

## Pyrrolidines From Olefins Via Radical Cyclization

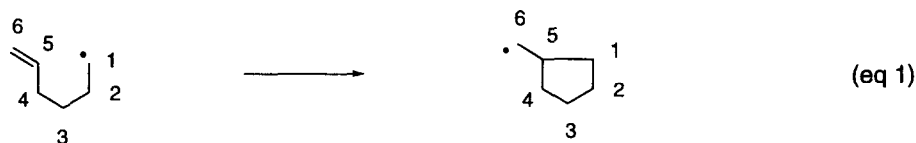
Vijay Gupta, Magnus Besev and Lars Engman\*

Uppsala University, Institute of Chemistry, Department of Organic Chemistry, Box 531, S-751 21, Uppsala, Sweden.

Received 9 December 1997; accepted 23 January 1998

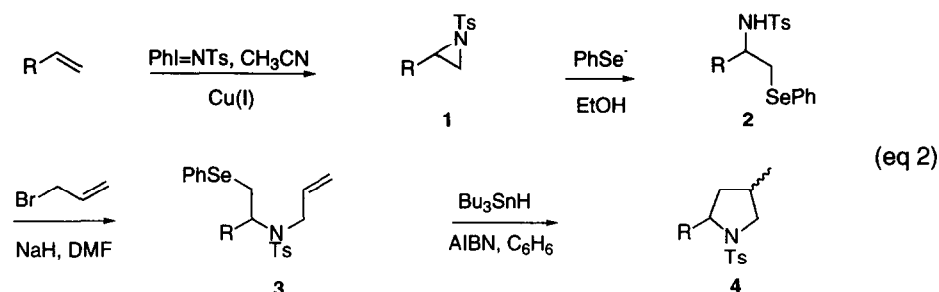
**Abstract:** 2,4-Disubstituted *N*-tosylpyrrolidines were prepared from olefins via *N*-tosylaziridination, benzeneselenolate ring-opening and reductive radical cyclization. Azidoselenation of olefins, followed by reduction, *N*-tosylation, *N*-allylation and reductive radical cyclization, afforded 3,4-disubstituted *N*-tosylpyrrolidines. © 1998 Elsevier Science Ltd. All rights reserved.

Free radical cyclization is an attractive method for ring construction in synthetic organic chemistry.<sup>1</sup> The facile and highly regioselective cyclization of the 5-hexenyl radical (eq. 1) has not only been useful for the construction of cyclopentanes, but also been applied extensively for the preparation of tetrahydrofuran<sup>2</sup> and pyrrolidine derivatives. The interest in pyrrolidine synthesis is largely motivated by the many interesting biological activities of substituted pyrrolidine derivatives.<sup>3</sup> There are synthetically useful radical cyclizations described where nitrogen has been introduced into all six positions<sup>4–9</sup> of the 5-hexenyl radical. Among the five



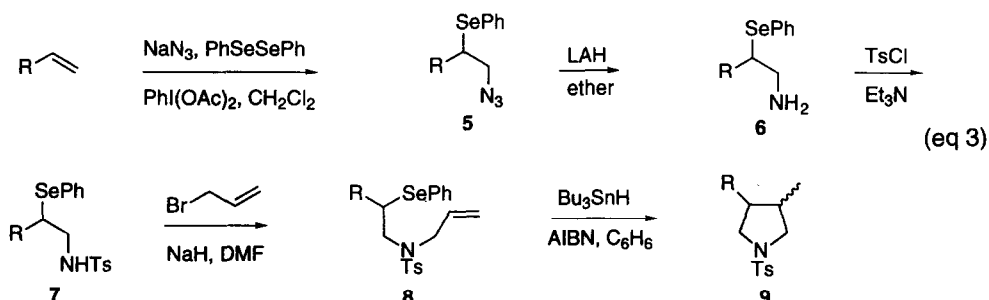
reactions affording pyrrolidines, the 3-aza-5-hexenyl radical cyclization has received only limited interest.<sup>6</sup> Although early calculations predicted that the radical cyclization would give a 99/1 ratio of *exo* and *endo* products,<sup>10</sup> it was only recently confirmed by experiment for the *N*-methyl derivative that the 3-aza-5-hexenyl radical cyclizes with a low activation energy (22 kJ mol<sup>-1</sup>) giving the 5-*exo trig* product exclusively.<sup>11</sup> Thus, it undergoes ring-closure some 70 times faster than the parent 5-hexenyl radical.

We recently reported radical-based methodology for tetrahydrofuran synthesis.<sup>2</sup> In the newly developed procedure, epoxides were regiospecifically ring-opened by selenolate or telluroate reagents and the carbon chalcogen bonds of the O-allylated  $\beta$ -hydroxyalkyl aryl chalcogenides used as sources of 3-oxa-5-hexenyl radicals. In view of the efficient methods recently developed for *N*-tosylaziridination of olefins,<sup>12</sup> we thought it would be interesting to try to adopt the above methodology to pyrrolidine synthesis. Ring-opening of aziridines by selenolate reagents is essentially an unexplored<sup>13</sup> reaction. As shown in eq. 2 and the Table, *N*-tosylaziridines 1, prepared by *N*-tosylaziridination of terminal olefins, were regiospecifically ring-opened by benzeneselenolate ion from the sterically least hindered side to afford *N*-tosyl- $\beta$ -aminoalkyl phenyl selenides 2.



*N*-allylation to give radical precursors **3** occurred efficiently at ambient temperature in DMF containing allyl bromide and sodium hydride. AIBN-induced reductive radical cyclization in benzene containing tributyltin hydride afforded 2,4-disubstituted pyrrolidines **4** as a mixture of diastereomers. Unfortunately, the *N*-tosylaziridine from styrene (**1**; R=Ph) was ring-opened to give an inseparable 1/3 mixture of compound **2d** and its regioisomer. The pure compound **2d** was instead prepared by *N*-tosylamidoselemination of styrene.<sup>13</sup> Unexpectedly, according to NOESY and NOE difference experiments, the *cis*-2,4-disubstituted pyrrolidines were predominantly formed in the radical cyclizations.<sup>14</sup> We hypothesize that this is due to an unfavourable interaction between the tosyl group and the equatorial 2-substituent in the chair-like transition state of the cyclization reaction. *N*-tosylaziridinated 1,3-cyclohexadiene (**1e**) was ring-opened at the allylic position by benzeneselenolate ion. Allylation and ring-closure afforded pyrrolidine **4e** as a 1.6/1 mixture of *exo* and *endo* isomers. In contrast, the *exo/endo* ratio was 1/2.7 for pyrrolidine **4f** obtained similarly from cyclohexene (Table).

In azidoselenation of terminal olefins a radical mechanism accounts for the introduction of selenium at the most substituted carbon (eq 3).<sup>15</sup> Thus, the regiochemistry of double bond functionalization is opposite to that



observed in ring-opening of aziridines. Reduction of azides **5** to the corresponding amines **6** was effected using lithium aluminum hydride or triphenylphosphine/hydrolysis. Following *N*-tosylation and *N*-allylation, reductive radical cyclization of compounds **8** afforded 3,4-disubstituted *N*-tosylpyrrolidines **9** as a mixture of diastereomers (Table).<sup>16</sup> Except for compound **9b**, carrying a bulky phenyl group in the 3-position, *cis*-3,4-disubstituted products were predominantly formed (Table). The ring-closure of compound **8d** (derived from 3,4-dihydropyran) was highly diastereoselective affording a 10/1 mixture of *endo* and *exo* products. As shown for the conversion of methylenecyclopentane to pyrrolidine **9e**, the methodology is also suitable for the construction of quaternary centers.

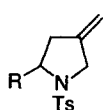
In both types of radical cyclization described, it would be desirable to increase the diastereoselectivity. We are presently trying to run the reactions at lower temperature using triethyl borane as an initiator.

Table Pyrrolidines from olefins via N-tosylaziridination/azidoselenation

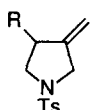
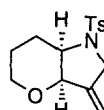
N-tosylaziridine/ azidoselenation product	$\beta$ -Aminoalkyl phenyl selenide (% yield <sup>a</sup> )	N-tosyl $\beta$ -amino- alkyl phenyl sele- nide (% yield <sup>a</sup> )	N-Allyl-N-tosyl $\beta$ - aminoalkyl phenyl selenide (% yield <sup>a</sup> )	Pyrrolidine (% yield <sup>a</sup> )
<b>1a</b> R=C <sub>6</sub> H <sub>13</sub>	-	<b>2a</b> R=C <sub>6</sub> H <sub>13</sub> (84)	<b>3a</b> (83)	<b>4a</b> R=C <sub>6</sub> H <sub>13</sub> (92) cis/trans=3/1
<b>1b</b> R=CH <sub>2</sub> Ph	-	<b>2b</b> R=CH <sub>2</sub> Ph(81)	<b>3b</b> (87)	<b>4b</b> R=CH <sub>2</sub> Ph (77) cis/trans=3/1
<b>1c</b> R=CH <sub>2</sub> OPh	-	<b>2c</b> R=CH <sub>2</sub> OPh(81)	<b>3c</b> (92)	<b>4c</b> R=CH <sub>2</sub> OPh(79) cis/trans=2/1
-	-	<b>2d</b> R=Ph <sup>b</sup>	<b>3d</b> (89)	<b>4d</b> R=Ph (79) cis/trans=2.5/1
	-			
<b>1e</b>	-	<b>2e</b> (83)	<b>3e</b> (85)	<b>4e</b> (71) exo/endo=1.6/1
	-			
<b>1f</b>	-	<b>2f</b> (77)	<b>3f</b> (84)	<b>4f</b> (90) exo/endo=1/2.7
<b>5a</b> R=C <sub>6</sub> H <sub>13</sub>	<b>6a</b> (81)	<b>7a</b> R=C <sub>6</sub> H <sub>13</sub> (84)	<b>8a</b> (88)	<b>9a</b> R=C <sub>6</sub> H <sub>13</sub> (85) cis/trans=2/1
<b>5b</b> R=Ph	<b>6b</b> (92)	<b>7b</b> R=Ph (62)	<b>8b</b> (98)	<b>9b</b> R=Ph(82) cis/trans=1/2
<b>5c</b> R=CH <sub>2</sub> OPh	<b>6c</b> (68)	<b>7c</b> R=CH <sub>2</sub> OPh (60)	<b>8c</b> (71)	<b>9c</b> R=CH <sub>2</sub> OPh(90) cis/trans=2/1
<b>5d</b>	<b>6d</b> (75)	<b>7d</b> (64)	<b>8d</b> (53)	<b>9d</b> (89) exo/endo=1/10
<b>5e</b>	<b>6e</b> (91)	<b>7e</b> (52)	<b>8e</b> (81)	<b>9e</b> (85)

<sup>a</sup> isolated yields <sup>b</sup> prepared according to ref. 13

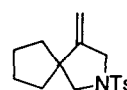
Pyrrolidines can also be efficiently prepared by 5-*exo-dig* cyclization of 3-aza-5-hexynyl radicals. The precursors to such species were conveniently prepared by replacing allyl bromide for propargyl bromide in equations 2 and 3. Thus, compounds **10** - **13** were prepared in 50-70 % yields from the appropriate phenylselenenides.



10 R=hexyl

11 R=Ph, CH<sub>2</sub>OPh

12



13

In conclusion, we have developed novel procedures for pyrrolidine synthesis. With enantiomerically pure aziridines becoming increasingly more available, we feel that the methodology described would also prove attractive for asymmetric synthesis.

**Acknowledgement:** Financial support by the Swedish Natural Science Research Council is gratefully acknowledged.

## References and notes

- Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds. Pergamon Press: Oxford, 1991; Vol 4, p 779. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley, New York, 1995.
- Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157. and refs cited therein.
- Pinder, A. R. In *The Alkaloids*, Grundon, M. F., Ed. Chemical Society: London, 1982; Vol 12.
- For 1-aza-5-hexenyl radical cyclization see: Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295. Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Tetrahedron*, **1990**, *46*, 2345. Tokuda, M.; Yamada, Y.; Takagi, T.; Sugimoto, H. *Tetrahedron* **1987**, *43*, 281.
- For 2-aza-5-hexenyl radical cyclization see: Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc. Perkin Trans. 1* **1996**, 219. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
- For 3-aza-5-hexenyl radical cyclization see: Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529. Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45. Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc. Chem. Commun.* **1986**, 78. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *Tetrahedron Lett.* **1985**, *26*, 957.
- For 4-aza-5-hexenyl radical cyclization see: Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417. Ziegler, F. E.; Jeroncio, L. O. *J. Org. Chem.* **1991**, *56*, 3479. Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269.
- For 5-aza-5-hexenyl radical cyclization see: Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123.
- For 6-aza-5-hexenyl radical cyclization see: Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623. Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514.
- Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
- Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1995**, *48*, 2047.
- Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897.
- Barton, D. H. R.; Britten-Kelly, M. R.; Ferreira, D. *J. Chem. Soc. Perkin Trans. 1*, **1978**, 1682.
- Compound **4d** has previously been prepared by reductive 3-aza-5-hexenyl radical cyclization. However, we were unable to confirm the assignment of the major isomer as *trans*-**4d**. Watanabe, Y.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. *Tetrahedron Lett.* **1987**, *28*, 3953.
- Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809.
- A similar protocol was recently used to prepare 2-amino-2-deoxy- $\alpha$ -D-C-glycosides: Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193.