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Diastereocontrol by a Hydroxyl Auxiliary in the Synthesis of Pyrrolidines via Radical Cyclization

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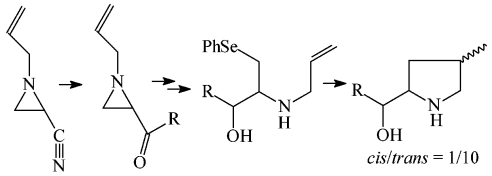
ABSTRACT



Organoselenium precursors of 3-aza-5-hexenyl radicals carrying a 1-hydroxyalkyl group in the 2-position were prepared by addition of organometallic reagents to *N*-allyl-2-aziridinecarbonitrile, reduction of the resulting aziridine ketone, and regioselective benzeneselenol ring opening of the aziridine. Reductive radical cyclization was highly selective, affording the corresponding *trans*-2,4-disubstituted pyrrolidine (*cis*/*trans* ca. 1/10) as the major diastereomer. Recrystallization afforded material that was substantially more enriched in the *trans* isomer (*cis*/*trans* < 1/25).

Radical carbon−carbon bond-forming reactions,[1] especially of the intramolecular type (radical cyclizations), are nowadays so versatile that they are routinely considered in retrosynthetic analysis of complex organic molecules. These reactions are not only restricted to carbocycle construction but also well suited for the preparation of various heterocycles such as tetrahydrofurans and pyrrolidines and derivatives thereof. However, a problem frequently encountered in the application of these radical cyclization reactions is that of diastereocontrol.[2]

By assuming a chairlike transition state, Beckwith and Houk have provided a model that could predict the stereochemical outcome of cyclization of variously substituted 5-hexenyl radicals (including oxa and aza derivatives).[3] However, it turns out that the selectivity (*cis*/*trans*) in simple disubstituted systems rarely exceeds 4/1 in favor of the predominating isomer.[4] We therefore thought it would be interesting to try to develop a methodology that would allow preparation of either of the *cis* and *trans* isomers of a particular system with higher selectivity. Thus, we recently found that trialkylaluminums directed radical cyclization of

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(2) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions—Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996.

(3) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun*. **1980**, 482. Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun*. **1980**, 484. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem*. **1987**, *52*, 959.

(4) For examples of 3-aza-5-hexenyl radical cyclizations of varying diastereoselectivity, see: Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem*. **1999**, *64*, 4273. Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem*. **1999**, *64*, 4282. Bertrand, M.-P.; Gastaldi, S.; Nouguier, R. *Tetrahedron* **1998**, *54*, 12829. De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T. *Synlett* **1993**, 871. Keusenkothen, P. F.; Smith, M. B. *Tetrahedron* **1992**, *48*, 2977. Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945. Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1992**, *48*, 9373. Soucy, F.; Wernic, D.; Beaulieu, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2885. Gennari, C.; Poli, G.; Scolastico, C.; Vassallo, M. *Tetrahedron: Asymmetry* **1991**, *2*, 793. Bachi, M. D.; De Mesmaeker, A.; Stevenart-De Mesmaeker, N. *Tetrahedron Lett*. **1987**, *28*, 2637. Watanabe, Y.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. *Tetrahedron Lett*. **1987**, *28*, 3953.

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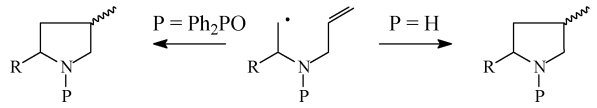
2-substituted 3-oxa-5-hexenyl radicals to occur in a highly *cis*-selective fashion (the unperturbed reaction is *trans*-selective).[5] Similarly, cyclization of 2-substituted 3-aza-5-hexenyl radicals **1** (Scheme 1) was found to occur in a highly

Scheme 1



Predominantely 2,4 - *cis* **1** Predominantely 2,4 - *trans*

cis-selective fashion (*cis*/*trans* = 10/1−20/1) if the nitrogen was carrying a bulky substitutent[6] (the best results were obtained with a diphenylphosphinoyl group), whereas cyclization of the corresponding N-unsubstituted radical provided the *trans*-2,4-disubstituted pyrrolidine as the major product. Sterically demanding 2-substituents afforded a large excess of *trans*-disubstituted pyrrolidine (Scheme 1; *cis*/*trans* < 1/20 for R = *t*-Bu and P = H).

With less bulky substituents (R = methyl, *n*-hexyl, isopropyl), the *cis*/*trans* ratio was usually close to 1/4 when the reaction was carried out at 15 °C. One notable exception was the case with a phenoxymethyl substituent (Scheme 1; *cis*/*trans* = 1/14 for R = CH_2OPh and P = H). We hypothesized that this high *trans*-selectivity could be due to intramolecular hydrogen bonding,[7] favoring an equatorial orientation of the 2-substituent in a chairlike transition state **2** (Figure 1).

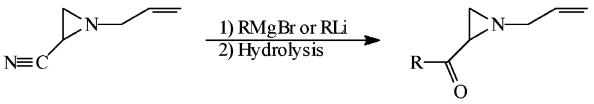
2 **3**

Figure 1. Hydrogen bonding in the transition state of the radical ring closure.

As a further extension of this reasoning, it occurred to us that it might be possible to employ a hydroxyl substitutent in the side chain as an auxiliary (favoring transition state **3**) to increase *trans*-selectivity in the cyclization of 2-substituted 3-aza-5-hexenyl radicals. Provided the auxiliary could be smoothly removed, a rather general synthesis of *trans*-2,4-disubstituted pyrrolidines would be achieved.

We envisioned suitable organoselenium radical precursors could be prepared from readily available[8] *N*-allyl-2-aziridinecarbonitrile (**4**) by addition of an organometallic reagent[9] and hydrolysis of the resulting imine (Scheme 2).

Scheme 2



4

5a R = Ph (92%)
b R = 2-thienyl (68%)
c R = *n*-pentyl (60%)
d R = *i*-propyl (52%)
e R = 2-(1,3-dioxolan-2-yl) ethyl (73%)

PhLi added to compound **4** already at −78 °C. PhMgBr was less reactive but provided a similar yield (92%) of compound **5a**. When aliphatic Grignard reagents were employed, addition of a catalytic amount (0.1 equiv) of CuBr was found to give cleaner and higher yielding reactions (compounds **5c**−**e**).[10] Intermediate imines obtained from addition of aliphatic organometallic reagents were hydrolyzed during ammonium chloride workup. Those obtained from aromatic reagents were hydrolyzed with lithium hydroxide in methanol/water. The resulting ketoaziridines can be diastereoselectively reduced to the corresponding alcohols[11] and a phenylseleno group introduced by benzeneselenol ring opening of the aziridine[12] (Scheme 3).

After zinc complexation, aziridine ketones **5** on sodium borohydride reduction afforded only the corresponding *erythro*-configured aziridine alcohols **6**. The following ring-opening of the aziridine with benzeneselenol occurred regioselectively from the sterically least hindered side to give *erythro*-configured amino alcohols **7**.

Reductive radical cyclization of compounds **7** was effected in high yield by photolysis in benzene in the presence of AIBN and tri-*n*-butyltin hydride. As shown in Table 1, the diastereomeric mixtures of 2,4-disubstituted pyrrolidines **8** obtained were highly enriched in the *trans* isomer (1/12 < *cis*/*trans* < 1/9). Although the level of selectivity does not quite match the one obtained with a phenoxymethyl substituent in the 2-position (Figure 1, structure **2** *cis*/*trans* = 1/14; vide supra), it is clear that cyclization of radical

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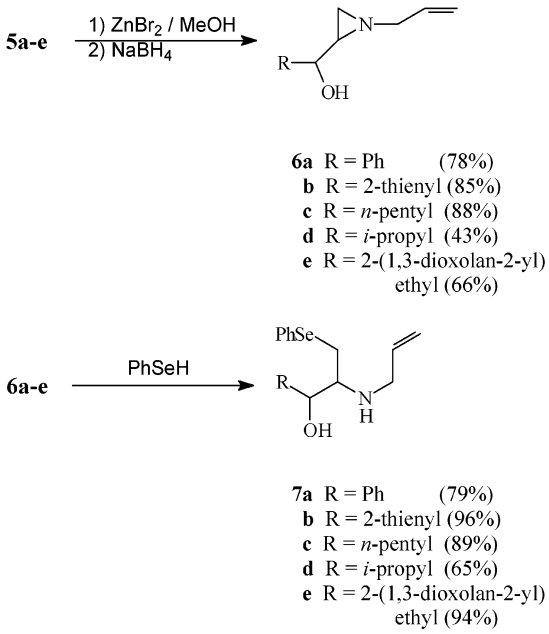
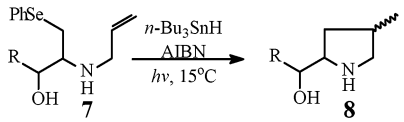
(6) Besev, M., Engman, L. *Org. Lett.* **2000**, *2*, 1589.
(7) For an example of hydrogen bonding in the synthesis of 2,3-disubstituted pyrrolidines, see: Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Mendiguchia, P. *Eur. J. Org. Chem.* **2000**, 3727. See also: Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507. Kündig, E. P.; Xu, L.-H.; Romanens, P. *Tetrahedron Lett.* **1995**, *36*, 4047.
(8) US Pat. 4,321,197, 1983.
(9) Deng, S. X.; Huang, D. W.; Landry, D. W. *Tetrahedron Lett.* **2001**, *42*, 6259. Sugimura, T.; Koguro, K.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 509. Apen, P. G.; Rasmussen, P. G. *J. Heterocycl. Chem.* **1992**, *29*, 1091. De Kimpe, N.; Sulmon, P.; Schamp, N. *Bull. Soc. Chim. Belg.* **1986**, *95*, 567. Fuerstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. Kao, K.-H.; Sheu, R.-S.; Chen, Y.-S.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2383. Paquette, L. A.; Mendez-Andino, J. L. *J. Org. Chem.* **1998**, *63*, 9061. Estieu, K.; Ollivier, J.; Salaun, J. *Tetrahedron* **1998,** *54*, 8075.
(10) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.
(11) Bartnik, R.; Laurent, A.; Lesniak, S. *J. Chem. Res., Miniprint* **1982**, 2701.
(12) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323. See also ref 6.

Scheme 3



precursors carrying a hydroxyl auxiliary in the side chain are much more *trans*-selective than they would be if the hydroxyl was missing. As a further bonus of the hydroxyl auxiliary, pyrrolidines **8** were found to be highly crystalline. Thus, recrystallization of crude compound **8a** from cyclohexane and sublimation of **8d** afforded material substantially more enriched in the *trans*-isomer (*cis*/*trans* < 1/25). Several protocols (including radical deoxygenation and displacement of a suitable sulfonate ester with lithium aluminum hydride) could be considered for removal of the hydroxyl auxiliary. As an example, compound **8a** was *N*-tosylated, converted to a xanthate, and then subjected to treatment with AIBN and tri-*n*-butyltin hydride (Barton−McCombie method[13]). The product was a 1/9 mixture of *cis* and *trans* *N*-tosyl-2-benzyl-4-methylpyrrolidine, the spectral characteristics of which were in excellent agreement with those of authentic samples of the materials.[6]

Table 1. Diastereoselective Reductive Radical Cyclization of 3-Aza-5-hexenyl Phenyl Selenides **7**



R	product	yield[a](%)	*cis*/*trans* ratio[b]
Ph	**8a**	82	1/9
2-thienyl	**8b**	80	1/9
n-pentyl	**8c**	96	1/10
i-propyl	**8d**	81	1/12
2-(1,3-dioxolan-2-yl)ethyl	**8e**	84	1/9

[a] Isolated yield. [b] As determined by ^{1}H NMR.

Figure 2. Oxazolidinones.

The ring closure shown in the first entry of Table 1 (R = Ph) was also tried in a protic solvent (*tert*-butyl alcohol). However, the diastereoselectivity did not differ from that observed in benzene. Also, ^{1}H NMR studies of the radical precursor **7a** did not provide any evidence for hydrogen bonding. This suggests that structure **3** (or a similar arrangement where the hydroxyl is donating a proton) does not contribute to preorganize the molecule prior to cyclization. Rather, the observed *trans*-directing effect of the auxiliary seems to be the result of increased steric bulk of the side chain. In an effort to somehow mimic the effect of intramolecular hydrogen bonding, amino alcohol **7a** was converted into oxazolidinone **9** (Figure 2) by heating in dimethyl carbonate with sodium hydride. Although reductive radical cyclization produced mostly the diastereomer of oxazolidinone **10** where the 2,4-substituents of the pyrrolidine moiety are oriented *trans*, the *cis*/*trans* selectivity (1/6) could not match the one seen in the cyclization of compound **7a**. Cyclization of compound **7a** was also carried out in the presence of various aluminum-based Lewis acids that could be expected to chelate to the amino alcohol moiety. However, as compared with the unperturbed reaction, none of these additives caused a notable change in the diastereoselectivity of radical cyclization.

In conclusion, we have found that 5-*exo*-cyclization of readily available organoselenium precursors of 3-aza-5-hexenyl radicals carrying a 1-hydroxyalkyl group in the 2-position gives the corresponding 2,4-*trans*-disubstituted pyrrolidines as the predominating products (*cis*/*trans* ratio ca. 1/10). By recrystallization, the diastereoselectivity could then be further improved. Since the hydroxyl auxiliary can be easily removed, the methodology nicely complements strategies for diastereocontrol that are based on variation in the *N*-substituent (which provide *cis*-2,4-disubstituted pyrrolidines with high selectivity[6]).

Acknowledgment. We thank the Swedish Research Council for financial support.

Supporting Information Available: Experimental procedures and characterization data for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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