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A Novel Rearrangement of *N*-Propargyl Vinylaziridines. Mechanistic Diversity in the Aza-[2,3]-Wittig Rearrangement

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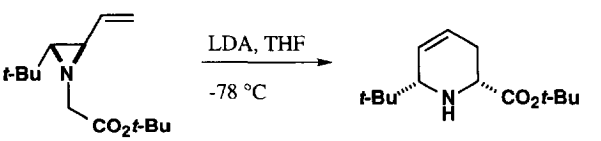
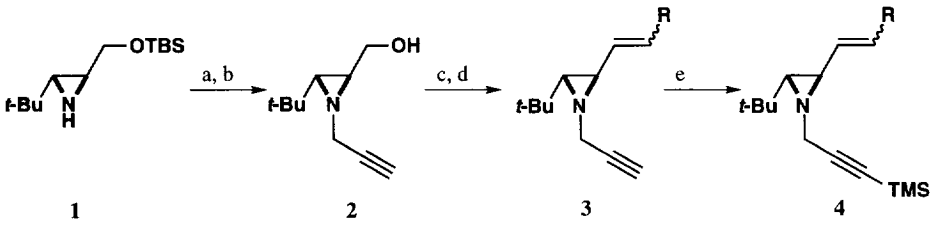
Abstract: *N*-Propargyl vinylaziridines **4a-c** have been prepared. The anionic rearrangement of **4a,b** gives the *trans*-2,6-disubstituted tetrahydropyridines **5a,b**, respectively, as the major products while **4c** gives 1-pyrroline **7c** exlusively. The mechanism for the formation of pyrrolines in these reactions is discussed.

Pericyclic reactions in which a σ bond is translocated over a π system are normally associated with a high degree of stereoselectivity and predictability. As a consequence sigmatropic rearrangement reactions provide a powerful strategy in organic synthesis. In this context we recently described an aza-[2,3]-Wittig rearrangement of *trans*-2,3-disubstituted *N-tert*-butylacetyl vinylaziridines which, when subjected to LDA at -78 °C, were transformed to the corresponding *cis*-2,6-disubstituted tetrahydropyridines in high yields and as a single detectable diastereomer in each case (Scheme 1).[1,2] The potential of this reaction was demonstrated by employing it as a key step in an enantioselective total synthesis of Indolizidines 209B and 209D, and later the Coldham group obtained analogous results when rearranging structurally similar vinylaziridines.[3,4] The stereochemical outcome of these transformations was explained by invoking a transition state geometry that closely resembles that calculated for the parent [2,3]-Wittig rearrangement in allylic ethers. For that case it has been shown, and later rationalized by computational methods, that the stereochemical outcome of the reaction can be controlled by a judicious choice of anion-stabilizing group.[5,6] For example, α-alkoxy anions derived from (*E*)-allylic propargylic ethers rearrange to give the product with high *anti* selectivity while the corresponding acetic acid enolate preferentially gives the *syn* product.[5b,7] Consequently, as a part of an ongoing investigation of the aza-[2,3]-Wittig rearrangement in vinylaziridines we became interested in the possibility of reversing the previously observed selectivity, i. e. to obtain *trans*-2,6-disubstituted tetrahydropyridines, by using *N*-propargyl vinylaziridines as substrates and herein communicate our results.



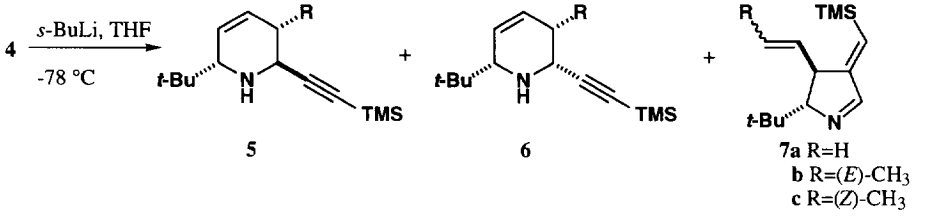
Scheme 1. Stereoselective aza-[2,3]-Wittig rearrangement.

The vinylaziridines **3** and **4** required for the present study were prepared from **1**[1] in good overall yield (Scheme 2). Alkylation of **1** with propargyl bromide followed by removal of the silyl protecting group gave the primary alcohol **2**.[8] Swern oxidation of **2** gave the corresponding aldehyde which was immediately subjected to Wittig olefination to furnish vinylaziridines **3**. Finally, deprotonation of this material with *n*-BuLi and quenching the resultant anion with TMSCl yielded the TMS-propargyl derivatives **4a-c**. It should be noted that vinylaziridines like **3** and **4** are particularly well suited for this type of study since they exist as single nitrogen invertomers at room temperature, thus simplifying the spectroscopic and mechanistic analysis.



Scheme 2. **a** R=H, **b** R=(*E*)-CH_3, **c** R=(*Z*)-CH_3. a) $CHCCH_2Br$, K_2CO_3, 18-crown-6, THF, 92%; b) *n*-Bu_4NF, THF, 92%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; d) **a** Ph_3PCH_3Br, KHMDS, THF, 83%, **b** $Ph_3PCH_2CH_3Br$, KHMDS, THF, 81%, **c** $Ph_3PCH_2CH_3Br$, PhLi, MeOH, toluene, 32% (*E*:*Z* 3.2:1); e) *n*-BuLi, TMSCl, -78 °C, 70-86%.

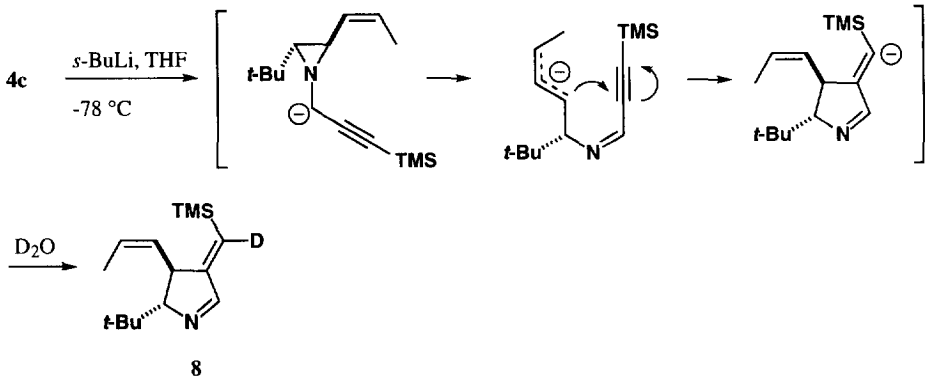
Somewhat surprisingly, attempts to rearrange vinylaziridine **3a** by using *n*-BuLi, *n*-BuLi/TMEDA or *s*-BuLi (3 eq.) gave none of the expected products and **3a** was recovered unaffected, or with complete incorporation of deuterium at the terminal alkyne position when the reaction was quenched with D_2O. This is in contrast to the behaviour of allylic propargyl ethers which are smoothly deprotonated and rearranged by the action of *n*-BuLi,[7a] and seems to indicate that the α-amino anion derived from **3a** should be of considerably higher energy compared to the analogous species derived from an ether.[9] However, subjecting the TMS derivative **4a** to *s*-BuLi (THF, -78 °C) resulted in formation of the *trans*-2,6- and *cis*-2,6-tetrahydropyridines **5a** and **6a** along with considerable amounts of 1-pyrroline **7a** (**5a**:**6a**:**7a** 1.8:1.2:1) in a combined isolated yield of 64% (Scheme 3).[10,11] The relative stereochemistry of **5a** and **6a** was assigned by inspection of the relevant coupling constants in the ^1H NMR spectra and verified by NOESY experiments, while the structure elucidation of **7a** required more extensive NMR investigation (NOESY, COSY, HETCOR and long-range HETCOR). Similarly, rearrangement of **4b** (*E*:*Z* 3.2:1) gave tetrahydropyridines **5b** and **6b** together with 1-pyrrolines **7b** and **7c** in 49% combined yield (**5b**:**6b**:**7b**:**7c** 4.9:2.4:1:1.4) while aziridine **4c** under identical conditions gave **7c** as a single detectable isomer in 30% isolated yield. The isolated yields in these reactions are low because compounds **5-7** are air sensitive and decompose to some extent even when flash chromatographed under an argon atmosphere on deactivated silica.



Scheme 3. Rearrangement of vinylaziridine **4** (**a** R=H, **b, c** R=CH_3).

These results are significant for several reasons, even though a detailed mechanistic analysis of these findings is premature at this stage. It has thus been demonstrated that the stereochemical outcome of the aza-[2,3]-Wittig rearrangement in vinylaziridines can be controlled by the choice of anion-stabilizing group. The present results also show that the previously described[1] *cis*-selectivity in formation of 2,6-disubstituted tetrahydropyridines can be reversed by using the TMS-propargyl moiety as an activating group to yield the *trans*-2,6-disubstituted tetrahydropyridine in a ratio of 2-1.5:1.

The formation of 1-pyrrolines **7a-c** in these reactions is surprising and represents an unprecedented reaction manifold in the vinylaziridine system.[12] Some valuable information about the formation of the 1-pyrrolines was obtained by repeating the experiment with aziridine **4c** (*s*-BuLi, -78 °C, THF) and quenching the reaction with D_2O. This yielded compound **8** as a single diastereomer with complete deuterium incorporation which suggests a mechanism in which the initially formed propargylic anion, derived from **4c**, opens the aziridine ring to form the corresponding allylic anion (Scheme 4). Intramolecular addition of this anion to the alkyne moiety (5-exo-dig) then gives a vinylic anion (species known to be configurationally stable)[13] which is then quenched by D_2O to give **8**, thus accounting for the exclusive formation of an (*E*)-vinylsilane in this process.



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Scheme 4. Proposed mechanism for formation 1-pyrroline **8**.

In conclusion, we have shown that the stereochemical outcome of the aza-[2,3]-Wittig rearrangement in vinylaziridines can be controlled by a proper choice of nitrogen substituent. Furthermore, 1-pyrrolines are formed in varying amounts by a novel reaction pathway in the rearrangement of *N*-TMS-propargyl vinylaziridines. While this limits the synthetic applicability of the aza-[2,3]-Wittig rearrangement in these systems, it clearly warrants further mechanistic investigations.

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10. **5a**: IR (neat): ν=2900, 2160, 1460, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, referenced to residual solvent peak): δ 5.53 (br s, 2H), 4.04 (dd, 1H, *J*=2.1, 6.1 Hz), 3.27 (m, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.68 (br s, 1H), 0.93 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, referenced to residual solvent peak): δ 127.3, 123.6, 108.2, 86.2, 58.9, 43.7, 33.7, 30.8, 26.2, 0.16; [a]$_D$ -77.01 (*c* 2.78, $CHCl_3$); HRMS (CI+) calcd for $C_{14}H_{26}NSi$ (M+H): 236.1835, found: 236.1835.
6a: IR (neat): ν=2980, 2160, 1540, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, referenced to residual solvent peak): δ 5.77 (m, 1H), 5.67 (m, 1H), 3.65 (dd, 1H, *J*=4.3, 10 Hz), 3.10 (m, 1H), 2.30-2.11 (m, 2H) 1.65 (br s, 1H), 0.93 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, referenced to residual solvent peak): δ 127.8, 125.6, 107.8, 86.7, 64.3, 46.2, 33.8, 32.8, 26.1, 0.02; [a]$_D$ +26.5 (*c* 0.773, $CHCl_3$); HRMS (CI+) calcd for $C_{14}H_{26}NSi$ (M+H): 236.1835, found: 236.1831.
7a: IR (neat): ν=2960, 1580, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, referenced to residual solvent peak): δ 7.60 (d, 1H, *J*=2.2 Hz), 5.99 (d, 1H, *J*= 2.1 Hz), 5.69 (ddd, 1H, *J*=7.9, 10.2, 17.2 Hz), 5.02-4.96 (m, 2H), 3.76 (t, 1H, *J*=2.2 Hz), 3.19 (m, 1H), 0.92 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, referenced to residual solvent peak): δ 167.1, 159.5, 140.8, 129.2, 114.6, 90.3, 45.2, 35.5, 26.4, -0.51; HRMS (CI+) calcd for $C_{14}H_{26}NSi$ (M+H): 236.1835, found: 236.1839.
11. *n*-BuLi and *n*-BuLi/TMEDA are also effective in this deprotonation and gives an identical product composition compared to *s*-BuLi.
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