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Sugar-Derived Aziridines: Functionalization via Lithiation of the Aziridine Ring

Philippe Bisseret,*,† Claire Bouix-Peter, Olivier Jacques, Stéphanie Henriot, and Jacques Eustache*

Laboratoire de Synthèse Organique et de Chimie Microbienne - CNRS UPRESA 7015, Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse, 3, Rue Alfred Werner, F-68093 Mulhouse Cedex, France

j.eustache@univ-mulhouse.fr

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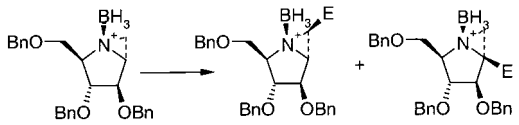
ABSTRACT



Stereoselective preparation of a new arabinose-derived aziridine and functionalization of the corresponding *N*-BH_3 complex are described. Regio- and stereoselective aspects are discussed.

In the course of a project aimed at identifying inhibitors of mycobacterial arabinosyltransferases, we needed to prepare a series of bicyclic sugar-derived aziridines (**1**; Figure 1).

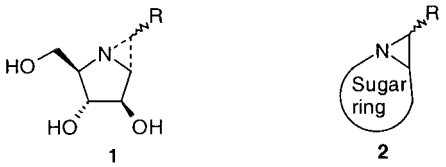


Figure 1. Sugar-derived bicyclic aziridines.

Although simple 1-azabicyclo[3.1.0] octanes are known,[3a] few nonsubstituted sugar-derived aziridines (**2**, R = H) have been found[1] and, to the best of our knowledge, only two examples of substituted analogues (**2**, R ≠ H) have been reported.[2] The key step in the synthesis of the latter compounds was an intramolecular 1,3-dipolar cycloaddition of *δ*-azidoalkenes. This reaction, however, is not general[3] and may lead to imines or diazo compounds besides (or instead of) the desired aziridines. In addition, the use of 1,3-dipolar cycloadditions for the preparation of *each* member of a series of functionalized aziridines, as required in a medicinal chemistry program, would obviously be cumbersome.

Vedejs and Kendall's recent report on the functionalization of simple aziridine−BH_3 complexes by sequential deproto-

† E-mail: p.bisseret@univ-mulhouse.fr.

(1) (a) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett.* **1995**, *36*, 4027−4030. (b) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett.* **1995**, *36*, 799−802. (c) Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.* **1990**, 953−963. (d) Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1988**, *110*, 312−313.

(2) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683−4687.

(3) The thermal decomposition of olefinic azides is still not well understood and may yield mixtures of products; see for instance: (a) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749−753. (b) Bernet, B.; Bulusu Murty, A. R. C.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 940−958. (c) Krülle, T. M.; dela Fuente, C.; Pickering, L.; Aplin, R. T.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. K.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3807−3820.

(4) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941−6942.

(5) Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **1998**, *39*, 825−828.

(6) (a) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chem. Acta* **1991**, *74*, 2073−2077. (b) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *34*, 6029−6032. The thermal lability of azide **4** (previously prepared once by another route) has been noted: Pearson, W. H.; Hines, V. A. *Tetrahedron Lett.* **1991**, *32*, 5513−5516.

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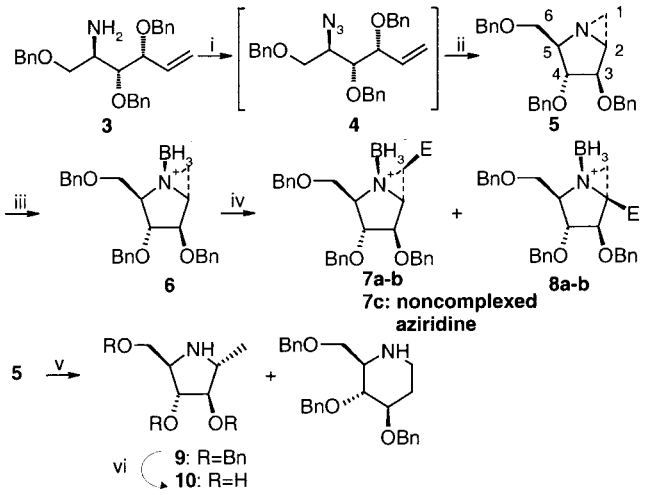
nation and quenching with electrophiles[4] suggested an alternative strategy (Scheme 1). In this approach, a common

Scheme 1[a]



[a] Legend: (i) TfN_3, DMAP, CH_3CN, 20 °C, 30 min; (ii) 3 h, 40 °C; (iii) BH_3-THF, 0 °C, 30 min; (iv), sBuLi (4 equiv), (−)-sparteine (4 equiv), cumene, −78 °C, 4 h, then electrophile, 30 min, −78 to 20 °C (electrophile: (a) D_2O, E = D; (b) Bu_3SnCl, E = $SnBu_3$; (c) $P(O)(OEt)_2Cl$ or $P(OEt)_2Cl$, E = $P(O)(OEt)_2$); (v) H_2 (P = 5 bar), $Pd(OH)_2$/C 10%, AcOEt; (vi) H_2 (P = 50 bar), Pd $(OH)_2$/C 10%, iPrOH.

nonsubstituted aziridine is converted to the desired analogues in one step. We report here the facile preparation of the new aziridine **5** and its functionalization via the corresponding borane complex.

Thus, the known primary amine **3**[5] was treated with freshly prepared triflic azide in the presence of DMAP, to afford the unstable azide **4**,[6] which was directly converted to a single bicyclic aziridine (**5)** in 55% yield (two steps) upon warming to 40 °C. The 2*R* configuration in **5** was established by nOe measurements and by chemical correlation: hydrogenolysis of the aziridine ring in **5** and removal of the benzyl groups afforded pyrrolidine **10**, whose NMR data were identical with those previously described.[7] Treatment of **5** with borane in THF gave complex **6** in 90% yield.

(7) Wang, Y.-F.; Dumas, D. P.; Wong, C.-H. *Tetrahedron Lett.* **1993**, *34*, 403−406.

(8) Whereas **7a**,**b** were isolated as aziridine−BH_3 complexes, **7c** was directly obtained as a free, noncomplexed aziridine. We attribute the difference between the stability of complexes **7a**,**b** and that of **7c** to reduced electron density on the nitrogen atom in the latter case.

Table 1. Functionalization of Aziridine−BH_3 Complex **6**

solvent	electrophile	**7**:**8**	yield (%)
THF	D_2O	1:0	10
cumene	D_2O	1:1	80
cumene	Bu_3SnCl	5:1	50
cumene	$P(O)(OEt)_2Cl$	1:0	15
cumene	$P(OEt)_2Cl$	1:0	20

Functionalization of **6** was then examined (see Table 1). Whereas deprotonation/quenching with D_2O was sluggish in THF, switching to cumene and using (−)-sparteine as a lithium chelating agent afforded a high yield of deuterated aziridine−BH_3 complexes **7a** and **8a** in a 1:1 ratio. The poor regioselectivity was surprising in light of earlier results[4] but was expected to improve for bulkier electrophiles. Accordingly, trapping of lithiated **6** with Bu_3SnCl gave a 50% yield of the 1*S* and 2*R* stannylated aziridine−BH_3 complexes **7b** and **8b** in a 5:1 ratio. This expected stereoselectivity is the result of a lithiation step *syn* to the N−B bond followed by electrophilic attack with retention of configuration, in line with Vedejs's results.

Phosphorylation was examined next: using $P(O)(OEt)_2Cl$ or $P(OEt)_2Cl$, the same *noncomplexed* 1*S* phosphonate **7c** was obtained in modest yield.[8] In the experiment using $P(OEt)_2Cl$, a spontaneous oxidation obviously takes place during the workup and/or purification steps.

Thus, the above studies show that functionalization of sugar-derived aziridine−borane complexes can be effected by deprotonation followed by quenching with electrophiles. The reaction appears to be both regio- and stereoselective, and although the (nonoptimized) yields are modest in some cases, the approach is competitive in terms of versatility and should allow a ready access to various classes of substituted sugar-derived aziridines.

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Supporting Information Available: Experimental procedures for compounds **4**−**7** and **9**−**10** and corresponding ^1H NMR spectra and HRMS data for **7b** and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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