The Mechanism of Nucleophilic Substitution of 1-Alkyl-2-(tosyloxymethyl)-aziridines

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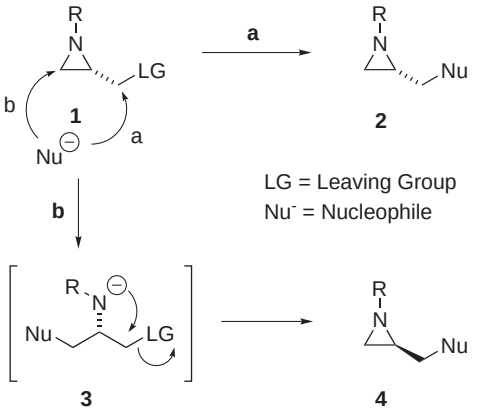
Abstract: The stereochemical course of nucleophilic substitution of 1-alkyl-2-(tosyloxymethyl)aziridines has been elucidated by a study using a chiral substrate, which confirmed that no initial ring opening and subsequent ring closure occurred but that instead direct substitution at the exocyclic methylene function took place. Consequently, these *N*-alkylaziridines exhibit a totally different reactivity towards nucleophiles as compared to the corresponding activated aziridines with an electron-withdrawing group at nitrogen, which has important stereochemical implications.

Key words: 2-(bromomethyl)aziridines, nucleophilic substitution, diastereoselectivity, nitrogen, heterocycles

The chemistry of *N*-tosylaziridines has been explored extensively in the past.[1] 1-(Arenesulfonyl)-2-(tosyloxymethyl)aziridines in particular constitute an interesting class of compounds for further elaboration due to the inherent reactivity of the constrained heterocycle and the exocyclic methylene function connected to a good leaving group.[2–7] It has already been demonstrated that these aziridines **1** (Scheme 1, R = arenesulfonyl or diphenylphosphinyl, LG = Tos or diphenylphosphinyloxy ODpp) undergo attack at the least substituted carbon atom of the aziridine moiety upon reaction with organocuprate reagents.[4] The resulting ring opened intermediates **3** give further ring closure by displacement of the tosylate or ODpp, furnishing substituted aziridines **4** with the inverted stereochemistry as compared to the chirality of the starting aziridine (Scheme 1, pathway b).[4] A different and very promising, but for the major part yet unexplored field of chemistry concerns the reactivity of 1-alkylaziridines, functionalized at the 2-position with a methylene function connected to a good leaving group. The absence of an electron-withdrawing group at nitrogen makes the aziridine moiety less susceptible towards nucleophiles than the *N*-(arenesulfonyl) analogues or the corresponding aziridinium salts. Athough in this case an opposite reactivity can be expected, no irrefutable proof has been provided up to now. Therefore, a detailed study concerning the mechanistic course of the substitution reaction of 1-alkylaziridines **1** urged itself, with particular interest in the stereochemistry of the substitution product.



Scheme 1

As outlined in Scheme 1, two possible pathways can occur upon treatment of an aziridine such as **1** (R = alkyl and LG = arenesulfonyl) with a nucleophile, resulting in either an aziridine **2** with the same absolute configuration as the starting material, or furnishing a substituted aziridine **4** in which the asymmetric carbon atom of the aziridine ring has the opposite stereochemistry as compared to the starting compound. In a third possibility both pathways might be competitive, and a mixture of isomers **2** and **4** would then be formed. To unravel the yet unknown mechanism of nucleophilic substitution of 1-alkyl-2-(tosyloxymethyl)aziridines and analogues, we applied a method based on the comparison of the stereochemistry of an aziridine obtained via a substitution reaction with a structurally analogous aziridine of known absolute configuration. Thus we synthesized an easy accessible racemic aziridine to evaluate the attainability of this concept, i.e. 1-*tert*-butyl-2-(hydroxymethyl)aziridine (**6**), prepared starting from methyl acrylate (**5**), which was converted into methyl (1-*tert*-butylaziridinyl)-2-carboxylate upon consecutive bromination and aziridination with *tert*-butylamine (Scheme 2).[8] The reduction of the latter ester was performed using $LiAlH_4$, resulting in the desired alcohol **6** in good yield.[8] When compound **6** was subjected to a Williamson ether synthesis using sodium hydride and iodomethane in THF, the corresponding methyl ether **7** was isolated in 90% yield as the single reaction product (Scheme 2).[9] In an alternative pathway, aziridine **6** was easily tosylated with tosyl chloride in dichloromethane in the presence of triethylamine and a catalytic amount of DMAP. The tosylated aziridine **8**, thus obtained, was

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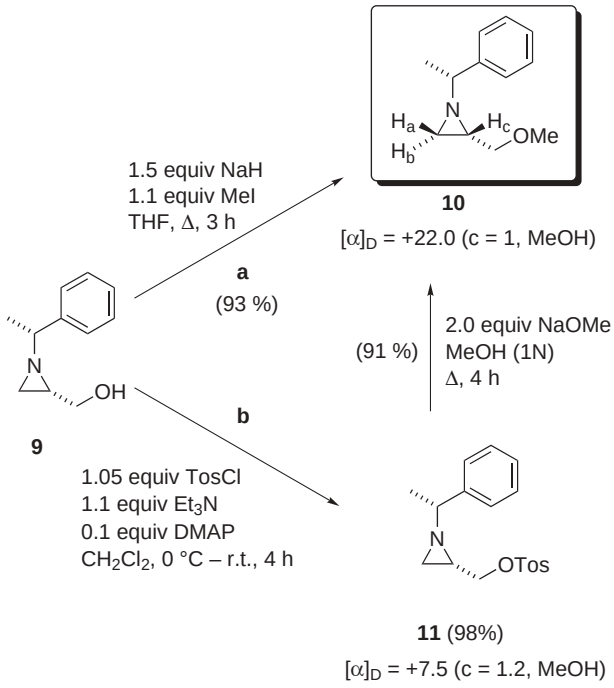
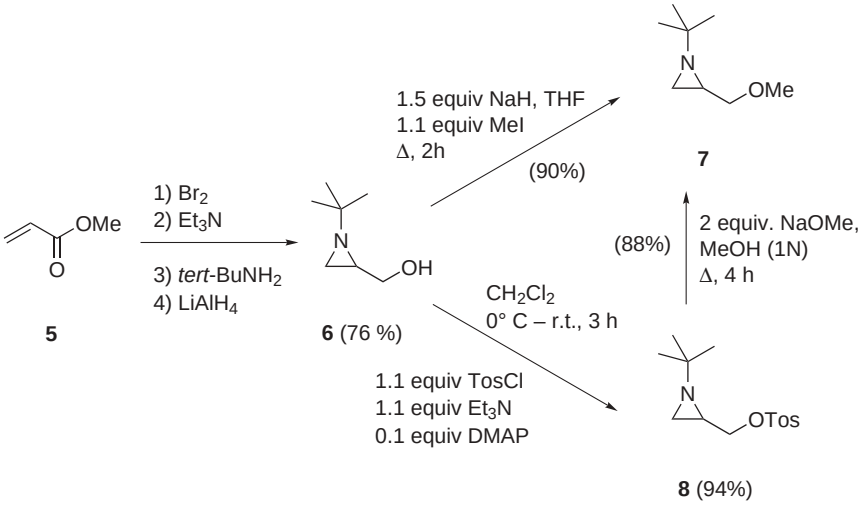
smoothly converted into 2-(methoxymethyl)aziridine (**7**) upon substitution with sodium methoxide in methanol under reflux in 88% yield (Scheme 2).

The same procedures were applied to a similar but enantiomerically pure and commercially available substrate, i.e. (1*R*,2*S*)-1-(α-methylbenzyl)-2-(hydroxymethyl)aziridine (**9**). In order to discriminate between the different possible pathways in a nucleophilic substitution with an aziridine such as **1** (Scheme 1), a substrate was chosen that contains two chiral centers. Since only one of these asymmetric carbon atoms might undergo inversion during the reaction, the substituted product will either be identical to the reference compound, prepared from the substrate, or a diastereomer of the reference aziridine. Thus, reference compound **10** was synthesized from aziridine **9** by a Williamson ether synthesis with sodium hydride and iodomethane in THF in 93% yield (Scheme 3, method a). Parallel, the chiral aziridine **9** was tosylated with tosyl chloride in dichloromethane in an excellent yield in the presence of triethylamine and a catalytic amount of DMAP, and subsequently subjected to a substitution with sodium methoxide in methanol resulting in a single reaction product **10** (Scheme 3, method b).[10] To distinguish between both possible pathways for the substitution reaction (Scheme 1), the reference aziridine **10** and the substitution product **10** were compared by means of different techniques, and judged to be one and the same compound. All spectroscopic data, i.e. ^{1}H NMR, ^{13}C NMR, IR and MS were identical for both compounds. Furthermore, chromatographic analysis resulted in identical retention factors upon column chromatography (SiO_2) and identical retention times upon gas chromatography (HP-5MS). These observations allowed to conclude that no diastereomer of the reference aziridine was formed during the substitution reaction. In other words, no ring opening occurred and the nucleophilic substitution proceeded via pathway a (Scheme 1), furnishing a substitution product with the same absolute configuration at the asymmetric aziridine carbon atom as compared to the starting aziridine and the reference compound. To confirm the stereochemical identity of the substitution product and the reference compound, the optical rotation of both compounds was measured and identical values were obtained {in both cases $[\alpha]_D$ +22.0° (*c* 1, MeOH)}. As a supplementary test, these two compounds were analyzed by gas chromatography on a chiral column (CYDEX-B), resulting in identical retention times. When the mixture of both compounds was injected, the chromatogram showed only one single peak.

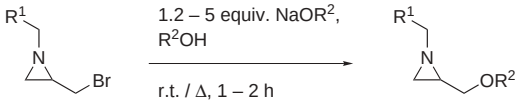


Scheme 3



Scheme 2

The general applicability of this concept in organic synthesis can be derived from the synthesis of some 2-(alkoxymethyl)aziridines (**13**) in good yields, prepared from 2-(bromomethyl)aziridines (**12**)[11] upon treatment with sodium alkoxides (Scheme 4). This methodology offers an easy and efficient alternative for the procedure developed by Deyrup.[8]



12a (R^1 = Ph)
12b (R^1 = $C(Me)_2CH_2Ph$)
12c (R^1 = *t*Bu)
12d (R^1 = *n*Pr)

13a (R^1 = Ph, R^2 = Me, 100%)
13b (R^1 = Ph, R^2 = Et, 81%)
13c (R^1 = $C(Me)_2CH_2Ph$, R^2 = Me, 96%)
13d (R^1 = *t*Bu, R^2 = Me, 72%)
13e (R^1 = *n*Pr, R^2 = Me, 92%)

Scheme 4

In conclusion, it has been demonstrated that 1-alkylaziridines, functionalized at the 2-position with a methylene function bound to a good leaving group, exhibit a different reactivity towards nucleophiles than the corresponding 1-(arenesulfonyl)aziridines. The former aziridines undergo attack at the exocyclic methylene carbon atom with displacement of the leaving group, instead of an initial ring opening and subsequent ring closure due to attack at the aziridine moiety. This implied that the stereochemistry of the substituted aziridine carbon atom is retained throughout the reaction. These preliminary results offer new perspectives in targeted organic synthesis, and extensive research in this area is currently in progress, about which will be communicated in due course.

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(9) The synthesis of 1-*tert*-butyl-2-(methoxymethyl)aziridine **7**, starting from 1-*tert*-butyl-2-(tosyloxymethyl)aziridine **8**, has been reported in the past.[8] This substitution was accomplished using methanolic sodium hydroxide (1 N) upon a prolonged reaction time (2 d). The procedure reported here with 2 equiv of sodium methoxide in MeOH (1 N) was much more effective, resulting in the desired compound in 88% yield after reflux for 4 h. Furthermore, the reported ^{1}H NMR data are partially incorrect and incomplete,[8,12] and for that reason all obtained spectroscopic data are mentioned here. Spectroscopic data of 1-*tert*-butyl-2-(methoxymethyl)aziridine **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 [9 H, s, $(CH_3)_3C$], 1.41 (1 H, d, *J* = 3.0 Hz, H_b), 1.57 (1 H, d, *J* = 6.3 Hz, H_a), 1.84–1.91 (1 H, m, H_c), 3.31 and 3.37 [2 H, 2 × d × d, *J* = 10.5, 5.6, 5.2 Hz, (HCH)O]; 3.38 (3 H, s, CH_3O). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.94 (CH_2N), 26.52 [$(CH_3)_3C$], 30.94 (CHN), 52.67 [$(CH_3)_3C$], 58.85 (CH_3O), 75.58 (CH_2O). IR (NaCl): ν_{max} = 2970, 2930, 2875, 1364, 1110, 734 cm^{-1}. MS (70 eV): *m/z* (%) = 144 (100) [M^+ + 1], 88(23). TLC: R_f = 0.40 (hexane/EtOAc 1:1).
(10) **Method a:** To an ice-cooled solution of (1*R*,2*S*)-1-(α-methylbenzyl)-2-(hydroxymethyl)aziridine **9** (0.27 g, 1.5 mmol) in THF (2 mL) was added NaH (0.09 g, 1.5 equiv, 60% dispersion in mineral oil) and the mixture was stirred for 30 min at r.t. Subsequently, MeI (0.23 g, 1.1 equiv) was added dropwise to the ice-cooled reaction mixture, which was then refluxed for 3 h. Extraction with Et_2O (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded (1*R*,2*S*)-1-(α-methylbenzyl)-2-(methoxymethyl)aziridine **10** (0.27 g, 93%).
Method b: To a solution of (1*R*,2*S*)-1-(α-methylbenzyl)-2-(tosyloxymethyl)aziridine **11** (0.50 g, 1.5 mmol) in MeOH (2.25 mL), prepared from the commercially available (1*R*,2*S*)-1-(α-methylbenzyl)-2-(hydroxymethyl)aziridine **9** via a standard tosylation reaction with 1.1 equiv TosCl, 1.1 equiv Et_3N and 0.1 equiv DMAP in 98% yield, was added sodium methoxide in MeOH (0.75 mL, 4 N in MeOH, 2 equiv) at r.t. and the reaction mixture was refluxed for 4 h. Extraction with CH_2Cl_2 (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded (1*R*,2*S*)-1-(α-methylbenzyl)-2-(methoxymethyl)aziridine **10** (0.26 g, 91%).
Spectroscopic data of (1*R*,2*S*)-1-(α-methylbenzyl)-2-(methoxymethyl)aziridine **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (3 H, d, *J* = 6.6 Hz, CH_3CH), 1.49 (1 H, d, *J* = 6.6 Hz, H_a), 1.63–1.70 (1 H, m, H_c), 1.86 (1 H, d, *J* = 3.6 Hz, H_b), 2.49 (1 H, q, *J* = 6.6 Hz, CHMe), 3.18 (3 H, s, CH_3O), 3.24 and 3.38 [2 H, 2 × d × d, *J* = 10.6, 5.8, 5.2 Hz, (HCH)O], 7.22–7.39 (5 H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.15 (CH_2N), 32.07 (CH_c), 37.45 (CH_3CH), 58.44 (CH_3O), 69.80 (CHMe), 74.03 (CH_2O), 126.75 (C_{para}), 127.02 and 128.28 (2 × C_{ortho} and 2 × C_{meta}), 144.49 (C_{quat}). IR (NaCl): ν_{max} = 2977, 2927, 1494, 1450, 1109, 701 cm^{-1}. MS (70 eV): *m/z* (%) = 191 (1) [M^+], 176 (3), 146 (100), 118 (8), 105 (79), 104 (11), 103 (13), 91 (16), 86 (40), 79 (13), 77 (20). $[\alpha]_D$ +22.0 (*c* 1, MeOH). TLC: R_f = 0.28 (hexane/EtOAc 1/1). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.47; H, 9.11; N, 7.20.
Spectroscopic data of (1*R*,2*S*)-1-(α-methylbenzyl)-2-(tosyloxymethyl)aziridine **11**: ^{1}H NMR (300 MHz, $CDCl_3$):

δ = 1.37 (3 H, d, *J* = 6.6 Hz, CH_3CH), 1.52 (1 H, d, *J* = 6.3 Hz, H_a), 1.66–1.73 (1 H, m, H_c), 1.79 (1 H, d, *J* = 3.3 Hz, H_b), 2.43 (3 H, s, CH_3Ar), 2.48 (1 H, q, *J* = 6.6 Hz, CHMe), 3.84 and 3.93 [2 H, 2 × d × d, *J* = 10.7, 6.2, 6.1 Hz, (HCH)O], 7.22–7.36 and 7.63–7.66 (7 H and 2 H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.74 (CH_3Ar), 23.37 (CH_2N), 32.33 (CH_c), 35.95 (CH_3CH), 69.43 (CHMe), 72.17 (CH_2O), 126.67, 127.28, 127.98, 128.47 and 129.86 [$CH(Me)CH_{para}$, 4 × C_{ortho} and 4 × C_{meta}], 133.06 (CCH_3), 144.09 and 144.78 (2 × C_{quat}). IR (NaCl): ν_{max} = 3061, 3030, 2972, 2927, 2869, 1599, 1494, 1450, 1363, 958 cm^{-1}. MS (70 eV): *m/z* (%) = 331 (1) [M^+], 316 (8), 226 (11), 176 (3), 160 (10), 144 (8), 105 (100), 91 (27), 79 (9), 77 (13), 55 (10). $[\alpha]_D$ +7.5 (*c* 1.2, MeOH). TLC: R_f = 0.36 (hexane/EtOAc 1:1).

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