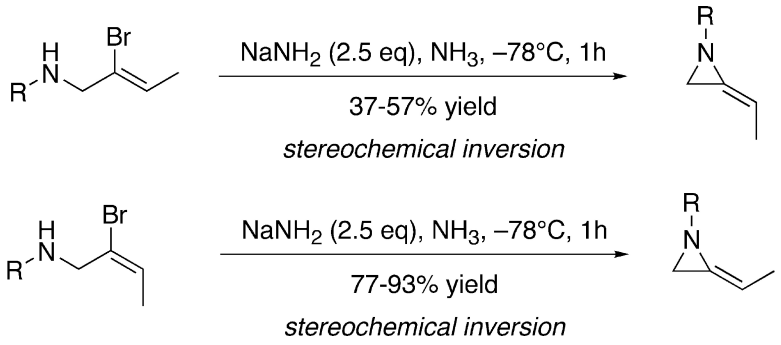
Communication

# Rare Example of Nucleophilic Substitution at Vinylic Carbon with Inversion: Mechanism of Methyleneaziridine Formation by Sodium Amide Induced Ring Closure Revisited

Jason J. Shiers, Michael Shipman, Jerome F. Hayes, and Alexandra M. Z. Slawin

*J. Am. Chem. Soc.*, **2004**, 126 (22), 6868-6869• DOI: 10.1021/ja0482684 • Publication Date (Web): 13 May 2004






## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 05/13/2004

# Rare Example of Nucleophilic Substitution at Vinylic Carbon with Inversion: Mechanism of Methyleneaziridine Formation by Sodium Amide Induced Ring Closure Revisited

Jason J. Shiers,[†] Michael Shipman,*[,†] Jerome F. Hayes,[‡] and Alexandra M. Z. Slawin[§]

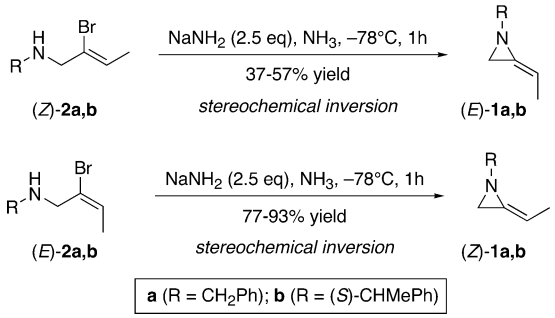
*Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, U.K., GlaxoSmithKline, Old Powder Mills, Tonbridge, Kent, TN11 9AN, U.K., and School of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife, KY16 9ST, U.K*

Received March 26, 2004; E-mail: m.shipman@warwick.ac.uk

Nucleophilic substitution reactions are very commonly encountered in mechanistic and synthetic chemistry. Bimolecular nucleophilic substitution ($S_N2$) at a saturated carbon atom ($sp^3$) proceeds with inversion of configuration.[1] Both stepwise and concerted processes at vinylic carbon ($sp^2$) normally afford substitution with retention of configuration although when the carbanion intermediate is long-lived, partial or complete stereoconvergence can result.[2] Examples of nucleophilic substitutions at vinylic carbon proceeding with inversion of configuration are rare. Typically, these involve substrates bearing very good leaving groups such as vinyl triflates[3] or vinyl iodonium salts.[4] Inversion of configuration has not been observed in unactivated systems such as vinyl chloride even though high-level computational studies suggest that in-plane, $\sigma$-approach of the nucleophile to the backside of the C−Cl bond is the preferred pathway.[5] *Herein, we report examples of stereochemical inversion occurring during substitution at an unactivated vinylic carbon atom.* Specifically, we show that intramolecular substitution of the C−Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom leads to 2-ethyleneaziridines by way of stereochemical inversion. In conjunction with deuterium-labeling experiments, these results indicate that the accepted mechanism[6] for ring closures of this type is flawed.

The reaction of 2-bromoallylamines with sodium amide in liquid ammonia is known to provide 2-methyleneaziridines in high yields.[7] As part of studies aimed at delineating the synthetic scope of these highly strained heterocycles,[8] we became interested in establishing if this reaction could be extended to the synthesis of derivatives bearing stereochemically defined substituents on the exocyclic double bond.[9] To this end, we set about the synthesis of (*E*)- and (*Z*)-2-ethyleneaziridines **1**. Derivatives containing either a simple benzyl (R = $CH_2Ph$) or chiral α-methylbenzyl (R = (*S*)-CHMePh) group on nitrogen were chosen. Four cyclization precursors (*E*)- and (*Z*)-**2a**,**b** were made by treatment of the (*E*)- and (*Z*)-isomers of 2-bromobut-2-en-1-ol[10] with methanesulfonyl chloride and further alkylation with either benzylamine or (*S*)-α-methylbenzylamine. The stereochemistry about the double bond within (*E*)-**2a**,**b** and (*Z*)-**2a**,**b** was confirmed by NOE difference experiments. Treatment of (*E*)- and (*Z*)-**2a**,**b** with sodium amide in liquid ammonia provided 2-ethyleneaziridines (*E*)- and (*Z*)-**1a**,**b** in moderate to excellent yields (Scheme 1).[11] Several aspects of these cyclizations are of special interest. First, the reactions are highly stereoselective with the aziridines being obtained as essentially single isomers about the double bond.[12,13] Second, lower yields were observed for the formation of (*E*)-**1a**,**b** as alkyne formation via antiperiplanar E2-elimination of HBr from (*Z*)-**2a**,**b** was competitive. Finally, and most significantly, the reactions proceed by net inversion at the alkene carbon atom undergoing substitution.

***Scheme 1.*** Ring Closure to Ethyleneaziridines with Stereochemical Inversion at the Vinylic Carbon Atom




The stereochemistry of (*Z*)-**1a** and (*Z*)-**1b** have been unambiguously established by derivatization and subsequent crystallographic analysis. Lithiation of (*Z*)-**1b**, and separately (*Z*)-**1a**, with *sec*-BuLi (THF, 5 h, −78 °C) and further reaction with benzophenone provided (*Z*)-**3** and (*Z*)-**4** in 83% and 62% yields, respectively (Figure 1). Importantly, in a control experiment, lithiation/protonation of (*Z*)-**1a** was shown to occur without isomerization of the double bond. Single crystals of **3** and **4** grown from diethyl ether were analyzed by single-crystal X-ray diffraction, which revealed that they both possess the (*Z*)-stereochemistry. For **3**, the major diastereomer (crude dr 93:7) possessed the expected (*S*)-configuration at C-3.[14] Lithiation of (*E*)-**1a** and alkylation with benzophenone produced the (*E*)-isomer of **4**.

Bottini and Olsen produced evidence indicating that the formation of methyleneaziridines proceeds primarily if not exclusively by an elimination−addition mechanism (Scheme 2).[6] Performing the reaction using tritium-enriched ammonia as solvent, they cyclized amine **5** to methyleneaziridine **6** (R = Pr) which was tritium labeled exclusively at C-3. In further crucial experiments, they reported that the hydrogens bonded to carbon of **5** and **6** do not undergo exchange with the solvent under the reaction conditions. Thus, they concluded that the reaction was proceeding through aziridinyl anion **9** by way of allenes **7** and **8**. The observation that (*E*)- and (*Z*)-**2a** yield different aziridine products is inconsistent with this elimination−addition mechanism as both these substrates would be expected to yield the same allene intermediate.

To further investigate the mechanism, deuterated 2-bromoallylamine **10** (95% D incorporation) was prepared in two steps from ethyl 2-bromoacrylate [(i) $LiAlD_4$, $AlCl_3$, $Et_2O$, 75%; (ii) MsCl, $Et_3N$, 0 °C, THF, then (*S*)-$PhCHMeNH_2$, 69%]. Treatment of **10** with sodium amide (1.25 equiv) for 5 min at −33 °C yielded (*S*)-**11** (92% D) (Scheme 3).[15] Thus, anion **9** cannot be an intermediate in the production of methyleneaziridines. Performing the cyclization

[†] University of Warwick.
[‡] GlaxoSmithKline, Tonbridge.
[§] University of St. Andrews.


10.1021/ja0482684 CCC: $27.50 

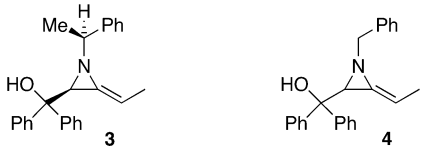
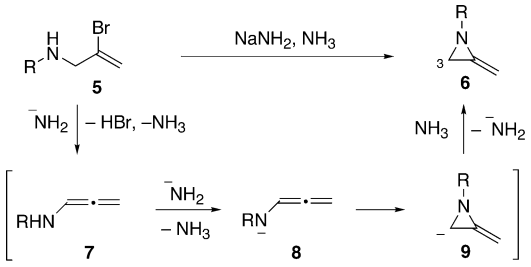
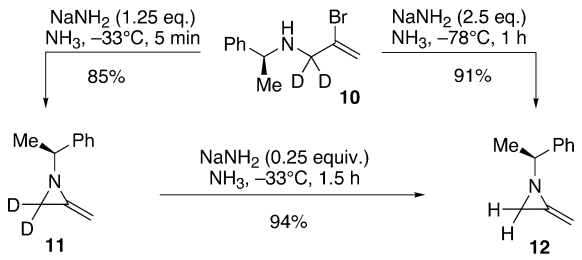



***Figure 1.*** Derivatives produced from (*Z*)-ethyleneaziridines used to confirm the alkene geometry by X-ray crystallography.

***Scheme 2.*** Original Ring Closure Mechanism Proposed by Bottini and Olsen[6]




***Scheme 3.*** Cyclization Studies Using Deuterium-Labeled Substrates




for a longer time using excess sodium amide (2.5 equiv, 1 h, −78 °C) resulted in conversion to (*S*)-**12** wherein virtually all the deuterium had been lost (12% D). Consistent with this finding, resubjection of deuterated methyleneaziridine (*S*)-**11** (92% D) to the cyclization conditions resulted in clean conversion to nondeuterated (*S*)-**12** (2.5% D). These results indicate that this methyleneaziridine, formed quickly under the cyclization conditions ($t_{1/2} \approx 10$ s at −78 °C using 2.5 equiv of $NaNH_2$), undergoes slow reversible exchange with the solvent by way of deprotonation at C-3 by the excess sodium amide.[16]

The question remains what is the mechanism of ring closure? Our evidence discounts the earlier proposal of an elimination−addition reaction. Furthermore, stereochemical inversion seems to rule out the possibility of an addition−elimination process wherein retention or stereoconvergence would be expected.[2] Substitution with inversion by in-plane $\sigma$-attack from the backside of the C−Br bond fits all the available experimental data. It remains to be seen if the constraints imposed on the reaction trajectory by the formation of a three-membered ring are important in encouraging this pathway.

To conclude, a rare example of substitution at a vinylic carbon proceeding with inversion has been unearthed. Efforts to explore the utility of the geometrically defined 2-ethyleneaziridines in synthesis will form the basis of future studies.

**Acknowledgment.** We thank the Engineering and Physical Sciences Research Council and GlaxoSmithKline for financial support of this work.

**Supporting Information Available:** Crystallographic data of **3** and **4** (CIF) experimental procedures and spectroscopic data for **1**−**4** and **10**−**12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Katritzky, A. R.; Brycki, B. E. *Chem. Soc. Rev.* **1990**, 83−105. (b) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, 71−167.

(2) (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7−15. (b) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474−479.

(3) (a) Clarke, T. C.; Kelsy, D. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 3626−3627. (b) Summerville, R. H.; Senkler, C. A.; Schleyer, P. v. R.; Dueber, T. E.; Stang, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 1100−1110. (c) Summerville, R. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 1110−1120.

(4) (a) Ochiai, M.; Oshima, K.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 7059−7061. (b) Okuyama, T.; Ochiai, M. *J. Am. Chem. Soc.* **1997**, *119*, 4785−4786. (c) Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* **1999**, 1363−1364. (d) Ochiai, M.; Yamamoto, S. *Chem. Commun.* **2002**, 2802−2803. (e) Okuyama, T.; Lodder, G. *Adv. Phys. Org. Chem.* **2002**, *37*, 1−56.

(5) Bach, R. D.; Baboul, A. G.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 5787−5793. Kim, C. K.; Hyun, K. H.; Kim, C. K.; Lee, I. *J. Am. Chem. Soc.* **2000**, *122*, 2294−2299 and references therein.

(6) Bottini, A. T.; Olsen, R. E. *J. Am. Chem. Soc.* **1962**, *84*, 195−199.

(7) (a) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925−2927. For the correct structural assignments, see: (b) Ettlinger, M. G.; Kennedy, F. *Chem. Ind.* **1956**, 166−167. (c) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1957**, *79*, 1462−1464.

(8) (a) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935−942. (b) Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383−2385. (c) Hayes, J. F.; Shipman M.; Twin, H. *Chem. Commun.* **2001**, 1784−1785.

(9) All previous routes to 2-methyleneaziridines have led to products in which both substituents on the exocyclic double bond are identical. For example, the synthesis of 2-isopropylidineaziridines is known: Wijnberg, J. B. P. A.; Wiering, P. G.; Steinberg, H. *Synthesis* **1981**, 901−903.

(10) For the preparation of (*E*)-2-bromobut-2-en-1-ol, see: (a) Hiskey, C. L.; Slates, H. L.; Wendler, N. L. *J. Org. Chem.* **1956**, *21*, 429−433. For (*Z*)-2-bromo-but-2-en-1-ol, see: (b) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453−1456.

(11) Sodium amide was made in situ by adding sodium metal to liquid ammonia at −33 °C containing a small quantity (2.5 mol %) of an Fe(III) source. Identical results were obtained using either $Fe(NO_3)_3 \cdot 9H_2O$ or $FeCl_3$.

(12) Substrates (*E*)- and (*Z*)-**2a**,**b** contained traces of the double bond isomer (≤8%). This was relayed into the aziridines which also contained a small quantity of the stereoisomer (≤9%). See Supporting Information.

(13) No appreciable racemisation occurred during the formation of (*Z*)-**1b** (90% ee) and (*E*)-**1b** (94% ee) as determined by chiral shift NMR experiments using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Racemic materials made and used as controls.

(14) Hayes, J. F.; Prévost, N.; Prokes, I.; Shipman M.; Slawin, A. M. Z.; Twin, H. *Chem. Commun.* **2003**, 1344−1345.

(15) The level of deuterium incorporation was measured using $^1H$ NMR spectroscopy and is the average of three experimental runs.

(16) It is unclear why Bottini and Olsen (ref 6) were unable to detect exchange with the solvent under their experimental conditions. However, we suspect that an insufficient amount of base was added. This conclusion was reached on the basis of the following observations. First, for the exchange experiment, they used just a catalytic quantity (0.26 equiv) of commerical sodium amide, whereas cyclisations were conducted using $NaNH_2$ made in situ from sodium metal and $FeCl_3$. In our experience, the activity of commercial material is far inferior and often necessitates the use of a large excess of reagent. Second, **6** used in the experiment was contaminated with 7% of the corresponding alkyne which would have consumed a significant proportion of the added base.

JA0482684