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Direct Access to L-Azetidine-2-carboxylic Acid

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A straightforward synthesis of L-azetidine-2-carboxylic acid is described, leading to both orthogonally protected versions or totally deprotected L-Aze. The starting material is a commercially available aspartic acid derivative, whose chirality is conserved. The (2-trimethylsilyl)ethanesulfonyl protecting group (SES) acts as a leaving group on the hydroxy function and serves as an activator for the amine function, which is the key-step of the reaction.

Introduction

L-Azetidine-2-carboxylic acid (**1**) (L-Aze, Figure 1) is a naturally occurring non-proteogenic amino acid, first isolated from *Convallaria majalis* in 1955.[1] This cyclic amino acid is the key component of nicotianamine and mugineic acid derivatives, which are natural potent iron transporters in plants[2] (Figure 1).

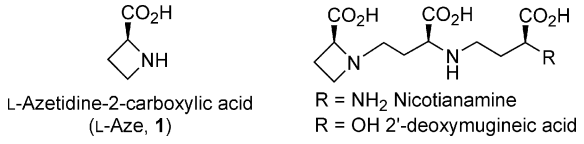


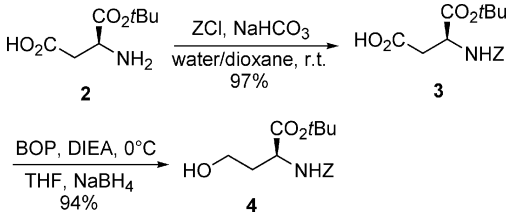
Figure 1. L-Azetidine carboxylic acid and nicotianamine structures.

Several syntheses of racemic **1** have been reported and reviewed[3] since its first preparation in 1969.[4,5] Synthesis of the pure (*S*)-enantiomer has been achieved mainly by enzymatic resolution[6] or by asymmetric induction.[7–10] Various L-amino acids were used as starting materials for the preparation of L-Aze, including L-homoserine by using hydrogen bromide under drastic conditions,[11] L-methionine in 11% yield,[12] or L-aspartate derivatives in 38% overall yield.[13] Access to **1** and its analogues has been recently reviewed.[14]

The work in this paper describes a direct method to synthesize **1** in high yield from the chiral pool.

Results and Discussion

Ring closure towards the preparation of the azetidine requires intramolecular cyclization of the open-chain starting material to form the C–N bond. Thus, we chose commercially available L-*tert*-butyl aspartate (**2**), as it is easy to handle in comparison to homoserine, which is prone to lactonization. Two steps, N-protection followed by reduction of carbonyl moiety in the side chain, were necessary to afford desired starting compound **4** in 91% yield (Scheme 1).



Scheme 1. Synthesis of suitably protected starting compound **4**.

For the intramolecular cyclization, two strategies were envisioned, Mitsunobu reaction or direct N-alkylation. The first strategy required the nitrogen atom to bear an acidic proton. This was achieved by switching from Z to SES protection [Z = benzyloxycarbonyl; SES = (2-trimethylsilyl) ethanesulfonyl],[15] with more efficient electron-withdrawing properties. At low temperature, the SES group was introduced at the nitrogen atom selectively. Resulting derivative **5** can be submitted to Mitsunobu conditions to afford protected derivative **6** of the desired azetidine carboxylic acid in 86% yield and more than 50% overall yield from **4** (Scheme 2).

Despite this conclusive result, we thought that direct N-alkylation could be possible by changing the hydroxy moiety into a leaving group. This can be attained in one pot with N-protection by using SES chloride. Indeed, the reaction carried out at room temperature yielded expected derivative **7** bearing two SES groups, one for N-activation and one for creating the leaving group at the hydroxy moiety of the side chain. Cyclization occurred under smooth basic conditions with excellent yield (97%) within

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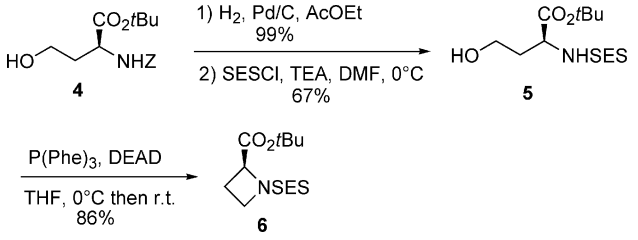
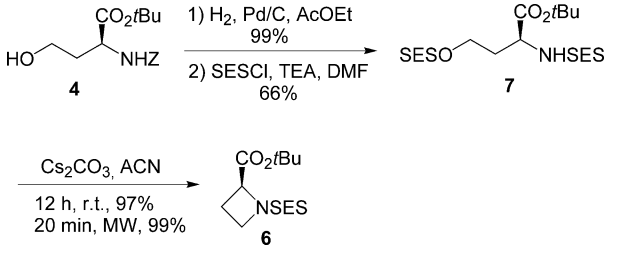


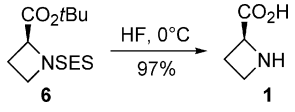
Scheme 2. Cyclization under Mitsunobu conditions.

12 h at room temperature (Scheme 3). Similar intramolecular displacement was described from a differently protected aspartate derivative to occur in only 58% under optimized conditions (Cs_2CO_3 in refluxing acetonitrile),[13] thus demonstrating the efficiency of the double role of the SES group in our strategy. In addition, we improved the cyclization yield up to 99% in 20 min by using nonconventional microwave heating (Scheme 3), thus bringing the overall yield to 65%.



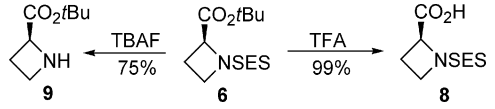
Scheme 3. Cyclization by direct intramolecular N-alkylation.

This cyclization reaction was also performed without solvent in a grinding ball,[16] and compound **6** was obtained in 97% yield within 3 h. Protected derivative **6** was converted in one step into targeted azetidine carboxylic acid **1** under strong acidic conditions [HF or trifluoromethanesulfonic acid (TFMSA)] (Scheme 4).



Scheme 4. Total deprotection of azetidine carboxylic acid **6**.

However, the orthogonality of the protections allowed the obtention of monoprotected derivatives **8** and **9**, depending on the reaction conditions (Scheme 5). Moreover, the combination of both successive deprotection steps could afford **1**, avoiding the problematical use of HF.



Scheme 5. Selective deprotection of azetidine carboxylic acid **6**.

Conclusions

In conclusion, we successfully achieved a convenient and rapid synthesis of L-azetidine carboxylic acid. Two strategies were investigated starting from the L-aspartic acid derivative. The most efficient route involved a direct N-alkylation step, made possible by the original double use of the SES group. This original methodology led to quantitative yield for the intramolecular cyclization key step, with the assistance of microwave heating. The overall yield of deprotected azetidine-2-carboxylic acid (**1**) reached 65% from alcohol derivative **4** and 59% from commercially available aspartic acid derivative **2**.

Experimental Section

General Methods: Trimethylsilylethylsulfonyl chloride[17] was prepared according to a literature procedure. Microwave-assisted reactions were performed in sealed vessels with a Biotage initiator 60 EXP instrument. The temperatures were measured with an IR sensor on the outer surface of the reaction vial. Ball milling experiments were performed in a Retsch MM 200 mixer mill with two stainless steel balls 7.0 mm in diameter into a stainless jar (10 mL) at a rate of 1800 rounds per minute (30 Hz) at room temperature.

Z-Asp-O*t*Bu (3): To a stirred solution of H-Asp-O*t*Bu (1 g, 5.3 mmol, 1 equiv.) in water/dioxane (2:1, 20 mL) was added $NaHCO_3$ (1.3 g, 15.9 mmol, 3 equiv.) at room temperature, followed by benzyl chloroformate (1.18 mL, 6.9 mmol, 1.3 equiv.) in dioxane (7 mL) over 2 h. The reaction mixture was stirred at room temperature overnight. The solution was extracted with ethyl acetate (3 × 10 mL). The aqueous layer was acidified to pH 2 with 6 N HCl. The product was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo to provide **3** (1.67 g, 97%) as a colorless oil. $[\alpha]_D^{24} = -8.9$ (c = 2.9, CH_2Cl_2).[18] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.55 (s, 1 H), 7.35 (m, 5 H), 5.92 (d, J = 8.32 Hz, 1 H), 5.11 (s, 2 H), 4.55 (td, J = 4.44, 4.44, 8.55 Hz, 1 H), 2.96 (dd, J = 4.41, 17.2 Hz, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 169.5, 156.1, 136.1, 128.2, 128.1, 127.9, 82.8, 67.1, 50.7, 36.7, 28.0, 27.8 ppm. MS (ESI): m/z = 346.1, 324.1, 268.1.

Z-Hse-O*t*Bu (4): *N*,*N*-Diisopropylethylamine (DIEA; 1.05 mL, 6.04 mmol, 1.3 equiv.) was added to a stirred suspension of Z-Asp-O*t*Bu (**3**; 1.5 g, 4.64 mmol, 1 equiv.) and benzotriazole-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP; 2.7 g, 6.04 mmol, 1.3 equiv.) in anhydrous THF (20 mL) at room temperature. The resulting solution was stirred for 10 min, cooled to 0 °C and $NaBH_4$ (230 mg, 6.04 mmol, 1.3 equiv.) was added in small portions. After stirring for 3 h, the solvent was evaporated, and the residue was taken up in ethyl acetate (25 mL) and washed with 1 N HCl (3 × 8 mL), saturated $NaHCO_3$ (3 × 8 mL), and brine (8 mL), then dried with Na_2SO_4, and concentrated in vacuo. The resulting viscous oil was purified by column chromatography (silica gel; petroleum ether/Et_2O, 3:7) to give alcohol **4** (1.38 g, 96%) as a colorless oil. $[\alpha]_D^{24} = -5.1$ (c = 1.6, CH_2Cl_2).[18] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 5.61 (d, J = 7.47 Hz, 1 H), 5.10 (s, 2 H), 4.29–4.40 (m, 1 H), 3.50–3.71 (m, 2 H), 3.10 (s, 1 H), 2.02–2.15 (m, 1 H), 1.49–1.65 (m, 1 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 156.8, 136.1, 128.5, 128.31, 128.1, 128.1, 82.4, 67.0, 58.4, 51.9, 35.4, 27.9 ppm. MS (ESI): m/z = 332.2, 310.2, 254.1.

SES-Hse-O*t*Bu (5): To a solution of Z-Hse-O*t*Bu (**4**; 1.5 g, 4.85 mmol) in EtOAc (15 mL) was added 10% Pd/C (300 mg), and the mixture was stirred for 3 h under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through Ce-

lite, and the filtrate was concentrated under reduced pressure to give an intermediate amine as a colorless oil (832 mg, 98%).To this amine (200 mg, 1.14 mmol, 1 equiv.) dissolved in anhydrous DMF (4.5 mL) was directly added triethylamine (204 μL, 1.48 mmol, 1.3 equiv.), and the mixture was cooled to –40 °C in an immersion-cooler cold bath. A solution of SESCl (228 mg, 1.14 mmol, 1 equiv.) in anhydrous DMF (1.5 mL) was added dropwise. The mixture was stirred overnight at –40 °C. DMF was removed by evaporation under low pressure. The residue was taken up in water (20 mL) and ethyl acetate (20 mL). The organic layer was washed with brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo to give **5**, which was purified by column chromatography (silica gel; petroleum ether/Et_2O, 3:7) to afford sulfonamide **5** (254 mg, 66%) as a white solid. M.p. 65 °C. $[\alpha]_D^{24}$ = –75.4 (*c* = 1.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.6 (d, *J* = 9.16 Hz, 1 H), 4.08 (dt, *J* = 4.32, 9.33, 9.35 Hz, 1 H), 3.68–3.84 (m, 2 H), 2.82–2.99 (m, 2 H), 2.35 (s, 1 H),1.98–2.12 (m, 1 H), 1.62–1.78 (m, 1 H), 1.42 (s, 9 H), 1.04 (m, 2 H), 0.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 85.0, 60.1, 55.8, 51.3, 37.9, 30.0, 12.4, 0.00 ppm. MS (ESI): *m*/*z* = 362.1, 340.1, 284.1, 220.2, 192.1.

SES-Hse(OSES)-O*t*Bu (7): To a solution of Z-Hse-O*t*Bu (**4**; 800 mg, 2.58 mmol) in EtOAc (9 mL) was added 10% Pd/C (200 mg), and the mixture was stirred for 3 h under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give an intermediate amine as a colorless oil (448 mg, 99%). To this intermediate amine (200 mg, 1.14 mmol, 1 equiv.) dissolved in anhydrous DMF (5 mL) was added triethylamine (637 μL, 4.58 mmol, 4 equiv.), and the mixture was cooled to 0 °C in an immersion-cooler cold bath. A solution of SESCl (456 mg, 2.28 mmol, 2 equiv.) in anhydrous DMF (2 mL) was added dropwise. The mixture was stirred overnight at 0 °C. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo to give **7**, which was purified by column chromatography (silica gel; petroleum ether/Et_2O, 8:2) to afford sulfonamide **7** (327 mg, 65%) as slightly yellow crystals. M.p. 75 °C. $[\alpha]_D^{24}$ = –108.0 (*c* = 6.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.09 (d, *J* = 9.18 Hz, 1 H), 4.27 (m, 2 H), 4.06 (dt, *J* = 4.45, 8.93, 9.97 Hz, 1 H), 2.97–3.10 (m, 2 H), 2.80–2.92 (m, 2 H), 2.18–2.32 (m, 1 H), 1.90–2.03 (m, 1 H), 1.45 (s, 9 H), 0.95–1.1 (m, 4 H), 0.05 (s, 9 H), 0.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 85.6, 67.5, 51.6, 49.0, 35.4, 29.9, 12.3, 12.1, 0.0, –0.05 ppm. MS (ESI): *m*/*z* = 526.26, 521.2, 448.1, 384.2, 356.1.

SES-Aze-O*t*Bu (6)

Method A: To a solution of PPh_3 (62 mg, 0.24 mmol, 2 equiv.) in THF (2 mL) under an argon atmosphere was added dropwise diethyl azodicarboxylate (DEAD; 47 μL, 0.24 mmol, 2 equiv.) at 0 °C. The mixture was stirred at 0 °C for 30 min. Compound **5** (40 mg, 0.118 mmol, 1 equiv.) in THF (3.5 mL) was added dropwise at 0 °C over 30 min. The mixture was stirred at 20 °C for 12 h. The solution was concentrated in vacuo, and the residue was purified by column chromatography (silica gel; petroleum ether/EtOAc, 20:1) to afford **6** as a colorless oil (32.6 mg, 86%).

Method B: To a solution of sulfonamide **7** (25 mg, 0.05 mmol, 1 equiv.) in anhydrous acetonitrile (1.2 mL) was added Cs_2CO_3 (60 mg, 0.2 mmol, 4 equiv.). The resulting mixture was irradiated by microwave-assisted heating (20 min, 90 °C). The mixture was taken up in water (2 mL) and ethyl acetate (1 mL). The mixture was extracted with ethyl acetate (3 × 1 mL) dried with Na_2SO_4, and concentrated in vacuo to afford **6** (15.8 mg, 99%) as a colorless oil.

Method C: A ball-mill vessel was charged with sulfonamide **7** (90 mg, 0.18 mmol, 1 equiv.) and Cs_2CO_3 (235 mg, 0.72 mmol, 4 equiv.). Stirring was started in a grinding bowl by using the ball mill with a vibration speed of 30 vib s^{-1}. After 3 h, the crude product was washed off the reaction vessel with EtOAc (4 × 2 mL) and the combined organic fractions were washed with water (3 × 2 mL) and dried with Na_2SO_4 and concentrated in vacuo to give **6** (56 mg, 97%). $[\alpha]_D^{24}$ = –90.4 (*c* = 6.7, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.72 (m, 1 H), 4.12 (dd, *J* = 8.56, 16.18 Hz, 1 H), 3.42–3.71 (m, 1 H), 2.89–3.10 (m, 2 H), 2.23–2.44 (m, 2 H), 1.45 (s, 9 H), 0.92–1.12 (m, 2 H), 0.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 84.2, 62.8, 51.7, 48.6, 30.0, 21.5, 16.1, 11.7, –0.3 ppm. MS (ESI): *m*/*z* = 344.0, 322.1, 266.1, 202.1, 174.2. HRMS (FAB+): calcd. for $C_{13}H_{27}NO_4SSi$ 322.1464; found 322.1516.

H-Aze-OH (1): SES-Aze-O*t*Bu (**6**; 150 mg, 0.5 mmol, 1 equiv.) was treated with anhydrous HF (2 mL) at 0 °C for 1.5 h in a Teflon apparatus. HF was removed by distillation. The residue was washed with Et_2O and then dissolved in water, which was removed by lyophilization to afford product **1** as its hydrofluoride salt (49 mg, 97%). M.p. 210 °C. $[\alpha]_D^{24}$ = –107.6[19] (*c* = 3.1, H_2O). ^1H NMR (300 MHz, D_2O): δ = 4.07 (dd, *J* = 9.46, 18.73 Hz, 1 H), 3.89 (dt, *J* = 6.11, 10.16, 10.24 Hz, 1 H), 2.65–2.85 (m, 1 H), 2.37–2.61 (m, 1 H), remaining signal obscured by H_2O peak at 4.7 ppm. ^{13}C NMR (75 MHz, D_2O): δ = 173.8, 42.2, 58.9, 23.2 ppm. MS (ESI): *m*/*z* = 225.1, 130.2, 103.1. HRMS (FAB+): calcd. for $C_4H_8NO_2$ 102.0555; found 102.0561.

SES-Aze-OH (8): A solution of SES-Aze-O*t*Bu (**6**; (50 mg, 0.15 mmol) in CH_2Cl_2/trifluoroacetic acid (TFA; 7:3, 0.5 mL) was stirred for 3 h at room temperature. The CH_2Cl_2/TFA mixture was removed by evaporation under reduced pressure, and the resulting residue was taken up in ethyl acetate (1 mL) and 1 N HCl (2 mL). The mixture was extracted with ethyl acetate (3 × 1 mL), dried with Na_2SO_4, and concentrated in vacuo to afford **8** (39.5 mg, 99%) as a colorless oil. $[\alpha]_D^{24}$ = –70.4 (*c* = 4.3, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 4.92 (t, *J* = 9.02 Hz, 1 H), 4.12 (m, 1 H), 3.42–3.71 (m, 1 H), 2.90–3.12 (m, 2 H), 2.23–2.44 (m, 2 H), 0.92–1.12 (m, 2 H), 0.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 61.7, 51.7, 48.6, 31.5, 21.4, 11.7, 0.3, –0.0, –0.3 ppm. MS (ESI): *m*/*z* = 294.9, 283.1, 268.0, 267.0, 266.0.

H-Aze-O*t*Bu (9): To a solution of sulfonamide **6** (50 mg, 0.15 mmol, 1 equiv.) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (TBAF; 1 M in THF, 0.45 mL, 0.45 mmol, 3 equiv.). The resulting mixture was stirred for 24 h at room temperature. The solution was concentrated in vacuo, and the residue was purified by chromatography (silica gel; EtOAc/MeOH, 90:10) to afford **9** (17.55 mg, 75%) as a pale-yellow oil. $[\alpha]_D^{24}$ = –57.4 (*c* = 2.1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.22 (s, 1 H), 4.45 (m, 1 H), 3.52–3.81 (m, 2 H), 2.65 (m, 1 H), 2.29 (m, 1 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 81.2, 58.8, 44.7, 28.0, 23.7 ppm. MS (ESI): *m*/*z* = 179.6, 157.8, 101.4.

Supporting Information (see footnote on the first page of this article): NMR spectra of compounds **1**, **3**–**9**.

Acknowledgments

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