Organolithium-mediated conversion of β-functionalised aziridines into alkynyl amino alcohols and diamines

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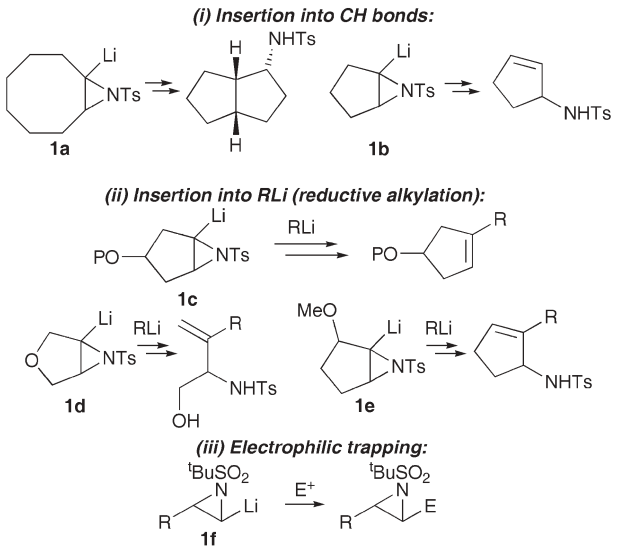
The direct conversion of dihydrofuran and dihydropyrrole *N*-triisopropylbenzenesulfonyl aziridines into alkynyl amino alcohols and diamines respectively can be achieved using 3 equiv. *sec*-butyllithium–PMDETA in THF; use of *n*-butyllithium and (−)-sparteine in Et_2O gave an alkynyl amino alcohol in 60% ee.

Following the ample precedent with epoxides,[1] there is much current interest in the development of novel transformations of lithiated *N*-sulfonyl aziridines **1**. To date, for lithiated aziridines **1** generated by aziridine deprotonation using strong bases, three different reaction modes are known (Scheme 1): (i) insertion into CH bonds—transannular CH insertions of **1a** generate polycyclic amines[2–5] whereas insertion of **1b** into adjacent β-CH bonds gives allylic amines;[3–5] (ii) insertion into organolithium reagents (also referred to as reductive alkylation)—insertions of **1c** can occur with loss of the amino group to give substituted alkenes as we have described[5] but the amino group can be retained to generate substituted allylic amines if there is a β-alkoxy group present, first demonstrated by Hodgson *et al.* with **1d**[6] and then by ourselves with **1e**;[7] and (iii) electrophilic trapping of lithiated terminal aziridines **1f**.[8] In this paper, we disclose a new organolithium-mediated transformation of aziridines, namely the conversion of dihydrofuran and dihydropyrrole aziridines into alkynyl amino alcohols and diamines respectively. Such a reaction has not been reported before for epoxides or aziridines and it could find preparative utility (*vide infra*).

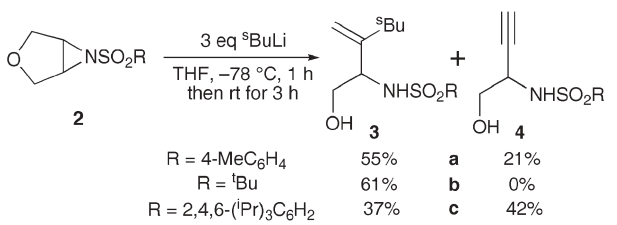


Scheme 1

As part of our ongoing studies into the chemistry of lithiated aziridines,[4,5,7] we investigated the effect of different *N*-sulfonyl groups on the conversion of dihydrofuran aziridines **2** into amino alcohols **3**. To our surprise, treatment of aziridines **2a–c** (readily prepared using our two-step procedure[9]) with 3 equiv. *sec*-butyllithium (using a procedure similar to that reported by Hodgson *et al.*[6]) resulted in the formation of significant quantities of alkynyl amino alcohols **4a** and **4c** (up to 42% yield) as well as the expected amino alcohols **3a–c** (Scheme 2).

Our suggested rationale for the formation of amino alcohols **3** and alkynes **4** from dihydrofuran aziridines **2** is summarised in Scheme 3. We suspect that lithiated aziridine **5** is a common intermediate and two carbenoid insertion processes are then competitive. Insertion of lithiated aziridine **5** into *sec*-butyllithium would give **6** which can eliminate alkoxide to give amino alcohols **3** after work-up. Alternatively, insertion of lithiated aziridine **5** into an adjacent CH bond would give a lithiated allylic sulfonamide intermediate **7**. Such a process is known for the corresponding carbocycle (*e.g.* **1b**, Scheme 1)[3–5] but vinyl ether **7** could also be generated from aziridine **2** by a β-elimination process. Then, vinyl ether **7** could undergo α-lithiation[10] to **8** followed by alkyne formation to give **4** (*via* a Fritsch–Buttenberg–Wiechell rearrangement[11] or direct elimination). Presumably, 3 equiv. of *sec*-butyllithium are needed since alkyne deprotonation would occur after the alkyne forms. Evidence in support of the intermediacy of both **5** and **7** in the formation of alkynes **4** is discussed later.

We then set about optimising conditions for the formation of alkynyl amino alcohols **4**. For this, we used the *N*-2,4,6-triisopropylbenzenesulfonyl aziridine **2c** since alkyne **4c** was obtained in the highest yield in our initial study (Scheme 2). The results are summarised in Table 1. With primary alkyllithium reagents such as (trimethylsilyl)methyllithium and *n*-butyllithium, only the reductive alkylation products, **3d** and **3e** respectively, were



Scheme 2

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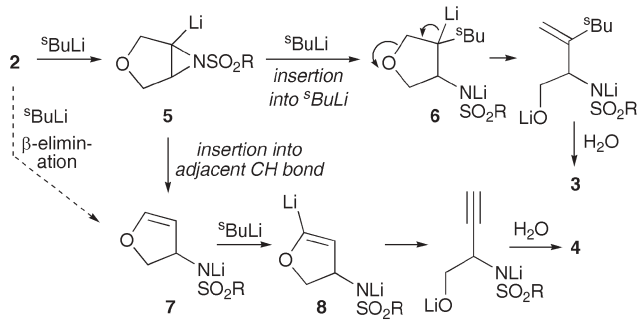


Scheme 3

formed (Entries 1 and 2). For *sec*-butyllithium, there was little difference between THF and Et_2O as solvent (Entries 3 and 4). In a previous study on the α-lithiation–rearrangement of *N*-sulfonyl aziridines, we had suggested that use of sterically hindered diamine ligands [*e.g.* (−)-sparteine] with *sec*-butyllithium led to a reduced degree of reductive alkylation compared to adjacent CH bond insertion.[5] Since we hoped to divert more of the lithiated aziridine **5** towards vinyl ether **7**, the effect of different diamine and triamine ligands was investigated (Entries 4–9). TMEDA was moderately successful, producing alkyne **4c** in 41% yield together with vinyl ether **9** in 19% yield (presumably generated from **7** or **8** upon quenching) (Entry 5). The use of (−)-sparteine in THF led to alkyne **4c** (5% ee) in a much improved 63% yield (Entry 6). Finally, use of pentamethyldiethylenetriamine (PMDETA) generated a 71% yield of alkyne **4c**† with no detectable amounts of the reductive alkylation product (Entry 7). These conditions were preferable to *sec*-butyllithium–PMDETA in Et_2O (Entry 8) and *n*-butyllithium–PMDETA in THF (Entry 9). Lower yields and mixtures of products were obtained when less than 3 equiv. of *sec*-butyllithium were used.

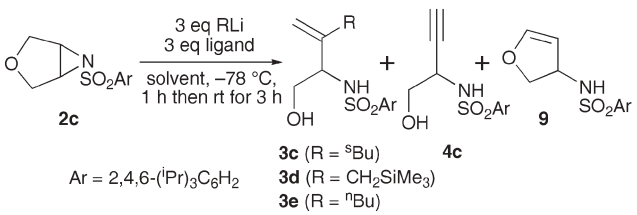
To provide support for our proposed mechanism for converting aziridine **2c** into alkyne **4c** (Scheme 3), aliquots of the reaction mixture were removed, quenched and analysed by ^1H NMR spectroscopy. After only 1 minute of mixing aziridine **2c** with *sec*-butyllithium–PMDETA at −78 °C, there was no starting material remaining and a 40:60 mixture of vinyl ether **9** and alkyne **4c** was obtained (together with <5% of amino alcohol **3c**). This ratio of products did not change during the next 1 hour at −78 °C. However, on warming to room temperature over 1 hour and quenching, only alkyne **4c** was present (with <5% **3c**). In a separate experiment, reaction with *sec*-butyllithium–PMDETA at −78 °C for 1 hour gave a 40:60 mixture of vinyl ether **9** and alkyne **4c** (by ^1H NMR spectroscopy of the crude product mixture) from which we isolated **9** (36% yield) and **4c** (46% yield). Thus, we believe that lithiated vinyl ether **7** (Scheme 3) is an intermediate in the transformation of aziridine **2c** into alkyne **4c**. However, all attempts at converting vinyl ether **9** into alkyne **4c** (using *sec*-butyllithium with or without PMDETA) have so far failed[12] and other mechanistic interpretations cannot be ruled out.

We also achieved alkyne formation from a dihydropyrrole aziridine but the alkyne product was only observed when both of the *N*-substituents were furnished with the 2,4,6-triisopropylbenzenesulfonyl group, namely aziridine **10**.[13] When aziridine **10** was reacted with (trimethylsilyl)methyllithium or *n*-butyllithium, only reductive alkylation was observed to give **11a** and **11b** respectively (Table 2, Entries 1 and 2). However, simply switching the organolithium reagent to *sec*-butyllithium led to the exclusive formation of alkyne **12** (72% yield) (Entry 3). Use of *sec*-butyllithium–PMDETA generated alkyne **12** in 81% yield (Entry 4).

Finally, enantioselectivity in the transformation of dihydrofuran aziridines **2** into alkynyl amino alcohols **4** was briefly studied using organolithiums–(−)-sparteine in Et_2O (more dilute conditions than in THF due to the moderate solubility of aziridines **2** in Et_2O). *N*-Tosyl aziridine **2a** gave alkyne (*S*)-**4a** in 35% yield and ~30% ee (by optical rotation data) using *sec*-butyllithium–(−)-sparteine (Scheme 4).

The absolute configuration of **4a** was verified as (*S*) by independent synthesis of alkyne (*R*)-**4a** from (*S*)-serine[14] and indicated that the reaction proceeds *via* lithiated aziridine **13**. This is the same sense of induction that we[4,5] and others[3] have reported for the generation of lithiated *N*-tosyl aziridines such as **1a** and **1b** using *sec*-butyllithium–(−)-sparteine. However, to our surprise, the *opposite* sense of induction was observed with *N*-triisopropylbenzenesulfonyl aziridine **2c**. Thus, aziridine **2c** gave

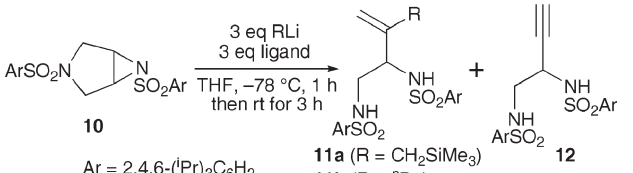
Table 1 Optimisation of formation of alkyne **4c** from aziridine **2c**



Entry	RLi	Solvent	Ligand	**3**, yield (%)[a]	**4c**, yield (%)[a]
1	Me_3SiCH_2Li	THF	—	77 (**3d**)	0
2	^{n}BuLi	THF	—	63 (**3e**)	0
3	^{s}BuLi	THF	—	37 (**3c**[b])	42
4	^{s}BuLi	Et_2O	—	36 (**3c**[b])	32
5	^{s}BuLi	THF	TMEDA	20 (**3c**[b,c])[c]	41[c]
6	^{s}BuLi	THF	(−)-Sparteine	15 (**3c**[b,c])[d]	63[e]
7	^{s}BuLi	THF	PMDETA	0	71
8	^{s}BuLi	Et_2O	PMDETA	0	60
9	^{n}BuLi	THF	PMDETA	24 (**3e**[b])	38

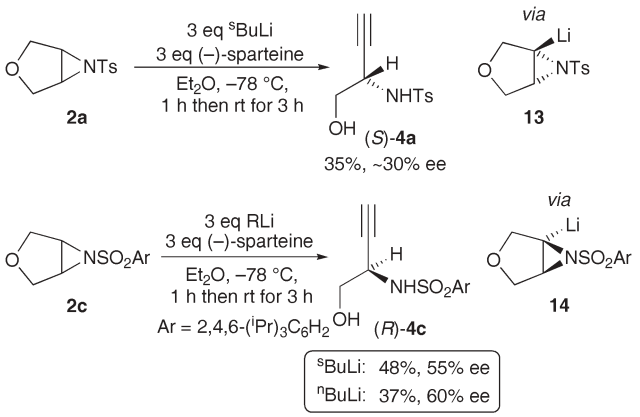
[a] Isolated yield after chromatography. [b] Amino alcohol **3c** obtained as a 50:50 mixture of diastereomers. [c] Vinyl ether **9** isolated in 19% yield. [d] % ee not determined. [e] Alkyne (*R*)-**4c** had 5% ee by chiral HPLC.

Table 2 Conversion of dihydropyrrole aziridine **10** into alkyne **12**



Entry	RLi	Ligand	**11**, yield (%)[a]	**12**, yield (%)[a]
1	Me_3SiCH_2Li	—	33 (**11a**)	0
2	^{n}BuLi	—	67 (**11b**)	0
3	^{s}BuLi	—	0	72
4	^{s}BuLi	PMDETA	0	81

[a] Isolated yield after chromatography.



Scheme 4

alkyne (*R*)-**4c** [stereochemistry established by independent synthesis from (*S*)-serine] in 48% yield and 55% ee (by chiral HPLC) using *sec*-butyllithium and in 37% yield and 60% ee using *n*-butyllithium (Scheme 4). These reactions presumably proceed *via* lithiated aziridine **14** and clearly indicate that the nature of the *N*-sulfonyl group has a significant effect on the sense and degree of lithiation of *N*-sulfonyl aziridines using organolithiums and (−)-sparteine.[15] This observation also lends support to our suggestion that vinyl ether **7** arises from lithiated aziridine **5** (*via* insertion into an adjacent CH bond) and not by a β-elimination process from **2**.

To conclude, a direct organolithium-mediated conversion of dihydrofuran and dihydropyrrole aziridines into alkynyl amino alcohols and diamines respectively has been developed. Optimum results were obtained using *sec*-butyllithium–PMDETA and *N*-2,4,6-triisopropylbenzenesulfonyl aziridines. Our methodology provides an alternative and more direct route to protected alkynyl amino alcohols which are normally prepared in 4–6 steps from serine and have proved useful in the synthesis of natural and unnatural amino acids containing alkynyl, alkenyl and cyclopropyl functionality.[16] Other reactions of *N*-2,4,6-triisopropylbenzenesulfonyl aziridines with organolithium reagents are currently under investigation in our laboratory.

Notes and references

† **Representative procedure: *N*-[1-(hydroxymethyl)prop-2-ynyl]-2,4,6-triisopropylbenzenesulfonamide 4c.** *sec*-Butyllithium (0.82 cm^3 of 1.05 M solution in cyclohexane, 0.86 mmol) was added dropwise to a stirred solution of PMDETA (0.18 cm^3, 0.86 mmol) in THF (2 cm^3) at −78 °C under nitrogen. After stirring for 15 min at −78 °C, the solution was added dropwise *via* cannula to a stirred solution of aziridine **2c** (100 mg, 0.285 mmol) in THF (3 cm^3). After stirring for 1 h at −78 °C, the solution was allowed to warm to rt over 3 h and saturated aqueous ammonium chloride solution (10 cm^3) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with petrol–EtOAc (4:1) as eluent gave alkyne **4c** (71 mg, 71%) as a white solid, mp 117–120 °C (from 4:1 petrol–EtOAc); R_F (1:2 petrol–Et_2O) 0.4; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3285 (OH and NH), 1322 (SO_2), 1152 (SO_2) and 662; δ_H (400 MHz; $CDCl_3$) 7.16 (2 H, s, *m*-$C_6H_4SO_2$), 5.10 (1 H, d, *J* 8.5 Hz, NH), 4.26–4.20 (1 H, m, CHN), 4.10 (2 H, sept, *J* 7.0 Hz, CH), 3.79 (1 H, dd, *J* 11.0 and 4.0 Hz, CH_AH_BO), 3.74 (1 H, dd, *J* 11.0 and 5.0 Hz, CH_AH_BO), 2.90 (1 H, sept, *J* 7.0 Hz, CH), 2.24 (1 H, br s, OH), 2.08 (1 H, d, *J* 2.5 Hz, CH), 1.27 (6 H, d, *J* 7.0 Hz, Me), 1.25 (6 H, d, *J* 7.0 Hz, Me) and 1.24 (6 H, d, *J* 7.0 Hz, Me); δ_C (100.6 MHz; $CDCl_3$) 153.0 (*ipso*-Ar), 150.2 (*ipso*-Ar), 132.6 (*ipso*-Ar), 123.7 (Ar), 79.2 (*C*≡CH), 73.7 (C≡*C*H), 65.3 (CH_2O), 47.2 (CHN), 34.1 (CH), 29.7 (CH), 24.8 (Me), 24.7 (Me) and 23.6 (Me); *m/z* (CI; NH_3) 369 [65%, $(M + NH_4)^+$], 352 (60), 301 (40), 272 (15), 251 (20), 235 (10), 203 (15), 103 (5), 86 (100), 70 (10) and 54 (30) [found $(M + H)^+$ 352.1946. $C_{19}H_{29}NO_3S$ requires *M* + H, 352.1946].

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