Introduction

As part of our work in the preparation of aziridine-allylsilanes\(^1\) we had need of a method for the preparation of simple monosubstituted, scalemic aziridines such as 1. The preparation of scalemic aziridines has been well covered in a number of reviews.\(^2\) Two methods seemed particularly well suited for the preparation of the types of aziridines needed for our work. First, an amino acid can be converted into a substituted aziridine.\(^3\) The use of amino acids, however, is quite limiting as to the identity of R. Second, the aziridination of an olefin with PhI=NTs and a copper catalyst has been shown to be useful in some cases.\(^4\) While this method can be extremely useful, again the choice of R can be limited. For example, other defins in the molecule can be a problem, and optimal yields are only obtained with cyclic or strained olefins.

Our plan (Scheme 1) was to prepare the aziridine 2 and to examine the reactivity of this molecule with a variety of organometallic reagents. The reaction of the aziridine ring with cuprates, organolithium reagents, and Grignard reagents is well known.\(^5\) We were not certain where nucleophilic attack would take place with an aziridine such as 2, and a variety of products are possible. If nucleophilic attack takes place at the tosyl ester, (S)-1 would be the result. We had hoped that attack would take place on the aziridine ring and lead to intermediate 3, which would then recylize to form aziridine (R)-1. A similar strategy has been used in reactions of glycidyl tosylate.\(^6\) In that case, when glycidyl tosylate was reacted with heteroatom nucleophiles, displacement of the tosylate was observed to be the major reaction pathway. Reaction of glycidal tosylate with organometallic reagents, however, gave products resulting from exclusive epoxide ring opening. In our case, such a strategy would allow the preparation of a variety of monosubstituted aziridines from a single aziridine precursor. The preparation of the precursor aziridine 10 in optically pure form from (S)-serine is well known.\(^7\)

Results and Discussion

The preparation of aziridine 10 was carried out as shown in Scheme 2. The readily available (S)-serine was esterified and tosylated, and the free hydroxyl was protected as a tert-butyldimethylsilyl ether. Reduction of the methyl ester was most efficiently carried out with lithium borohydride to produce 7.\(^8\) The aziridine ring was then formed via a Mitsunobu reaction.\(^9\) Desilylation of 8 yields aziridine 9 in 44% overall yield from (S)-serine. Tosylation produces the desired N-tosyl-O-tosylaziridine 10.


\(^{3}\) Reaction of glycidol tosylate with organometallic reagents, however, gave products resulting from exclusive epoxide ring opening. In our case, such a strategy would allow the preparation of a variety of monosubstituted aziridines from a single aziridine precursor.
We were pleased to find that the reaction of 10 with n-Bu₂CuLi gave only a single product (11a) in good yield (Scheme 3). As 11a could have either the S or R configuration, or a mixture of the two, the absolute stereochemistry needed to be determined. In order to unambiguously assign the absolute stereochemistry, the aziridine 11a with the R configuration was prepared by an alternate route (Scheme 4). Starting from aziridine 8, reaction with n-Bu₂CuLi gave a single ring-opened product 12. Desilylation and aziridine formation via a Mitsunobu reaction gave 11a with the R configuration. This compound was identical with respect to optical rotation with 11a prepared via the single-step aziridine opening/aziridine reformation reaction. Further proof of the stereochemical integrity of 11a was desired. For this purpose, the enantiomer of 11a, aziridine 23, was prepared from the aziridine tosylate 22. A number of routes which could lead us to 22 from (S)-serine were examined (Scheme 5). The aziridine ester 14 was prepared from 5 via a Mitsunobu reaction. Reduction of the ester using LiAlH₄ resulted in decomposition products. Reduction using LiBH₄ gave only the completely reduced product 15. Another route which was attempted involved protection of the free hydroxyl of 7 with a trityl group. Desilylation followed by a Mitsunobu reaction gave the trityl-protected aziridine 16. Hydrogenation of 16 using Pd on charcoal gave a mixture of products. The major product 17 was found to be the one arising from hydrogenolysis of the aziridine ring.¹⁰

The method which ultimately worked is depicted in Scheme 6. The methyl ester of (S)-serine was N-tosylated, followed by tritylation of the free hydroxyl group to provide 18. Reduction of the methyl ester and protection of the resulting alcohol with tert-butylmethylsilyl chloride gave 19. Removal of the trityl group proved to be difficult. Use of palladium on activated charcoal resulted in long reaction times and low yields of 20. Hydrogenation using 100 wt % of Pearlman's catalyst provided 20 in a 33% yield (60% considering recovered starting material). Use of more vigorous conditions resulted in complete removal of the trityl as well as the silyl protecting group. Dehydration using formic acid in ether provided the desired product in only 39% yield.¹¹ As before, the aziridine 21 was formed via a Mitsunobu reaction of the vicinal amido alcohol. Deprotection of the silyl group, followed by tosylation of the alcohol, produced 22. Aziridine 22 was then treated with n-Bu₂CuLi to provide 23.

The comparison of 11a and its enantiomer, 23, showed clear differentiation in the 1H NMR when combined with the chiral solvating reagent (S)- or (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The identification of the peaks arising from the (S) enantiomer 23 allowed us to assign

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an optical purity of >97% to the (R)-aziridine 11a.12 Chiral shift agent (+)-Eu(hfc)3 was not as effective as the chiral solvating agent in resolving the two enantiomers.

Satisfied that the reaction of 10 with a cuprate would provide 11 via a ring-opening-ring-closing sequence, we turned our attention to the use of other organometallic reagents. Neither n-BuLi nor n-BuMgBr provided any of the desired product; only decomposition of 10 was seen.

We next wished to examine the use of other organocuprate reagents. The cuprates derived from commercially available methylthiium, hexyllithium, and [(tri-methylsilyl)methyl]lithium gave acceptable yields of the corresponding aziridines 11–11d (Scheme 3). When methyl lithium was used, an additional product that we have identified as N-tosyl-3-pentanal was formed. We believe that this product arises from the reaction of Me2CuLi with the product 11b.13 Through the use of the chiral solvating agent, the enantiomeric purity of aziridines 11–11d was determined to be >97%.

We now turned our attention to the use of noncommercially available organolithium reagents in this reaction. To this end the known alkyl iodide 6-iodo-1-(trimethylsilyl)-2-hexene14 was prepared starting from butane-400 mesh ASTM) according to the general procedure using DMAP (180 mg, 1.5 mmol) in CH2Cl2 (15 mL) at 0 °C. The mixture was stirred for 40 min. The reaction was diluted with CH2Cl2 (20 mL) and washed with Saturated NH4Cl solution at 78 °C, and the aqueous solution was warmed to rt and allowed to stir for another 90 min. The reaction was diluted with CH2Cl2 (20 mL) and quenched by the addition of 1 M HCl (15 mL). The two layers were separated, and the aqueous layer was extracted with CH2Cl2 (5 mL). The organolithium was recovered with saturated NaOH solution (15 mL) and brine, dried (MgSO4), and concentrated. Chromatography (35% EtOAc in hexanes) gave 42.8% (10) as a white solid. [α]D +18.7° (c 8.4, EtOAc).

**Experimental Section**

(2R)-2-[(4-Methylphenyl)sulfonyl]oxy][2-methyl-1-(4-methylphenyl)sulfonyl]aziridine (10). Et3N (2.9 g, 29.2 mmol) was added to a solution of 99 (13.6 g, 14.6 mmol) and DMF (180 mg, 1.5 mmol) in CH2Cl2 (5 mL). CuI (85 mg, 0.5 mmol) and Toulensulfonyl chloride (2.9 g, 15.3 mmol) was added to the reaction over a period of 5 min. After the addition was complete, the solution was warmed to rt and allowed to stir for another 90 min. The reaction was diluted with CH2Cl2 (20 mL) and quenched by the addition of 1 M HCl (15 mL). The two layers were separated, and the aqueous layer was extracted with CH2Cl2 (5 mL). The organolithium was recovered with saturated NaOH solution (15 mL) and brine, dried (MgSO4), and concentrated. Chromatography (35% EtOAc in hexanes) gave 42.8% (10) as a white solid.

**General Procedure for the Preparation of Aziridines 11a–d.** A solution of the desired organolithium (1–1.35 mmol) was added to a cold (−78 °C) suspension of CuI (95 mg, 0.5 mmol) in THF (1 mL). The reaction mixture was stirred for 10 min and allowed to stir for another 10 min after which it was cooled to −78 °C. A solution of 10 (195 mg, 0.5 mmol) dissolved in THF (1 mL) was added to the reaction via cannula under a positive pressure of nitrogen. The reaction was allowed to stir at −78 °C for 60 min after which it was quenched by the addition of saturated NH4Cl solution at −78 °C, and the aqueous solution was extracted with Et2O (5 mL). The organolithium was recovered with saturated NaOH solution (15 mL) and brine, dried (MgSO4), and concentrated. Chromatography gave the aziridines 11a–d.

(2R)-2-Pentyl-N-[(4-methylphenyl)sulfonyl]aziridine (11a). Prepared by the general procedure using n-BuLi (1 mmol, 0.43 mL of a 2.3 M solution in hexanes) to give 99 mg (74%) of 11a as a colorless oil. [α]D 0.23 (6% EtOAc in hexanes), [α]D19 +18.5° (c 3.0, EtOAc), 1H NMR (CDCl3, 250 MHz) δ 7.79 (d, 2H, J = 8.2 Hz), 7.12 (d, 2H, J = 8.2 Hz), 7.04 (d, 2H, J = 8.2 Hz), 7.02 (d, 1H, J = 4.4 Hz), 4.48, 3.20 (d, 1H, J = 4.4 Hz). Anal. Calcd for C17H19NO2S: C, 67.63; H, 5.92; N, 3.07. Found: C, 67.63; H, 5.92; N, 3.07.

(2R)-2-Ethyl-N-[(4-methylphenyl)sulfonyl]aziridine (11b). Prepared by the general procedure using MeLi (1.2 mmol, 0.14 M solution in Et2O) to give 60% of 11b as a colorless oil. [α]D19 +7.9° (c 3.2, EtOAc). 1H NMR (CDCl3, 250 MHz) δ 7.82 (d, 2H, J = 8.35), 7.33 (d, 2H, J = 7.96), 2.69 (m, 1H, J = 8.35), 2.61 (d, 1H, J = 6.97), 2.44 (s, 3H), 2.07 (d, 1H, J = 4.84), 1.6 (m, 1H, J = 1.35), 0.83 (t, 3H, J = 6.84). 13C NMR (CDCl3, 62.5 MHz) δ 144.3, 135.5, 129.5, 128.0, 140.4, 33.6, 31.2, 31.1, 26.3, 22.5, 15.3. Anal. Calcd for C17H19NO2S: C, 62.88; H, 7.91; N, 5.20. Found: C, 62.86; H, 7.81; N, 5.20.

(2R)-2-(Triethylsilyl)ethyl-N-[(4-methylphenyl)sulfonyl]aziridine (11c). Prepared by the general procedure using [trimethylsilyl]methyl]lithium (1.2 mmol, 1.53 mL of a
0.78 M solution in pentane) to give 102 mg (69%) of 11e as a colorless oil. R: 0.27 (6% EtOAc in hexanes), [a]_D25 +32.7° (c 3.0, EtOAc), Η NMR (CDCl3, 250 MHz), δ 7.78 (d, 2H, J = 8.58), 2.69 (m, 1H), 2.55 (d, 1H, J = 6.91), 2.39 (s, 3H), 2.01 (d, 1H, J = 4.58), 1.39 (m, 2H), 0.36 (t, 2H, J = 8.67) –0.11 (s, 9H). 13C NMR (CDCl3, 62.5 MHz) 144.1, 135.3, 129.4, 127.9, 42.7, 33.7, 25.8, 21.4, 13.1, –2.1. Anal. Calcld for C17H17NO3Si: C, 56.22; H, 7.82; N, 4.71. Found: C, 56.34; H, 7.96; N, 4.68.

(R)-2-Heptyl-N-[(4-methylphenyl)sulfonyl]jazidirine (11d).
Prepared by the general procedure using n-heptyllithium (1.35 mmol, 0.75 ml of a 1.8 M solution in hexanes) to give 100 mg (68%) of 11d as a colorless oil. [α]_D25 +23.8° (c 3.9, EtOAc), Η NMR (CDCl3, 270 MHz), δ 7.79 (d, 2H, J = 8.29), 7.29 (d, 2H, J = 8.58), 2.55 (d, 1H, J = 6.97), 2.40 (s, 3H), 1.38 (m, 2H), 0.79 (s, 3H), 1.03 (d, 1H, J = 4.48), 0.65 –1.1 (m, 13.1H), 0.68. IC NMR (CDCl3, 67.5 MHz) δ 144.3, 135.3, 129.5, 128.0, 40.4, 34.7, 31.6, 31.3, 29.0, 28.9, 26.7, 22.5, 21.5, 14.0. Anal. Calcld for C14H15NO3S: C, 56.05; H, 8.52; N, 4.74. Found: C, 64.87; H, 8.24; N, 4.74.

(R)-2-(7-(Trimethylsilyl)hept-5-ynyl)-N-[(4-methylphenyl)sulfonyl]jazidirine (11e).
Bu3P (0.75 mL, 3.0 mmol) in Et2O (5 mL) was added to the reaction via cannula. The reaction was warmed to 70°C for 10 min after which it was warmed to rt and allowed to stir for 1 h. The reaction was recooled to 70°C, and a solution of CuI (119 mg, 0.63 mmol) and nBu3P (0.75 mL, 3.0 mmol) in Et2O (5 mL) was added to the reaction via cannula. The reaction was warmed to 40°C for 10 min after which it was cooled to 70°C and allowed to stir for another 40 min. A solution of 240 mg (0.63 mmol) in THF-Et2O (1:1) was added to the above solution, and the reaction was stirred for another 60 min after which it was quenched by the addition of saturated NH4Cl solution at 70°C. The aqueous solution was extracted with EtOAc (2 × 5 mL), dried (MgSO4), and concentrated. Chromatography (7% EtOAc in hexanes) gave 173 mg (75%) of 11e as a colorless oil. R_f 0.26 (6% EtOAc in hexanes). [α]_D25 +5.0° (c 3.0, EtOAc), Η NMR (CDCl3, 270 MHz), δ 7.79 (d, 2H, J = 8.28), 7.30 (d, 2H, J = 8.51), 5.35 (m, 1H), 5.15 (m, 1H), 2.69 (m, 1H), 2.59 (d, 1H, J = 6.98), 2.41 (s, 3H), 2.02 (d, 1H, J = 4.49), 1.85 (m, 2H), 1.39 (d, 2H, J = 8.18), 1.61 –1.1 (m, 6H), –0.03 (s, 9H). IC NMR (CDCl3, 67.5 MHz) δ 144.3, 135.4, 129.5, 127.9, 127.0, 125.6, 40.3, 33.6, 31.2, 29.1, 26.7, 26.4, 21.5, 18.4, –1.8. Anal. Calcld for C19H19NO3S: C, 62.42; H, 8.55; N, 3.83. Found: C, 62.4; H, 8.51; N, 3.84.

Alternate Preparation of (R)-2-Pentyl-N-[(4-methylphenyl)sulfonyl]jazidirine (11a).
nBu3P (1.21 mL of a 2.3 M solution in hexanes, 2.8 mmol) was added to a suspension of CuI (270 mg, 1.4 mmol) in THF (2.8 mL) at 40°C. The bluish black solution that was formed was allowed to stir at 40°C for 40 min. A solution of 8 (1 mL) in THF was added to the cuprate solution, and the solution was allowed to stir at 70°C for 40 min after which it was warmed to rt and stirred for another 60 min. The reaction was quenched by the addition of saturated NH4Cl solution (10 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, dried (MgSO4), and concentrated. Chromatography (8% EtOAc in hexanes) gave 249 mg (75%) of 11a as a colorless oil. R_f 0.26 (6% EtOAc in hexanes). [α]_D25 +22.0° (c 3.0, EtOAc), Η NMR (CDCl3, 250 MHz), δ 7.65 (d, 2H, J = 8.27), 7.35 (m, 17H), 4.90 (d, 1H, J = 7.61), 3.81 (dd, 1H, J = 3.60, 9.88), 3.63 (dd, 1H, J = 6.07, 9.86), 3.37 (m, 1H), 3.28 (dd, 1H, J = 4.52, 8.95), 3.0 (dd, 1H, J = 6.18, 8.97), 2.41 (s, 3H), 0.83 (s, 9H), 0.0 (d, 6H). IC NMR (CDCl3, 62.5 MHz) δ 143.6, 143.0, 138.0, 129.5, 128.5, 127.7, 127.0, 126.9, 86.8, 62.1, 61.9, 54.6, 25.8, 21.4, 18.1, –5.6.

O-(tert-Butyldimethylsilyl)-O-[(tert-Butyldimethylsilyl) hydrochloride (310 mg, 5.4 mmol) was added to the cold solution, and the mixture was then stirred overnight at rt. The mixture was then diluted with CH2Cl2 (5 mL), washed successively with 1 M HCl, saturated NaHCO3 and brine, dried (MgSO4), and concentrated. Chromatography (10% EtOAc in hexanes) provided 1.42 g (87%) of 19 as a white solid. [α]_D25 +58.8° (c 7.9, EtOAc), Η NMR (CDCl3, 250 MHz), δ 7.67 (d, 2H, J = 8.30), 7.35 (m, 17H), 5.51 (d, 1H, J = 9.15), 4.05 (m, 3.54 (s, 3H), 3.43 (dd, 1H, J = 3.4, 9.06), 3.34 (dd, 1H, J = 3.58, 9.07), 2.39 (s, 3H), 1.3 IC NMR (CDCl3, 62.5 MHz) δ 170.2, 143.4, 143.2, 137.2, 129.6, 128.5, 127.8, 127.2, 86.7, 77.5, 77.0, 76.5, 64.6, 56.1, 52.4, 21.4. HMRS Calcld for C25H32NO5S 515.1767, found 515.1757.

Notes

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