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Remote chiral induction in the thio-Claisen rearrangement of bicyclic thiolactams

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Abstract

A remote steric effect in the bicyclic lactam oxazolidine ring has been shown to affect the stereochemical outcome in the thio-Claisen rearrangement taking place in the piperidone ring.

The use of chiral bicyclic lactams as templates in asymmetric synthesis has proven to be a powerful tool for the construction of a variety of natural and unnatural products.[1] A previous report from this laboratory described the asymmetric synthesis of highly branched 4,4-disubstituted cyclohexenones via an asymmetric thio-Claisen rearrangement.[2] These studies demonstrated that the chiral non-racemic thiolactams **2** could be readily prepared from their corresponding bicyclic lactams **1** using thionating reagents[3a,3b]. Interestingly, in the absence of substituents on the carbon bearing oxygen in the oxazolidine ring, we observed introduction of sulfur displacing the ring oxygen as the major by-product (Scheme 1).[4] We later employed the more heavily substituted (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol to access chiral bicyclic lactam 4.[2a] To our surprise the presence of the *endo* phenyl substituent in the latter lactam prevented sulfur from displacing oxygen and provided thiolactam **5** in 98% yield. Our earlier studies showed that alkylation of the sulfur thioenolate with various allyl bromides provided *N*,*S*-ketene acetal **6** which underwent a [3,3]-sigmatropic rearrangement at elevated temperatures to give thiolactams **7a**–**d** with excellent *exo*-facial selectivity.

We now report an interesting and unexpected steric effect in the thio-Claisen rearrangement of these bicyclic lactams. During our studies of these thio-Claisen rearrangements, it was observed that the *nor*-ephedrine derived lactam mixture **8**[5,6] underwent a sigmatropic rearrangement with crotyl bromide to generate the desired thiolactams **9** in moderate selectivity (3:1). In addition, rearrangement of **10** with various allylic bromides provided monoallyl derivatives **11a**–**c** in variable diastereoselectives **6** (Scheme 2, Table 1). Allyl bromide, the smallest allylic halide employed, gave the lowest selectivity (1.7:1), whereas crotyl bromide gave only a 1.8:1 ratio of products. Rearrangement to afford the prenyl

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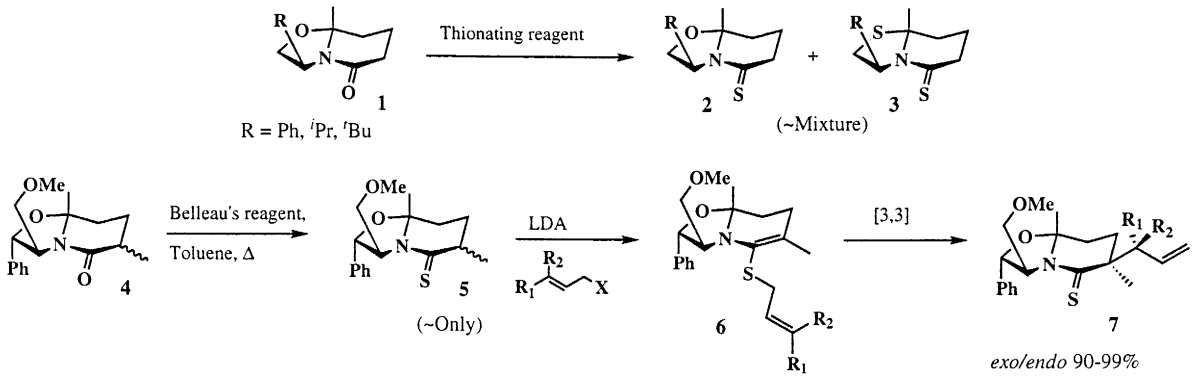
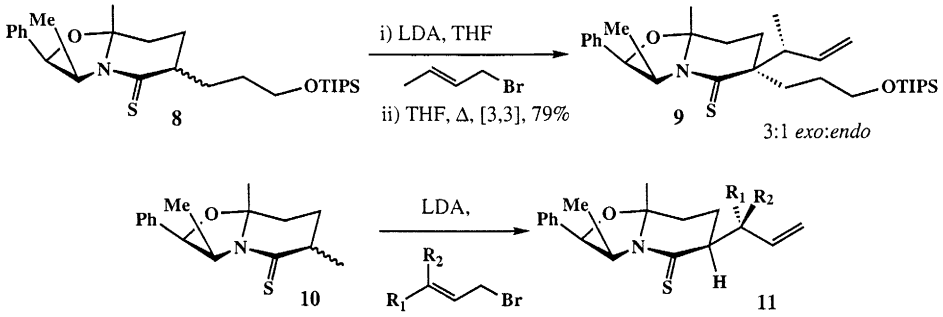


Scheme 1.

derived thiolactam **11c** gave higher diastereoselectivity (15:1), however this is somewhat lower than the selectivity observed with lactams **7a**–**d** (allyl 3:1, crotyl 9:1, prenyl >99:1, Scheme 1). Furthermore, longer reaction times were necessary to effect the rearrangement to **11**. It occurred to us that the substitution pattern on the oxazolidine ring of the bicyclic lactam may play a pivotal role in the *exo* and *endo* diastereoselectivity during [3,3]-sigmatropic rearrangement, even though it is seemingly remote from the sites of rearrangement. The *nor*-ephedrine lactam **10** posseses a *cis* substitution pattern on the oxazolidine ring compared to the *trans* substitution observed with bicyclic lactam **5**. The fact that no *endo* substituent is present in **8** may be responsible for the profound steric effect noted in the thio-Claisen rearrangement.



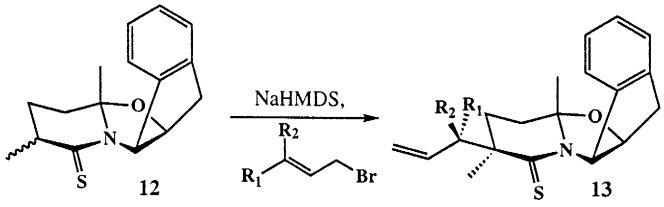
Scheme 2.

Table 1
Thio-Claisen rearrangement of **10** to **11**

Entry	R_1	R_2	Solvent	Temperature (°C)	Time (h)	Yield (%)	d.r. *exo*:*endo*
a	H	H	THF	r.t.	17	74	1.7:1
b	CH_3	H	THF	65	11	70	1.8:1
c	CH_3	CH_3	DMF, K_2CO_3	90	96	35	15:1

In an effort to shed some light on this effect, we carried out the thio-Claisen rearrangements with the (1*R*,2*S*)-*cis*-aminoindanol derived lactam **12** (Scheme 3). As expected with no *endo* substituent in the oxazolidine ring, the selectivity of the rearrangement was rather poor (Table 2). Thio-Claisen rearrangement of the bicyclic lactam **12** with allyl bromide provided **13a** in 62% yield (2:1 diastereomeric

mixture). Employing the more hindered crotyl bromide, the [3,3]-sigmatropic rearrangement occurred only at elevated temperatures and led to the allyl derivative **13b** in 40% yield and 1:1 diastereomeric mixture. In both cases, longer reaction times were required. The low yield of thiolactam **13b** (40%) was due to unrearranged *S*-allyl derivative recovered. *S*-allyl lactams from cinnamyl and prenyl bromide were found not to rearrange at all (Table 2, entries c, d). Presumably, the large indanol substituent in **13** severely limits any *exo*-rearrangement when the allyl moiety has substituents larger than a single methyl group.

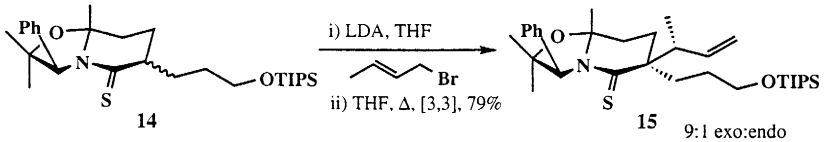


Scheme 3.

Table 2
Thio-Claisen rearrangement — selectivity to **13**

Entry	R_1	R_2	Solvent	Temperature (°C)	Time (h)	Yield (%)	d.r. *exo*:*endo*
a	H	H	THF	25	40	62	2:1
b	CH_3	H	THF	65	48	40	1:1
c	Ph	H	THF	66	-	0	-
d	CH_3	CH_3	THF	66	-	0	-

The *gem*-dimethyl phenylglycine derived bicyclic lactams **14** and **16**[2a] were prepared from condensation of *gem*-dimethyl phenylglycine amino alcohol[7] with 4-acetylbutyric acid or as described in Ref. 5. These thiolactams (**14** and **16**) possess methyl groups in both the β- and α-face at the carbon bearing oxygen in the oxazolidine ring and were anticipated to improve the selectivity for the thio-Claisen rearrangements. In the event, **14** and **16**, on alkylation with various allyl bromides proceeded with good selectivities favoring the *exo* diastereomer (Scheme 4, Table 3).

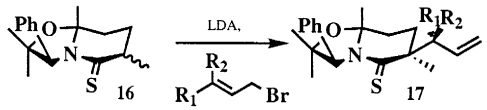


Scheme 4.

Only the sterically less demanding allyl bromide gave poor selectivity (Table 3, entry a). The other examples in Table 3 required hot toluene (~110°C) to affect the rearrangement which augurs well for the fact that *endo* substituents in the oxazolidine ring of **16**, as remote as they appear to be, somehow play a key role in reaching the transition state of this rearrangement (Scheme 5). The fact that the major diastereomer is *exo* (**17**) is consistent with the argument that the *endo* face provides some steric barrier to *endo* products.[8]

Table 3

Entry	R_1	R_2	Solvent	Temperature (°C)	Time (h)	Yield (%)	d.r. *exo*:*endo*
a	H	H	THF	0	2	93	2:1
b	Ph	H	Toluene	110	14	52	>95:5
c	CH_3	CH_3		110	14	55	>95:5



Scheme 5.

Acknowledgements

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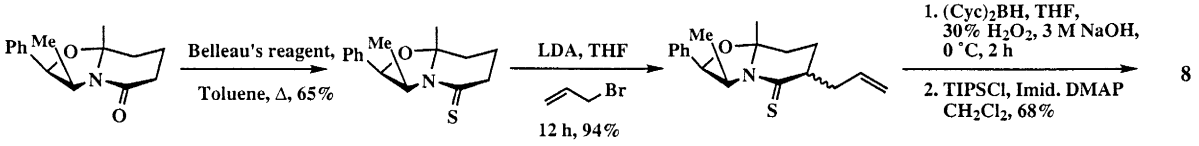
3. (a) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (b) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron* **1983**, *24*, 3815.
4. Munchhof, M. J.; Devine, P. D.; Meyers, A. I. Unpublished results.
5. Bicyclic thiolactam **8** was prepared from the *nor*-ephedrine derived bicyclic lactam[6] according to the synthetic sequence shown below. Lactam **14** was prepared utilizing the same synthetic sequence and with comparable yields.



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8. We carried out solvent studies and found that THF, alkanes, and other relatively non-polar solvents had little effect on the rearrangements and the resulting diastereoselectivities. Except for providing wider temperature ranges, little else was observed. This is in agreement with the generally accepted non-polar nature of the rearrangements. No studies were carried out in highly polar solvents (e.g. alcohols, acids).