and phenol **2a** (0.3 mmol) in the indicated solvent (2.0 mL) was stirred under an air atmosphere for 4 days. [b] Isolated yield after column chromatography. [c] The reaction was performed under a N_2 atmosphere. [d] The reaction was performed under an O_2 atmosphere. n.r. = no reaction.

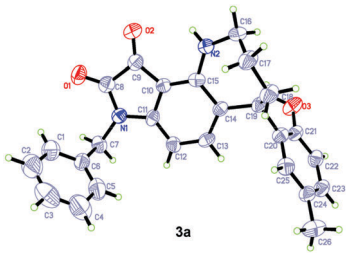
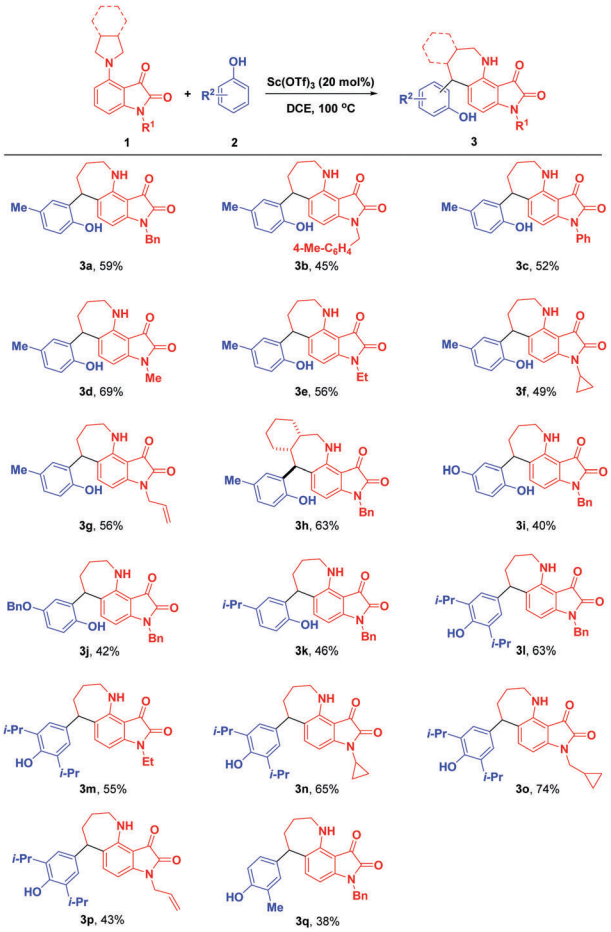


Fig. 2 The X-ray crystal structure of **3a**.

and 100 °C were the optimal reaction conditions (Table 1, entries 10–17). Notably, the reaction under a N_2 atmosphere only gave the desired product in less than 8% yield (Table 1, entry 18), implying the importance of molecular oxygen in this transformation. However, the following experiment under an O_2 atmosphere provided **3a** in 38% yield, which suggested that the avoidance of the oxidation of phenols was vital for this reaction (Table 1, entry 19). Consequently, the best reaction conditions were selected as indicated in entry 10.

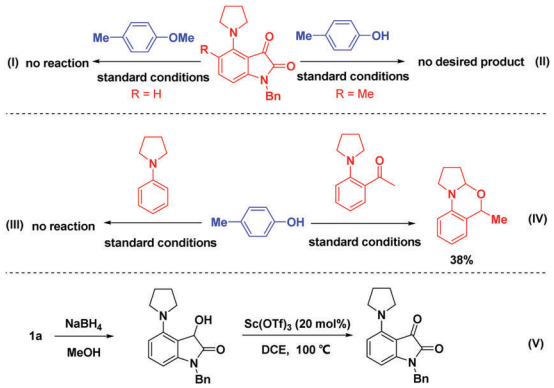
With the optimized reaction conditions in hand, the scope of this ring expansion methodology was evaluated over a wide array of substrates (Scheme 2). At the outset, we sought to investigate the substrate scope with respect to the isatins. As shown in Scheme 2, a variety of alkyl and aryl substituents were installed on the N-atoms of the isatins to evaluate the general applicability of this transformation (**3a–g**). Remarkably, the isatins bearing the benzyl (**3a–b**), phenyl (**3c**), cyclopropyl (**3f**) and allyl (**3g**) groups were totally tolerable, delivering the corresponding tetrahydro-1-benzazepines in decent yields. It is worth mentioning that the strained cyclopropane and alkene moieties were also compatible with this system. Notably, *N*-methyl isatin exhibited the best efficiency and delivered the desired ring expansion product **3d** in 69% yield. More intriguingly, the successful assembly of the cyclohexane-fused polycyclic amine product **3h** from octahydro-isoindole implied the potential application of this approach in building complex polycyclic compounds. Subsequently, the scope of the phenol derivatives was examined (**3i–q**). As expected, the reactions of hydroquinone, 4-benzyloxyphenol and 4-isopropylphenol with 1-benzyl-4-pyrrolidinyl isatin **1a** proceeded well, giving rise to the corresponding products **3i–k** in acceptable yields. Notably, when 2,6-diisopropylphenol was used as a reaction candidate, the reaction occurred at the *para*-position of the hydroxyl group, yielding different products **3l–p** in 43–74% yields. Finally, it was found that *o*-cresol could also engage in this transformation, affording **3q** in acceptable yield. However, for phenol and other substituted phenols, the yields were low. Further examination of other nucleophiles such as *p*-xylene, aniline and indole met with failure (see the ESI†).

In order to shed light on the mechanism of the transformation, some control experiments were performed (Scheme 3). Protection of *p*-cresol **2a** with a methyl group totally suppressed this reaction (Scheme 3, I), indicating the importance of the free OH group. When the 5-position was occupied by a methyl group in substrate **1a**, no desired product was observed (Scheme 3, II).

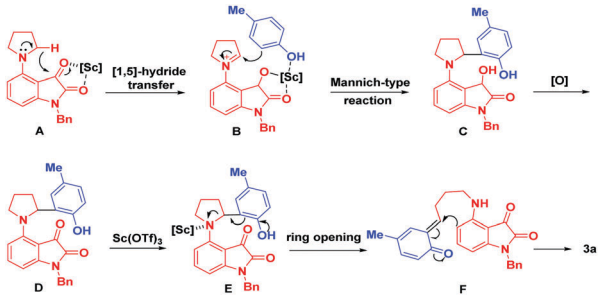


Scheme 2 The scope of tetrahydro-1-benzazepines. Reaction conditions: a solution of **1** (0.1 mmol), $Sc(OTf)_3$ (0.02 mmol), and phenol **2** (0.3 mmol) in DCE (2.0 mL) was stirred at 100 °C under an air atmosphere for 4 days. The yields are for the isolated products.

Intriguingly, the replacement of **1a** with 1-phenylpyrrolidine also impeded this reaction (Scheme 3, III), implying that the 1, 2-dicarbonyl moiety of the isatin was indispensable. For the 1-phenylpyrrolidine substrate with an acetyl group on the 2-position of the phenyl ring, the cascade [1,5]-hydride transfer/cyclization occurred with the oxygen anion as a nucleophile



Scheme 3 Control experiments.



Scheme 4 Proposed reaction mechanism.

(Scheme 3, IV).[13] Reduction of **1a** afforded the alcohol intermediate, which could be fully oxidized to **1a** under the standard conditions in 10 minutes (Scheme 3, V).

On the basis of the above experiments and literature precedents, a plausible reaction mechanism of this transformation is proposed as shown in Scheme 4. Activated by $Sc(OTf)_3$, 1-benzyl-4-pyrrolidinyl isatin **1a** undergoes [1,5]-hydride transfer to furnish intermediate **B**.[13,14] The subsequent intermolecular Mannich-type reaction delivers intermediate **C**, which is easily oxidized to isatin derivative **D** by air. Then intermediate **D** engages in the key ring-opening step *via* transition state **E** catalyzed by $Sc(OTf)_3$ to give *ortho*-quinone methide (*o*-QM) intermediate **F**.[15] The following intramolecular nucleophilic addition toward *o*-QM generates the desired product **3a** as the final ring expansion product. In the whole process, the $Sc(OTf)_3$ catalyst plays the key role in initiating the [1,5]-hydride transfer as well as the ring-opening processes.

In summary, a novel hydride transfer induced ring expansion of 4-pyrrolidinyl isatins has been developed to synthesize tetrahydro-1-benzazepines in one step, which represents the first example of ring expansion from a pyrrolidine ring to a seven-membered azacycles. A range of substituted phenols and 4-pyrrolidinyl isatins were tolerated to afford the highly functionalized tetrahydro-1-benzazepine derivatives in decent yields. This methodology provides an efficient protocol to one-step assembly of seven-membered polycyclic amines *via* ring expansion of readily available pyrrolidine derivatives. We believe that this report will not only offer a distinctive protocol for ring-expansion of five-membered azacycles, but also find wide application in the construction of biologically significant tetrahydro-1-benzazepine derivatives.

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Conflicts of interest

There are no conflicts to declare.

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