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Synthesis of 6-substituted tetrahydropyridinones and cyclization to indolizidine and quinolizidine structures

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Abstract—3-Sulfolenes **1** with various substituents at C-2 underwent [4+2] cycloaddition reactions with *p*-toluenesulfonyl isocyanate to give the teterahydropyridinones **4**. Through N-detosylation and Hg(II)-mediated electrophilic addition/intramolecular cyclization of **4e** and **4f**, the indolizidine and quinolizidine compounds **7a**/**7b** and **8** were synthesized, respectively.

The piperidine ring is among the most abundant molecular fragments in both natural and synthetic compounds with various biological activities.[1] The aza-Diels–Alder reaction is one of the most versatile routes to substituted piperidines.[2–7] In general, the use of strongly electron-deficient imines is a prerequisite. We have also used this method to synthesize some thio-substituted piperidine derivatives.[8,9]

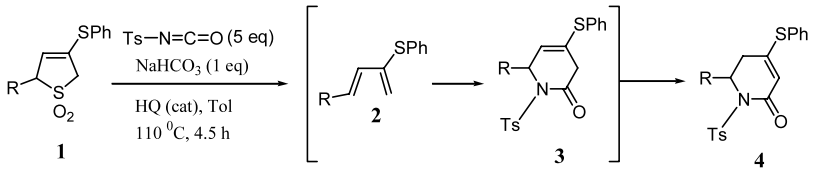
Although arylsulfonyl isocyanates have an electron-deficient C=N moiety, their aza-Diels–Alder reactions with dienes were rarely reported[10–12] because the [2+2] cycloaddition or electrophilic substitution predominates.[13–15] We have recently reported the first aza-Diels–Alder reactions of thio-substituted dienes with arylsulfonyl isocyanates to give the cyclized products with complete control of chemo- and regioselectivity.[16,17] We now describe the extension of this reaction to the synthesis of many 6-substituted tetrahydropyridinones. Two of these compounds are further converted to the indolizidine and quinolizidine structures, which are important natural products.[18]

Thio-substituted 3-sulfolenes **1**[19,20] can undergo in situ thermal desulfonylation and [4+2] cycloaddition reaction[21–25] with *p*-toluenesulfonyl isocyanate (PTSI) to give the cyclized products **4**. The results are summarized in Table 1.

Table 1. Aza-Diels–Alder reactions of 3-sulfolenes **1** with PTSI

Entry	Compound **1**	Product	Yield (%)
1	**1a** R = H	**4a**	71[a]
2	**1b** R = Me	**4b**	81[a]
3	**1c** R = Et	**4c**	80
4	**1d** R = $CH_2CH{=}CH_2$	**4d**	74
5	**1e** R = $(CH_2)_2CH{=}CH_2$	**4e**	79
6	**1f** R = $(CH_2)_3CH{=}CH_2$	**4f**	70[a]
7	**1g** R = $(CH_2)_2CH_2Cl$	**4g**	70
8	**1h** R = CH_2Ph	**4h**	71
9	**1i** R = $(CH_2)_3$	**4i**	58
10	**1j** R = $(CH_2)_4$	**4j**	19[b]
11	**1k** R = $(CH_2)_5$	**5b**	38[c]

[a] Results reported in Ref. 17.
[b] **2j** (12%) and **5a** (35%) were also obtained.
[c] **2k** (21%) was also obtained.



Keywords: thio-substituted 3-sulfolenes; aza-Diels–Alder reactions; Hg(II) ions; quinolizidines; indolizidines.
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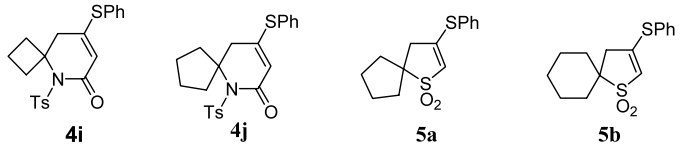
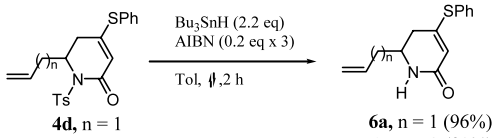


4i **4j** **5a** **5b**

The desulfonylation of 3-sulfolenes **1** was carried out in refluxing toluene in the presence of $NaHCO_3$ (1 equiv.) to remove the sulfur dioxide generated, and a catalytic amount of hydroquinone (HQ) to prevent polymerization of the dienes **2**. The in situ generated dienes **2** would then react with PTSI (5 equiv.) to give the cycloaddition products **3**, which upon treatment with acid or base gave the more stable conjugated products **4**. By comparing the yields of entries 1–8, it can be seen that varying the carbon number of the side chain or having a terminal double bond or a chlorine substituent does not affect the efficiency of the cycloaddition. However, 3-sulfolene **1i** (entry 9) containing a spiro butane moiety gave a slightly lower yield of product **4i**. The steric effect of the spiro pentane (entry 10) was even greater so that only a low yield of cyclization product **4j** was obtained together with some unreacted diene **2j** and isomerized 2-sulfolene **5a**. In the case of 3-sulfolene **1k** (entry 11) containing a spiro hexane moiety, only the diene **2k** and isomerized 2-sulfolene **5b** were obtained.

In order to synthesize the indolizidine and quinolizidine bicyclic compounds, we used Parsons' method of Bu_3SnH/AIBN to cleave the *N*-tosyl group of amides.[26] The lactams **6a**–**c** were obtained in high yield.

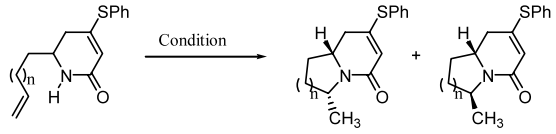
We investigated Harding's method[27] of using Hg(II) ion to facilitate the synthesis of indolizidines and quinolizidines from lactams **6b**–**c**. The results are summarized in Table 2.



4d, n = 1
4e, n = 2
4f, n = 3

6a, n = 1 (96%)
6b, n = 2 (83%)
6c, n = 3 (95%)

Comparing entries 1–2, greater amounts of $Hg(OAc)_2$ leads to higher yield of product **7**. Using the more reactive mercuric trifluoroacetate, $Hg(OTFA)_2$, the yield was much higher (compare entry 3 with entry 1). When these reactions were carried out at room temperature (entries 1–3), the diastereomeric ratios of products **7a**/**7b** were 1:1. Although these two isomers could not be separated by column chromatography, the ratio of these two isomers was determined by ^1H NMR. The NOESY spectrum of product **7b** showed cross signals between the methyl group and the hydrogen at the ring junction, thus establishing its stereochemistry. We also



6b, n = 1
6c, n = 2

7a (*cis*) **7b** (*trans*)
8 (*trans*)

found that the amount of *cis*-**7a** decreases at lower temperature and increases at higher temperature (compare entries 3–6). Theoretical calculation[28] shows that *cis*-**7a** has a slightly lower energy (6.9977 kcal/mol) than *trans*-**7b** (7.0977 kcal/mol). This means that *cis*-**7a** is the thermodynamic product. On the other hand, *trans*-**7b** is the kinetic product.

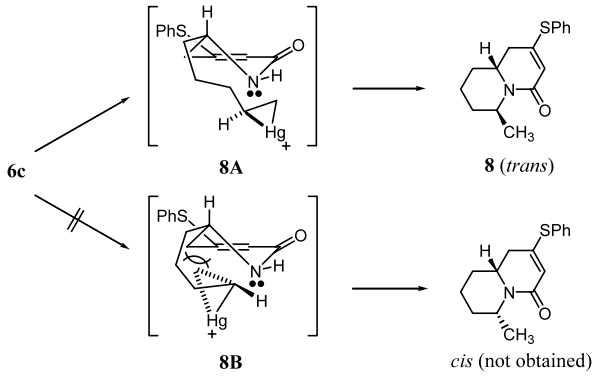
The $Hg(OAc)_2$-mediated cyclization of **6c** gave only a single product *trans*-**8**, albeit in low yield (entry 7). Increasing the amount of $Hg(OAc)_2$ improved the yield to 40% (entry 8). However, using $Hg(OTFA)_2$ gave product **8** in very good yield (entry 9). The structure of **8** was confirmed by its NOESY spectrum, which showed cross signals between the methyl group and the hydrogen at the ring junction. Therefore, the cycliza-

Table 2. Mercuric ion-promoted cyclization of **6b** and **6c**

Entry	6	Condition[a]	Yield (%)	(*cis*:*trans*)[b]
1	**6b**	$Hg(OAc)_2$ (1.2 equiv.), CH_3CN, rt, 24 h	**7a**/**7b** (60)	(1:1)
2	**6b**	$Hg(OAc)_2$ (2.4 equiv.), CH_3CN, rt, 24 h	**7a**/**7b** (76)	(1:1)
3	**6b**	$Hg(OTFA)_2$ (1.2 equiv.), CH_3CN, rt, 24 h	**7a**/**7b** (88)	(1:1)
4	**6b**	$Hg(OTFA)_2$ (1.2 equiv.), CH_3CN, 0°C, 12 h	**7a**/**7b** (78)	(5:6)
5	**6b**	$Hg(OTFA)_2$ (1.2 equiv.), CH_3CN, −25 to −15°C, 12 h	**7a**/**7b** (75)	(4:6)
6	**6b**	$Hg(OTFA)_2$ (1.2 equiv.), CH_3CN, reflux, 3 h	**7a**/**7b** (74)	(6:4)
7	**6c**	$Hg(OAc)_2$ (1.2 equiv.), CH_3CN, rt, 24 h	**8** (18)	
8	**6c**	$Hg(OAc)_2$ (2.4 equiv.), CH_3CN, rt, 24 h	**8** (40)	
9	**6c**	$Hg(OTFA)_2$ (1.2 equiv.), CH_3CN, rt, 24 h	**8** (84)	

[a] After the reaction of **6b** or **6c** with Hg(II) reagent, the resulting solution was treated with $NaBH_4$ (3 equiv.)/3 M NaOH in CH_3CN at room temperature for 2 h.

[b] The diastereomeric ratio of *cis*:*trans* was determined by ^1H NMR.



Scheme 1.

tion of **6c** to **8** is both regio- and stereospecific; only the 6-*exo* addition and *trans* product was obtained. Theoretical calculation[28] shows that *trans*-**8** has a much lower energy (5.9388 kcal/mol) than the corresponding *cis* isomer (8.8462 kcal/mol). Besides its thermodynamic stability the selective formation of *trans*-**8** may be related to the activation energies involved (Scheme 1).

Assuming that the lone pair electrons of nitrogen must attack from the back side of the mercurinium ion, the reaction of intermediate **8A** would give the *trans* product, and the intermediate **8B** would lead to the *cis* product. It can be seen that **8B** is sterically more hindered than **8A**. Hence only the *trans*-**8** was obtained.

In summary, we have synthesized many 6-substituted tetrahydropyridinones **4** from the aza-Diels–Alder reactions of 3-sulfolenes **1** with *p*-toluenesulfonyl isocyanate. We have also successfully converted the cycloaddition products **4e** and **4f** to the indolizidine and quinolizidine compounds **7a**/**7b** and **8** with the mediation of Hg(II) ions.

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28. The minimized steric energy is calculated by the program CS Chem3D using MM2 and its default parameter.