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Substituted Aziridines by Lithiation–Electrophile Trapping of Terminal Aziridines

David M. Hodgson,* Philip G. Humphreys, and John G. Ward†

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

david.hodgson@chem.ox.ac.uk

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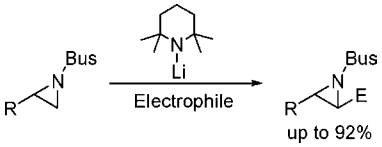
ABSTRACT



Regio- and stereoselective deprotonation of *N*-Bus (Bus = *tert*-butylsulfonyl)-protected terminal aziridines with lithium 2,2,6,6-tetramethylpiperidide generates a nonstabilized (H-substituted) aziridinyl anion that undergoes in situ or external electrophile trapping under experimentally straightforward conditions to give *trans*-disubstituted aziridines in good to excellent yields.

Aziridine chemistry, although lagging somewhat in its development compared to analogous studies with epoxides, is seeing increasing research interest.[1] The ready availability of terminal aziridines (typically accessed from terminal alkenes[2] or imines[3]), together with recent disclosures on the preparation of enantiomerically pure terminal aziridines from epoxides,[4] suggests that straightforward methods to elaborate such aziridines (while retaining the aziridine ring) would be of considerable value.[5] We recently reported the synthesis of *trans*-disubstituted epoxides by organolithium-induced deprotonation and subsequent electrophile trapping of terminal epoxides at −90 °C,[6] as well as the lithium 2,2,6,6-tetramethylpiperidide (LTMP)-induced in situ silylation of terminal epoxides at 0 °C.[7] In the present communication we report the adaptation and advancement of this methodology for the direct synthesis of substituted aziridines from terminal aziridines.

Aggarwal and co-workers have recently highlighted the synthetic potential of α,β-aziridinylsilanes,[8] and we initially sought to access them by applying our aforementioned in situ silylation methodology. Although Quast and Vélez reported the lithiation−silylation of a methyleneaziridine,[9] to the best of our knowledge there is only one isolated report concerning the silylation of a simple terminal aziridine.[10] In this latter work, the *N*-Boc aziridine of propene together with TMEDA and an excess of Me_3SiCl in ether at −78 °C were treated with a precooled solution of *s*-BuLi to give a *trans*/*cis* mixture of α,β-aziridinylsilanes.[11] Preliminary evaluation of our LTMP-mediated in situ silylation protocol with

† GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, U.K.

(1) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258.
(2) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845.
(3) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587−1589.
(4) (a) Kim, S. K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952−3954. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973−3975. Also, for reviews on enantioselective aziridination, see: (c) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 607−618. (d) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919.
(5) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) McCoull, W. M.; Davis, F. A. *Synthesis* **2000**, 1347−1365.
(6) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Org. Lett.* **2004**, *6*, 4187−4189.
(7) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Tetrahedron Lett.* **2002**, *43*, 7895−7897.
(8) (a) Aggarwal, V. K.; Ferrara, M. *Org. Lett.* **2000**, *2*, 4107−4110. (b) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335−2344.
(9) (a) Quast, H.; Vélez, C. A. W. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 342−343. For a recent example, see: (b) Hayes, J. F.; Prévost, N.; Proke×f0, I.; Shipman, M.; Slawin, A. M. Z.; Twin, H. *Chem. Commun.* **2003**, 1344−1345.
(10) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276−277.

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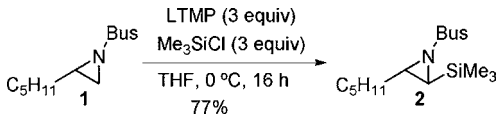
terminal aziridines bearing *N*-tosyl protection gave none of the corresponding α,*β*-aziridinylsilanes.[12] Our attention therefore turned to the use of the *tert*-butylsulfonyl (Bus) group[13] for aziridine protection, as we have recently found the latter useful in other lithiated aziridine chemistry.[14] Pleasingly, terminal aziridine **1** (prepared by the method of Sharpless and co-workers[15] from 1-heptene and BusNClNa with catalytic $PhMe_3NBr_3$ in 89% yield) underwent successful silylation using our earlier conditions[7] to give the desired α,*β*-aziridinylsilane **2** as a single isomer in 77% yield (Scheme 1).

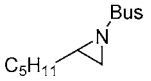
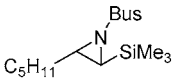
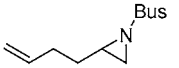
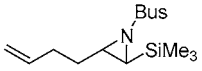
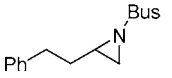
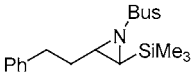
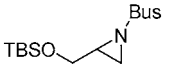
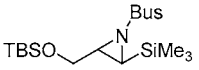
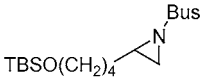
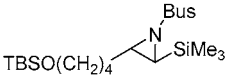
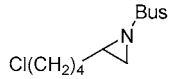
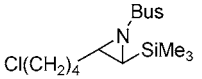
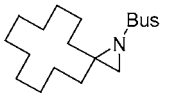
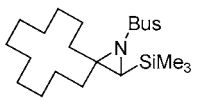
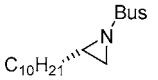
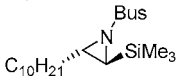
Scheme 1. Deprotonation−in Situ Silylation of Aziridine **1**



The *trans* stereochemistry was supported by comparison of aziridinyl $^3J_{HH}$ values with related literature compounds,[16] a crystal structure of a *trans*-α,*β*-aziridinyl sulfone synthesized by a similar route (vide infra) and by analogy with the *trans*-selective lithiation[17] and silylation of terminal epoxides when using LTMP.[7]

The yield of α,*β*-aziridinylsilane **2** could be improved to 86% by carrying out the reaction at −78 °C for 1 h (conditions otherwise as Scheme 1). These latter conditions were then applied to a variety of other terminal aziridines to assess the scope of the method (Table 1).

Table 1. α,*β*-Aziridinylsilanes from Terminal Aziridines[21]

entry	aziridine **3**	α,β-aziridinylsilane **4**	yield (%)
1			86
2			80
3			79
4			52
5			83
6			79
7			63[a]
8			81

[a] Reaction carried out at 0 °C for 16 h.

Complications arising from potentially competing allylic deprotonation[18] (and/or intramolecular cyclopropanation[19]) or benzylic deprotonation were not observed (entries 2 and 3). Proximal and distal silyl ether functionality were also tolerated (entries 4 and 5), as was a potentially eliminable (and/or displaceable) primary chloride substituent (entry 6). In contrast with the analogous epoxide, a 2,2-disubstituted aziridine underwent successful silyation at 0 °C (entry 7);[20] however, the reaction was clearly more sluggish than with monosubstituted aziridines, since the starting aziridine was recovered (91%) following attempted reaction at −78 °C.

Importantly for asymmetric synthesis, no significant degradation of ee was observed during the deprotonation-in situ silylation of an enantioenriched terminal aziridine (entry 8).[22] Attempts to deprotonate-silylate cyclic or acyclic *cis*-2,3-disubstituted aziridines were unsuccessful at both 0 °C and −78 °C, presumably due to reduced acidity and/or unfavorable interactions between the sterically demanding LTMP and the substituted aziridine.[23]

The deprotonation−in situ silylation of terminal epoxides and aziridines is possible as a result of compatibility between LTMP and Me_3SiCl under the reaction conditions. In other studies, LTMP has also been shown to coexist with electrophiles other than Me_3SiCl at −78 °C,[24] so we considered whether in situ aziridinyl anion generation-trapping would

(11) We obtained 52% (lit.[10] 80%) of a 1.7:1 *trans*/*cis* mixture of α,*β*-aziridinylsilanes.

(12) Using LTMP (3 equiv) and Me_3SiCl (3 equiv) in THF, the *N*-Boc aziridine of 1-hexene could be successfully silylated at −78 °C (silylation was unsuccessful at 0 °C) in 1 h (69%, >99% *trans*:*cis*), but this could not be usefully extended to other electrophiles.

(13) Sun, P.; Weinreb, S. M.; Shang, M. J. *J. Org. Chem.* **1997**, *62*, 8604−8608.

(14) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234−2235.

(15) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783−786.

(16) $^3J_{HH}$ = 6 Hz for α,*β*-aziridinylsilane **2** and those listed in Table 1. Reference 8a reports *trans* $^3J_{HH}$ = 6 Hz and *cis* $^3J_{HH}$ = 8 Hz for related *N*-Ts α,*β*-aziridinylsilanes.

(17) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2103−2104.

(18) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1691−1697.

(19) Hodgson, D. M.; Chung, Y. K.; Paris, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 8664−8665.

(20) All other reactions shown in Table 1 also proceeded to completion at 0 °C within 16 h; however, all of the yields were lower and ^{1}H NMR analysis of the crude reaction mixtures showed substantial byproduct formation.

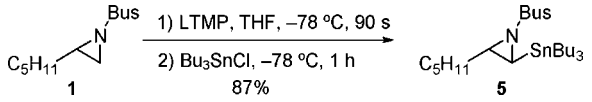
(21) **General Procedure.** *n*-BuLi (1.6 M in hexanes, 0.94 mL, 1.5 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (3.8 mL) at −78 °C under argon. The mixture was warmed to room temperature over 30 min and then cooled to −78 °C. To this solution was added Me_3SiCl (0.19 mL, 1.5 mmol), followed rapidly by a solution of aziridine (0.5 mmol) in THF (1.5 mL). Following 1 h of stirring at −78 °C, saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether/Et_2O or EtOAc) gave the α,*β*-aziridinylsilane.

(22) Determined by specific rotation comparison of the starting enantioenriched (*S*)-1-(*tert*-butylsulfonyl)-2-decylaziridine and a sample prepared by TBAF-mediated desilylation of the enantioenriched α,*β*-aziridinylsilane (see Supporting Information).

(23) For examples of related observations between LTMP and 2,3-disubstitued epoxides, see: (a) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513−6514. (b) Reference 7.

be limited to Me_3SiCl. Following the optimized procedure for in situ silylation,[7] a range of other electrophiles were screened.[25] Unfortunately, all but one of the electrophiles screened with aziridine **1** were unsuccessful. Bu_3SnCl (3 equiv) was the only successful electrophile, giving 69% of the desired α,β-aziridinylstannane **5** (after chromatography using Florisil),[26] along with 10% of recovered **1** (Scheme 2). This suggested at least partial compatibility between

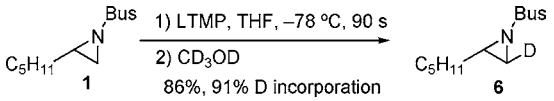
Scheme 2. Synthesis of α,β-Aziridinylstannane **5**



LTMP and Bu_3SnCl at −78 °C. In an attempt to increase the yield, the order of reagent addition was altered so that there was a 90 s pause after mixing the aziridine and LTMP (3 equiv) prior to addition of Bu_3SnCl (3 equiv). This resulted in complete consumption of aziridine **1** and an improved yield (87%) of the desired stannane **5** as a single diastereomer, tentatively assigned *trans* stereochemistry by analogy with the above silylation studies.

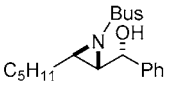
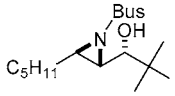
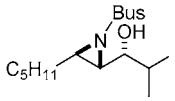
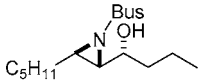
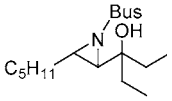
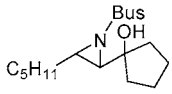
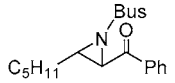
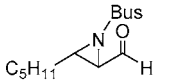
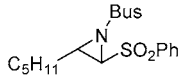
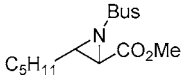
To establish whether the reaction shown in Scheme 2 was a true external electrophile trapping reaction, deuteration studies were undertaken using aziridine **1** as the model substrate (Scheme 3).

Scheme 3. Deuteration of Aziridine **1**



Quenching the putative aziridinyl anion after 90 s with CD_3OD resulted in an 86% yield with 91% D incorporation (by ^1H NMR) of the desired *trans*-deuterated aziridine **6**.[27] It is significant that LTMP was capable of generating a nonstabilized (H-substituted) aziridinyl anion at −78 °C within 90 s and that this anion was then able to undergo subsequent external electrophile trapping at −78 °C.[28] As no compatibility between the electrophile and LTMP would be required for an external electrophile trap, we anticipated that a wide range of electrophiles could be trapped by a nonstabilized aziridinyl anion. To examine the scope of this external electrophile trapping process, a range of LTMP-incompatible electrophiles were subsequently investigated (Table 2).

Table 2. Substituted Aziridines from Terminal Aziridine **1**[35]

entry	electrophile	product **7**		yield (%)
1	PhCHO		**7a**	38[a]
2	*t*-BuCHO		**7b**	54[a]
3	*i*-PrCHO		**7c**	43[a]
4	*n*-PrCHO		**7d**	54[a]
5	Et_2CO		**7e**	76[b]
6	Cyclopentanone		**7f**	59[b]
7	$PhCONMe_2$		**7g**	57[b]
8	DMF		**7h**	63
9	$PhSO_2F$		**7i**	92[c]
10	CO_2		**7j**	63[d]

[a] Reaction quenched after 90 s. [b] Using 3 equiv of LTMP and 6 equiv of electrophile. [c] Using 6 equiv of LTMP and 4 equiv of electrophile. [d] After CO_2 trapping, the crude reaction mixture was treated with CH_2N_2 to give the ester shown. Yield is the final isolated yield over two steps.

Pleasingly, both enolizable and nonenolizable aldehydes could be trapped remarkably quickly (no starting material was observed 90 s after electrophile addition at −78 °C), albeit in modest yields (Table 2, entries 1−4). In these cases single diastereomers of the aziridinyl alcohols **7a**−**d** were isolated,[29] which were tentatively assigned *anti* stereochemistry on the basis of the diastereoselectivity (dr 98:2) observed by Aggarwal and co-workers in a desilylation electrophile trapping reaction between a *trans*-α,β-aziridinylsilane and benzaldehyde.[8b] Potentially enolizable ketones (3-pentanone and cyclopentanone) reacted well as electrophiles, giving the desired tertiary alcohols **7e,f** in moderate to good yields (76% and 59%, respectively, entries 5 and 6). Electrophile trappings using comparatively unreactive amides (*N*,*N*-dimethylbenzamide and *N*,*N*,-dimethylformamide) were successful (57% and 63%, respectively, entries 7 and 8). Benzenesulfonyl fluoride[30] was trapped in excellent yield (92%, entry 9),

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(25) Electrophiles investigated were PhCHO, Ph_2CO, *t*-BuCOCl, $ClCO_2Et$, MeI, cyclohexyloxirane, and Bu_3SnCl.

(26) Using SiO_2 resulted in contamination with undesired tin byproducts.

(27) Quenching with CD_3OD after 5 min gave a lower yield of aziridine **6**.

(28) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325.

(29) We suspect that the modest yields in these cases are due to the other diastereomer being formed competitively, but undergoing degradation via *N*- to *O*- Bus migration.

and X-ray crystallographic analysis of the product supported the assigned *trans* stereochemistry.[31] Aziridinyl sulfones are potentially useful synthetic intermediates, as suggested by the chemistry of the analogous epoxysulfones.[32] Trapping with CO_2 was successful, although attempts to directly isolate the acid were unsuccessful, whereas subsequent esterification with diazomethane led to an ester that could be isolated in good yield (63% over 2 steps, entry 10).[33] α,*β*-Aziridinyl-esters are useful synthetic intermediates for the synthesis of both α- and *β*-amino acids.[34]

In conclusion, we have shown a new, experimentally straightforward method for the stereocontrolled formation of α,*β*-aziridinylsilanes by aziridine lithiation−in situ silylation. Also, we have demonstrated that *N*-Bus-protected terminal aziridines can be deprotonated with a hindered lithium amide and subsequently trapped with a variety of electrophiles. While there are other indirect methods for aziridinyl anion generation and electrophile trapping[28] (for example, from aziridinyl stannanes,[36] sulfoxides,[37] or aziridine borane complexes[38]), the present procedure is attractive because it proceeds directly from simple terminal aziridines to give *trans*-disubstituted aziridines. The latter retain a useful nitrogen protecting group[13] to enable further synthetic transformations. Additional studies in the area of aziridine functionalization and synthetic utility of the substituted aziridine products are currently underway.

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Supporting Information Available: Characterization data for aziridines **3**, α,*β*-aziridinylsilanes **4**, and substituted aziridines **7**, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) (a) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897−908. (b) Jackson, R. F. W.; Dunn, S. F. C. McCamley, A.; Clegg, W. *Org. Biomol. Chem.* **2003**, *1*, 2527−2530.

(33) Attempted trapping with other electrophiles, such as allyl bromide, BnBr, BuOTf, and MeI, has so far been unsuccessful.

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(35) **General Procedure.** *n*-BuLi (1.6 M in hexanes, 0.47 mL, 0.75 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.13 mL, 0.75 mmol) in THF (1.9 mL) at −78 °C. Following warming to room temperature over 20 min, the reaction was cooled to −78 °C and a solution of aziridine (0.25 mmol) in THF (0.75 mL) added, followed after 90 s by the electrophile (0.75 mmol). Following 30 min of stirring at −78 °C (90 s for entries 1−4), saturated aqueous NH_4Cl (5 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, or Florisil for the aziridinyl aldehyde in entry 8) gave the substituted aziridine.

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