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Tetrahedron Letters 46 (2005) 8551–8554
Tetrahedron Letters

Synthesis and transformations of sulfur-substituted indolizidines and quinolizidines

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Received 1 September 2005; revised 29 September 2005; accepted 30 September 2005
Available online 14 October 2005

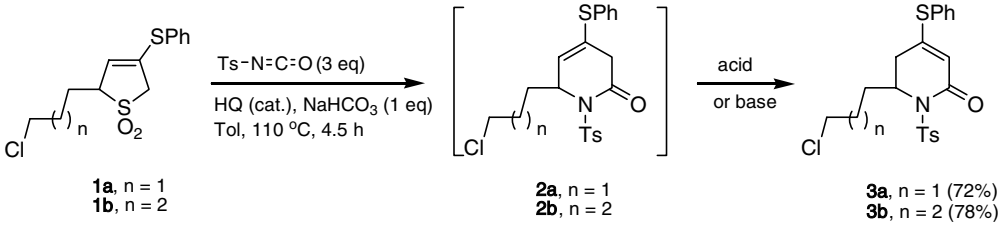
Abstract—3-Sulfolenes **1a**–**b** underwent [4+2] cycloaddition reactions with *p*-toluenesulfonyl isocyanate to give tetrahydropyridinones **3a**–**b**. Through *N*-detosylation of **3a**–**b** and subsequent intramolecular cyclization, indolizidine **5a** and quinolizidine **5b** were synthesized. Useful functional group transformations of compounds **5a**–**b** were also investigated.

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.[8–10]

Although arylsulfonyl isocyanates have an electron-deficient C=N moiety, their aza-Diels–Alder reactions with dienes were rarely reported[11–13] because the [2+2] cycloaddition or electrophilic substitution predominates.[14–16] 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.[17,18] We have also used this methodology to synthesize many 6-substituted 2-piperidinones.[19] Two of these compounds were further converted to the indolizidine and quinolizidine structures, which are important framework of many natural products.[20–26] We now report a new method for the synthesis of sulfur-substituted indolizidines and quinolizidines, and some of their functional group transformations.

Thio-substituted 3-sulfolenes **1a**–**b**[27] can undergo in situ thermal desulfonylation and [4+2] cycloaddition reaction[19] with *p*-toluenesulfonyl isocyanate (PTSI) to give the cyclized products **3a**–**b** (Eq. 1).

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 **3a**–**b**.[28] Lactams **4a**–**b** were obtained in moderate yield (Eq. 2). It should be noted that slow addition of Bu_3SnH to a dilute solution of **3a**–**b** was necessary in order to avoid simultaneous cleavage of the chloro group of **3a**–**b**. Upon treatment of lactams **4a**–**b** with NaH in refluxing THF indolizidine **5a** and quinolizidine **5b** were



1a, n = 1
1b, n = 2

2a, n = 1
2b, n = 2

3a, n = 1 (72%)
3b, n = 2 (78%)

(1)

Keywords: Thio-substituted 3-sulfolenes; Aza-Diels–Alder reaction; Indolizidines; Quinolizidines.
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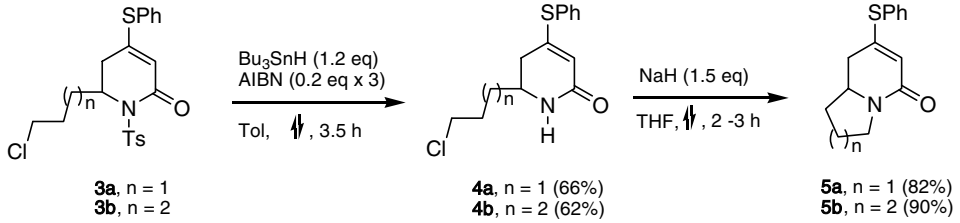
doi:10.1016/j.tetlet.2005.09.191

synthesized by intramolecular cyclization[29–31] in good yield. It is important to note that the use of potassium *t*-butoxide as the base led only to the recovered starting material or elimination of HCl to form the terminal alkenes.

Following a reported procedure,[39] treatment of compounds **5a**–**b** with methyllithium, followed by acidification with acetic acid and reduction with sodium borohydride, gave stereospecifically the *cis* products **10a**–**b** in fair to good yields (Eq. 5).



3a, n = 1
3b, n = 2

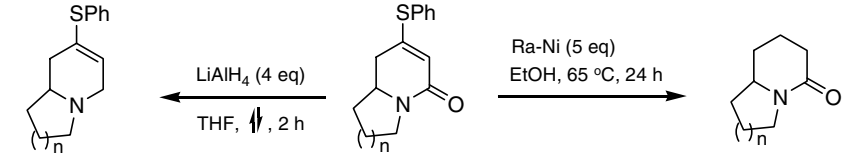
4a, n = 1 (66%)
4b, n = 2 (62%)

5a, n = 1 (82%)
5b, n = 2 (90%)

(2)

With indolizidine **5a** and quinolizidine **5b** in hand, we have also carried out some functional group transformations. The lactam functional group of compounds **5a**–**b** was reduced by $LiAlH_4$ to give the amines **6a**–**b** (Eq. 3). Treatment of compounds **5a**–**b** with W-2 Raney nickel both cleaved the C–S bond and reduced the C=C bond to give products **7a**[32] and **7b**.[33]

The stereochemistry of compounds **10a** and **10b** was clearly established by 2D-NOESY experiments (Fig. 1). For compound **10a**, the proton at C-8a (δ 2.25–2.34) has cross signals with the proton at C-5 (δ 2.78–2.90) and the H_β at C-3 (δ 2.00, q, $J = 9.0$ Hz). This indicates that the hydrogen at C-8a is *cis* to the hydrogen at C-5. The IR spectrum of compound **10a**



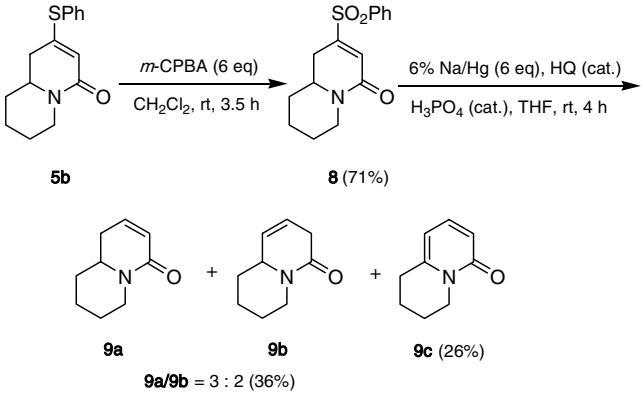
6a, n = 1 (58%)
6b, n = 2 (50%)

5a, n = 1
5b, n = 2

7a, n = 1 (35%)
7b, n = 2 (30%)

(3)

Compound **5b** was oxidized by *m*-CPBA to give sulfone **8** (Eq. 4), which upon treatment with sodium amalgam led to the sulfone-cleavaged products: an inseparable mixture of **9a**[34] and **9b**,[35] together with some oxidation product **9c**[36] which was obtained during chromatographic purification of compounds **9a**–**b**. Attempted desulfurization using the standard procedure,[37] $Na(Hg)/MeOH/Na_2HPO_4$, did not proceed at all. Thus, catalytic amount of H_3PO_4 in THF was used in this reaction.[38]



5b

8 (71%)

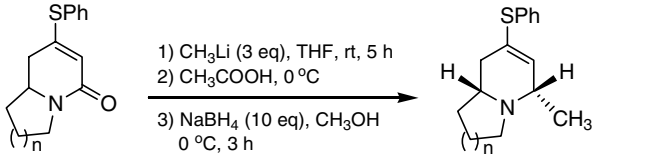
9a

9b

9c (26%)

9a/9b = 3 : 2 (36%)

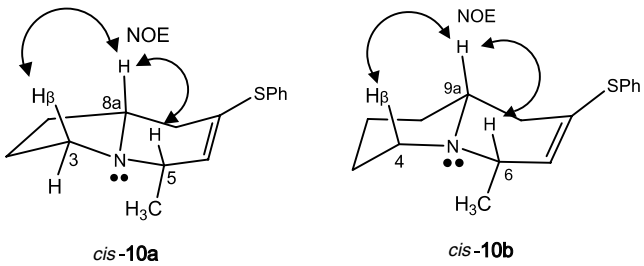
(4)



5a, n = 1
5b, n = 2

10a, n = 1 (77%)
10b, n = 2 (55%)

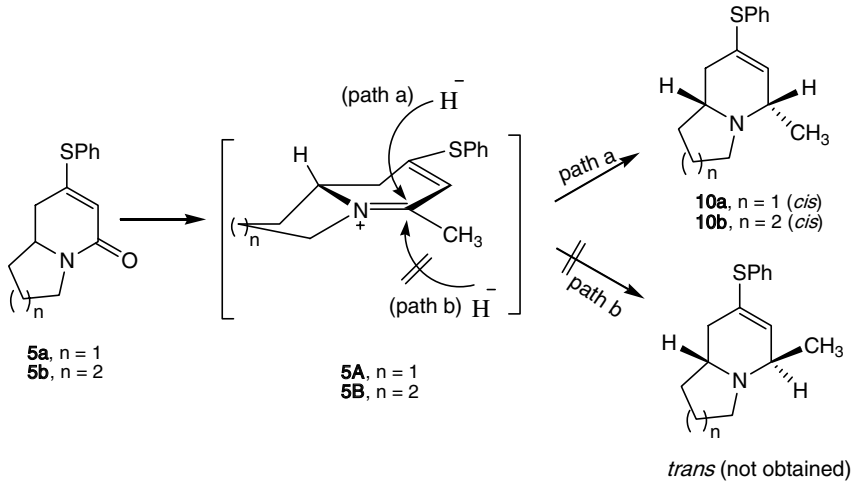
(5)



cis-**10a**

cis-**10b**

Figure 1. NOESY correlations of *cis*-**10a** and *cis*-**10b**.



Scheme 1. Preferred pathway for the diastereoselective formation of *cis*-**10a**–**b** from **5a**–**b**.

shows a Bohlmann band at 2783 cm^{-1}, indicating the presence of one or more α-hydrogens oriented *trans*-biaxially to the nitrogen lone pair.[40,41] Likewise, for compound **10b**, the proton at C-9a (δ 2.12–2.28) has cross signals with the proton at C-6 (δ 2.73–2.86) and the H_β at C-4 (δ1.79, t, $J = 11.3$ Hz), indicating the *cis* relationship of the hydrogens at C-9a and C-6. The IR spectrum of **10b** also shows a Bohlmann band at 2788 cm^{-1}.

To explain the stereospecific formation of *cis*-**10a** and *cis*-**10b**, we postulated that the iminium ions **5A** and **5B** were first formed as the intermediate. The hydride ion would then prefer to attack from the axial direction due to the stereoelectronic effect (Scheme 1).[42,43] In addition, approach of the hydride from the β-face leading to a chair conformation is favored over that from the α-face, because the latter will lead to a less stable boat conformation.

In summary, we have synthesized 6-substituted 2-piperidinones **3a**–**b** from the aza-Diels–Alder reactions of 3-sulfolenes **1a**–**b** with *p*-toluenesulfonyl isocyanate, and have successfully converted them to indolizidine **5a** and quinolizidine **5b**. We have also carried out some useful functional transformations of compounds **5a** and **5b**.

Acknowledgements

Financial support of this work by the National Science Council of the Republic of China is gratefully acknowledged (NSC 93-2113-M-030-004).

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