An improved procedure for the preparation of chiral nonracemic *N*-tosyl-2-alkylaziridines and *N*,*2*-dialkylaziridines on multigram-scale

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Dedicated to Prof. Joan Bosch on his 60th birthday

Abstract

A modified and improved procedure has been developed for the preparation of chiral nonracemic *N*-tosyl-2-alkyl aziridines in a single step starting from readily available β-amino alcohols. The procedure relies on a one pot *N*-tosylation/*O*-tosylation/intramolecular S_N displacement, which furnishes the target heterocycles in excellent yields. The application of this protocol on a multigram scale has also been explored with excellent results. In addition, the application of a similar methodology has also allowed the preparation of *N*-benzyl-2-alkyl aziridines.

Keywords: Aziridines, β-amino alcohols

Introduction

Chiral aziridines have shown to be extremely interesting and useful compounds in organic synthesis,[1] due to their known ability to undergo highly regio- and diastereoselective ring-opening reactions with a wide variety of nucleophiles.[2] In addition, they have also been employed as sources of chirality in stereocontrolled reactions and some examples of their use as chiral auxiliaries or ligands in asymmetric synthesis can be found in the literature.[3] For these reasons, many methods have been developed for the asymmetric synthesis of such important chiral intermediates, most of them focused on transformation of substrates from the chiral pool, like α-amino acids or derivatives.[4]

Very recently we have reported a very efficient stereoselective ring-opening reaction of aziridines with chiral enolates under double stereodifferentiation conditions, which allowed us to obtain α-methyl-γ-amino amide derivatives in a highly stereoselective way (scheme 1).[5] During our studies, we found that the presence of an electron withdrawing group such as a *para*-

toluenesulfonyl group at the aziridine nitrogen atom which stabilizes the developing negative charge during the reaction was crucial for the ring-opening reaction to occur. After identifying the *matched* and *mismatched* combination of reagents, we found that the ring opening reaction proceeded in excellent yields and diastereoselectivities in all cases tested and the obtained adducts could be successfully converted into enantiomerically pure α-methyl-γ-amino acids and esters and the latter could be easily transformed into the corresponding γ-lactams, showing the high potential of this methodology in asymmetric synthesis.
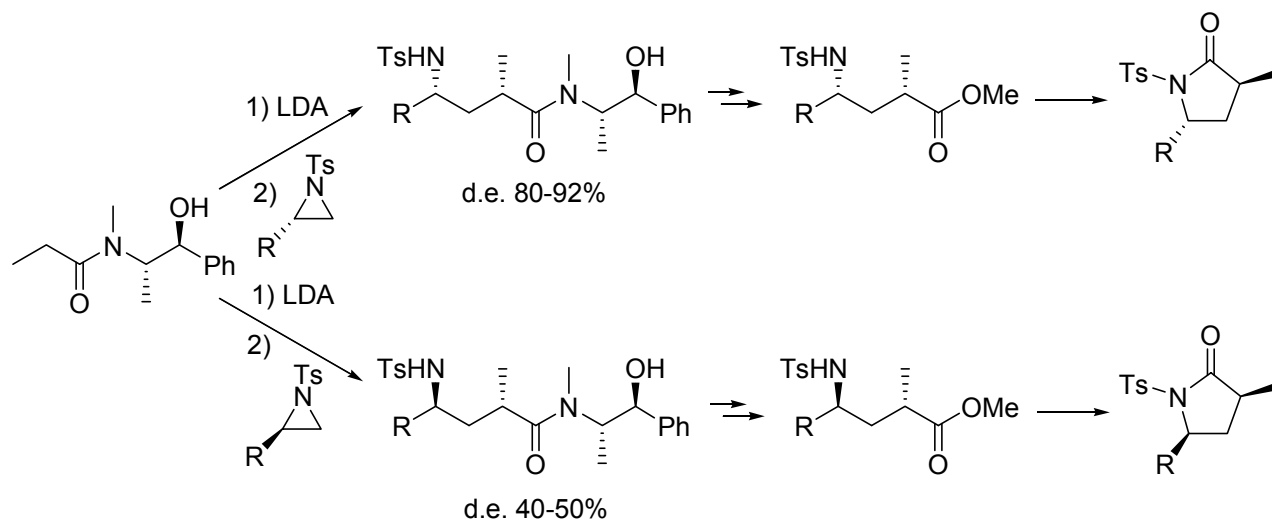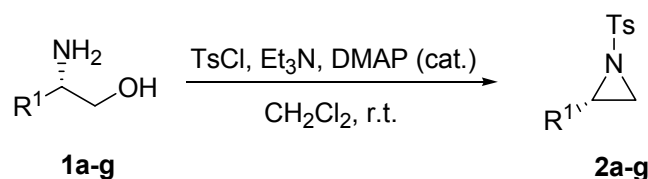

Scheme 1

In this context, and in connection with these studies, we needed a simple protocol for the preparation of chiral nonracemic aziridines in multigram quantities. Related to this topic, most of the methods reported in the literature for the preparation of chiral 2-alkyl aziridines suffer from important drawbacks, especially related to the low yields generally obtained when performing the described transformations on large scale, mainly due to the number of steps required or to problems found during the work-up procedure or during the purification of the final or intermediate products. For that reason, we decided to develop an improved protocol for the preparation of chiral *N*-tosyl 2-alkyl aziridines in multigram quantities, which we wish to preset in this paper. This procedure consists of the transformation of commercially available enantiopure β-amino alcohols into the target aziridines in a single step.

Results and Discussion

We started our study based on conditions reported in a previous paper in which *N*-tosyl β-amino alcohols were successfully transformed into the corresponding aziridines by *O*-tosylation/base-promoted cyclization.[6] The substrates needed for this transformation had to be prepared in a two

step sequence by *N*-tosylation of the corresponding α-amino acid followed by reduction. With this precedent in mind, we thought that the *N*-tosylation and cyclization could also be performed in a single operation starting from the analogous *N*-unprotected β-amino alcohol and therefore we proceeded to react 100 mg of (*S*)-alaninol with 2.5 eq. of tosyl chloride and excess (3.0 eq.) triethylamine in CH$_2$Cl$_2$ and in the presence of a catalytic amount of DMAP, observing that the expected *N*-tosyl-2-methyl aziridine was formed in a clean way after 24h. When we applied these conditions to higher amounts of the starting substrate (1g or 10g) the reaction showed to be equally effective, giving comparable yields of the final compound. Other differently substituted β-amino alcohols were subjected to these conditions.

Scheme 2

Table 1. Synthesis of *N*-tosyl aziridines **2a-g** from β-amino alcohols **1a-g**

| Entry[a]	Prod.	R^1	Yield[b]	$[\alpha]_D^{20}$	Lit. $[\alpha]_D^{20}$	Ref.
1	**2a**	Me	89	+33.1 (*c*=0.3, CH$_2$Cl$_2$)	+32.1 (*c*=1.0, CH$_2$Cl$_2$)	6
2	**2b**	Et	93	+13.1 (*c*=1.0, CH$_2$Cl$_2$)	+11.0 (*c*=1.4, CHCl$_3$)	7
3	**2c**	*i*-Pr	86	+14.8 (*c*=0.5, CH$_2$Cl$_2$)	+14.8 (*c*=1.0, CH$_2$Cl$_2$)	6
4	**2d**	Ph	93	+51.5 (*c*=0.3, CH$_2$Cl$_2$)	+65.5 (*c*=1.0, C$_6$H$_6$)	8
5	**2e**	CH$_2$Ph	91	+10.7 (*c*=0.3, CH$_2$Cl$_2$)	+10.1 (*c*=1.0, CH$_2$Cl$_2$)	6
6	**2f**	CH$_2$=CHCH$_2$	90	+20.1 (*c*=0.3, CH$_2$Cl$_2$)	+18.9 (*c*=4.3, AcOEt)	9
7	**2g**	CH$_2$=CHCH$_2$CH$_2$	88	+27.5 (*c*=0.3, CH$_2$Cl$_2$)	+27.8 (*c*=3.6, AcOEt)	9

[a] All reactions were run on a 10.0 g. scale
[b] Yield of pure compound after flash column chromatography purification.

As it is shown in table 1, the employed protocol furnished the corresponding aziridines in excellent yields in all cases tested, showing that these were consistently high regardless of the nature of the R^1 substituent at the chiral β-amino alcohol substrate. All the analytical and spectroscopic data of the prepared aziridines **2a-g** matched with those reported in the literature. In particular, the fact that the $[\alpha]_D^{20}$ values obtained by us for the aziridines prepared were in good agreement with those reported, allowed us to conclude that the stereochemical integrity of the center of chirality present at the starting materials had been maintained during the *N*-tosylation/cyclization process. It is important to point out that the reaction was performed in all cases on a 10 g. scale, which allowed us to prepare high quantities of the target aziridines in a single step and using a very simple protocol.

The advantages of this procedure compared to the original methodology reported by Berry and Craig,[6] are mainly those derived from the lower number of steps employed in our case. If we consider that β-amino alcohols are normally prepared from the corresponding α-amino acids, our procedure consists of two synthetic steps, starting from the same kind of substrate, while the aforementioned procedure needs an additional step consisting of the *N*-tosylation of the starting α-amino acids. Moreover, if we take into account that most chiral β-amino alcohols are usually commercially available, the target aziridines could be obtained by us in a single step using this very simple protocol.

We have also tested the synthesis of other *N*-substituted aziridines employing this methodology. For this purpose we first had to convert starting β-amino alcohols into the corresponding *N*-alkyl derivatives **3a-g** by condensation with the corresponding aldehyde followed by *in situ* reduction of the obtained oxazolidine. These *N*-alkyl β-amino alcohols furnished cleanly the expected aziridines **4a-g** upon treatment with tosyl chloride and triethylamine in the presence of catalytic amounts of DMAP (scheme 3).

1a (R^1=Me)
1c (R^1=*i*-Pr)
1d (R^1=Ph)
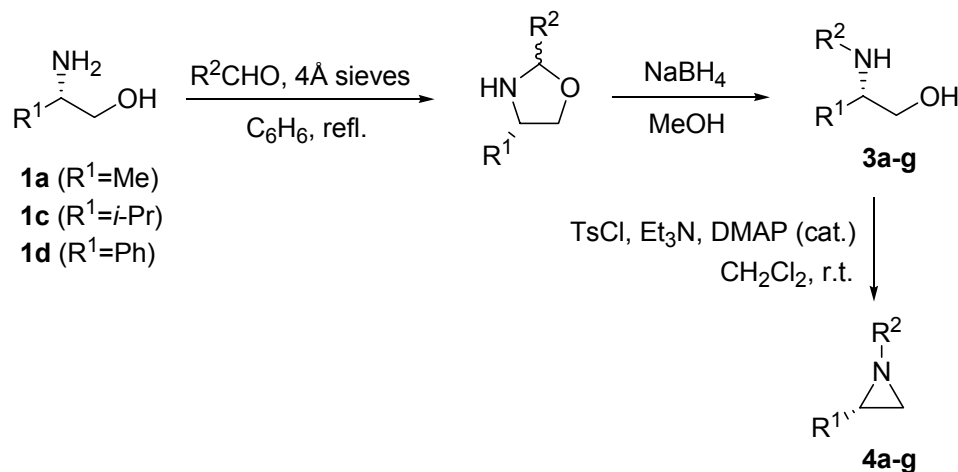
Scheme 3

Table 2. Synthesis of *N*-Alkyl aziridines **4a-g** from β-amino alcohols **1a**, **1c** and **1d**

Entry[a]	R^1	R^2	Prod.	Yield[b]	Prod.	Yield[b]
2	Ph	Me	**3a**	95	**4a**	85
3	Ph	CH$_2$CH=CH$_2$	**3b**	92	**4b**	86
4	Ph	*i*-Pr	**3c**	94	**4c**	82
5	Ph	*n*-Bu	**3d**	90	**4d**	87
1	Ph	CH$_2$Ph	**3e**	88	**4e**	90
6	Me	CH$_2$Ph	**3f**	92	**4f**	87
7	*i*-Pr	CH$_2$Ph	**3g**	90	**4g**	91

[a] All reactions were run at 1.0 g. scale
[b] Yield of pure compound after flash column chromatography purification.

In conclusion, we have set up a very efficient and simple procedure for the preparation of chiral nonracemic *N*-tosyl 2-alkyl aziridines in a single step starting from the corresponding chiral β-amino alcohols. The designed protocol involves a sequential one-pot *N*-tosylation/*O*-tosylation and a final intramolecular nucleophilic substitution step, which delivers the target heterocycles in excellent yields. The same procedure can also be applied for the preparation of other *N*-alkyl substituted aziridines, although in this case performing first an *N*-alkylation procedure prior to the cyclization step.

Experimental Section

General Procedures. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20-25ºC, running at 250 MHz for ^{1}H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances are reported in ppm relative to tetramethylsilane unless otherwise stated. Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm. thick silica gel plates (Merck Kiesegel GF_{254}) and visualization was accomplished by UV light or by spraying with phosphomolybdic acid. Flash column chromatography on silica gel was performed with Merck Kiesegel 60 (230-400 mesh). All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140ºC) overnight and purged with argon prior to use.

General procedure for the one-pot synthesis of *N*-Tosyl-2-alkylaziridines 2a-g
Et_3N (0.30 mol) was added to a cooled (0ºC) solution of the starting β-amino alcohol **1a-g** (0.1 mol), TsCl (0.25 mol) and DMAP (20mg) in dry CH_2Cl_2 (400 mL). The mixture was allowed to reach to r.t. and stirred at this temperature for 24h, after which a saturated NH_4Cl solution (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 70 mL) and the organic fractions were collected, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* affording the desired aziridines **2a-f** after flash column chromatography purification (hexanes/AcOEt 8:2).
(2*S*)-(+)-*N*-(p-toluenesulfonyl)-2-methylaziridine (2a). The reaction of (*S*)-(+)-alaninol (10.00 g, 0.13 mol), TsCl (50.45 g, 0.27 mol), DMAP (30 mg) and Et_3N (50.7 mL, 0.40 mol) following the general procedure furnished aziridine **2a** (25.0 g, 0.11 mol) after flash column chromatography purification. Yield: 89% . Mp. 56-58 ºC (Et₂O:Hexanes 1:1), (Lit.[6] 58-59 ºC). $[\alpha]_D^{20}$: +33.1 (c=0.3, CH_2Cl_2). (Lit.[6] +32.1 c=1.0, CH_2Cl_2). IR (KBr): 1340, 1150 (SO_2). ^{1}H-NMR (δ, ppm): 1.15 (d, 3H, *J*=5.6 Hz); 1.93 (d, 1H, *J*=4.6 Hz); 2.34 (s, 3H); 2.50 (d, 1H, *J*=7.0 Hz); 2.72 (m, 1H); 7.24 (d, 2H, *J*=8.0 Hz); 7.73 (d, 2H, *J*=8.0 Hz). ^{13}C-NMR (δ, ppm): 16.4; 21.2; 34.3; 35.5; 127.4, 129.4; 134.8; 144.1. MS (EI) *m/z* (Rel. Int.): 155 (1), 139 (1), 105 (2), 91 (13), 65 (12), 56 (100), 51 (2).

The other aziridines were prepared according to the general procedure. Analytical and spectroscopic data for **2b**,[7] **2c**,[6] **2d**,[8] **2e**,[6] **2f**[9] and **2g**[9] matched with those reported in the literature:

General procedure for the *N*-alkylation of β-amino alcohols

A suspension of the corresponding β-amino alcohol **1a**, **1c** or **1d** (10mmol) and the corresponding aldehyde (10mmol) in 80 mL of benzene was refluxed for 12h. in the presence of powdered 4Å mol. sieves (5g). Then, the mixture was cooled to r.t., filtered and the solvent was removed *in vacuo*. The resulting yellowish oil was next dissolved in MeOH (50mL) and $NaBH_4$ (20mmol) was added in three portions. The mixture was stirred until TLC indicated full conversion (typically 12h) and sat. NH_4Cl (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3x 80mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to afford the target *N*-alkyl β-amino alcohol **3a-g** after flash column chromatography purification (hexanes/ethyl acetate 3:7).

(2*S*)-(+)-2-amino-*N*-benzyl-2-phenylethanol (3e). The reaction of (*S*)-(+)-phenylglycinol (1.00 g, 7.30 mmol), benzaldehyde (0.77 g, 7.30 mmol), and $NaBH_4$ (0.55 g, 14.60 mmol) following the general procedure furnished *N*-benzyl β-amino alcohol **3e** (1.46 g, 6.42 mmol) after flash column chromatography purification. Yield: 88%. mp 88 °C (Et_2O). $[\alpha]_D^{20}$: +82.3 (*c* = 1.0, $CHCl_3$). (Lit.[10] −82.5, *c*=1.0, $CHCl_3$ for the *R* isomer). IR (KBr): 3445 (NH + OH). ^{1}H-NMR (δ, ppm): 2.75 (bs, 2H); 3.53 (dd, 1H, *J* = 8.7, 11.0 Hz), 3.55 (d, 1H, *J*= 13.0 Hz), 3.66 (dd, 1H, *J*= 4.2, 11.0 Hz), 3.70 (d, 1H, *J* =13.0 Hz), 3.80 (dd, 1H, *J*= 4.2, 8.7 Hz), 7.45-7.20 (m, 10H), ^{13}C-NMR (δ, ppm): 51.2; 63.9, 66.8, 128.5; 128.7; 129.0; 129.2; 129.6; 127.1, 140.0, 140.5.

The other *N*-alkyl β-amino alcohols were prepared according to the general procedure. Analytical and spectroscopic data for **3a**,[11] **3b**,[12] **3c**,[13] **3d**,[14] **3f**[15] and **3g**[16] matched with those reported in the literature.

General procedure for the synthesis of aziridines 4a-g

Et_3N (1.5 mmol) was added over a cooled (0ºC) solution of the starting *N*-alkyl β-amino alcohol **1a-d** (1.0 mmol), TsCl (1.2 mmol) and DMAP (5mg) in dry CH_2Cl_2 (100 mL). The mixture was allowed to reach r.t. and stirred at this temperature for 24h., after which a saturated NH_4Cl solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the organic fractions were collected, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* affording the wanted aziridines **4a-g** after flash column chromatography purification (hexanes/AcOEt 8:2).

(2*S*)-(+)-*N*-(Benzyl)-2-phenylaziridine (4e). The reaction of (*S*)-(+)-*N*-benzylphenylglycinol **3e** (1.00 g, 4.40 mmol), TsCl (1.00 g, 5.29 mmol), DMAP (10 mg) and Et_3N (0.92 mL, 6.60 mmol) following the general procedure furnished aziridine **4e** (0.83 g, 3.96 mmol) after flash column chromatography purification. Yield: 90% . $[\alpha]_D^{20}$: +50.1 (c=1.0, CH_2Cl_2). (Lit.[17] +49.0 *c* =2.0, EtOH);). ^{1}H-NMR (δ, ppm): 1.84 (d, 3H, *J* = 6.6 Hz), 1.98 (d, 1H, *J* = 3.2 Hz), 2.50 (dd, 1H, *J* =

3.2, 6.6 Hz), 3.58 (d, 1H, J = 13.8 Hz), 3.69 (d, 1H, J = 13.8 Hz), 7.18-7.42 (m, 10H). ^{13}C-NMR (δ, ppm): 38.3; 41.9; 65.1; 126.7; 127.6; 128.2; 128.7; 129.8; 139.2; 140.5; 145.4.

The other aziridines **4** were prepared according to the general procedure. Analytical and spectroscopic data **4a**,[18] **4b**,[19] **4c**,[19] **4d**,[20] **4f**[21] and **4g**[22] matched with those reported in the literature.

Acknowledgements

References and Footnotes

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