Aza-[2,3]-Wittig Rearrangements of Vinylaziridines

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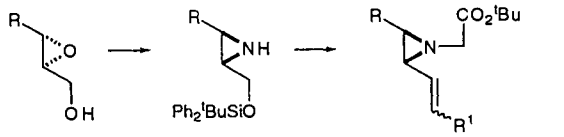
The [2,3]-Wittig rearrangement (eq 1, X = O) has become a powerful strategy in organic chemistry as demonstrated by its numerous applications in natural product synthesis.[1] Generally the reaction is considered to proceed *via* a concerted mechanism involving a five-membered envelope-like transition state in which the breaking C–O and forming C–C bonds are almost eclipsed,[2,3] the high stereoselectivity often observed being rationalized in terms of steric effects and electronic interactions.[2] Despite the documented utility of this reaction, the corresponding aza-[2,3]-Wittig rearrangement (eq 1, X = NR″) has received considerably less attention. Although some attempts in this area have been made,[4,5] to date only one unequivocal example of this transformation has been reported, involving the base-promoted rearrangement of 1-benzyl-4-vinyl-2-azetidinone to the corresponding seven-membered unsaturated lactam.[6] For that case it was also noted that the ease with which the ring expansion occurred undoubtedly was associated with the considerable relief of ring strain on going from a four- to a seven-membered ring. In an analogous vein we have investigated the aza-Wittig rearrangement of vinylaziridines **3** to the corresponding tetrahydropyridine derivatives **4** (Scheme 2) and herein detail our preliminary findings.[7]

(1)

X=O, NR″
G=Ph, CO_2R, CCTMS, CN, ...

Scheme 1 summarizes the preparation of the vinylaziridines used in the present study. Opening of epoxides **1**, obtained in high enantiomeric purity by the Sharpless epoxidation,[8] with sodium azide[9] (89–95%) followed by selective protection of the primary hydroxyl (88–94%) and reductive cyclization[10] gave aziridines **2** (73–94%), their absolute configuration being inverted as compared to that of the parent epoxides. *N*-Alkylation of **2**

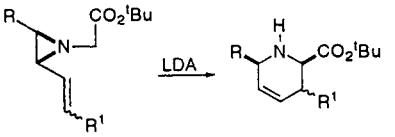
Scheme 1



1 **2**

3a. R=BnOCH$_2$, R^1=H
b. R=C_6H_{13}, R^1=H
c. R=^{t}Bu, R^1=H
d. R=^{t}Bu, R^1=(*Z*)-CH_3
e. R=^{t}Bu, R^1=(*E*)-CH_3

Scheme 2



3

		Yield
4a.	R=BnOCH$_2$, R^1=H	93%
b.	R=C_6H_{13}, R^1=H	98%
c.	R=^{t}Bu, R^1=H	95%
d.	R=^{t}Bu, R^1=α-CH_3	92%
e.	R=^{t}Bu, R^1=β-CH_3	92%

with *tert*-butyl bromoacetate (61–82%),[11] removal of the silyl group (85–89%), and then exposure of the resultant alcohol to a Swern oxidation[12] followed by a Wittig olefination[13,14] (56–81%) yielded vinylaziridines **3a–e** in good overall yield. Since it was noted that aziridines **3** are prone to undergo thermal [1,5]-hydrogen shifts,[15] these compounds were prepared and processed as quickly as possible, any prolonged storage at room temperature being avoided. The ^{1}H NMR spectra of aziridines **3c–e** all indicate the presence of a single nitrogen invertomer, presumably with the *tert*-butyl acetate group *trans* to the sterically most demanding ring substituent in each case. In contrast, the spectra of **3a** and **3b** consist of two sets of lines in a ratio of about 2–4/1 at room temperature, suggesting an equilibrium of two invertomers.[16]

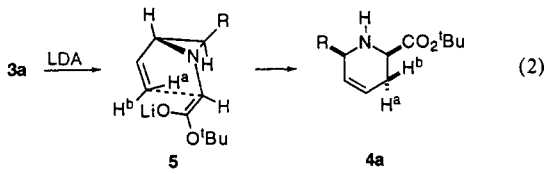
The results from the [2,3] rearrangements of vinylaziridines **3** are collected in Scheme 2. Subjecting vinylaziridine **3a** to LDA in THF at –78 °C resulted in the rapid (<5 min) formation of tetrahydropyridine **4a** in 93% yield and as a single isomer,[17] the relative stereochemistry of which was established by its conversion into *cis*-2,6-bis(hydroxymethyl)piperidine.[18] In a similar way compounds **3b–e** could be transformed into **4b–e**, respectively, and in all cases only a single isomer of the products could be detected. As for their relative stereochemistry, compound **4b** was assigned in analogy with **4a**, while that of **4c–e** could be determined by analyzing the relevant coupling constants in the ^{1}H NMR spectra, assuming, in each case, that the unsaturated six-membered ring adopts a half-chair conformation and that the *tert*-butyl group functions as a conformational lock, occupying

(1) (a) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.11. (b) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594–604.
(2) Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421–1423.
(3) For a somewhat different transition state structure, see ref 1b.
(4) (a) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981–2984. (b) Murata, Y.; Nakai, T. *Chem. Lett.* **1990**, 2069–2072. (c) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275–1276.
(5) The rearrangement described in ref 4a has been shown to proceed by a [1,2] mechanism; see ref 4b.
(6) Durst, T.; Elzen, R. V. D.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261–9263.
(7) For recent applications of vinylaziridines in organic synthesis, see: (a) Hudlicky, T.; Tian, X.; Königsberger, K.; Rouden, L. *J. Org. Chem.* **1994**, *59*, 4037–4039. (b) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652–654. (c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619. (d) Hudlicky, T.; Reed, J. W. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 8.1.
(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
(9) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696–5704.
(10) (a) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271–4273. (b) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619–624.
(11) Ahman, J.; Somfai, P. *Synth. Commun.* **1994**, *24*, 1121–1127.
(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(13) Tanner, D.; Somfai, P. *BioMed. Chem. Lett.* **1993**, *3*, 2415–2418.
(14) Compound **3e** was prepared from the corresponding aldehyde by a Schlosser modification of the Wittig reaction, affording **3e** in 56% yield (*E*/*Z*: 1/1). Schlosser, M.; Christmann, K. F. *Angew. Chem.* **1965**, *77*, 682–683.
(15) (a) Borel, D.; Gelas-Mialhe, Y.; Vessière, R. *Can. J. Chem.* **1976**, *54*, 1590–1598. (b) Sauleau, J.; Sauleau, A.; Huet, J. *Bull. Soc. Chim. Fr.* **1978**, 97–103. (c) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755–3762. (d) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527–3530.
(16) The inversion barrier for $\mathbf{3a}_{major \rightarrow minor}$ was calculated by using the DNMR 5 program: $\Delta G^{\ddagger}$ = 16.5 kcal/mol and ΔG° = 0.77 kcal/mol. (Stephenson, D. S.; Binsch, G. *QCPE* **1978**, *11*, 365.)
(17) Compounds **4a–e** readily darken upon standing and are not stable to extensive chromatography on silica gel. However, the crude products from the [2,3] rearrangments are normally sufficiently pure, as determined from their ^{1}H NMR spectra, to be used directly. For a related experience, see: Overman, L. E.; Flan, C. J.; Malone, T. C. *Org. Synth.* **1989**, *68*, 188–197.
(18) Kasuga, S.; Taguchi, T. *Chem. Pharm. Bull.* **1965**, *13*, 233–240.

0002-7863/94/1516-9781$04.50/0

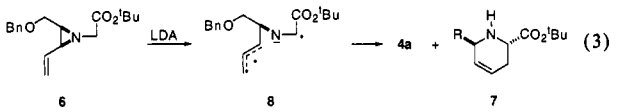
a pseudoequatorial position. Further support for this assignment was obtained by hydrogenation of compound **4c**, which yielded the corresponding *cis*-2,6-disubstituted piperidine derivative as evident from its spectral data.[19]

In line with the calculated transition structure for the [2,3]-Wittig rearrangement,[2] as well as for the homodienyl-[1,5]-hydrogen shift to which this reaction bears resemblance,[20] we suggest structure **5** as a possible transition state conformation (eq 2). In **5** the *tert*-butyl acetate group and the alkene moiety are *cis* in order to facilitate bond formation. In addition, the vinylic group adopts an *endo* orientation, projecting over the ring, while the enolate moiety is oriented so as to minimize steric interaction with the aziridine ring substituents (*exo*). Bond formation between the rearrangement origin and terminus and accompanying opening of the aziridine moiety then yields the observed products. This model helps to explain (1) the exclusive formation of *cis*-2,6-disubstituted tetrahydropyridines and (2) the stereochemical outcome when using substrates **3d** and **3e**. It should be noted that, in the rearrangement of vinylaziridines **3a** and **3b**, existing as mixtures of invertomers, the suggested model requires a facile mechanism for the inversion at nitrogen in order to account for the high yields observed. We are currently investigating the possibility of this inversion taking place after formation of the corresponding enolate.



(2)

The rearrangement of a *cis*-2,3-disubstituted vinylaziridine results in the formation of an almost equal mixture of the corresponding *cis*- and *trans*-2,6-disubstituted tetrahydropyridines, in sharp contrast to the examples discussed above. Thus, the racemic vinylaziridine **6**, prepared from the corresponding epoxide as detailed above, exists as a single nitrogen invertomer, presumably with the *tert*-butyl acetate group *trans* to the other ring substituents. Exposing **6** to LDA at −78 °C resulted in the rapid formation of racemic **4a** and **7** in 93% yield and in a ratio of 1.8/1 (eq 3). The reaction outcome is readily accounted for by assuming cleavage of the initially formed anion, in which the distance between the rearrangement origin and terminus is too far to allow for an efficient orbital overlap, into diradical anion **8**. Ring closure of **8** then gives the observed product mixture, the lack of stereoselectivity being due to a rapid inversion of the radical center in **8**.[21,22]



(3)

In summary, we have shown that properly substituted vinylaziridines are excellent substrates in the aza-[2,3]-Wittig rearrangement, and we are currently investigating the scope and limitations of this reaction. In addition, the tetrahydropyridines obtained from these rearrangements should provide a novel entry to biologically significant alkaloids and pipecolic acid derivatives.

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Supplementary Material Available: A procedure for the rearrangement of vinylaziridine **3c** and spectroscopic data for compounds **3a–e**, **4a–e**, **6**, and **7** (4 pages). This material is contained in many 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.

(19) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.17 (dd, 1H, J = 11.2, 2.8 Hz, C*H*$CO_2{}^t$Bu), 2.16 (dd, 1H, J = 11.0, 2.2 Hz, ^{t}BuC*H*).

(20) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089–2092.

(21) Similar arguments have previously been invoked to account for the lack of selectivity in the aza-Wittig rearrangement; see ref 6.

(22) We cannot exclude the possibility that **7** is formed by a mechanism involving nitrogen inversion followed by a [2,3] rearrangement.