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New methodology for the preparation of *N*-tosyl aziridine-2-carboxylates

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Abstract—*N*-Tosyl aziridine-2-carboxylate methyl esters were prepared from methyl *N*-tosyl-L-serinate or *N*-tosyl-L-threoninate, tosyl chloride, and K_2CO_3, under phase-transfer catalysis (PTC) conditions. The same methodology, as applied to the *tert*-butyl *N*-tosyl-L-serine amide, afforded the corresponding newly prepared aziridine-2-carboxamide, as an enantiomerically pure compound.

Aziridines, three-membered nitrogen heterocycles, are constituents of several molecules presenting biological activity, for example, azinomycins and mytomycins.[1] In analogy to epoxides, aziridines react with nucleophiles, via ring opening reactions, allowing the introduction of an ethylamino group in a wide range of substrates.[1,2a–g,k] The preparation of substituted aziridines has been extensively reviewed.[1,2a–d,i–l] In particular, *N*-tosyl aziridines, used for chemical fixation of CO_2,[3] as ligands,[4] and as precursors of aminoacids[5] and of other synthetic targets,[2f,g] have been prepared from (i) alkenes via nitrene insertion[6] or aminohalogenation,[7] (ii) sulfinimines via aza-Darzens type additions,[8] (iii) β-hydroxy-α-aminoesters by intramolecular Mitsunobu cyclization,[9] and by ring closure of the corresponding N,O-ditosylated derivatives[10] or of the *N*-trityl-*O*-tosyl derivative.[2e,5] However, for the preparation of enantiomerically pure **1** and **2**, only two methods[2e,5,10] are described in the literature (Scheme 1).

By the first method,[2e,5] **1** and **2** were obtained in ca. 50% yield, after a rather long sequence. The applicability of method 2[10b] is limited by the instability of the N,O-ditosylated intermediate **3**, prone to β-elimination.[5,10a] However, we were able to circumvent such drawbacks performing a one step phase-transfer catalyzed aziridination of *N*-tosyl-L-serine or *N*-tosyl-L-threonine methyl esters.

In our hands, the attempted preparation of *N*,*O*-ditosyl-L-serine ethyl ester[10a] (**3**, R = H, R′ = Et; Scheme 1; method 2), to be used as precursor of the corresponding aziridine, failed due to the easy formation of *N*-tosyl dehydroalanine ethyl ester. It should be mentioned that a similar result was described by Baldwin et al.[5] for the direct bis-tosylation of methyl L-serinate hydrochloride in homogeneous medium. However, when we submitted methyl *N*-tosyl-L-serinate or methyl *N*-tosyl-L-threoninate (Scheme 2; **4a**,**b**) to reaction with tosyl chloride and K_2CO_3, in a PTC solid–liquid system, the ring closure reaction of a putative N,O-di-tosylated intermediate was prevalent over any competitive reaction, including racemization of the stereogenic centers (Scheme 2).

Under these conditions, compounds **1** and **2** could be prepared either from the amino esters hydrochlorides or from the N-tosylated aminoesters in moderate to good yield (Table 1).

Considering the aziridination reactions of **4a** and **4b**, performed in the presence of the quaternary ammonium catalyst Aliquat 336 (Table 1, entries 3 and 4), a straightforward reaction mechanism may be envisaged, as consisting of: (i) deprotonation of the tosylated nitrogen of **4** at the water liquid film that coats the solid potassium carbonate, the so called 'omega phase',[11]

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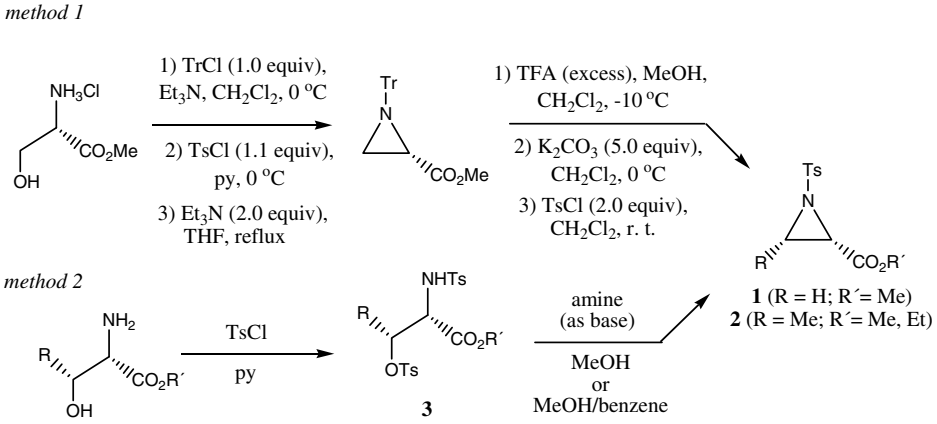
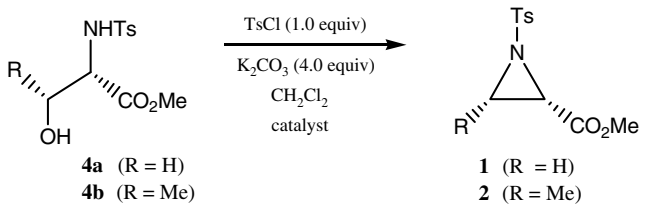


Scheme 1. Preparation of optically active *N*-tosyl aziridine-2-carboxylates **1** and **2**.



Scheme 2. PTC preparation of *N*-tosyl aziridine-2-carboxylates **1** and **2** from **4a**,**b**.

leading to an anionic intermediate **A**. Although this intermediate may exist as three species in equilibrium (Scheme 3), the more lipophilic charge delocalized cyclic structure (**II**) should be the one, that is, easily transported to the organic phase by exchange between potassium and the quaternary ammonium cations ($\mathbf{Q}^+$; Scheme 4);

(ii) O-tosylation of the transported intermediate **A** in the organic phase; (iii) deprotonation of the tosylated nitrogen of the N,O-ditosylated aminoester **3** and (iv) S_N ring closure of the deprotonated intermediate **B** in the organic phase (Scheme 4).

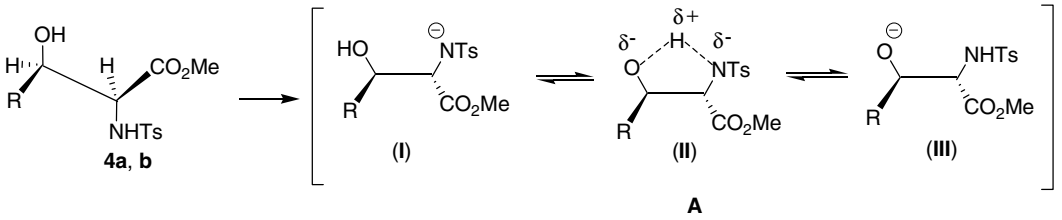
It should be mentioned that although the tosylate anion associates strongly with the quaternary cation in the organic phase, catalyst poisoning seems to be avoided by continuous formation of insoluble potassium tosylate that accumulates on the surface of potassium carbonate.

In order to ascertain the intermediancy of (**II**), we decided to compare the relative extension of the aziridination reactions of two epimers, that is, methyl *N*-tosyl-L-threoninate (**4b**) and methyl *N*-tosyl-D-*allo*-threoninate (**4c**). In the case of **4c**, the anionic intermediate would exist predominantly as open chain species, at the expenses of the more lipophilic but sterically hindered cyclic form **C**. Therefore, the aziridination reaction would proceed at a slower rate as compared to the one for the L-threonine derivative. Both reactions were performed in the presence of Aliquat 336 in $CDCl_3$ contain-

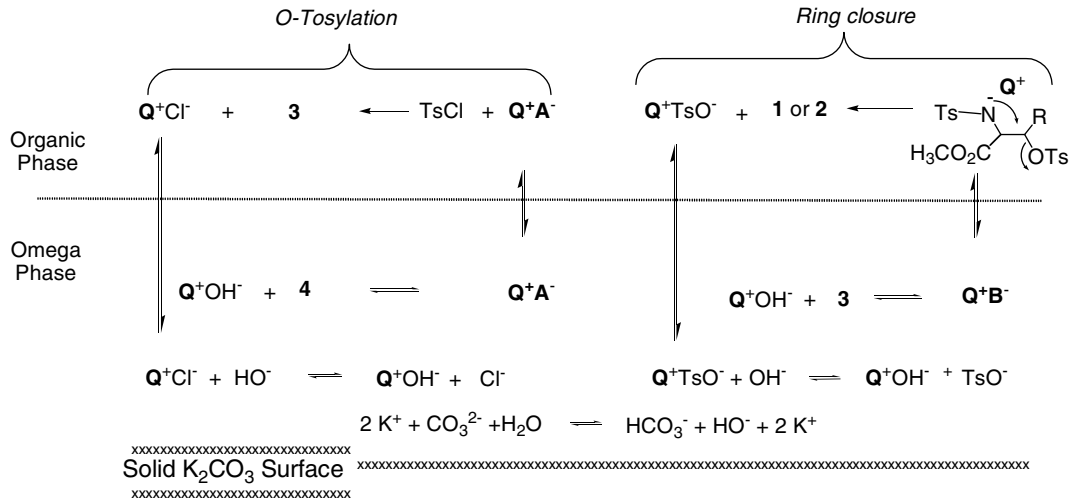
Table 1. Preparation of methyl *N*-tosyl aziridine-2-carboxylates **1** and **2**

Entry	Starting material	Product	Isolated yield[a] (%) Catalyst	
			Aliquat 336	18-Crown-6
1	Methyl L-serinate·HCl	**1**	52	54
2	Methyl L-threoninate·HCl	**2**	28	38
3[b]	Methyl *N*-tosyl-L-serinate (**4a**)	**1**	54	73
4[c]	Methyl *N*-tosyl-L-threoninate (**4b**)	**2**	49	50

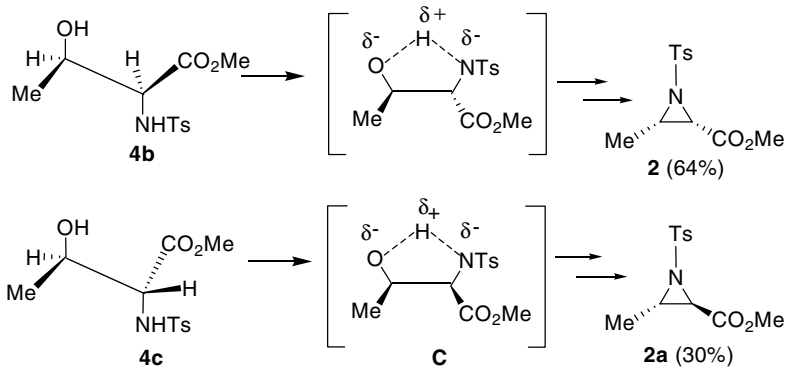
[a] Reaction time: 1 h for **1** and 9 h for **2**.
[b] In the absence of catalyst, 49% after 1 h.
[c] In the absence of catalyst, 12% after 6 h.



Scheme 3. Deprotonation of **4** leading to **A**.



Scheme 4. Reaction mechanism for the transformation of **4** into **1** or **2**, by PTC.



Scheme 5. Deprotonated intermediates in the conversion of **4b** and **4c** into **2** and **2a**.

ing a known amount of dibenzyl ether, to be used as an internal standard for the estimation of crude yields, and quenched after 23 h. As expected, the yield of the *trans* aziridine **2a**[9b] was significantly lower than that for the cis derivative (Scheme 5).

As a whole, the rate of the aziridination process could be limited either by the transfer of the anionic intermediates into the organic phase, or by the organic phase reactions (O-tosylation and S_N cyclization). The structure of the catalyst plays a fundamental role in determining the ease of occurrence of each of these mechanistic steps. Table 2 summarizes the results for the aziridination reactions of **4a** and **4b**, performed under the same conditions, but employing catalysts of increasing q values,[12a] and therefore of increasing quaternary ammonium cation accessibility for ion-pair formation.[13]

The aziridination of **4a** seems to be a transfer rate limited reaction[12b] favored by open-faced accessible catalysts (Table 2, entries 3 and 4; $q > 1$[12a]), being the yield of the reaction performed with an anion activating catalyst[12c] (entry 1) the same as that in the absence of catalyst (entry 6). For the analogous reactions of **4b**, the anions transfer and the displacement reactions seem to equally contribute to overall kinetics, as expected considering that the cyclization reaction should be slower for **3b** as compared to **3a**.

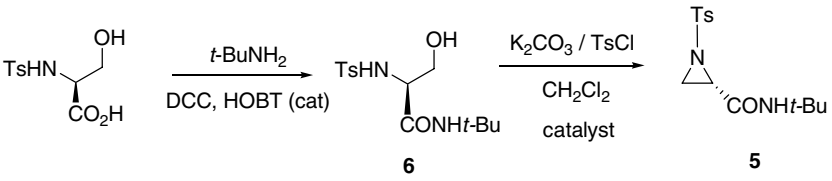
Table 2. Catalyst performance for the transformation of **4a** or **4b** into **1** or **2**

Entry	Catalyst[a]	q	Yield[b] (%)		
			1		**2**
			15 min	60 min	23 h
1	Oc_4NBr	0.50	34	58	59
2	Bu_4NBr	1.00	33	68	56
3	Aliquat 336	1.38	52	81	64
4	$C_{16}H_{33}Me_3NBr$[b]	3.06	62	76	60
5	18-Crown-6	—	59	69	55
6	None		32	59	40

[a] 10 mol %.

[b] Crude yield estimated after 23 h by ^1H NMR in $CDCl_3$ using dibenzyl ether as internal standard.

As an ongoing investigation of a new route for the preparation of N-tosylated piperazines, we decided to apply our PTC methodology to the preparation of *tert*-butyl 1-tosyl-aziridine-2-carboxamide (**5**) (Scheme 6).



Scheme 6. PTC preparation of **5**.

Table 3. Catalyst efficiency screening for the preparation of **5**

Entry	Catalyst	*q*	Yield[a,b] (%)
1	$C_{16}H_{33}Me_3NBr$	3.06	98
2	Aliquat 336	1.38	99
3	Bu_4NHSO_4	1.00	57
4	18-Crown-6	—	54
5	None		0

[a] 4 equiv of K_2CO_3, 1.0 equiv of TsCl, catalyst (10 mol %), dibenzyl ether as internal standard.
[b] After 5.5 h.

tert-Butyl *N*-tosyl-L-serine amide **6**, to be used as a precursor of **5**, was prepared[14] from *N*-tosyl-L-serine[15] and *tert*-butylamine. As for the cyclization of **6**, the efficiencies of four catalysts were evaluated by comparison of crude yields determined by ^{1}H NMR (Table 3).

As can be seen, more accessible catalysts[13] (Table 3, entries 1 and 2) are more efficient as compared to the lipophilic Bu_4NHSO_4 (Table 3, entry 3), suggesting that the rate of transfer of the anionic intermediates plays a major role in the overall kinetics. In a preparative experiment, 18-Crown-6 was employed on the basis of a compromise between yield (60%) and easy of purification of the desired enanatiomerically pure aziridine **5**.[16]

In summary, we have developed a facile PTC protocol[17] for the preparation of some synthetically valuable enantiomerically pure *N*-tosyl aziridine-2-carboxylates **1** and **2**, starting from readily available β-hydroxy-α-amino-esters. Moreover, the new aziridine carboxamide **5** could be also prepared by the same methodology.

Acknowledgment

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14. Amidation was performed using 1 equiv of DCC and 10 mol % of 1-hydroxybenzotriazole as coupling reagents, in THF yielding 82% of **6**, as a solid, still containing traces

of 1-hydroxybenzotriazole. Mp: 135.5–137 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (9H, s), 2.43 (3H, s), 3.35 (1H, dd, $J = 11$ and 5.2 Hz), 3.59–3.67 (1H, m), 3.92 (1H, dd, $J = 11$ and 3.9 Hz), 5.74 (1H, d, $J = 7.4$ Hz), 6.44 (1H, br s), 7.32 (2H, d, $J = 8.3$ Hz), 7.76 (2H, d, $J = 8.3$ Hz). MS (EI 70 eV) 214(34), 197(26), 157(19), 155(67), 133(22), 92(19), 91(90), 65(30), 60(42), 58(32), 57(100). Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.50; H, 7.06; N, 8.91. Found: C, 53.53; H, 6.93; N, 9.08.

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16. Enantiomeric purity (100%) was evaluated using 25 mol % of (−)Eu(tfc)$_3$ in $CDCl_3$.
17. Representative procedure for PTC aziridination: *Methyl (2S)-1-[(4-methylphenyl)sulfonyl]aziridine-2-carboxylate* (**1**). A mixture of methyl *N*-tosyl-L-serinate (**4a**) (3.0 mmol), tosyl chloride (3.0 mmol), K_2CO_3 (12 mmol), Aliquat 336 (0.30 mmol) in dichloromethane (5 mL) was vigorously stirred for 1 h at room temperature. The resulting suspension was filtered under reduced pressure (water pump) over a pad of silica gel (70–230 mesh) and the solid was rinsed with dichloromethane (10 mL). Alternatively, water (10 mL) was added to the suspension, and the aqueous solution was extracted with dichloromethane (10 mL). The combined organic extract was dried with anhydrous Na_2SO_4. Removal of solvent under reduced pressure yielded a viscous oil that was purified by *dry-flash* chromatography on TLC grade silica gel (eluent: *n*-hexane–ethyl acetate 3:1) to give **1** as a colorless oil. Yield 54%. ^{1}H NMR ($CDCl_3$): δ 2.44 (3H, s), 2.56 (1H, d, $J = 4.1$ Hz), 2.76 (1H, d, $J = 7.2$ Hz), 3.34 (1H, dd, $J = 7.1$ and 4.1 Hz), 3.72 (3H, s) 7.35 (2H, d, $J = 8.3$ Hz), 7.85 (2H, d, $J = 8.3$ Hz). $[\alpha]_D^{25}$ −52.7 (*c* 1.18, $CHCl_3$) (lit.[5] $[\alpha]_D^{20}$ −55.2 (*c* 1.17, $CHCl_3$)). *Methyl (2S,3S)-3-methyl-1-[(4-methylphenyl)sulfonyl]aziridine-2-carboxylate* (**2**). As described above, from methyl *N*-tosyl-L-threoninate (**4b**) (3.5 mmol), tosyl chloride (3.5 mmol), K_2CO_3 (14 mmol), Aliquat 336 (0.35 mmol) in dichloromethane (30 mL). Reaction time 9 h. The crude product was purified by *flash* chromatography on silica gel (230–400 mesh) (eluent: hexane–ethyl acetate 6:1). Yield 49%. Mp 58–59 °C (lit.[10b] 59–60 °C). $[\alpha]_D^{25}$ −40.4 (*c* 2.0, MeOH) (lit.[10b] $[\alpha]_D^{26}$ −41.0 (*c* 2.1, MeOH)). ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, d, $J = 5.8$ Hz), 2.45 (3H, s), 3.10 (1H, dq, $J = 7.5$ and 5.8 Hz), 3.39 (1H, d, $J = 7.5$ Hz), 3.73 (3H, s), 7.35 (2H, d, $J = 8.1$ Hz), 7.85 (2H, d, $J = 8.1$ Hz). ^{13}C NMR ($CDCl_3$): δ 12.4, 21.9, 40.3, 41.4, 52.8, 128.2, 130.1, 134.8, 145.2, 166.5. IR (KBr): cm^{-1} 1750, 1596, 1441, 1404, 1381, 1358, 1326, 1202, 1161, 1089, 1015, 895, 865, 812, 685, 560. *(2S)-N-(tert-Butyl)-1-[(4-methylphenyl)sulfonyl]aziridine-2-carboxamide* (**5**). As described above, from *tert*-butyl *N*-tosyl-L-serine amide[14] **6** (1.9 mmol), tosyl chloride (1.9 mol), K_2CO_3 (7.6 mmol), 18-Crown-6 (0.19 mmol) in dichloromethane (30 mL). Reaction time 5 h. The crude product was purified by *gravity* chromatography on silica gel (70–230 mesh) (eluent: petroleum ether–ethyl acetate 4:1) to give **5** as a white solid. Mp 105.5–108 °C. Yield 60%. ^{1}H NMR ($CDCl_3$): δ 1.27 (9H, s), 2.39 (1H, d; $J = 4.3$ Hz), 2.45 (3H, s), 2.69 (1H, d, $J = 7.5$ Hz), 3.18 (1H, dd, $J = 7.5$ and 4.3 Hz), 6.14 (1H, s), 7.37 (2H, d, $J = 8.3$ Hz), 7.83 (2H, d, $J = 8.3$ Hz). ^{13}C NMR ($CDCl_3$): δ 22.4, 29.2, 33.8, 38.8, 51.5, 127.8, 129.9, 133.0, 145.0, 165.0. Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.30; H, 6.63; N, 9.21. $[\alpha]_D^{20}$ −51.4 (*c* 3.0, $CHCl_3$).