A Highly Stereoselective Aza-[3,3]-Claisen Rearrangement of Vinylaziridines as a Novel Entry to Seven-Membered Lactams

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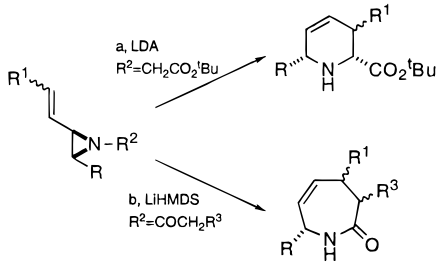
Sigmatropic rearrangements provide a powerful tool for stereocontrolled bond construction. Of these reactions, those variants in which a carbon−heteroatom bond, which is normally easily formed, is transformed into a carbon−carbon bond have proven particularly useful, prominent examples being the [2,3]-Wittig and [3,3]-Claisen rearrangements.[1,2] The often excellent stereoselectivities obtained in these reactions are usually rationalized by assuming cyclic transition states in which the stereochemical information embedded in the substrate is effectively communicated, for steric or stereoelectronic reasons, to the product. The main thrust in this area has traditionally been directed toward substrates in which the migrating bond is a C−O σ-bond, while other heterologs have received considerably less attention. In this respect we,[3] and others,[4] have recently documented the use of variously *N*-substituted vinylaziridines as substrates in the aza-[2,3]-Wittig rearrangement to yield the corresponding di- or trisubstituted tetrahydropyridines in high yield (a, eq 1), the driving force being the relief of ring strain.[5] It was also demonstrated that the stereochemical outcome of the reaction is dependent on the substitution pattern of the aziridine nuclei. In an effort to expand the synthetic potential of vinylaziridines we became interested in the possibility of using them in an aza-[3,3]-Claisen rearrangement,[2b,6] thus providing a novel entry to seven-membered lactams (b, eq 1),[7,8] compounds that are of interest in natural product synthesis[9] and as peptide turn mimetics.[10] Herein we disclose our preliminary findings in this area.



(1)

N-Alkyl and *N*-sulfonyl vinylaziridines have received considerable interest as intermediates in the stereoselective synthesis of alkaloids and peptidomimetics, and, as a consequence, several efficient routes toward them have been developed.[11,12] Somewhat surprisingly, the corresponding *N*-acyl and *N*-H vinylaziridines, which might serve as a precursor for all types of vinylaziridines, have received less attention, and, prior to this investigation, no general and enantioselective synthesis of them has been documented. The *N*-acyl vinylaziridines **4a**−**g** required for the present study were prepared from the corresponding vinylepoxides **1a**−**d**[13] (ee >95%) as outlined in Scheme 1. Acid-catalyzed aminolysis of **1** resulted in a stereospecific and highly regioselective ring-opening to give amino alcohols **2** (69−93%).[14] The subsequent ring closure was best effected using the standard Mitsunobu protocol,[15] affording aziridines **3** (49−54%) and treatment of these materials with acetic anhydride, propionic anhydride, benzyloxyacetic anhydride, or *N*-Boc glycine anhydride[16] gave the *N*-acyl vinylaziridines **4a**−**g**, the precursors for the projected rearrangement. The crude products from the acylation step were judged to be >95% pure according to ^{1}H NMR spectroscopy. However, attempts to purify **4b** on silica gel resulted in a quantitative rearrangement into the corresponding *trans*-4,5-disubstituted oxazoline **5**,[17] and, consequently, the crude products from the acylation step were used directly in the subsequent Claisen rearrangements, the yields of which thus refer to such two-step sequences.

The results of the aza-[3,3]-Claisen rearrangements are collected in Scheme 2. When *N*-acetyl vinylaziridine **4a** was added to LiHMDS in THF at −78 °C followed by slowly warming the resultant mixture to room temperature, lactam **6a**

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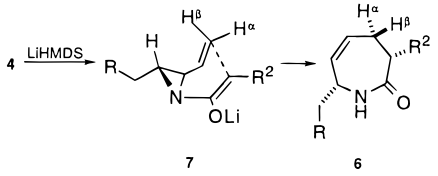
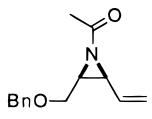
was formed in 83% yield. Repeating the procedure with **4b** gave **6b** in equally good yield (83%). Having thus established the feasibility of the rearrangement our next concern was the stereochemical outcome when using more highly substituted substrates. Deprotonation of **4c**, the α-benzyloxy derivative **4d** and the glycine amide **4e**, which are known to give preferentially the corresponding (*Z*)-enolates,[18] and rearrangement gave the seven-membered lactams **6c** (85%, α:*β* 22:1), **6d** (81%), and **6e** (76%), respectively. For the last two cases only single diastereomers of the products could be detected. Similarly, (*Z*)- and (*E*)-alkenyl derivatives **4f** and **4g** were rearranged into **6f** (73%) and **6g** (73%), respectively, as the only detectable diastereomers in each case,[19] indicating that the stereochemistry of the olefinic moiety is retained throughout the reaction. The relative stereochemistry of **6c**−**g** was secured by NOE analysis in each case, showing an interaction between the C3 and C7 methine protons, while that of **6f** and **6g** also required an inspection of the relevant coupling constants in their ^{1}H NMR spectra.[20]

The results from the rearrangements of vinylaziridines **4** can be rationalized by assuming that the reaction proceeds through the six-membered boat-like transition-state assembly **7** (eq 2). It should be noted that boat transition states have been invoked previously to explain the outcome in Claisen-type rearrangements of certain cyclic substrates, while the acyclic cases are generally believed to involve chair-like structures.[2d,e] The main features of **7** are that the olefin and enolate moieties are *cis* in order to facilitate bond formation and that both these groups adopt an *endo* conformation, projecting over the three-membered ring. Bond formation between the enolate and the alkene and concomitant opening of the aziridine gives the observed products. This model then correctly accounts for (i) the formation of α-isomers **6c**−**e** when deprotonating and rearranging **4c**−**e**, the sound assumption being that (*Z*)-enolates are involved in each case,[18,21] and (ii) the stereochemical outcome when using the alkenyl derivatives **4f** and **4g**. It is also presumed that the ease with which these transformations occur is a consequence of the considerable relief of ring strain when going from a three- to a seven-membered ring.



7 6 (2)

Some additional support for the above model was obtained when trying to rearrange vinylaziridine **8**, prepared from the corresponding *cis*-vinylepoxide by the route shown in Scheme 1. Deprotonation of **8** (LiHMDS, −78 °C) followed by warming to room temperature and quenching with D_2O gave only recovered starting material (10%), with complete incorporation of deuterium at the α-position, along with decomposed material, indicating that for steric reasons the enolate derived from **8** is not capable of attaining the required transition state structure to participate in the [3,3]-rearrangement.



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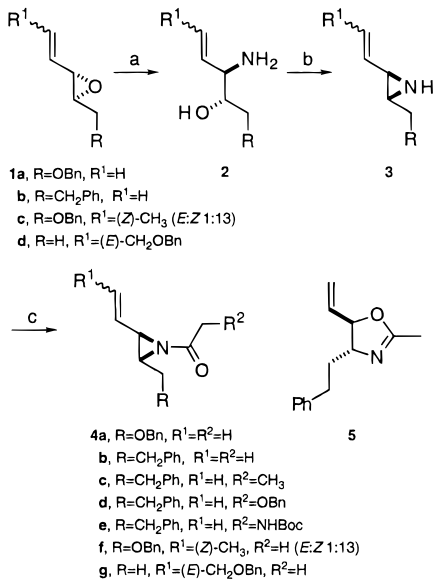
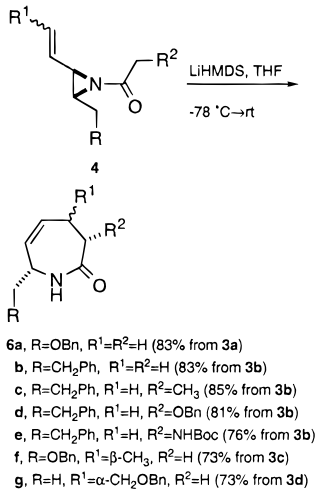
Scheme 1[a]



[a] Conditions: (a) NH_3, $TsOH\cdot H_2O$, 130 °C, 4 days, 69−93%. (b) DEAD, Ph_3P, THF, Δ, 49−54%. (c) $(R^2CH_2CO)_2O$, Et_3N, DMAP, CH_2Cl_2.

Scheme 2



In conclusion, we have described a novel and highly stereoselective aza-[3,3]-Claisen rearrangement of *N*-acyl vinylaziridines into the corresponding tetrahydroazepin-2-ones. Work is in progress to investigate the scope of this reaction and to apply it in natural product synthesis and for the preparation of peptidomimetics.

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Supporting Information Available: A procedure for the rearrangement of vinylaziridine **4b** and spectroscopic data for compounds **4a**−**g** and **6a**−**g** (5 pages). See any current masthead page for ordering and Internet access instructions.

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(19) The isomeric ratio of **4f** (*E*:*Z* 1:13) was retained in the rearrangement to give **6f** (α:*β* 1:13).

(20) Compounds **6a**−**g** adopts a "boat-like" conformation in which H-3*β* and H-7 are in close proximity, as judged from NOE experiments and confirmed by conformational analysis using MacroModel 5.5 (MM2). Selected ^{1}H NMR data for **6f**: *δ* 2.37 (ddd, *J* = 12.1, 6.2, 1.7 Hz, H-3α), 2.73 (t, *J* = 12.1 Hz, H-3*β*). **6g**: *δ* 2.60 (ddt, *J* = 13.3, 5.4, 1.5 Hz, H-3α), 3.00 (dd, *J* = 13.3, 4.0 Hz, H-3*β*).

(21) This explains why the enolates derived from **4d**,**e**, which have the possibility of forming chelated (*Z*)-enolates, rearrange with higher selectivities than the enolate derived from **4c**.