Synthesis of *cis*-4,5-Diarylazepanes

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Abstract: Substituted *cis*-4,5-diarylazepanes are synthesized in modest overall yields starting from 5,5-diarylazepan-4-ones by a reduction, mesylation, rearrangement, and hydrogenation reaction sequence.

Key words: *cis*-4,5-diarylazepanes, boron trifluoride etherate, heterocycles, 1,2-sigmatropic shift, spiro compounds

The seven-membered azepane ring is a prevalent scaffold that serves as a crucial building block for numerous syntheses of useful compounds, and it has been previously reviewed.[1] Depending on the substitution pattern and functionalization, different derived substitutents in the structural skeleton of azepane have been shown to be effective biologically active compounds, such as benzazepine or phenazepane analogues.[2,3] Consequently, a significant effort has been directed toward the development of new methods for the synthesis of substituted azepanes.[4] In addition, the chiral azepane system can be a synthetically useful ligand in the asymmetric reactions.[5] Due to the particular pharmaceutical interest concerning specific substitution pattern of the great number of azepanes and their derivatives, new methods for their preparation are needed. The adopted synthetic strategies of substituted azepanes are summarized in Figure 1.[5–7] In this paper, we intend to report the 1,2-sigmatropic shift methodology for the synthesis of substituted *cis*-4,5-diarylazepanes from known 5,5-diarylazepan-4-ones.

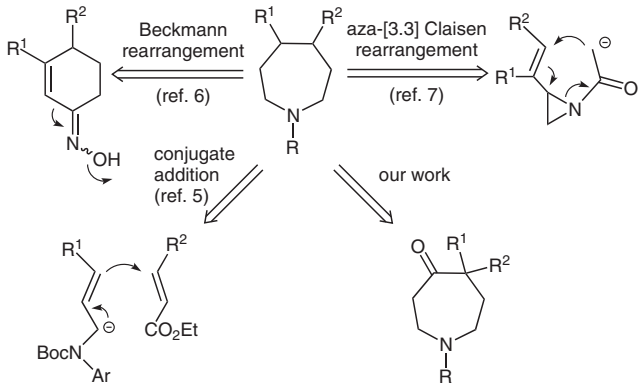
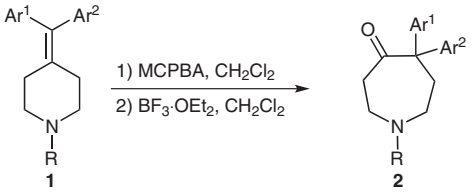


Figure 1 Synthetic strategies toward substituted azepane

The synthesis of substituted 5,5-diarylazepan-4-ones **2** started with tetrasubstituted *exo*-olefins **1** via ring expansion with MCPBA and $BF_3{\cdot}OEt_2$. Skeleton **1** was easily yielded from commercially available piperidine-4-carboxylic acid ethyl ester via sulfonylation with sulfonyl chloride, Grignard addition with arylmagnesium bromide, and dehydration. Skeleton **2** was chosen as the starting material for synthesizing substituted *cis*-4,5-diarylazepanes, as shown in Scheme 1.[8]



Ar^1, Ar^2 = Ph, 4-FPh, 4-MeOPh
R = Ms (SO_2Me), Bs (SO_2Ph), Ts (SO_2Tol)

Scheme 1 Synthesis of starting material **2**

Initially, the azepanol **3c** was prepared by reduction of model substrate **2c** (Ar^1 = Ar^2 = Ph; R = Ts) with sodium borohydride in methanol at room temperature for 2–3 hours in 89% yield. As shown in Table 1, treatment of azepanol **3c** with MsCl (3.0 equiv) and Et_3N (alkylamine) in DCE (10 mL) generated a mixture of mesylate **4c** and olefin **1c**. After adjusting the reaction temperature, time and equivalents of Et_3N, two products (**4c/1c** = 7:1 to 2:1) were isolated from the reaction mixture (Table 1, entries 1–4). Under the reflux temperature and prolonged time (5 h or 30 h), compound **1c** was yielded as the major product (Table 1, entries 5 and 6). This showed that higher temperature prompted the in situ rearrangement to occur and controlled the yield ratios of major product **1c**. To increase the yield ratio of compound **4c**, other bases with different basicity were examined in the next step. Mesylation of azepanol **3c** with 5 equivalents of DBU (amidine) gave **1c** as the major product (**4c/1c** = 1:6) at room temperature (Table 1, entry 7). When pyridine or imidazole (aromatic amine) was chosen as the base or solvent (for pyridine) at room temperature, the major product **4c** was isolated in good yields along with a trace amount of rearranged product **1c** (Table 1, entries 8–10).

With the above results, compounds **4a**,**b** and **4d**–**h** were also isolated in 82–92% yields under the conditions in entry 10 (Table 1). By treating the mesylate **3c** with different bases (alkyl amine, amidine, aromatic amine), we observed that there was an interesting selectivity for the dis-

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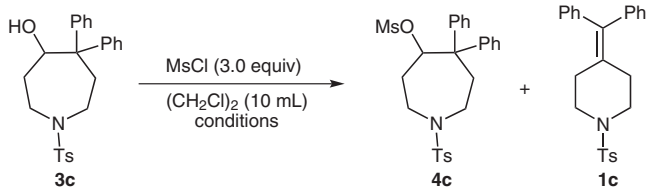
Table 1 Reaction of Alcohol **3c** with MsCl[a]



Entry	Base	Temp	Time (h)	Yield of **4c** (%)[b]	Yield of **1c** (%)[b]
1	Et_3N (3.0 equiv)	ice bath	5	72	10
2	Et_3N (3.0 equiv)	r.t.	5	62	15
3	Et_3N (3.0 equiv)	r.t.	30	47	31
4	Et_3N (5.0 equiv)	r.t.	30	50	24
5	Et_3N (5.0 equiv)	reflux	5	15	69
6	Et_3N (5.0 equiv)	reflux	30	trace	82
7	DBU (5.0 equiv)	reflux	5	10	63
8	pyridine (5.0 equiv)	r.t.	5	86	trace
9	imidazole (5.0 equiv)	r.t.	5	81	trace
10	pyridine (6 mL)	r.t.	5	90	trace

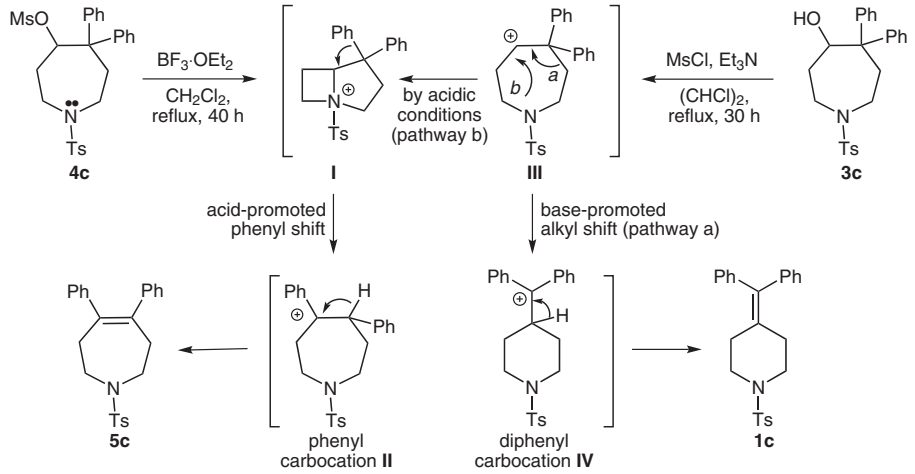
[a] The reactions were run on a 0.5 mmol scale with **3c**.
[b] The products were >95% pure as determined by ^1H NMR analysis.

tribution of product yields between the piperidine and the azapane frameworks.

As shown in Table 2, the 1,2-sigmatropic rearrangement of skeleton **4** (R = Ms, Bs, Ts; Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$) with $BF_3{\cdot}OEt_2$ (2.0 equiv) gave skeleton **5** as the major product at reflux for 40 hours.[9] The 1,2-sigmatropic shift procedure was monitored using TLC until the reaction was complete. Eight olefins, **5a**–**h**, were obtained in 55–89% yields. The structural frameworks of compounds **5b** and **5e** were determined using single-crystal X-ray analysis.[10] Furthermore, *cis*-4,5-diarylazepanes **6a**–**h** were achieved by hydrogenation of skeleton **5** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon at room temperature for 10 hours. After completing the above procedures, the vicinal *cis*-4,5-diarylazapane **6** was synthesized from the geminal 5,5-diarylazapan-4-one **2** in a modest total yield via reduction, mesylation, the 1,2-sigmatropic shift, and the hydrogenation reaction. Our typical experimental procedure suggested a general and efficient alternative for the preparation of symmetrical and unsymmetrical *cis*-4,5-diarylazepanes with the different electron-withdrawing and electron-donating aryl groups. Comparing the two kinds of products (e.g., $Ar^1 = Ar^2 = Ph$, R = Ts), we found that six-membered piperidine **1c** with a geminal diaryl *exo*-olefin was the major product generated from the treatment of alcohol **3c** with Et_3N under the basic conditions (Scheme 2). Under the Lewis acid promoted reaction, mesylate **4c** was easily converted into seven-membered azapane **5c** with vicinal diaryl *endo*-olefin.

The possible explanation for the interesting transformations from compound **4c** to **5c** was that the $BF_3{\cdot}OEt_2$-mediated demesylation of compound **4c** was controlled by the lone nitrogen pair on the azepane skeleton. The initial event may be the formation of intermediate **I**. Next, intermediate **II** was formed by an intramolecular ring closure of intermediate **I** and followed by the aryl group 1,2-shift of intermediate **II**. Then, compound **5c** was obtained by the proton abstraction of intermediate **II** under thermodynamic control. In another pathway, intermediate **III** would be first generated by the mesylation of compound **3c**. Furthermore, compound **1c** was easily formed by the migration of the alkyl group under the base-induced conditions via intermediate **IV** with a more stable diphenyl carbocation.

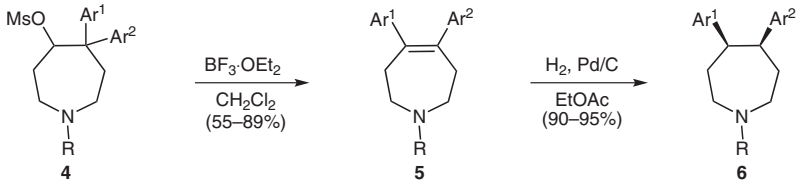
It was also found that spiropieridine **7a** or **7b** was obtained in low yields (34% and 26%) via the reaction of ketone **2a** or **2b** with Et_3N (5 equiv) in CH_2Cl_2 for 25 hours under reflux conditions.[11] Among the product mixtures, starting materials **2a** and **2b** were recovered in nearly 56% and 66% yields. As shown in Scheme 3, the ring system with the five-membered dioxa spiropiperidine skeleton was



Scheme 2 Possible rearrangement mechanism

found in the presence of CH_2Cl_2. The possible mechanism is as follows: the initial event was regarded as the formation of intermediate **A** with an oxonium ion with chloromethyl motif;[12] intermediate **B** with diphenyl carbocation was generated via the rearrangement. The intermediate **A** should be generated from reaction of ketone **2** with the chloromethyl quaternary ammonium chloride under high-pressure conditions in a sealed tube. Thus, skeleton **7** was afforded by water addition followed by the intramolecular ring closure.

Table 2 Synthesis of Substituted *cis*-4,5-Diarylazepanes **6**[a]



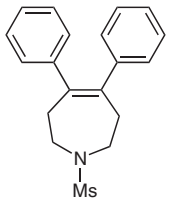
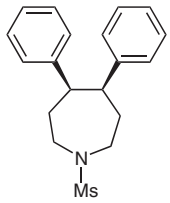
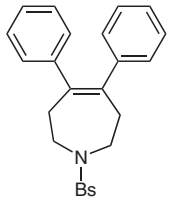
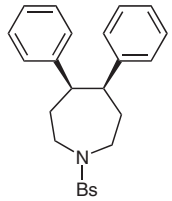
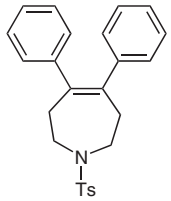
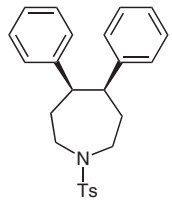
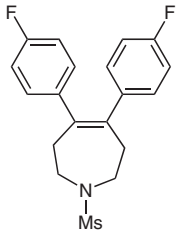
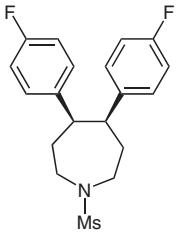
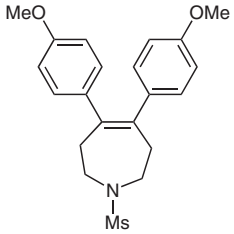
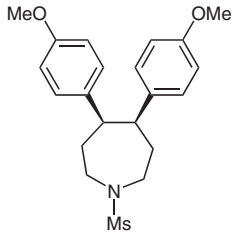
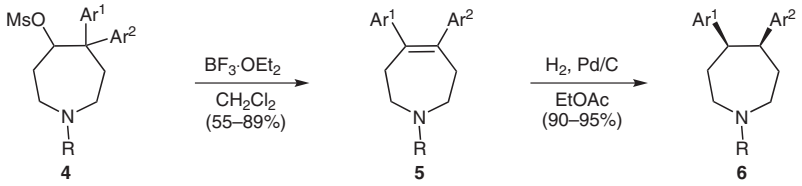
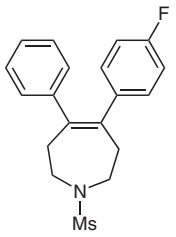
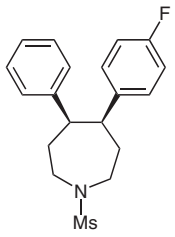
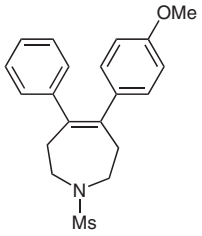
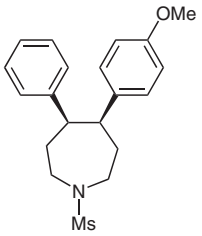
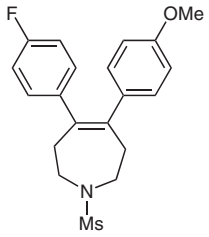
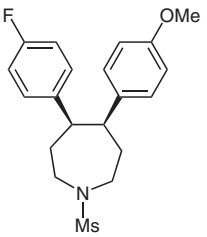
Entry	Product **5**	Yield of **5** (%)[a]	Product **6**	Yield of **6** (%)[a]
1	 **5a**	89	 **6a**	92
2	 **5b**	78	 **6b**	95
3	 **5c**	75	 **6c**	93
4	 **5d**	70	 **6d**	90
5	 **5e**	63	 **6e**	92

Table 2 Synthesis of Substituted *cis*-4,5-Diarylazepanes **6**[a] (continued)

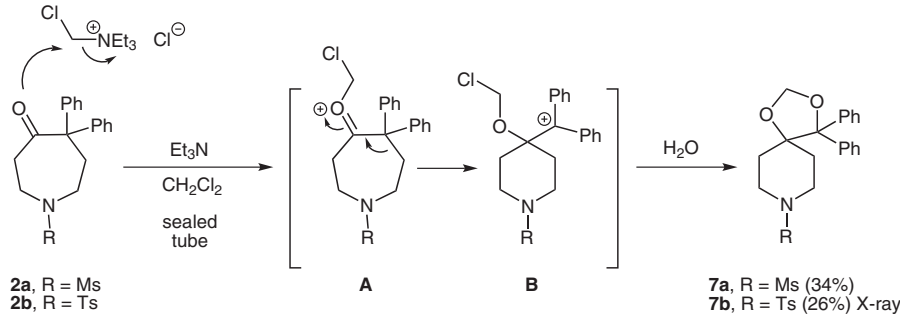


Entry	Product **5**	Yield of **5** (%)[a]	Product **6**	Yield of **6** (%)[a]
6	 **5f**	59	 **6f**	93
7	 **5g**	55	 **6g**	90
8	 **5h**	67	 **6h**	92

[a] The isolated products were >95% pure as judged by ^{1}H NMR analysis.

To increase the yield of skeleton **7**, reaction of ketone **2a** with diiodomethane or dibromomethane and Et_3N was further examined. But the desired spiro product **7a** was isolated in low yield (15% or 10%). The structural framework of compound **7b** was established by single-crystal X-ray analysis (Figure 2).[10] This study showed that the present synthetic approach could construct the spiro [4.5]-ring system from an azepanone skeleton.[13]

Attempts to establish the tetracyclic skeleton **8** via the trifluoroacetic acid mediated ring closure of skeleton **5**[14] failed, perhaps due to insufficient reactivity. In order to construct the phenanthrene system, photolysis of skeleton **5** was further examined in different solvents (e.g., methanol, benzene, ethyl acetate, tetrahydrofuran) and wavelengths (e.g., λ = 3600, 3060, 2540 nm).[15] When ethyl acetate and λ = 3060 nm were chosen as the solvent and



Scheme 3 Reaction of ketone **2** with Et_3N in CH_2Cl_2

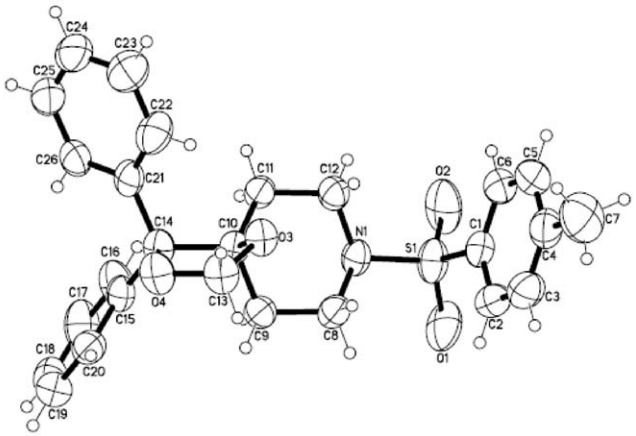
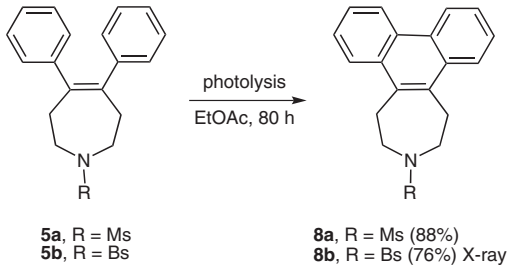


Figure 2 X-ray structure of compound **7b**

wavelength, respectively, under the irradiation conditions, we found that a single tetracyclic azacyclohepta[*l*]phenanthrene skeleton **8** was isolated in good yield, as shown in Scheme 4.[16] The structural framework of compound **8b** was constructed using single-crystal X-ray analysis (Figure 3).[10]



Scheme 4 Synthesis of tetracyclic skeleton **8**

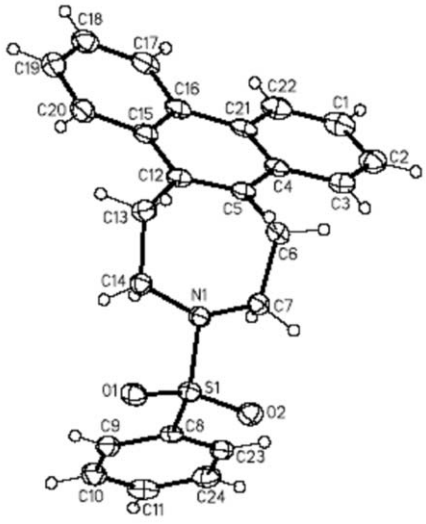


Figure 3 X-ray structure of compound **8b**

In summary, we presented an easy and straightforward synthesis of unsymmetrically *cis*-4,5-diarylazepanes by the treatment of 5,5-diarylazepan-4-ones with the reduction, mesylation, rearrangement, and hydrogenation. The tetracyclic azacyclohepta[*l*]phenanthrene skeleton was synthesized. We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of diarylazocane and its related derivatives.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Representative Procedure for Skeleton 5**
$BF_3{\cdot}OEt_2$ (1.0 mmol) was added to a stirring solution of the

skeleton **4** (0.5 mmol) in CH_2Cl_2 (10 mL) at r.t. The reaction mixture was stirred at reflux for 40 h. The total procedure was monitored by TLC until the reaction was completed. A sat. $NaHCO_3$ solution (1 mL) was added to the reaction mixture, and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane–EtOAc = 8:1 to 4:1) afforded skeleton **5**.

(10) CCDC 810260 (**5b**), 810167 (**5e**), 805710 (**7b**), and 817429 (**8b**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(11) **Representative Procedure for Skeleton 7**
Et_3N (500 mg, 5.0 mmol), skeleton **2** (1.0 mmol), and CH_2Cl_2 (6 mL) were added to a sealed tube at r.t. The reaction mixture was stirred at reflux temperature for 25 h and then cooled to r.t. CH_2Cl_2 (10 mL) was added to the reaction mixture, and then HCl solution (1 N, 10 mL) was also added to the reaction mixture. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane–EtOAc = 4:1 to 2:1) afforded skeleton **7**.

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(16) **Representative Procedure for Skeleton 8**
Skeleton **5** (0.13 mmol) was dissolved in EtOAc (10 mL; free of oxygen) and was irradiated under a nitrogen atmosphere with a lamp (λ = 3060 Å), using a Pyrex glass filter at r.t. for 80 h. The solvent was evaporated to afford crude product. Purification on silica gel (hexane–EtOAc = 4:1 to 2:1) afforded skeleton **8**.