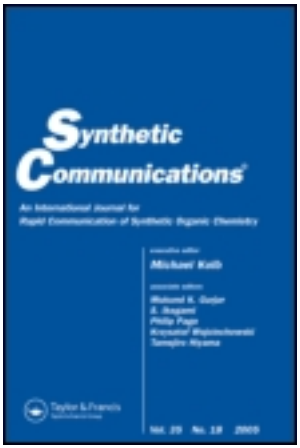

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EFFICIENT SYNTHESIS OF TOSYL-AZIRIDINE-2-*t*-BUTYL CARBOXYLATE

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Tosyl-aziridine-2-*t*-butyl carboxylate is easily synthesized from Tos-Ser-O-^{t}Bu by use of Mitsunobu conditions.

Aziridine-2-carboxylates are valuable precursors to both α- and ß-amino acids, as well as other useful synthetic targets,[1] and various approaches to these compounds have been reported.[2-18] Usually, aziridine-2-carboxylates are formed by cyclization of trityl protected mesylates or tosylates of serine and threonine, as originally described by Okawa et. al.,[13] or by closely related procedures.[14-16] Recently we developed a versatile synthesis of α, ß- diaminopropionic acid analogs from tosyl aziridine-2-*t*-butyl-carboxylate **1** and needed an efficient method to prepare this precursor.[19]

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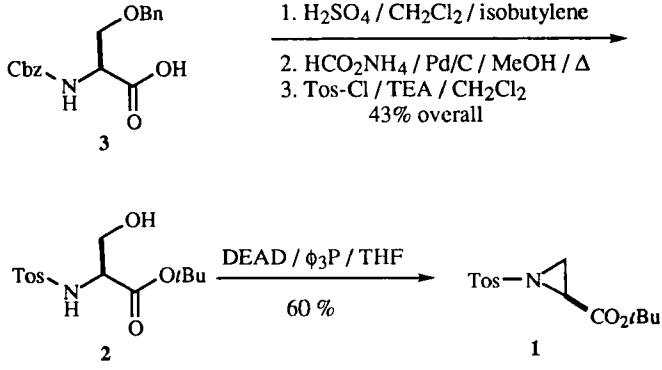
The most direct route to **1** involves reaction of the ester **2** under Mitsunobu conditions (Scheme 1), but prior reports suggested that this approach would not work. For example, Cbz-glycyl-threonine N-Me amide reacts under Mitsunobu conditions to afford the desired aziridine, but when a methyl ester is used, only the dehydroamino acid is formed.[17] Similarily, N,O-tosyl derivatives of serine can be transformed into the desired aziridine-2-carboxylates when the amide but not the ester is used.[14,18] The N-trityl, O-tosylate method[13-16] has been used many times to prepare aziridine-2-carboxylates, but this method requires exchange of the bulky trityl group and difficult chromatographies. Thus, we sought a more direct route to this compound. Initial experiments involving Mitsunobu cyclization of Tos-serine methyl ester confirmed that the dehydroamino acid ester is the major product formed. We have found that use of a *t*-butyl ester in place of other esters or amide derivatives suppresses the ß-elimination reaction and makes possible an efficient route to the title compound.

Scheme 1



Synthesis of the key intermediate Tos-Ser-O-*t*Bu **2** (Scheme 1)[20] was carried out by use of standard methods. Cbz-Ser(OBn) **3**[21] was esterified by use of isobutylene and H_2SO_4,[22] and the benzyl groups were cleaved under transfer hydrogenation conditions.[23] Tosylation of the resulting free amine gave Tos-Ser-O-*t*Bu **2** in moderate yield (43% from **3**) with limited chromatography. Mitsunobu ring closure then produced the desired aziridine **1** which was obtained in good yield (60%) after filtration through silica gel and crystallization. When these reactions were carried out on a small scale (30 mg) and the product was isolated by chromatography a higher yield (79%) of **1** is obtained.

The use of a *t*-butyl ester in place of an ethyl ester to protect the aziridine-2-carboxylate suppresses dehydroamino ester formation under Mitsunobu conditions and provides a convenient route to crystalline tosyl- aziridine-2-carboxylates from commercially available starting materials. The advantage of this method lies in the simplified purifications and elimination of protecting group exchanges.

EXPERIMENTAL

N-Tosyl-serine t-butyl ester (**2**)

Formation of t-butyl ester: Following a modification of the reported procedure[22], isobutylene was bubbled through a solution of Cbz-Ser(OBn) (4.18 g, 12.6 mmol) in CH_2Cl_2 (240 mL) until saturation was reached (~ 5 min). While the isobutylene was bubbling through the solution, H_2SO_4 (0.67 mL, 12.5 mmol) was added dropwise. The reaction was stirred at room temperature for 4 h. The reaction was quenched with 1N $NaHCO_3$ and concentrated in vacuo. The crude product was dissolved in Et_2O (200 mL) and washed with 1N $NaHCO_3$ (200 mL). The organic

phase was dried over Na_2SO_4 concentrated in vacuo to give 4.55 g of a yellow oil which was used without further purification: R_F 0.35 (20% EtOAc/hexane); ^1H NMR δ 7.38-7.25 (m, 10H, Ar), 5.61 (br d, J = 8.0, 1H, N-H), 5.11 (br s, 2H, Benzyl), 4.47, 4.55 (ABq, J = 12.07, 2H, Benzyl), 4.38 (m, 1H, α-CH), 3.87 (m, 1H, ß-CH), 3.67 (m, 1H, ß-CH), 1.44 (s, 9H, *t*-Bu); ^{13}C NMR δ 169.31, 155.93, 137.52, 136.30, 128.52, 128.41, 128.12, 128.08, 127.79, 127.64, 82.24, 73.35, 70.28, 66.91, 54.91, 27.99; LSIMS (3-NBA matrix) $[M + H]^+$ 386.2

Cleavage of Cbz and Benzyl Groups: MeOH (230 mL) was added to Cbz-Ser(OBn)-O*t*Bu (4.45 g), HCO_2NH_4 (3.68 g, 58.3 mmol) and Pd/C (5.97 g). The resulting suspension was refluxed until the starting material disappeared (8.5 h). The reaction was cooled to room temperature, filtered through celite and concentrated in vacuo to yield 1.94 g of a gold oil which was used without further purification: R_F 0.07 (100% EtOAc); ^1H NMR δ 3.76 (m, 1H, α-CH), 3.60 (m, 1H, ß-CH), 3.47 (m, 1H, ß-CH), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR δ 173.08, 81.65, 64.12, 56.38, 28.00; LSIMS (3-NBA matrix) $[M + H]^+$ 162.1

Tosylation: To a solution of Ser-O*t*Bu (1.94 g) in CH_2Cl_2 (23 mL) was added tosyl chloride (2.19 g, 11.4 mmol) and TEA (1.6 mL, 11.4 mmol). After being stirred at room temperature for 2 h, the reaction was diluted with CH_2Cl_2 (100 mL), washed with 5% HCl (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was triturated with hexane (30 mL) and recrystallized from toluene (20 mL) to give 1.3 g (33%) of a white solid. The mother liquor was recycled and purified by flash chromatography (50 g of silica gel, 40% EtOAc/hexane) to give 433 mg (10%) of additional product: R_F 0.72 (100% EtOAc); $[\alpha]^{22.5}_D$ +15° (c 1.02, $CHCl_3$); mp

105.5-107 °C; ^{1}H NMR δ 7.75 (d, J = 8.3, 2H, Ar), 7.31 (d, J = 8.1, 2H, Ar), 5.48 (m, 1H, α-CH), 3.89-3.78 (m, 2H, ß-CH_2), 2.42 (s, 3H, Ar-CH_3), 1.32 (s, 9H, *t*-Bu); ^{13}C NMR δ 168.52, 143.71, 136.39, 129.75, 127.31, 83.30, 64.01, 58.16, 27.71, 21.50; LSIMS (3-NBA matrix) m/z $[M + H]^+$ 316.1; HR-LSIMS exact mass calcd. for $C_{14}H_{22}NO_5S$: $[M + H]^+$ 316.1219; found 316.1219.

N-Tosyl-aziridine-2-t-butyl-carboxylate (**1**)

To a solution of Tos-Ser-O*t*Bu (3.54 g, 11.2 mmol) and triphenylphosphine (3.53 g, 13.4 mmol) in THF (150 mL) was added diethylazodicarboxylate (DEAD) (1.8 mL, 11.2 mmol). After being stirred at room temperature for 2 h, the reaction was concentrated in vacuo. The crude product was passed through a plug of silica (45 g of silica gel, 30% Et_2O/hexane) and recrystallized from 20% Et_2O/hexane to give 1.8 g (53%) of a white solid. The mother liquor was recycled to furnish 240 mg (7%) of additional product: R_F 0.38 (50% Et_2O/hexane); $[\alpha]^{25}_D$ -52.3° (c 1.0, CH_2Cl_2) [Lit.[14] $[\alpha]^{20}_D$ -45.3° (c 1.09, CH_2Cl_2)]; mp 97-99 °C [Lit.[14] mp 74-75 °C]; ^{1}H NMR δ 7.85 (d, J = 8.3, 2H, Ar), 7.35 (d, J = 8.5, 2H, Ar), 3.22 (dd, J = 7.0, 4.2, 1H, α-CH), 2.69 (d, J = 7.0, 1H, ß-CH), 2.50 (d, J = 4.2, 1H, ß-CH), 2.45 (s, 3H, Ar-CH_3), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR δ 165.70, 145.04, 134.30, 129.76, 128.15, 82.98, 36.81, 31.84, 27.83; LSIMS(3-NBA matrix) $[M + H]^+$ 298.

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