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Two-step syntheses of 2,4,6-triisopropylbenzenesulfonyl aziridines

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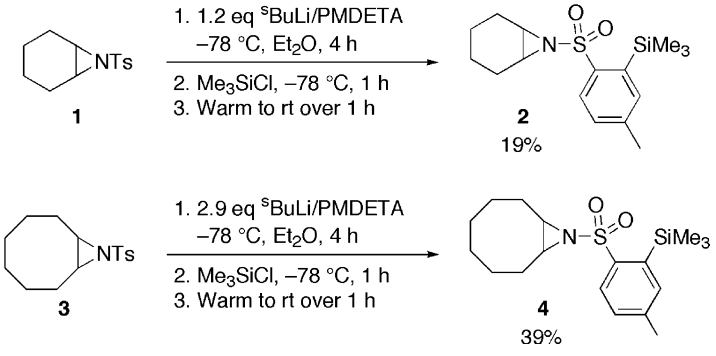
Abstract—In a continuing study on the α-lithiation of *N*-tosyl aziridines, it is reported that *ortho*-lithiation of the *N*-tosyl group is occurring under typical α-lithiation conditions (*s*-BuLi/PMDETA). Thus, a simple, two-step synthesis of *N*-2,4,6-triisopropylbenzenesulfonyl aziridines was optimised. The route involves epoxide ring opening using a sulfonamide, mesylation and base-mediated ring closure. The scope and limitations of this route were assessed and five new *N*-2,4,6-triisopropylbenzenesulfonyl aziridines were prepared in good yields. Since this method was unsuitable for the preparation of cyclooctene aziridine, an alternative two-step method was developed. This method involved aminobromination of cyclooctene using NBS/2,4,6-triisopropylbenzenesulfonamide.

Recent work in our group has focused on the alkyllithium-mediated α-lithiation of *N*-tosyl aziridines such as **1** and **3**.[1–3] Suspecting that lithiation *ortho* to the sulfonamide of the *N*-tosyl group[4–6] may be occurring under the reaction conditions, we decided to trap any intermediate organolithiums with Me_3SiCl. Thus, lithiation of *N*-tosyl aziridine **1** using *s*-BuLi in the presence of pentamethyldiethylenetriamine (PMDETA) at −78 °C for 4 h and subsequent trapping with Me_3SiCl gave substituted aziridine **2**[7] in 19% yield together with recovered starting aziridine **1** (25% yield). Under comparable conditions, aziridine **3** gave **4**[8] in 39% yield (with 35% recovered starting material). In contrast to cyclooctene oxide,[9] no trapping at the α-position of the aziridine was observed. Clearly, the *N*-tosyl-aziridino protecting group is not an innocent bystander in alkyllithium reactions and this is probably why an excess of alkyllithium is typically employed for lithiation of *N*-tosyl aziridines.[1–3]

With a view to developing aziridine α-lithiation conditions that avoid excess alkyllithium as the base, we considered using *N*-2,4,6-triisopropylbenzenesulfonyl aziridines **5**. The 2,4,6-triisopropylbenzenesulfonyl group is of course well known from its use in the Shapiro reaction.[4a,10] To our surprise, *N*-sulfonyl aziridines **5** have never previously been prepared and so a convenient route to these compounds needed to be devised.



Keywords: Aziridines; Epoxides; Sulfonamides.
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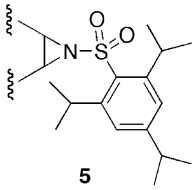
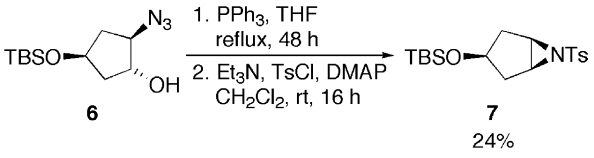
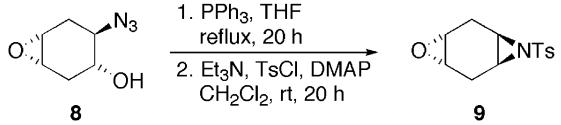


5

Despite extensive studies on aziridination methodology,[11] there are in fact few synthetic methods for the synthesis of 'non-tosyl' *N*-sulfonyl aziridines. The most obvious approach is sulfonylation of the parent NH aziridine (normally prepared by Staudinger reduction of the corresponding azido alcohol,[12] itself synthesised from the epoxide and sodium azide). We have utilised such an approach for proof of stereochemistry in some of our previous studies (e.g. **6** → **7** and **8** → **9**)[13,14] but these reactions have always proved low yielding in our hands (24% yield of **7** and 41% yield of **9** are representative).



6 **7**
24%



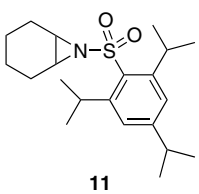
8 **9**
41%

Alternative and popular approaches for the direct synthesis of aziridines from alkenes involve use of iodinanes PhI = NSO_2R[15,16] (which can also be prepared in situ[17]) and *N*-chloramine sulfonamide salts $RSO_2NCl^-Na^+$,[18,19] both of which we have used in other studies.[1,13,20] With iodinanes, Andersson et al. have reported the preparation of a few *N*-sulfonyl aziridines[16] and the synthesis of *N*-SES-protected aziridines, pioneered by Dauban and Dodd, is well documented.[11a,17,21] For *N*-chloramine sulfonamide salts, commercially available Chloramine-T is almost always used[18] although Sharpless and co-workers have also had success with $^tBuSO_2NCl^-Na^+$.[19] Thus, these commonly employed methods each have their own limitations.

Due to the lack of widespread syntheses of different *N*-sulfonyl aziridines, we were attracted to a report by Albanese et al. on the three-step synthesis of *N*-tosyl aziridines starting from epoxides.[22,23] The epoxides were ring opened with *p*-toluenesulfonamide and the resulting amino alcohols were tosylated and cyclised using K_2CO_3. In one example, another sulfonamide (*p*-$NO_2C_6H_4SO_2NH_2$) was used. By slightly modifying Albanese's original methods,[22a] we have now successfully synthesised a range of *N*-2,4,6-triisopropylbenzenesulfonyl aziridines **5** using a simple two-step protocol. In addition, we also developed a two-step synthesis of *N*-2,4,6-triisopropylbenzenesulfonyl cyclooctene aziridine using an aminobromination approach.[24] Herein, we describe our results.

To start with, we optimised conditions for the synthesis of *N*-tosyl aziridine **1**, culminating in a two-step approach that delivered **1** in 75% overall yield. Thus, cyclohexene oxide was ring-opened using *p*-toluenesulfonamide in refluxing dioxane in the presence of K_2CO_3 and $BnNEt_3^+Cl^-$ to give amino alcohol **10** in 91% yield after chromatography. An extended reaction time (72 h) was necessary for a high conversion to **10**. In an improvement to Albanese's route, we mesylated **10** and the crude mesylate was then directly cyclised to *N*-tosyl aziridine **1**. In this way, **1** was produced in 82% yield after chromatography. Our approach to **1** benefits from use of less equivalents of sulfonamide, a shorter mesylation reaction time and the need for only two chromatographic purifications; in addition, our overall yield of **1** is higher.

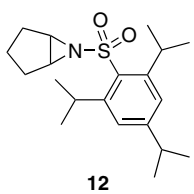
When *p*-toluenesulfonamide was replaced with *N*-2,4,6-triisopropylbenzenesulfonamide, some of the reaction times for step (i) were increased to 96 h to optimise the yields. Using this two-step approach, aziridines **11**–**15** were prepared in satisfactory yields over the two steps (29–69%).[25] Despite *N*-2,4,6-triisopropylbenzenesulfonamide being more sterically hindered, the results obtained compared well with *p*-toluenesulfonamide for each of **11**–**15**. Notably, the synthesis of the *N*-tosyl analogue of dihydrofuran aziridine **13** using our protocol (56% yield over two steps) is more efficient (in terms of yield and overall reaction time) than a recently



11

(i) 85% (68 h)
(ii) 78% (a: 5 h, b: 4 h)

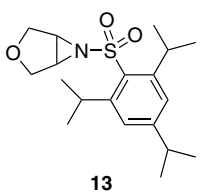
Ts: *(i)* 91% (72 h)
(ii) 82% (a: 5 h, b: 3 h)



12

(i) 47% (72 h)
(ii) 62% (a: 16 h, b: 16 h)

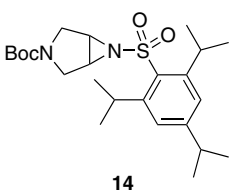
Ts: *(i)* 79% (72 h)
(ii) 77% (a: 16 h, b: 16 h)



13

(i) 86% (96 h)
(ii) 80% (a: 16 h, b: 16 h)

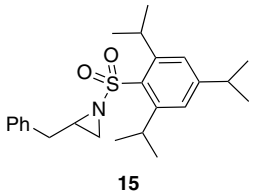
Ts: *(i)* 75% (72 h)
(ii) 74% (a: 16 h, b: 16 h)



14

(i) 63% (72 h)
(ii) 76% (a: 16 h, b: 16 h)

Ts: *(i)* 59% (72 h)
(ii) 54% (a: 16 h, b: 16 h)

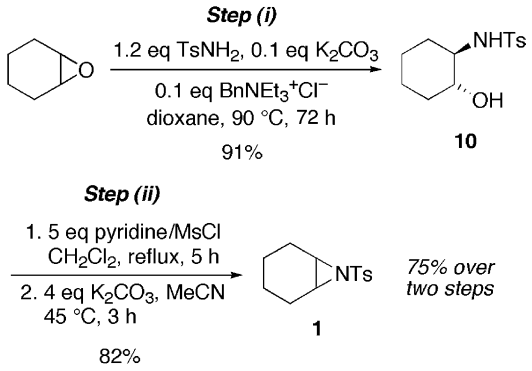


15

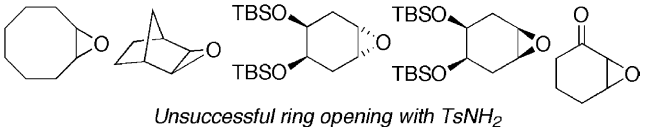
(i) 73% (96 h)
(ii) 86% (a: 16 h, b: 16 h)

Ts: *(i)* 73% (72 h)
(ii) 73% (a: 16 h, b: 16 h)

Conditions:
Step (i) 1.2 eq 2,4,6-triisopropylbenzenesulfonamide or $TsNH_2$, 0.1 eq K_2CO_3, 0.1 eq $BnNEt_3^+Cl^-$, dioxane, 90 °C, 68-96 h
Step (ii) (a) 5 eq pyridine/MsCl, CH_2Cl_2, reflux, 5-16 h; (b) 4 eq K_2CO_3, MeCN, 45 °C, 4-16 h

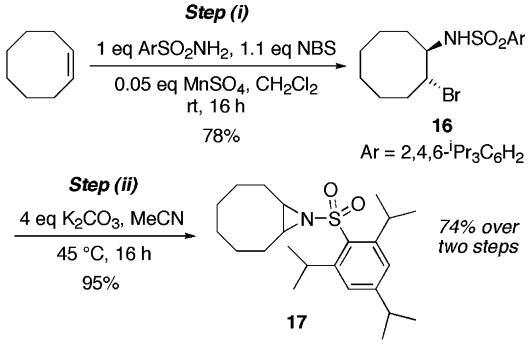


reported approach.[26] We briefly explored the scope of the approach and have identified some limitations. For example, ring opening of the five epoxides shown below using *p*-toluenesulfonamide were unsuccessful.



Unsuccessful ring opening with $TsNH_2$

For our planned lithiation studies, the preparation of *N*-2,4,6-triisopropylbenzenesulfonyl cyclooctene aziridine was of particular importance. Therefore, since ring opening of cyclooctene oxide was unsuccessful we investigated another route to this aziridine based on amino-bromination, as reported by Sudalai and co-workers.[24] Thus, reaction of cyclooctene with *N*-2,4,6-triisopropylbenzenesulfonamide in the presence of NBS and manganese sulfate gave amino bromide **16** in 78% yield after chromatography. In contrast to Sudalai's observation, we found that the yield of **16** was only moderately reduced (to 69%) if the manganese sulfate catalyst was omitted. Cyclisation of amino bromide **16** to aziridine **17** was readily accomplished in near-quantitative yield using K_2CO_3. Hence, this approach also represents a simple two-step synthesis of *N*-sulfonyl aziridines.



In summary, two straightforward routes to previously unknown *N*-2,4,6-triisopropylbenzenesulfonyl aziridines **11**–**15** and **17** have been developed. These approaches have utility for the preparation of 'non-tosyl' *N*-sulfonyl aziridines. The usefulness of such aziridines in alkyllithium-mediated reactions will be reported in due course.

Acknowledgements

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7. Data for **2**: colourless oil; R_f (1:1 petrol–Et_2O) 0.7; IR (CH_2Cl_2): 2957, 2856, 1320, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.85 (d, $J = 1.0$, 1H), 7.56 (d, $J = 8.0$, 1H), 7.29 (dd, $J = 8.0$, 1.0, 1H), 2.99–2.45 (m, 2H), 2.42 (s, 3H), 1.78–1.74 (m, 4H), 1.43–1.33 (m, 2H), 1.25–1.17 (m, 2H), 0.45 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.3, 141.1, 140.5, 137.3, 129.6, 129.1, 39.6, 22.7, 21.6, 19.5, 1.1; MS (CI, NH_3) *m/z* 324 [100%, $(M+H)^+$], 308 (70); HRMS (CI, NH_3) *m/z* calcd for $C_{16}H_{25}NO_2SiS$ $(M+H)^+$ 324.1452, found 324.1454.
8. Data for **4**: colourless oil; R_f (1:1 petrol–Et_2O) 0.7; IR (CH_2Cl_2): 2928, 2856, 1320, 1246, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.87 (d, $J = 8.0$, 1H), 7.55 (br s, 1H), 7.28 (dd, $J = 8.0$, 1.0, 1H), 2.82–2.73 (m, 2H), 2.42 (s, 3H), 2.03–1.98 (m, 2H), 1.58–1.25 (m, 10H), 0.42 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.5, 141.2, 140.4, 137.2, 129.6, 129.0, 43.7, 26.4, 26.1, 25.2, 21.6, 1.1; MS (CI, NH_3) *m/z* 352 [100%, $(M+H)^+$], 336 (40); HRMS (CI, NH_3) *m/z* calcd for $C_{18}H_{29}NO_2SiS$ $(M+H)^+$ 352.1770, found 352.1767.
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25. *Representative procedure for two-step synthesis of aziridines from epoxides.* 6-(2,4,6-Triisopropyl)-3-oxo-6-azabicyclo-[3.1.0]hexane **13**: a stirred mixture of 2,5-dihydrofuran epoxide (200 mg, 2.33 mmol), K_2CO_3 (32 mg, 0.23 mmol), $BnEt_3N^+Cl^-$ (52 mg, 0.23 mmol) and 2,4,6-triisopropylbenzenesulfonamide (784 mg, 2.80 mmol) in dioxane (1 mL) was heated at 90 °C under N_2 for 96 h. After cooling, CH_2Cl_2 (5 mL) was added and the solids were removed by filtration through Celite. The filtrate was 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 hydroxy sulfonamide (737 mg, 86%) as a white solid, mp 141–143 °C; R_f (1:1 petrol–Et_2O) 0.2; IR (CH_2Cl_2): 3496, 3250, 1314, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.17 (s, 2H), 4.83 (d, $J = 8.0$, 1H), 4.41 (td, $J = 5.0$, 3.0, 1H), 4.11 (sept, $J = 7.0$, 2H), 4.04 (dd, $J = 10.0$, 5.0, 1H), 3.96 (dd, $J = 10.0$, 5.0, 1H), 3.75–3.66 (m, 1H), 3.65 (dd, $J = 10.0$, 3.0, 1H), 3.52 (dd, $J = 10.0$, 3.0, 1H), 2.91 (sept, $J = 7.0$, 1H), 2.35 (br s, 1H), 1.29–1.25 (m, 18H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 153.3, 150.3, 132.3, 124.0, 73.6, 71.3, 61.1, 34.1, 29.7, 24.84, 24.76, 23.5; MS (CI, NH_3) *m/z* 387 [25% $(M+NH_4)^+$], 370 [100 $(M+H)^+$]; HRMS (CI, NH_3) *m/z* calcd for $C_{19}H_{31}NO_4S$ $(M+H)^+$ 370.2058, found 370.2052. A solution of hydroxy sulfonamide (500 mg, 1.36 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise to a stirred solution of pyridine (0.47 mL, 6.78 mmol) and mesyl chloride (0.45 mL, 6.78 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C under N_2. After 20 min, the solution was heated at reflux for 16 h. After cooling, the solution was washed with brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude mesylate. Then, a stirred mixture of the crude mesylate and K_2CO_3 (750 mg, 5.44 mmol) in MeCN (15 mL) was heated at 45 °C under N_2 for 16 h. After cooling, CH_2Cl_2 (15 mL) was added and the organic solution was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash chromatography on silica with petrol–EtOAc (9:1) as eluent gave aziridine **13** (380 mg, 80%) as a white solid, mp 177–180 °C; R_f (1:1 petrol–Et_2O) 0.6; IR(CH_2Cl_2): 3089, 2955, 1313, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.18 (s, 2H), 4.33 (sept, $J = 7.0$, 2H), 3.99 (d, $J = 10.0$, 1H), 3.71 (d, $J = 10.0$, 1H), 3.68 (s, 2H), 2.91 (sept, $J = 7.0$, 1H), 1.26 (d, $J = 7.0$, 18H); ^{13}C NMR (100.6 MHz, $CDCl_3$): 153.5, 150.9, 130.8, 123.8, 68.0, 44.6, 34.2, 29.6, 24.8, 23.5; MS (CI, NH_3) *m/z* 352 [100, $(M+H)^+$]; HRMS (CI, NH_3) *m/z* calcd for $C_{19}H_{29}NO_3S$ $(M+H)^+$ 352.1952, found 352.1946.
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