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Unprotected Vinyl Aziridines: Facile Synthesis and Cascade Transformations

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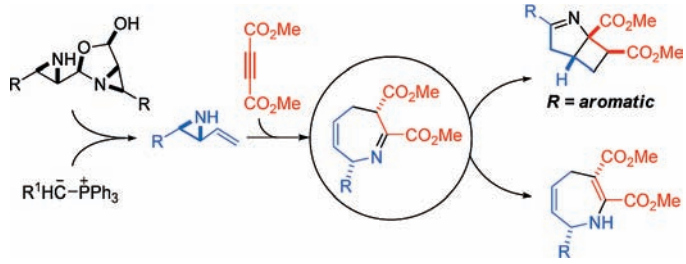
ABSTRACT



Functionalized vinylaziridines, readily available from water-stable aziridine aldehydes have led to the construction of a variety of stereochemically rich heterobicycles. A cascade ring-opening/ring-contraction mechanism operates in the course of the process. These results underscore the notion that interesting and useful nitrogen-mediated relay processes can arise when elements of strain are merged with the manifolds of enamine/iminium ion reactivity.

Cascade reactions give rise to products that may not be immediately obvious upon examination of the starting materials.[1] Elaborate structures can be derived from relatively simple molecules if a chemoselective and thermodynamically downhill sequence of bond-forming events has been secured. In this regard, strained functional groups are an unmatched source of inspiration for reaction design and development. As part of our efforts in the chemistry of heterocycles, we have now streamlined the syntheses of vinyl aziridines, azepines, and fused aminocyclobutanes. Several key features of nitrogen-containing functional groups have been central to forging this line-up of transformations. For our purposes, we resorted to unprotected amino aldehydes as precursors to vinyl aziridines.

Coupling the innate energy of cyclopropanes, aziridines, and epoxides with sigmatropic reactions can be useful in the synthesis of medium-sized rings. There are inherent advantages to this strategy: while the Cope rearrangement involving a [3,3]-sigmatropic shift in 1,5-dienes requires elevated temperatures,[2] the Cope homologues incorporating cyclopropane rings proceed at lower temperatures, giving rise to conformationally labile seven-membered rings.[3] For example, the *cis*-1,2-divinylcyclopropane rearrangement has been shown to proceed even at −40 °C.[4,5] Despite the utility of this approach for the construction of larger rings, the requirement for a *cis* stereochemical relationship between the olefin moieties attached to the cyclopropane is a notable limitation. An underexplored, but related, transformation incorporating an aziridine as the strain-release module does not suffer from the same stereochemical predicament due to the relatively low barrier to inversion at nitrogen. However, this chemistry relies on vinyl aziridines which are difficult to prepare.[6,7]

We were interested in developing cascade rearrangements that commence with vinyl aziridines.[8] Facile synthesis of unprotected vinyl aziridines soon became our number one priority. The available methods for the synthesis of unprotected C-vinyl aziridines include the ring closure of amino[9]

(1) For recent reviews on cascade reactions for heterocycle synthesis, see: (a) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (b) Bur, S. K.; Padwa, A. *Adv. Heterocycl. Chem.* **2007**, *94*, 1–105. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.

(2) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanism*, 4th ed.; Springer: New York, 2004.

(3) (a) Brown, J. M.; Golding, B. T.; Stofko, J. J., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 319–320. (b) Schneider, M. *Angew. Chem., Int. Ed.* **1975**, *14*, 707–708. (c) Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426–4427. (d) Vogel, E. *Angew. Chem., Int. Ed.* **1963**, *2*, 1–11.

(4) Doering, W. V. E.; Roth, W. R. *Angew. Chem., Int. Ed.* **1963**, *2*, 115–122.

(5) Rademacher, P. *Chem. Rev.* **2003**, *103*, 933–975.

(6) Nielsen, I. M. B. *J. Phys. Chem. A* **1998**, *102*, 3193–3201.

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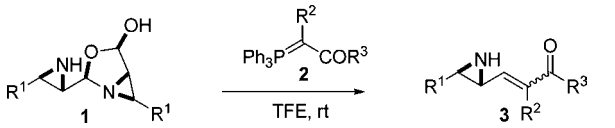
Table 1. One-Step Construction of Vinyl Aziridines from Unprotected Aziridine Aldehydes[a]



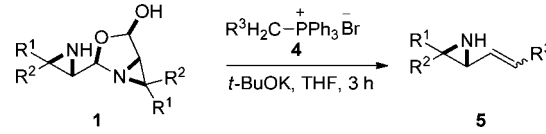
entry	R^1	R^2	R^3	product (*trans*/*cis*)	yield[b] [%]
1	Ph	H	OEt	**3a** (8/2)	98[c]
2	*p*-F-Ph	H	OEt	**3b** (8/2)	85
3	*p*-OMe-Ph	H	OEt	**3c** (>95/5)	65
4	Ph	Me	OEt	**3d** (>95/5)	95
5	*p*-F-Ph	Me	OEt	**3e** (>95/5)	80
6	*p*-OMe-Ph	Me	OEt	**3f** (>95/5)	63

[a] General conditions: reactions were performed on a 0.04 mmol scale in TFE using a ratio of 1:2.2 for the amino aldehyde dimer/Wittig reagent. [b] Isolated yields. [c] 1 mmol scale.

or azido alcohols[10] or the treatment of α,β-unsaturated oximes[11] or hydrazones[12] with Grignard reagents. Especially noteworthy is the pioneering study by Brois, in which the 1,2-divinylaziridine, prepared by the low-temperature addition of hexafluoro-2-butyne to the parent vinylaziridine, underwent ring expansion.[9] Protecting groups allow easier access to substituted C-vinyl aziridines, but their removal is difficult since the respective acidic conditions promote rapid and undesired S_N2' ring opening.[13] The lack of a mild approach prompted our investigation into olefination of amphoteric amino aldehydes recently developed in our lab.[14] These reagents can be prepared from simple starting materials such as α-amino acids and exist as dimers with the monomer/dimer equilibrium lying toward the latter in a variety of solvents. 2,2,2-Trifluoroethanol (TFE) has been shown to promote partial dissociation of the dimer. We happily noted that the dissolution of aziridine aldehydes in TFE allowed reactions with stabilized Wittig reagents to proceed smoothly (Scheme 1, path A). Despite the presence of the nucleophilic aziridine nitrogen, treatment of dimer **1a** with Wittig reagent **2** at room temperature in TFE furnished vinyl aziridine **3a** in 98% yield (Table 1, entry 1). Under optimized conditions, a variety of α,β-unsaturated vinyl aziridines can be prepared in one step from aziridine aldehyde dimers.

Conditions that allow the use of Wittig salts were also developed. Despite the fact that the dimeric amino aldehydes do not readily dissociate at high pH (there is no crossover between two structurally different dimeric amino aldehydes in the presence of base), treatment of **1** with a variety of Wittig salts **4** in the presence of *t*-BuOK at 0 °C afforded the corresponding vinylaziridines **5a**−**g** with high *cis* selectivity with respect to olefin geometry (Table 2). As free aldehyde is not observed in THF by NMR, we contend that *t*-BuOK promotes the reaction of the partially dissociated dimer (Scheme 1, path B). The latter has been implicated in

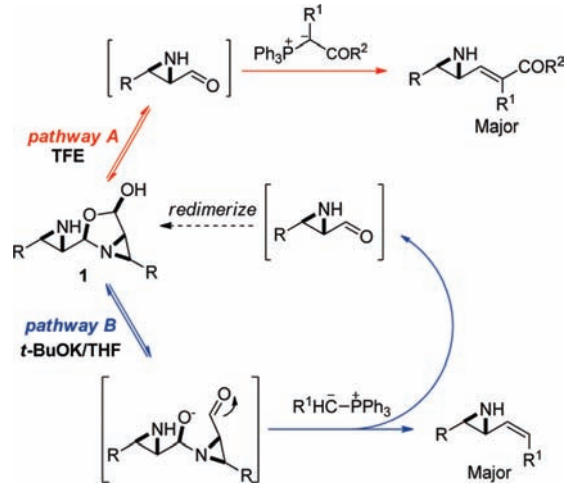
Table 2. Construction of Vinyl Aziridines Using Wittig Salts[a]



entry	R^1	R^2	R^3	product (*cis*/*trans*)	yield[b] [%]
1	Ph	H	H	**5a** (−)	88[c]
2	Ph	H	Me	**5b** (8/2)	85
3	Ph	H	Pr	**5c** (8/2)	80
4	Ph	H	$(CH_2)_2C'CPh$	**5d** (9/1)	70
5	*p*-F-Ph	H	Pr	**5e** (8/2)	80
6	*p*-OMe-Ph	H	Pr	**5f** (8/2)	70
7	Ph	Me	$(CH_2)_2C'CPh$	**5g** (9/1)	65

[a] General conditions: reactions were performed on a 0.1 mmol scale in THF using a reactant ratio of 1:4:4.5 for dimer/Wittig salt/*t*-BuOK. [b] Isolated yields. [c] 2 mmol scale.

Scheme 1. Vinyl Aziridine Synthesis: The Two Pathways



(7) (a) For a recent example of strain-release rearrangement of *N*-vinyl aziridines, see: Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370–10371. (b) For an excellent synthesis of seven-membered lactams from vinyl aziridines, see: Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385–8386. (c) Lewis acid-catalyzed rearrangements of vinyl aziridines: Brichacek, M.; Lee, D.; Njardarson, J. T. *Org. Lett.* **2008**, *10*, 5023–5026. (d) Dynamic kinetic resolution of vinyl aziridines: Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6123–6125.

(8) See Ohno, H. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; John Wiley & Sons: New York, 2006.

(9) Stogryn, E. L.; Brois, S. J. *J. Am. Chem. Soc.* **1967**, *89*, 605–609.

(10) (a) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 331–334. (b) Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109–117. (c) Olofsson, B.; Wijtmans, R.; Somfai, P. *Tetrahedron* **2002**, *58*, 5979–5982.

(11) Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett.* **1974**, *15*, 131–134.

(12) Chaabouni, R.; Laurent, A. *Synthesis* **1975**, 464–467.

(13) (a) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904–4914. (b) Zhou, J.; Magomedov, N. A. *J. Org. Chem.* **2007**, *72*, 3808–3815. (c) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Org. Lett.* **2004**, *6*, 2377–2380.

(14) (a) Yudin, A. K.; Hili, R. *Chem.—Eur. J.* **2007**, *13*, 6538–6542. (b) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772–14773. (c) Li, X.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14152–14153.

the course of our previous studies in reductive conjugation of amino aldehydes with amino acid derivatives.[15] An X-ray crystal structure was obtained for the *trans*-isomer **5a**. This vinyl aziridine features a dimeric arrangement in the solid state, which is driven by the stabilizing aromatic/aromatic interactions (Figure 1).

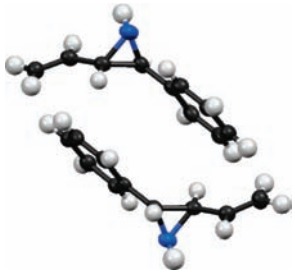
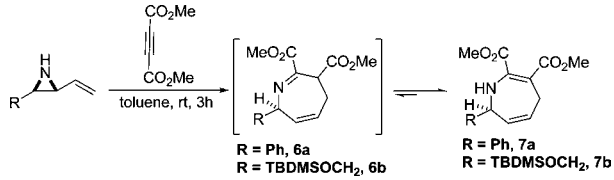


Figure 1. X-ray crystal structure of **5a**.

The pK_{aH} of NH aziridine is 8.0, which indicates substantial nucleophilicity. An enlargement into a medium-sized ring[16] upon converting the aziridine nitrogen into a transient enamine would produce a nitrogen center capable of partaking in an imine/enamine equilibrium. This intermediate can be regarded as a pivot point to undergo further transformations driven by the C═N bond strength.

Upon treatment of vinyl aziridine **5a** with DMAD at room temperature in toluene, azepine **7a** was obtained in excellent yield through nucleophilic attack of the aziridine nitrogen onto the electron-poor acetylene carbon, followed by a Cope rearrangement[9] (Scheme 2). Monitoring this reaction using

Scheme 2. Azepines from Unprotected Vinyl Aziridines and DMAD



^{1}H NMR revealed that the azepine was formed via intermediate **6a** through removal of the acidic α-ester proton. Examination of **6a** reveals another acidic proton alpha to

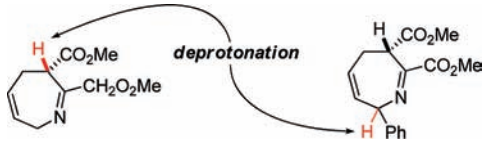


Figure 2. Potential deprotonation sites.

the amino group (Figure 2). In hopes of a subsequent rearrangement we examined a variety of reaction conditions to trigger selective removal of this proton and concomitant creation of a 6π-electron system. Gratifyingly, when the reaction was performed in DMSO, we observed the cascade formation of a heterobicycle (**8a**) as a single diastereoisomer arising from deprotonation at the benzylic position.

Aminocyclobutanes are important scaffolds that have found application as designer nucleotides as well as parts of constrained amino acids.[17] An X-ray structure of compound **8a** established the *cis* relationship between the bridgehead proton and two methyl ester groups (Figure 3). Subjecting

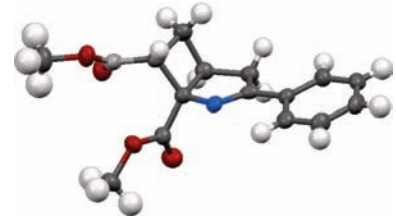
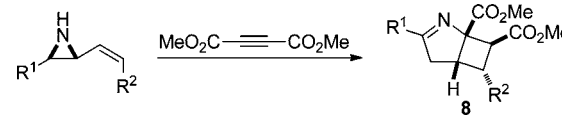


Figure 3. X-ray crystal structure of **8a**.

other vinyl aziridines with aromatic substituents to the reaction allowed us to prepare a variety of heterobicyclic molecules (Table 3). The aromatic substituent α to the vinyl

Table 3. Cascade Synthesis of Heterobicycles from Vinyl Aziridines[a]



entry	R^1	R^2	product	yield[d] [%]
1	Ph	H	**8a**	70
2	Ph	Me	**8b**	68
3	Ph	Pr	**8c**	65
4	Ph	$(CH_2)_2C'CPh$	**8d**	85
5	*p*-F-Ph	H	**8e**[b]	75
6	*p*-OMe-Ph	Me	**8f**[c]	68

[a] General conditions: reactions were performed on a 0.07 mmol scale in DMSO-d_6 using a reactant ratio of 1:1 for vinyl aziridine/DMAD. Each reaction was performed at room temperature for 12 h unless otherwise noted [b] 3 h, rt. [c] 45 °C, 12 h. [d] Isolated yields.

group of the aziridine was the ultimate key to this mode of reactivity. In its absence, the reaction did not proceed past conjugated azepine **7**.[16a]

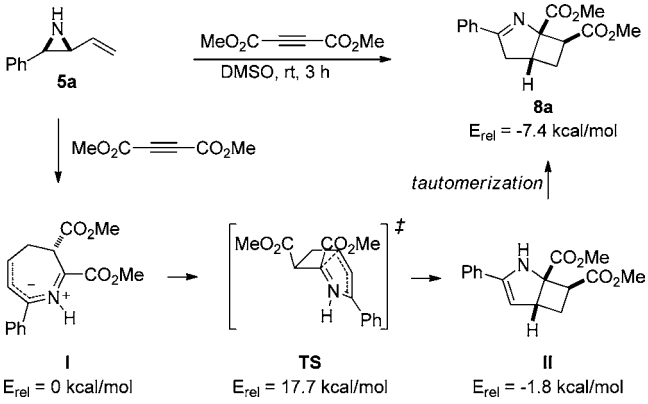
The initial step of the cascade sequence involves a nucleophilic attack of the vinyl aziridine onto the acetylene

(15) Once formed in the course of olefination, the monomeric aziridine aldehyde undergoes rapid redimerization.

(16) (a) Hassner, A.; D'Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett.* **1981**, *22*, 3691–3694. (b) Hassner, A.; Belinka, B. A., Jr.; Haber, M.; Munger, P. *Tetrahedron Lett.* **1981**, *22*, 1863–1866.

carbon. This step is followed by a Cope rearrangement into the azepine. Studies of the divinyl cyclopropane-to-cycloheptadiene rearrangement have shown that the reaction proceeds through an endo boat-like TS.[18] A similar endo boat TS likely generates the azepine. In our case, the conformational flexibility of the seven-membered ring is the factor that sets up subsequent ring contraction. Following deprotonation of the azepine at the benzylic position, a 6π-electron system is generated. The latter participates in a disrotatory electrocyclization[19] giving the aminocyclobutane containing the heterobicycle (Scheme 3).

Scheme 3. Proposed Mechanism for Aminocyclobutane Formation



We aimed to gather evidence for our proposed electrocyclization pathway using a combined computational and experimental approach. The rearrangement was found to take place in the absence of base, but methyl substitution at the benzylic position of the azepine precluded the bicycle formation. In addition, destabilization of the incipient benzylic anion through *p*-methoxy substitution on the arene retarded bicycle formation. The cascade process still proceeded in good yield but at a significantly decreased rate (Table 3, entry 6). Thus, elevated temperatures (45 °C) were required to force efficient conversion.

A zwitterionic intermediate (**I**) is the suspected species that undergoes electrocyclization. Gas-phase calculations performed at the B3LYP/6-31G(d,p) level of theory located a transition state for the electrocyclization proceeding from **I** to give **II** with a reasonable activation energy of 17.7 kcal/mol. Tautomerization from **II** yields the low-energy product **8a**. Interestingly, **8a** was found to be 7.4 kcal/mol lower in energy than its progenitor azepine. Thus, substitution of the aziridine ring with an aromatic group facilitates deprotonation at the benzylic position, generating an extended conjugated π-system capable of undergoing an electrocyclization to generate stereochemically complex bicyclic amines.

In summary, unprotected amino aldehydes allow easy, one-step access to a variety of N-unprotected vinyl aziridines, affording effective building blocks for the synthesis of heterobicycles through a cascade ring-opening/ring-contraction mechanism. The reactions are rooted in the readily available dimeric amino aldehydes which have been shown to participate in efficient olefinations even under highly basic conditions. Our results underscore the notion that interesting and useful nitrogen-mediated relay processes can arise when elements of strain are merged with the manifolds of enamine/iminium ion reactivity. Plans are on foot to explore a wider range of cascade processes triggered by unprotected vinyl aziridines.

Acknowledgment. We thank NSERC for financial support. We acknowledge Dr. T. Burrow for NMR analysis and Dr. A. Lough for X-ray structure analyses of compounds **5a** and **8a**.

Supporting Information Available: Experimental procedures, characterization, spectra, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Torres, E.; Gorrea, E.; Da Silva, E.; Nolis, P.; Branchadell, V.; Ortuño, R. M. *Org. Lett.* **2009**, *11*, 2301–2304. (b) Fernández, D.; Torres, E.; Avilés, F. X.; Ortuño, R. M.; Vendrell, J. *Bioorg. Med. Chem.* **2009**, *17*, 3824–3828.

(18) Özkan, Ï.; Zora, M. *J. Org. Chem.* **2003**, *68*, 9635–9642.

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