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Reductive Alkylation of β-Alkoxy Aziridines: New Route to Substituted Allylic Amines

Clare M. Rosser,[†] Susannah C. Coote,[†] Jonathan P. Kirby,[†] Peter O'Brien,*[,†] and Darren Caine[‡]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and GlaxoSmithKline Pharmaceuticals, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, U.K.

paob1@york.ac.uk

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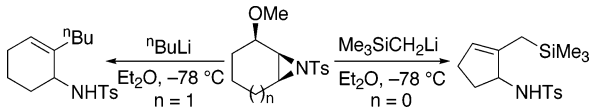
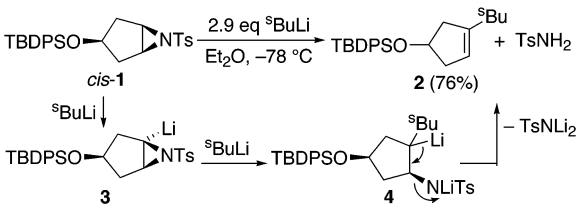
ABSTRACT



A new route to substituted cyclic allylic amines via the reductive alkylation of β-alkoxy aziridines using excess alkyllithium reagents is described.

Lithiated epoxides (oxiranyl anions) are now firmly established as useful synthetic intermediates.[1,2] In contrast, harnessing the synthetic utility of the corresponding lithiated aziridines has proved somewhat more problematic,[1a,d] and this is particularly true for lithiated aziridines generated by α-lithiation/deprotonation of aziridines that lack an anion-stabilizing group.[3] As part of our ongoing studies into reactions of lithiated aziridines,[4] we recently reported the *sec*-butyllithium-mediated reductive alkylation of *N*-tosyl aziridine *cis*-**1** to give cyclopentene **2** in 76% yield (together with *p*-toluenesulfonamide, $TsNH_2$) (Scheme 1).[5]

Scheme 1. Reductive Alkylation of an Aziridine



The formation of cyclopentene **2** presumably proceeds via lithiated aziridine **3** and subsequent elimination of $TsNLi_2$ from **4**, itself generated from carbenoid insertion into the C−Li bond of *sec*-butyllithium. Although well-known for epoxides,[6,7] we were surprised to find that this was the first report of reductive alkylation of aziridines. To extend the synthetic potential of lithiated aziridines and to further exploit the reductive alkylation of aziridines, we now report the conversion of β-methoxy aziridines **5** to substituted allylic amines **7** (via **6**) (Scheme 2). On the basis of the precedent with epoxides,[8,9] we incorporated a β-alkoxy group into the aziridine **5** so that it could undergo alkoxide elimination from **6** and not elimination of $TsNLi_2$ as in **4** (Scheme 1). In this

[†] University of York.
[‡] GlaxoSmithKline.

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(2) For recent examples, see: (a) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330. (b) Hodgson, D. M.; Paruch, E. *Tetrahedron* **2004**, *60*, 5185.

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(6) (a) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526. (b) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527.

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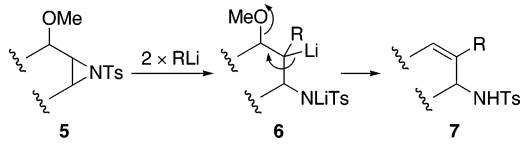
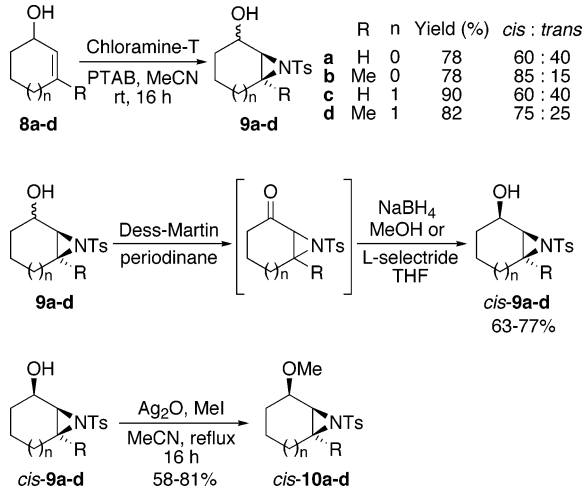
Scheme 2. Reductive Alkylation of β-Alkoxy Aziridines



way, the sulfonamide group is retained in the product **7**.[10] Herein, we report the stereoselective synthesis of cyclic β-methoxy aziridines *cis*-**5** and their reductive alkylation to substituted allylic amines **7**.

Our route to cyclopentene and cyclohexene β-methoxy aziridines *cis*-**10a**−**d** started with allylic alcohols **8a**−**d**, prepared by Luche reduction of the enones. Aziridination of **8a**−**d** using phenyltrimethylammonium tribromide (PTAB) and Chloramine-T[11] gave hydroxy aziridines **9a**−**d** in high yields (78−90%) and with a satisfactory degree of *cis* selectivity (Scheme 3).

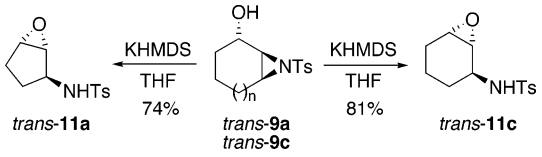
Scheme 3. Synthesis of β-Methoxy Aziridines *cis*-**10a**−**d**



The *cis*-selectivity of the aziridination presumably arises from preferential bromination on the less hindered face of the alkene (opposite to the hydroxyl group); similar stereoselectivity has been noted in an expanding number of related examples.[11,12] Aziridines *cis*- and *trans*-**9a**−**d** can be separated by chromatography to give 44−68% isolated yields of *cis*-**9a**−**d**. Alternatively, an oxidation−reduction sequence (via the keto aziridines[13]) can be utilized to produce single diastereomers of *cis*-hydroxy aziridines **9a**−**d**. For reduction of the keto aziridines, $NaBH_4$ in MeOH gave complete stereocontrol with the cyclopentenes, but high stereoselectivity with the cyclohexenes necessitated the use of L-selectride in THF at −78 °C. The high *cis*-selectivity of these reductions is mirrored in nucleophilic additions to the corresponding keto-epoxides[8,14] and results from attack on the least hindered C═O face *and* anti to the adjacent C−O bond. Finally, methylation using Ag_2O and MeI gave the required β-methoxy aziridines *cis*-**10a**−**d** (typical NaH/MeI conditions were much less successful).

The relative stereochemistry of hydroxy aziridines **9a** and **9c** was established unequivocally using an aza-Payne rearrangement.[15] Only the *trans*-hydroxy aziridines will undergo a base-mediated conversion into an amino epoxide. Thus, upon reaction with KHMDS, *trans*-**9a** ($n = 0$) gave epoxide *trans*-**11a** and *trans*-**9c** ($n = 1$) gave known[16] epoxide *trans*-**11c** (Scheme 4). The relative stereochemistry of hydroxy aziridines **9b** and **9d** was assigned by analogy.

Scheme 4. Aza-Payne Rearrangement of *trans*-**9a** and **-9c**



With β-methoxy aziridines *cis*-**10a**−**d** in hand, we were now ready to study their reductive alkylation using excess alkyllithiums. Our typical protocol involved reaction of the β-methoxy aziridine with 2.5 equiv of alkyllithium in Et_2O at −78 °C for 5 min followed by warming to room temperature over 1 h. In this way, β-methoxy aziridines *cis*-**10a**−**d** were converted into substituted allylic amines **12**−**15** in 6−67% yield (Scheme 5).

Two general conclusions can be made on the basis of these preliminary results. First of all, cyclopentene aziridines appear to be more susceptible to reductive alkylation and thus they generally give higher yields of allylic amines (e.g., **12a,b** and **13a**−**c**, 53−67% yield). This is consistent with our previous findings on the rearrangement of aziridines to allylic amines using *sec*-butyllithium and (−)-sparteine.[4,5]

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(10) A similar strategy using dihydrofuran aziridine and aziridines of acyclic allylic ethers has recently been disclosed: Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234.

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(13) Related *N*-alkyl and *N*-CO_2Et keto aziridines have been prepared using other routes. See: (a) Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P. A. *Tetrahedron* **2003**, *54*, 14105. (b) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron Lett.* **2002**, *43*, 4329.

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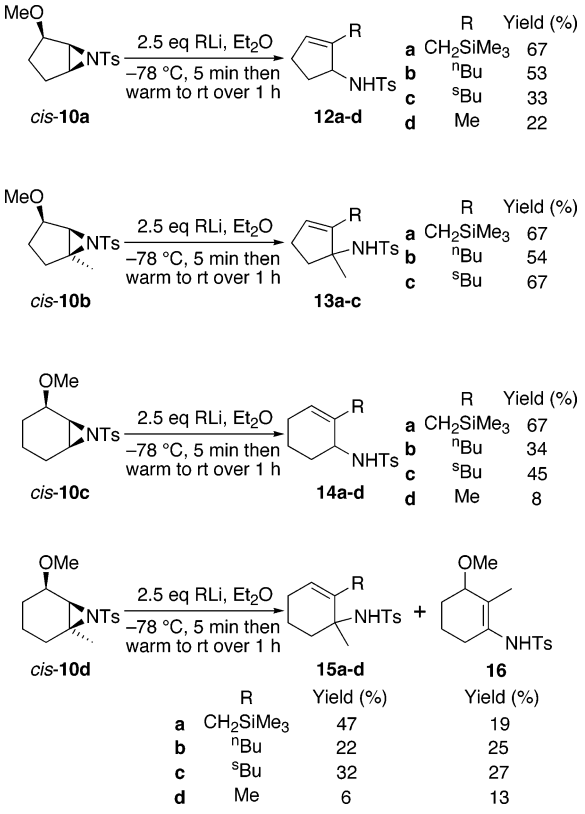
(15) (a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044. (b) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726.

(16) (a) O'Brien, P.; Childs, A. C.; Ensor, G.; Hill, C. L. Kirby, J. P.; Dearden, M. J.; Oxenford, S.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955. (b) Bäckvall, J.-E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953.

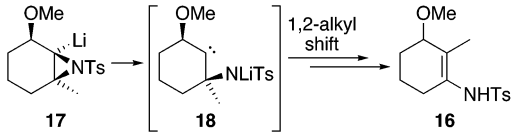
Scheme 5. Reductive Alkylation of β-Methoxy Aziridines



Second, the best alkyllithium reagent for reductive alkylation is trimethylsilylmethyllithium (e.g., **12a**, 67%; **13a**, 67%; **14a**, 67%; **15a**, 47%), and the worst is methyllithium. Unfortunately, we have been unable to prepare methoxy aziridines *trans*-**10a**−**d** by methylation (under a range of conditions), and this has so far precluded a study of their reductive alkylation.

On careful inspection of the product mixtures generated from β-methoxy aziridine *cis*-**10d**, we noticed the formation of the same byproduct, enamide **16** (13−27% yield). The regiochemistry of enamide **16** was confirmed by NOESY experiments, and it must be formed by a skeletal rearrangement process. Our suggested mechanism for the formation of **16**[17] is outlined in Scheme 6. Thus, initial lithiation occurs to give **17**, but reductive alkylation of **17** by the second alkyllithium (to give **6**, see Scheme 2) is competitive with α-elimination (to give carbene **18**) and subsequent 1,2-methyl

Scheme 6. Suggested Mechanism for Formation of **16**



shift (to give **16**). Such a 1,2-alkyl shift is well-established for alkoxy epoxides[18] and, in Et_2O, may have a more concerted mechanism, i.e., from **17** → **16**, without the intermediacy of the carbene **18**.[18a] However, the 1,2-alkyl shift was not observed with *cis*-β-methoxy epoxides,[8] analogous to the aziridines studied here. In addition, we did not isolate any enamides from aziridines *cis*-**10a**−**c**.

In summary, a new route to cyclic substituted allylic amines **12**−**15** via the reductive alkylation of β-methoxy aziridines has been established. Furthermore, as shown by the reactions of aziridine *cis*-**10d** and in contrast to the corresponding β-methoxy epoxides, two different reaction manifolds occur. Future work will focus on optimizing reaction conditions so that products of type **15** (reductive alkylation) and **16** (1,2-alkyl shift) can each be obtained in high yields.

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Supporting Information Available: Representative experimental procedures for the preparation of *cis*-**10d** and **12a**−**d**, **13a**−**c**, **14a**−**d**, and **15a**−**d**/**16** and full characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra of *cis*-**9d**, *cis*-**10d**, **12a**−**d**, **13a**−**c**, **14a**−**d**, **15a**−**d**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The isolation of an ene-sulfonamide from the reaction of *N*-tosyl cyclohexeneaziridine with *sec*-butyllithium and (−)-sparteine has been described previously. See: Müller, P.; Nury, P. *Helv. Chim. Acta* **2001**, *84*, 662. However, isolation of the ene-sulfonamide could not be reproduced by the same group; see ref 3d.

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