Simple Method for Controlling Stereoselection in Mannich Cyclization Reactions of Aldehydes

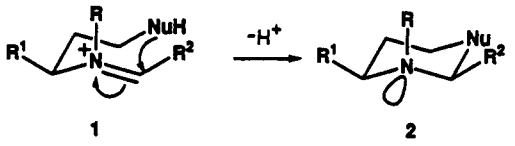
Dirk A. Heerding,[1a] Chang Y. Hong, Noriyuki Kado,[1b] Gary C. Look,[1c] and Larry E. Overman*

Department of Chemistry, University of California, Irvine, California 92717-2025

Received August 27, 1993®

Summary: By judicious choice of the nitrogen substituent, either stereoisomer of 1-substituted 1,2,3,4,6,7,8,8a-octahydroisoquinolines can be prepared by reactions of allylsilane amines **3** with aldehydes.

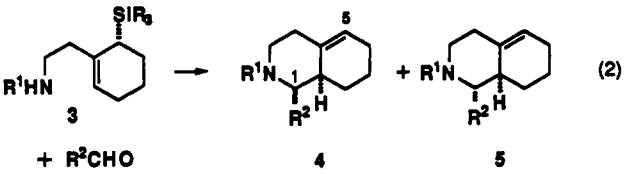
Reactions of iminium cations with tethered nucleophiles (Mannich cyclization reactions) are among the most important methods for preparing nitrogen heterocycles.[2] Although Mannich cyclizations have been employed for over 70 years,[3] stereochemical nuances of this chemistry have been revealed only recently. An antiperiplanar orientation of the developing nonbonded electron pair on nitrogen and the entering nucleophile is preferred, as are chair topographies in cyclizations that form piperidine rings.[2,4] These features are illustrated in eq 1, as is the



(1)

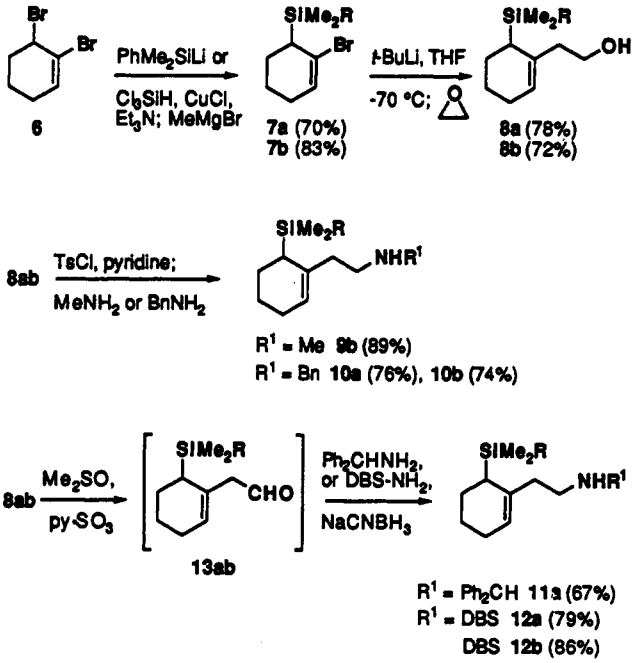
favored quasiequatorial orientation of the group R^2 in cyclizations of aldehyde-derived iminium ions.[5] In this paper, we disclose a new stereocontrolled synthesis of 1-substituted 1,2,3,4,6,7,8,8a-octahydroisoquinolines that introduces a potentially general method for controlling stereoselection at the site of nucleophilic attack in Mannich cyclization reactions.

As part of our investigations of opioid and morphinan synthesis,[6] we required access to 1-substituted 1,2,3,4,6,7,8,-8a-octahydroisoquinolines **4** having a trans relationship of the 1-substituent and the angular hydrogen. Cyclizations of iminium cations formed from the condensation of allylsilane amines **3** and aldehydes appeared to be a potentially general approach to octahydroisoquinolines of this type (eq 2).[2,7,8] We also anticipated that stereoselection in the key cyclization could be controlled by the proper choice of the nitrogen substituent R^1.



(2)

Scheme I[a]



[a]Key: **a**, R = Me; **b**, R = Ph.

Allylsilane amines **9–12** were prepared in three to four steps from readily available dibromide **6**[9] as summarized in Scheme I. Silylation of **6** at the allylic site with $PhMe_2SiLi$,[10] or with $HSiCl_3$ followed by treatment of the derived allyltrichlorosilane with MeMgBr,[11] provided **7a** and **7b** in good yields.[12] Reaction of the vinyllithium reagents derived from these vinylic bromides with ethylene oxide and $BF_3{\cdot}OEt_2$[13] at ≤ −70 °C then provided the silyl homoallylic alcohols **8a** and **8b**.[14] Conventional aminolysis of the tosylate derivatives of these intermediates with methylamine or benzylamine provided the allylsilane

® Abstract published in *Advance ACS Abstracts,* November 1, 1993.

(1) Current addresses: (a) Medicinal Chemistry Department, Smith-Kline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406-0939. (b) Central Research Laboratories, Hokuriku Seiyaku Co., Ltd., Inokuchi, Katsuyama, Fukui, 911, Japan. (c) Affymax Research Institute, 4001 Miranda Ave., Palo Alto, CA 94304.

(2) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.4.

(3) For summaries of important early work, see: (a) Blicke, F. F. *Org. React. (N. Y.)* **1942**, *1*, pp 303–341. Hellmann, H.; Optiz, G. α-Aminoalkylierung, Verlag Chemie: Weinheim, 1960.

(4) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 211–221.

(5) For representative examples, see: (a) Jacobsen, E. J.; Mendelson, L. T.; Overman, L. E. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (b) Darbre, T.; Nussbaumer, C.; Borschberg, H.-J. *Helv. Chim. Acta* **1984**, *67*, 1040. (c) Deng, L.; Czerwinski, K.; Cook, J. M. *Tetrahedron Lett.* **1991**, *32*, 175. (d) Czerwinski, K. M.; Deng, L.; Cook, J. M. *Ibid.* **1992**, *33*, 4721.

(6) Hong, C. Y.; Kado, N., Overman, L. E. *J. Am. Chem. Soc.*, in press.

(7) In contrast to the many examples of intramolecular reactions of allylsilanes with *N*-acyliminium cations, there are only a few reports of forming piperidines from the reaction of basic allylsilane amines with aldehydes.[2,8]

(8) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React (N.Y.)* **1989**, *37*, 57.

(9) Stevens, C. L.; Valicenti, J. A. *J. Am. Chem. Soc.* **1965**, *87*, 838.

(10) For use of this method to prepare **7a**, see: Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043. Due to the inconvenience in preparing Me_3SiLi on large scales, we found it preferable to prepare **7a** by the method of Itoh.[11]

(11) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267. Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1.

(12) All intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Unless noted otherwise, yields refer to purified products.

(13) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(14) These intermediates rearrange to the allyllithium isomers at higher temperature.

0022-3263/93/1958-6947$04.00/0 © 1993 American Chemical Society

Table I. Stereoselection in Iminium Ion–Allylsilane Cyclizations To Form 1-Substituted 1,2,3,4,6,7,8,8a-Octahydroisoquinolines

	allylsilane			aldehyde		octahydroisoquinoline products		
entry	compds	R	R^1	R^2	cycln condns[a]	yield,[b] %	compds	isomer ratio (4:5)[c]
1	**9b**	Ph	Me	Bn	A	88	**4a, 5a**	11:89
2	**9b**	Ph	Me	Bn	B	68	**4a, 5a**	20:80
3	**9b**	Ph	Me	Ph	A	55[d]	**5b**	only **5b**
4	**10b**	Ph	Bn	Bn	B	48[d]	**4c, 5c**	61:39
5	**10a**	Me	Bn	Bn	A	68	**4c, 5c**	58:42
6	**10a**	Me	Bn	Bn	C	72	**4c, 5c**	57:43
7	**11a**	Me	Ph_2CH	Bn	A	73	**4d**	only **4d**
8	**12a**	Me	DBS	Bn	A	67	**4e**	only **4e**
9	**12b**	Ph	DBS	Bn	C	79	**4e**	only **4e**
10	**12a**	Me	DBS	*o*-$IC_6H_4CH_2$	A	82	**4f**	only **4f**

[a] (A) The aldehyde (2 equiv), Me_3SiCN (2 equiv), and ZnI_2 (0.2 equiv) were mixed to form the silylcyanohydrin intermediate; the silylamine (1 equiv) and MeOH (*ca.* 5 mL/mmol) were added, and the reaction was heated at reflux. (B) The purified Strecker product was treated with ZnI_2 (1 equiv) in THF (10–20 mL/mmol) at room temperature. (C) A solution of the aldehyde (1.1 equiv), silylamine (1 equiv), ZnI_2 (0.05 equiv), and dry EtOH (10–20 mL/mmol) was warmed to 65 °C. [b] Isolated yield of purified product(s). [c] Determined from the yields of **4** and **5**. In all cases this ratio was similar to that obtained by ^1H NMR analysis of the crude reaction product. [d] The bulk of the remaining mass was recovered Strecker product.

amines **9b**, **10a**, and **10b**. Since the yield of similar displacements with hindered primary amines was low, the benzhydrylamine **11a** and the *N*-(5-dibenzosuberyl)amines (DBS)[15] **12a** and **12b** were prepared by reductive amination of the β,γ-unsaturated aldehydes **13a** and **13b**. These labile aldehydes were best prepared by Parikh–Doering[16] oxidation of **8a** and **8b** and were employed directly, without purification, in the reductive amination step.

Results obtained from the reaction of allylsilane amines **9–12** with representative aldehydes to form octahydroisoquinolines **4** and **5** are summarized in Table I. In our early studies, the amine and aldehyde were first condensed to form the Strecker product,[17] which was subsequently cyclized in MeOH or THF in the presence of ZnI_2. More recently, we have found that the condensation–cyclization of the allylsilane amines with aldehydes (1.1 equiv) is best accomplished directly in MeOH or EtOH in the presence of 5 mol % of ZnI_2. It is notable that sensitive arylacetaldehydes perform satisfactorily under these conditions.[18] Stereochemical assignments for the octahydroisoquinoline products followed directly from their ^1H NMR spectra. Particularly diagnostic were the upfield shifts (~1 ppm)[19] of the axial methine hydrogen at C(1) and the larger vicinal coupling constant of this hydrogen in stereoisomers **5**.[20]

As is apparent in Table I, the stereochemical outcome of this octahydroisoquinoline synthesis is dramatically effected by the size of the R^1 substituent on nitrogen.[21] When R^1 = Me, isomer **5** was formed preferentially (entries 1–3), while isomer **4** is the exclusive product of cyclizations of the benzhydrylamine and *N*-(5-dibenzosuberyl)amine substrates (entries 7–10).[22] Substrates **10a** and **10b**, containing *N*-benzyl substitution, cyclized with low stereoselectivity (entries 4–6). The observed stereoselection is readily rationalized as depicted in Figure 1. When R^1 is small, cyclization in chair conformer **15** having the R^2 substituent oriented in a quasiequatorial fashion is preferred.[5] However, when R^1 is large, nonbonded interactions between R^1 and R^2 destabilize the cyclization transition state related to conformer **15** sufficiently that cyclization takes place preferentially by way of the alternate iminium ion stereoisomer **14**.[23,24]

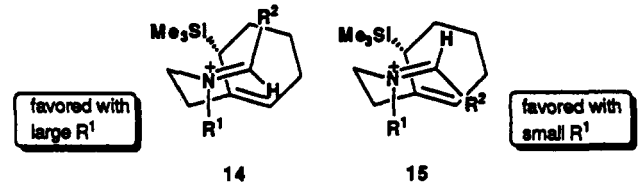


Figure 1. Control of stereoselection by the nitrogen substituent.

In summary, either stereoisomer of 1-substituted 1,2,3,4,6,7,8,8a-octahydroisoquinolines can be prepared by ZnI_2-promoted reaction of allylsilane amines **3** and aldehydes (eq 2). In light of the wide occurrence of reduced isoquinoline rings in natural alkaloids and pharmaceutical agents, this efficient new synthesis of octahydroisoquinolines could have numerous applications. Moreover, the ability to control the stereochemical outcome of iminium ion cyclizations by proper tuning of the geometry of the iminium ion component should find use as well in Mannich synthesis of other nitrogen heterocycles.

Acknowledgment. This investigation was supported by NIH Grant GM30859 and Hokuriku Seiyaku Co., Ltd. NMR and mass spectra were determined at Irvine using spectrometers purchased with the assistance of the NSF Shared Instrumentation program.

Supplementary Material Available: Characterization data for new compounds and experimental details for a representative condensation–cyclization reaction of **12b** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Pless J. *Helv. Chim. Acta* **1976**, *59*, 499.
(16) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(17) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583. Mai, K.; Patil, G. *Synth. Commun.* **1985**, *15*, 157.
(18) For a recent example of the difficulties often encountered in iminium ion chemistry of this important aldehyde class, see: Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *32*, 2995.
(19) Vierhapper, F. W.; Eliel, E. L.; Zuniga, G. *J. Org. Chem.* **1980**, *45*, 4844. Lambert, J. B.; Oliver, W. L. *J. Am. Chem. Soc.* **1969**, *91*, 7774.
(20) The stereochemical assignment for **4e** was confirmed by chemical correlation (HCO_2H, 70 °C; HCHO, HCO_2H, 110 °C) with **4a**.
(21) Solvent effects on diastereoselection are small; see entries 4–6.
(22) None of the stereoisomer **5** was detected in the crude cyclization product by ^1H NMR analysis, indicating that diastereoselection was at least 20:1.
(23) As stated, the mechanistic rationale assumes that interconversion of iminium ion stereoisomers (e.g., by nucleophile addition–elimination) is more rapid than cyclization. On the basis of previous studies of other Mannich cyclization reactions, we believe this is likely.[24] However, in the present case no experimental evidence bears on this issue.
(24) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.