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Substitution-Controlled Selective Formation of Hexahydrobenz[*e*]isoindoles and 3-Benzazepines via $In(OTf)_3$-Catalyzed Tandem Annulations

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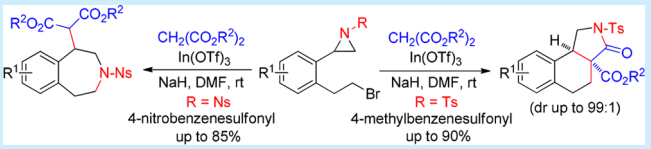
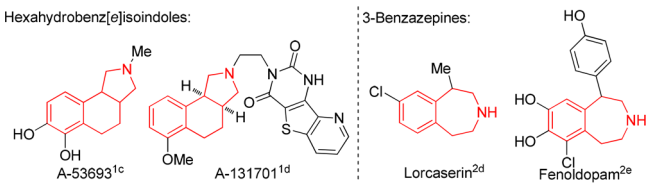
Supporting Information

ABSTRACT: A dramatic *N*-substituent controlled tandem annulation of 2-(2-(2-bromoethyl)phenyl)-1-sulfonylaziridines with 1,3-dicarbonyl compounds has been developed. When the *N*-substituent was a 4-methylbenzenesulfonyl group (Ts), sequential ring opening of aziridines, nucleophilic substitution, and lactamization took place to provide a series of hexahydrobenz[*e*]isoindole compounds in good yields with good diastereoselectivities. By contrast, 3-benzazepine compounds were afforded in good yields via ring opening of aziridines and nucleophilic substitution when the *N*-substituent was the 4-nitrobenzenesulfonyl group (Ns).



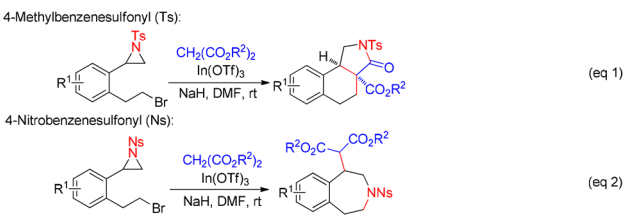
Hexahydrobenz[*e*]isoindoles[1] and 3-benzazepines,[2] as two important classes of heterocyclic skeletons containing the phenethylamine substructure, exist in a number of compounds with interesting biological and pharmacological properties (Scheme 1). Traditionally, these two skeletons have been constructed by different routes. In the literature, methodologies for the synthesis of 3-benzazepines are relatively abundant. Typical strategies include Heck-type cyclization,[3] Friedel−Crafts cyclization,[4] radical cyclization,[5] hydroamidation,[6] and ring-expansion reaction.[7] Recently, several elegant cascade reactions have been also developed for the synthesis of 3-benzazepines.[8] In contrast to many of the methods for the synthesis of 3-benzazepines, there are few reports on the assembly of hexahydrobenz[*e*]isoindoles. Several successful examples mainly include intramolecular Diels−Alder cycloadditions of benzocyclobutenes[9] and multistep synthesis starting from functionalized 1,2-dihydronaphthalenes.[10] Considering the continued synthetic requirement of hexahydrobenz[*e*]isoindoles and 3-benzazepines for bioactive evaluation in drug discovery, there is still a high demand for developing efficient and general methodologies for the synthesis of them.

Scheme 1. Representative Bioactive Molecules



Chemoselective construction of complex cyclic compounds from a multifunctional substrate via a tandem reaction is an attractive challenge for chemists. It is even more impressive if the reaction is effectively controlled to provide different cyclization products from the same starting materials.[11] Recently, we designed and synthesized a new type of substrates containing aziridines[12] and alkyl halides. Both of them are prone to react with various nucleophiles to afford ring-opened products and substitution products. When we employed 1,3-dicarbonyl compounds as the nucleophiles to initiate tandem reactions,[13−15] a dramatic substituent effect was observed. Tandem reactions delivered two different kinds of products via respective cyclization paths by subtle structure modification of *N*-substitution of the aziridine. For *N*-Ts-activated aziridines, sequential ring opening of aziridines, nucleophilic substitution, and lactamization took place, providing hexahydrobenz[*e*]-isoindoles in moderate to good yields with good diastereoselectivities (Scheme 2, eq 1). When *N*-Ns-activated aziridines were used, tandem reactions underwent ring opening of aziridines and nucleophilic substitution to furnish 3-benzazepines in good yields (Scheme 2, eq 2). Herein, we would like to

Scheme 2. Selective Formation of Hexahydrobenz[*E*]isoindoles and 3-Benzazepines



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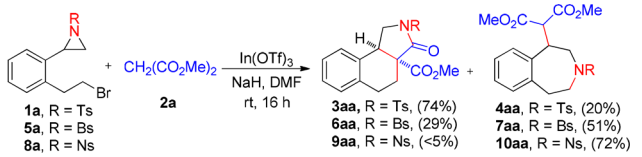
report the detailed results of these two pathway-controllable tandem reactions.

The reaction of aziridine **1a** with dimethyl malonate **2a** (see Scheme 3 for structures) was carried out for our initial

Scheme 3. Substituent Effect at the Nitrogen Atom

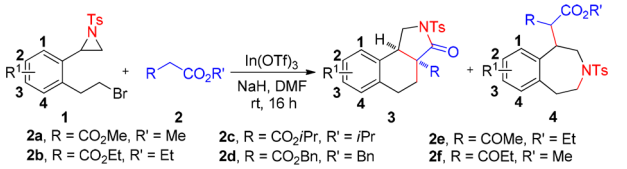


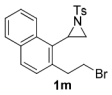
investigation (see Supporting Information for the optimization of the reaction conditions). When aziridine **1a** was treated with **2a** (3 equiv) in the presence of $In(OTf)_3$ (20 mol %) and NaH (3 equiv) at room temperature for 16 h in DMF, the best result was obtained. Tricyclic product **3aa** was afforded in 74% yield as a single diastereomer, along with bicyclic product **4aa** in 20% yield. With the optimal reaction conditions in hand, we synthesized aziridines **5a** and **8a** to investigate the influence of the protecting group of the N atom of aziridines on tandem reactions (Scheme 3). Unexpectedly, an obvious *N*-substituent effect was observed. With the enhancement of electron-withdrawing properties of substituent groups at the N atoms of the aziridine ring, the formation of tricyclic products was gradually suppressed under the optimal reaction conditions. Bicyclic products were isolated as the preponderant products. In particular, the tandem reaction of *N*-Ns-activated aziridine **8a** with **2a** furnished bicyclic product **10aa** in 72% yield, along with tricyclic product **9aa** in less than 5% yield. The unexpected *N*-substitution effect impelled us to develop two tandem reactions for the synthesis of tricyclic products **3** and bicyclic products **10**, respectively.

The tandem reactions of *N*-Ts-activated aziridines **1** with 1,3-dicarbonyl compounds **2** for the synthesis of tricyclic products **3** were first investigated (Table 1). In most cases, products **3** were obtained as the preponderant products with good diastereoselectivities, along with a small quantity of products **4**. It was found that malonic esters **2a**−**2d** successfully reacted with aziridine **1a** to provide products **3aa**−**3ad** in acceptable to good yields with good diastereoselectivities (Table 1, entries 1−4). The relative configuration of **3ac** was confirmed by X-ray crystal structure analysis. When *β*-ketoesters **2e** and **2f** were used to run tandem reactions, tricyclic products **3ae** and **3af** were afforded in low yields (Table 1, entries 5−6). After carefully analyzing the reaction of **2f** with **1a**, we isolated a bicyclic byproduct **3af′** in 36% yield (Scheme 4). The structure of **3af′** was confirmed by X-ray crystal structure analysis. It can be seen that lactamization did not occur when the nitrogen atom and the ester group were at different sides of the six-membered ring. Then *N*-Ts-activated aziridines **1b**−**1m** with various substituents on the aromatic ring were subjected to tandem reactions (Table 1, entries 7−19). In general, these aziridines underwent tandem reactions with **2a** or **2d** to generate the desired tricyclic products in good yields with good diastereoselectivities. As an exception, when we conducted the tandem reaction using aziridine **1b**, we isolated bicyclic product **4ba** as the major product.[16] The structure of **4ba** was confirmed by X-ray crystal structure analysis. In addition, it was found that the naphthalene-containing substrate **1m** reacted with **2a** to afford product **3ma** in 60% yield (Table 1, entry 20).

Subsequently, tandem reactions of *N*-Ns-activated aziridines **8** with 1,3-dicarbonyl compounds **2** were investigated for the

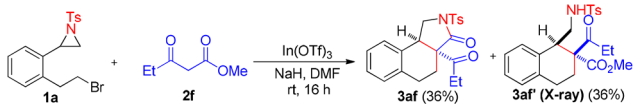
Table 1. Construction of Hexahydrobenz[*e*]isoindoles[a]



entry	1, R^1	2	3	yield/%[b,c]	4	yield/%[d]
1	**1a**, H	**2a**	**3aa**	74	**4aa**	20[b]
2	**1a**, H	**2b**	**3ab**	64	**4ab**	30[b]
3	**1a**, H	**2c**	**3ac**	45	**4ac**	40[b]
4	**1a**, H	**2d**	**3ad**	72	**4ad**	15
5	**1a**, H	**2e**	**3ae**	38	**4ae**	<5
6	**1a**, H	**2f**	**3af**	36	**4af**	<5
7	**1b**, 1-F	**2a**	**3ba**	<5[d]	**4ba**	80[b]
8	**1c**, 1-Me	**2a**	**3ca**	64	**4ca**	25
9	**1d**, 2-F	**2a**	**3da**	68	**4da**	18
10	**1e**, 2-Cl	**2a**	**3ea**	62	**4ea**	12
11	**1e**, 2-Cl	**2d**	**3ed**	66	**4ed**	15
12	**1f**, 2-Me	**2a**	**3fa**	72	**4fa**	24
13	**1g**, 2-OMe	**2a**	**3ga**	70	**4ga**	24
14	**1h**, 3-F	**2a**	**3ha**	60	**4ha**	12
15	**1i**, 3-Cl	**2a**	**3ia**	64	**4ia**	12
16	**1i**, 3-Cl	**2d**	**3id**	72	**4id**	15
17	**1j**, 3-Me	**2a**	**3ja**	68	**4ja**	25
18	**1k**, 4-Cl	**2a**	**3ka**	80	**4ka**	<5
19	**1l**, 4-OMe	**2a**	**3la**	90	**4la**	<5
20		**2a**	**3ma**	60	**4ma**	<5

[a]Reaction conditions: **1** (1 equiv, 0.2 mmol), **2** (3 equiv, 0.6 mmol), NaH (3 equiv, 0.6 mmol), $In(OTf)_3$ (20 mol %), DMF (2 mL), in Ar, rt, 16 h. [b]Yields of isolated products. [c]The products were obtained as single diastereomers. [d]Determined by ^1H NMR using 1-chloro-2,4-dinitrobenzene as the internal standard.

Scheme 4. Reaction of Aziridine 1a with *β*-Ketoester 2f



synthesis of 3-benzazepines (Table 2). In all cases, products **10** were afforded as the preponderant products, along with less than 5% yields of products **9**. It was found that the reactions of aziridine **8a** with malonic esters **2a**−**2d** proceeded smoothly to furnish the corresponding products **10aa**−**10ad** in 48−79% yields (Table 2, entries 1−4). The structure of **10aa** was confirmed by X-ray crystal structure analysis. Next, a series of aziridines **8b**−**8n** bearing various electron-accepting and -donating substituents on the aromatic ring were selected to react with malonic ester **2a** (Table 2, entries 5−15). To our delight, all of these aziridines successfully reacted with **2a** to give bicyclic products **10ba**−**10la** in good yields. At last, the reaction

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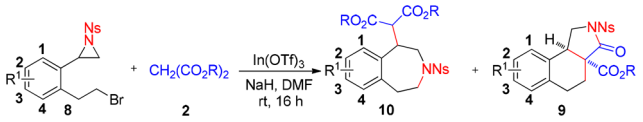
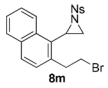
Table 2. Construction of 3-Benzazepines[a]



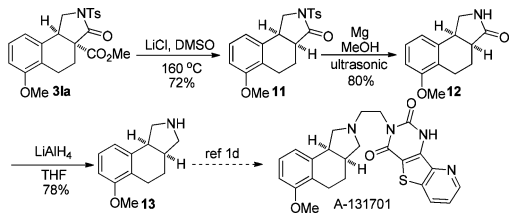
entry	8, R^1	2	10	yield/%[b]
1	**8a**, H	**2a**	**10aa**	72
2	**8a**, H	**2b**	**10ab**	65
3	**8a**, H	**2c**	**10ac**	48
4	**8a**, H	**2d**	**10ad**	79
5	**8b**, 1-F	**2a**	**10ba**	85
6	**8c**, 1-Me	**2a**	**10ca**	72
7	**8d**, 2-F	**2a**	**10da**	69
8	**8e**, 2-Cl	**2a**	**10ea**	72
9	**8f**, 2-Me	**2a**	**10fa**	75
10	**8g**, 2-OMe	**2a**	**10ga**	78
11	**8h**, 3-F	**2a**	**10ha**	65
12	**8i**, 3-Cl	**2a**	**10ia**	73
13	**8j**, 3-Me	**2a**	**10ja**	75
14	**8k**, 4-Cl	**2a**	**10ka**	72
15	**8l**, 4-OMe	**2a**	**10la**	60
16		**2a**	**10ma**	62

[a]Reaction conditions: **8** (1 equiv, 0.2 mmol), **2** (3 equiv, 0.6 mmol), NaH (3 equiv, 0.6 mmol), $In(OTf)_3$ (20 mol %), DMF (2 mL), in Ar, rt, 16 h. [b]Yields of isolated products.

of aziridine **8m** containing the naphthalene ring with **2a** was carried out under the optimal conditions (Table 2, entry 16). The desired product **10ma** was obtained in 62% yield.

To demonstrate the synthetic utility of the tandem reaction, construction of the key intermediate of A-131701 was targeted (Scheme 5). Krapcho decarboxylation of **3la** led to product **11** in

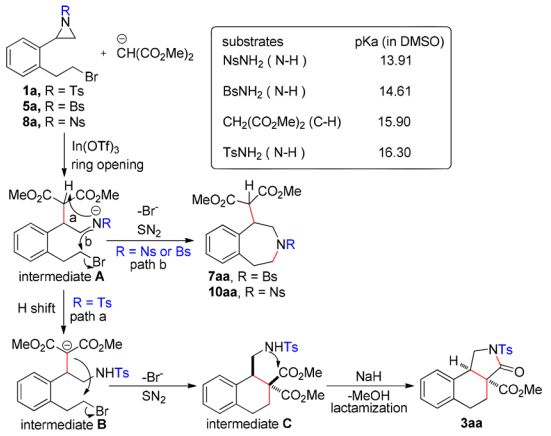
Scheme 5. Synthesis of the Key Intermediate of A-131701



72% yield. Treatment of **11** with magnesium powder under ultrasonic conditions resulted in cleavage of the *N*-Ts group, furnishing product **12** in 80% yield. Further $LiAlH_4$ reduction provided the final product **13**, which could be converted into A-131701 by using the method reported by Meyer and co-workers.[1d]

A possible mechanism is proposed in Scheme 6. The carbon nucleophile, generated from malonic ester **2a**, preferred to attack aziridine to provide ring-opening intermediate **A**. If R is a Ts group, a key 1,4-proton transfer would occur to deliver intermediate **B**. Subsequently, the newly generated carbanion

Scheme 6. Possible Mechanism for Tandem Reactions



underwent nucleophilic substitution and lactamization at the same side to provide product **3aa**. If R is a Ns or Bs group, the nitrogen anion in intermediate **A** would directly attack alkyl bromide to provide product **7aa** or **10aa**. The available data on the pK_a values allows a reasonable explanation for why tandem reactions followed respective paths to provide two different products. The pK_a value of $TsNH_2$ (N−H)[17a] is greater than the pK_a value of $CH_2(CO_2Me)_2$ (C−H).[17b] It meant that the carbanion in intermediate **B** is thermodynamically more stable than the nitrogen anion in intermediate **A** when R was a Ts group. As a result, 1,4-proton transfer occurred, and the tandem reaction followed *path a* to afford product **3aa**. By contrast, the pK_a values of $BsNH_2$ (N−H)[17c] and $NsNH_2$ (N−H)[17c] are less than the pK_a value of $CH_2(CO_2Me)_2$ (C−H). The nitrogen anion in intermediate A is predominant in the thermodynamic equilibrium when R was Bs or Ns group. Thus, the tandem reaction followed *path b* to afford product **7aa** or **10aa**.

In conclusion, we have developed a pathway-controllable strategy for the formation of two different of heterocyclic products by using the same starting material with only a single change of *N*-substitution. *N*-Ts-Activated aziridines underwent ring opening of aziridines, nucleophilic substitution, and lactamization to give hexahydrobenz[*e*]isoindoles in good yields with good diastereoselectivities. For *N*-Ns-activated aziridines, ring opening of aziridines and nucleophilic substitution took place to provide 3-benzazepines in good yields. As an example for demonstrating its potential, this tandem reaction was used to access the important intermediate of A-131701.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02406.

Experimental procedure, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1857267−1857270 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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