Propargyl Amines

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A Versatile Synthetic Platform Based on Strained Propargyl Amines**

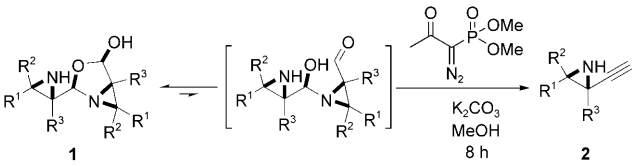
*Zhi He and Andrei K. Yudin**

Gabriel prepared ethylene imine in 1888.[1a] Despite the overall instability of this compound and other N–H aziridines, particularly under acidic conditions, their nitrogen center possesses some notable features. In 2006, we capitalized on the fact that aziridines are quite nucleophilic ($pK_{aH} = 8.0$) but do not easily form iminium ions when exposed to aldehydes. This allowed us to create a series of bench-stable unprotected amino aldehydes.[1] The present paper describes the development of a versatile platform for synthetic elaboration of strained propargyl amines. We show that unprotected amino aldehydes are one step away from unprotected N–H ethynylaziridines. Despite apparent simplicity and considerable synthetic potential of these molecules, they have eluded synthesis until now.[2]

Partial dissociation of aziridine aldehyde dimers previously enabled attack at the aldehyde carbon atom by soft nucleophiles such as organoindium reagents.[3] When subjected to the Corey–Fuchs procedure, the aziridine aldehyde dimer **1a** participated in the Wittig-type transformation, which afforded the corresponding dibromoolefin. However, the second step of this process, namely the *n*BuLi-promoted conversion of the dibromoolefin into the ethynyl end point, was plagued by rapid formation of intractable tars due to ring-opening. Fortunately, a one-step homologation with the Bestmann–Ohira reagent[4] in anhydrous methanol in the presence of K_2CO_3 did not trigger decomposition. The desired ethynylaziridine **2a** was furnished as a bench-stable solid in 95% yield. Several N–H ethynylaziridines having different substitution patterns were prepared using this method (Table 1). The reaction works well not only with alkyl-substituted aziridine aldehydes (**1g–h**), but also with electron-neutral (**1a**), electron-rich (**1b**), and electron-deficient (**1c**) aryl substrates. The thiophenyl-substituted aziridine aldehyde dimer (**1d**) also showed excellent reactivity. The hindered starting materials (**1e–f**) worked equally well in this process.

Interestingly, despite a possibility for decomposition through intermolecular attack of the nucleophilic aziridine nitrogen atom on the alkyne carbon atom (causing S_N2' scission), the unprotected N–H ethynylaziridines were found to be stable up to at least 100 °C. We were curious to examine the molecular structure[5] of these molecules as a way of probing their electronic properties. An X-ray structure of **2c**[12] confirms the presence of a stabilizing aziridine–alkyne interaction. The average length of the $C3_{(aziridine)}$–$C2_{(acetylene)}$ bond is 1.444 Å, which is significantly shorter than a typical $C(sp^3)$–C(sp) single bond (1.472 Å). Strained rings such as cyclopropanes, epoxides, and aziridines are known to partake in strong hyperconjugative interactions with sp^2- or sp-carbon-containing functional groups.[6] These interactions have been manifested not only in the ground-state stabilization, but also in lowering the activation barrier of chemical transformations.[7]

Table 1: N–H terminal ethynylaziridines from aziridine aldehyde dimers.[a]



1 2

Starting material	R^1	R^2	R^3	Product	Yield[b]
1a	Ph	H	H	**2a**	95%
1b	*p*-$MeOC_6H_4$	H	H	**2b**	70%
1c	*p*-FC_6H_4	H	H	**2c**	84%
1d		H	H	**2d**	76%
1e	Ph	Me	H	**2e**	74%
1f	H	H	Ph	**2f**	80%
1g		H	H	**2g**	90%
1h		H	H	**2h**	72%

[a] Reactions were carried out using 1.0 equiv of aziridine aldehyde dimer, 2.2 equiv of the Bestmann–Ohira reagent, and 4.0 equiv of K_2CO_3 in methanol at 25 °C. [b] Yield of isolated product.

Armed with an insight into the structural features of ethynylaziridines, we opted to exploit one-step transformations involving both amine and alkyne functional groups. First, we envisioned a possibility for direct preparation of unprotected α-amino allenes, versatile intermediates in aza-cycle synthesis,[8] by an S_N2' scission of N–H ethynylaziridines.[9] Of the hydride transfer reagents tested (DIBAL, 9-BBN, $[\{(Ph_3P)CuH\}_6]$, and $Cp_2Zr(H)Cl$),[10] 9-BBN showed optimal reactivity, giving the α-amino allene **3g** exclusively in high yield from the N–H ethynylaziridine **2g** (Table 2, entry 7) in just over one hour without any alkyne hydroboration by-products. We evaluated the generality of the reaction by treating ethynylaziridines with 9-BBN (Table 2).

To gain insight into the stereochemistry of this allene construction, the internal phenyl ethynylaziridine **4a** was first obtained from **2a** through a Sonogashira coupling with phenyl iodide (Scheme 1). The NH group did not interfere in this

[*] Z. He, Prof. Dr. A. K. Yudin
Davenport Research Laboratories, Department of Chemistry
University of Toronto
80 St. George St., Toronto, ON, M5S3H6 (Canada)
Fax: (+1) 416-946-7676
E-mail: ayudin@chem.utoronto.ca

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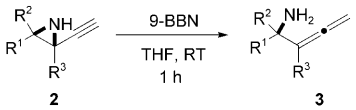
Table 2: Synthesis of α-amino allenes from N–H terminal ethynylaziridines.[a]

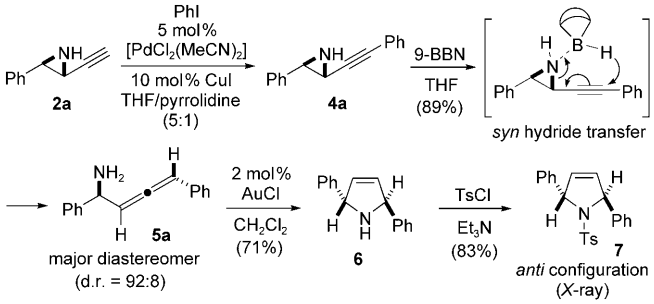


2 **3**

Entry	Ethynylaziridine	Allene	Yield[b]
1	**2a**	**3a**	84%
2	**2b**	**3b**	70%
3	**2c**	**3c**	76%
4	**2d**	**3d**	75%
5	**2e**	**3e**	88%
6	**2f**	**3f**	77%
7	**2g**	**3g**	77%
8	**2h** (98% ee)	**3h** (98% ee)	55%

[a] Reactions were carried out using 1.0 equiv of ethynylaziridine and 1.0 equiv of 9-BBN in THF at 25 °C. [b] Yield of isolated product. 9-BBN = 9-borabicyclo[3,3,l] nonane.

process. Treating phenyl ethynylaziridine **4a** under the hydride reduction conditions resulted in the corresponding internal α-amino allene **5a** (Scheme 1) as the predominant diastereomer (d.r. 92:8). It was subsequently converted into the dihydropyrrole **6** upon treatment with AuCl with complete transfer of chirality.[8c] The crystal structure of the tosylated derivative **7**,[12] revealing the *anti* configuration of the internal allene **5a**, indicates that the 9-BBN mediated allene formation is consistent with the *syn* hydride transfer from the boron to the distal alkyne carbon atom. It is likely

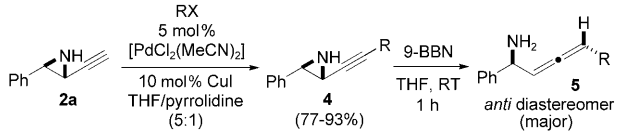


Scheme 1. Preparation of an internal α-amino allene for elucidation of the relative stereochemistry.

that significant pre-coordination of boron to the aziridine nitrogen atom contributes to the high diastereo- and regiocontrol of this allene synthesis.

A variety of substituted aryl ethynylaziridines, prepared by Sonogashira coupling, showed similar reactivity towards 9-BBN reduction, producing the corresponding *anti*-configured α-amino allenes with good to excellent diastereoselectivities (Table 3, entries 1–4). Notably, vinyl-substituted ethynylaziridines can also afford the corresponding *anti*-configured conjugated vinyl allenes with high yields and exclusive diastereoselectivities (Table 3, entries 5–7). Interestingly, the vinyl groups remained intact during the reduction.

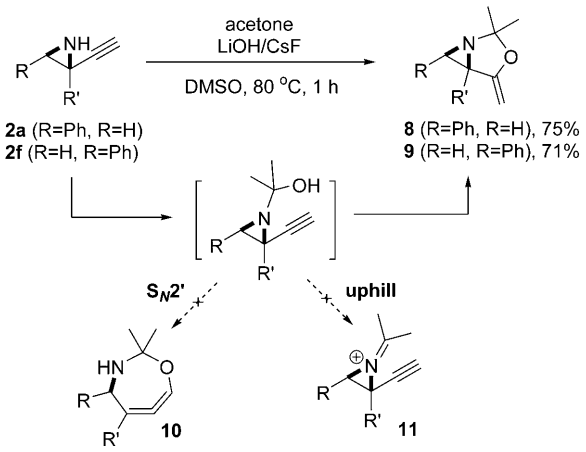
Table 3: Synthesis of internal α-amino allenes from N–H aryl or vinyl ethynylaziridines.[a]



Entry	Halide	Allene product	Yield[b]	d.r.[c]
1		**5b**	74%	>99:1
2		**5c**	81%	90:10
3		**5d**	75%	97:3
4		**5e**	84%	87:13
5		**5f**	83%	>99:1
6		**5g**	79%	>99:1
7		**5h**	82%	>99:1

[a] The allene preparation reactions were carried out using 1.0 equiv of ethynylaziridine and 1.0 equiv of 9-BBN in THF at 25 °C. [b] Yield of isolated **5**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. 9-BBN = 9-borabicyclo[3,3,l] nonane.

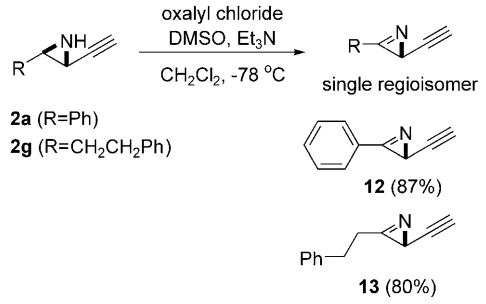
Encouraged by the above results, we have additionally investigated the extent of regiocontrol possible by way of nitrogen-mediated nucleophilic attack at the C–C triple bond. Interestingly, the ethynylaziridines **2a** and **2f** readily furnished fused bicycles **8** and **9**,[11] respectively, upon reaction with acetone in DMSO in the presence of a LiOH/CsF base combination (Scheme 2). In contrast to the boron reagents, no S_N2' attack forming cyclic allene species **10** was initiated in this case. The unique feature of aziridine nitrogen atom also



Scheme 2. Annulation of N–H ethynylaziridines with acetone.

prevents formation of the energetically uphill iminium ion **11**, enabling ring closure to afford the cyclic enol ether product.

The reactions considered thus far involved both aziridine and alkyne units. To our delight, we have also collected evidence for regio- and chemoselective oxidation of the aziridine moiety in N–H ethynylaziridine without touching the alkyne unit. Under the conditions normally prescribed for the Swern oxidation, compounds **2a** and **2g** afforded the corresponding bench-stable 2*H*-azirines **12** and **13**, respectively, with the C=N bond on the oposite side of the ring relative to the acetylene group (Scheme 3). Interestingly, in



Scheme 3. Chemoselective and regioselective azirine synthesis from N–H ethynylaziridines.

the presence of either aryl or alkyl groups, the regioselectivity remains high. This chemoselective transformation is intriguing, as is the stability of **12** and **13**. The structure of azirine alkyne **12** was confirmed by X-ray crystallographic analysis.[12]

In summary, N–H ethynylaziridines have been prepared from amphoteric aziridine aldehydes. Given recent interest in structural characterization of the unusual interactions involving unprotected amines and acetylenes,[13] molecules of this sort are noteworthy from the theoretical viewpoint. They also open up a plethora of synthetic opportunities. N–H terminal ethynylaziridines, together with their corresponding aryl- or vinyl-substituted internal analogues, can be directly converted into unprotected α-amino allenes by a highly diastereoselective *syn* hydride delivery. N–H ethynylaziridines are also distinguished by their chemo- and regioselective transformations into bicyclic aziridine/enol ethers and highly strained azirine alkynes. The ongoing renaissance in alkyne chemistry[14] should render these readily accessible chiral building blocks synthetically useful. On the basis of the dissected reactivity patterns, we anticipate that a myriad possibilities await these and related molecules.

Experimental Section

General procedure for the synthesis of α-amino allene **3** or **5**: N–H ethynylaziridine **2** or **4** (0.4 mmol) in 3 mL of anhydrous THF was added to a flame dried flask equipped with a magnetic stirring bar and a rubber septum. 0.5 M 9-BBN in THF solution (0.4 mmol) was then added at 0 °C. The reaction mixture was then warmed to room temperature and stirred under N_2 at room temperature for 1 h until the reaction was complete as indicated by TLC analysis. The reaction was cooled to 0 °C again, and then 0.6 mL of 10 % NaOH and 0.2 mL of 30 % H_2O_2 were added. The mixture was vigorously stirred for 2 h at room temperature. An additional 5 mL of 10 % NaOH solution was added to the reaction mixture, which was then extracted with diethyl ether (5 mL × 3). The combined ether layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified using flash column chromatography on silica gel, eluting with 2 %–5 % methanol (containing 2 M ammonia) in dichloromethane.

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