An efficient synthesis of (R)-3-aminothiolane

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An efficient synthesis of (R)-3-aminothiolane is described based on a one-pot tandem hydroxyl activation-intramolecular cyclisation of Ts-protected-D-methioninol in the presence of methanesulfonyl chloride/pyridine. Removal of the tosyl group then gave (R)-3-aminothiolane in good yield. (R)-3-Aminothiolane derivatives are important building blocks for the synthesis of biologically active compounds.

Keywords: (R)-3-aminothiolane, intramolecular cyclisation, pharmaceutical synthesis

(R)-3-Aminothiolane and the related sulfone derivatives have been used as important building blocks for the synthesis of biologically active compounds including pharmaceuticals[1–9]. Efforts have been made to develop a simple synthetic route for the preparation of this compound. In 1984, Jones and McElhinney synthesised racemic 3-aminothiolane from tetrahydrothiophen-3-one[10]. After zinc bromide catalysed condensation of D-methioninol with benzonitrile and subsequent acid cyclisation, basic hydrolysis, Ashton *et al*. produced optically pure (R)-3-aminothiolane.[3] However, given the relatively low yield and strict reaction condition, there is still room for improvement. We report here a novel synthetic route for the preparation of (R)-3-aminothiolane.

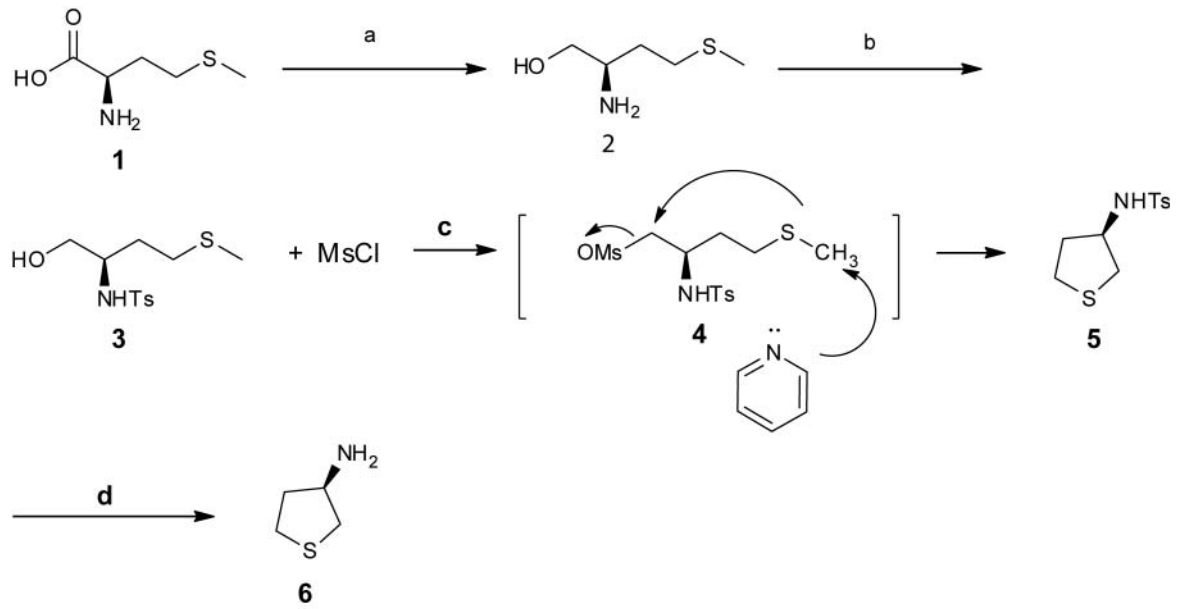
The synthesis was started from D-methionine **1** (Scheme 1), which on $NaBH_4/I_2$ reduction in THF gave D-methioninol **2** in 91% yield[11]. The amino group was protected as its tosyl derivative (TsCl, Et_3N, CH_2Cl_2, room temperature) **3**. The alcohol **3** was treated with methanesulfonyl chloride in pyridine at 0 °C and then at 70 °C. This activated the hydroxyl group to promote an intramolecular cyclisation, probably via the key intermediate **4** to produce (R)-4-methyl-N-(tetrahydrothiophen-3-yl)-benzenesulfonamide **5** in 89% yield. The tosyl group was removed by stirring the compound **5** in the presence of conc. HCl and AcOH under reflux. After vacuum distillation of the crude product, (R)-3-aminothiolane was isolated in 87% yield.

In conclusion, a highly efficient and practical approach to (R)-3-aminothiolane has been developed by a one-pot tandem hydroxyl activation and base catalysed intramolecular cyclisation. The overall yield of the route is 70% for four steps. Further application of this approach is currently underway in our laboratory.

Experimental

Melting points were determined with a SGW X-4 micro melting point apparatus. ^{1}H NMR spectras were recorded using Avance 400 MHz spectrometer. ESI-MS were recorded on Dionex MSOPlus mass spectrometer. High resolution mass spectra were recorded on Finnigan MAT XL95 mass spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter.

D-Methioninol **(2)**: A mixture of D-methionine **1** (14.9 g, 100 mmol) and sodium borohydride (2.28 g, 60 mmol) was stirred in tetrahydrofuran (100 mL) at 0 °C. This solution was kept below 10 °C while drops of iodine (13.97 g, 55 mmol) in tetrahydrofuran (10 mL) were added. After the addition, the mixture was stirred at refluxing temperature for 6 h. Then after cooling to ambient temperature, MeOH was added to the reaction mixture which was stirred until the evolution of gas had ceased. The mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (50 mL) and washed with sat. NaCl. Then the organic layer was dried, filtered, and concentrated under vacuum to give a pale yellow crude residue (12.3 g, 91%), which was directly used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (br s, 2H), 3.62–3.55 (m, 1H), 3.42–3.29 (m, 1H), 2.98–2.92 (m, 1H), 2.89 (br s, 1H), 2.60–2.51



Scheme 1 Reagents and conditions: (a) $NaBH_4$, I_2, THF, 0 °C, 91%; (b) TsCl, Et_3N, CH_2Cl_2, 99%; (c) MsCl, Pyridine, 0 °C then 70 °C, 89%; (4) conc.HCl, AcOH, reflux, 87%.

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(m, 2H), 2.14 (s, 3H), 1.94–1.85 (m, 1H), 1.81–1.77 (m, 1H). ESI-MS *m/z*: 136.2 $(M+H)^+$.

(R)-N-[1-Hydroxy-4-(methylthio)butan-2-yl]-4-methylbenzenesulfonamide **(3)**: A magnetically stirred solution containing D-methioninol **2** (3 g, 22.5 mmol) in dichloromethane (20 mL) and triethylamine (4.54 g, 45 mmol) was treated with toluene-*p*-1-sulfonyl chloride (5.13 g, 27 mmol) in dichloromethane (20 mL) dropwise below 10 °C. The mixture was then stirred at room temperature for 3 h before 1N HCl (50 mL) was added. The layers were separated, the organic layer was washed with sat. NaCl (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product. Recrystallisation from MeOH gave (R)-N-[1-hydroxy-4-(methylthio)-butan-2-yl]-4-methylbenzenesulfonamide **3 (**6.48 g) as a pale yellow solid. $[\alpha]_D^{20}$ = + 18.2 (c 1.0, MeOH); m.p. 105–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.01 (d, *J* = 8.6Hz, 1H), 3.88 (br s, 1H), 3.55–3.37 (m, 2H), 2.61–2.48 (m, 2H), 2.45 (s, 3H), 2.12 (s, 3H), 1.91–1.75 (m, 2H). ESI-MS (*m/z*) 312.1 $(M + Na)^+$. HRMS Calcd. for $C_{12}H_{19}NO_3S_2Na$ $(M + Na)^+$ requires 312.0704, found 312.0697.

(R)-4-Methyl-N-(tetrahydrothiophen-3-yl)-benzenesulfonamide **(5)**: A solution of (R)-N-(1- hydroxy-4-(methylthio)butan-2-yl)-4-methylbenzenesulfonamide **3** (5.78 g, 20 mmol) in pyridine (50 mL) was treated with methanesulfonyl chloride (2.74 g, 24 mmol) dropwise while keeping the internal temperature between 0 and 5 °C. After the addition was complete, stirring was continued for another 8 h at 70 °C. The system was then cooled to room temperature and quenched with 1N HCl until a pH of 5 was reached. The precipitate was removed by filtration, and the filtrate was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried over $MgSO_4$, and evaporated in vacuum. Recrystallisation from EtOH-H_2O (8:1) gave **5** (4.57 g, 17.8 mmol, 89%) as a bright yellow powder. $[\alpha]_D^{20}$ = + 58.31 (c 1.0, $CHCl_3$). M.p. 91–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.99 (d, *J* = 8.2 Hz, 1H), 4.08 (dt, *J* = 8.7, 4.4 Hz, 1H), 2.97-2.73 (m, 3H), 2.53 (dd, *J* = 11.2, 3.7 Hz, 1H), 2.46 (s, 3H), 2.02 (dt, *J* = 11.7, 4.9 Hz, 1H), 1.93 (ddd, *J* = 12.8, 8.1, 4.0 Hz, 1H). MS-ESI(*m/z*): 280.1 $[M+Na]^+$. HRMS calcd for $C_{11}H_{15}NNaO_2S_2$ $(M + Na)^+$ requires 280.0442, found 280.0437.

(R)-3-Aminothiolane **(6)**: A mixture of **5** (22 g, 85.6 mmol), conc. HCl (150 mL) and AcOH (50 mL) was stirred at 100 °C for 8 h. After cooling to room temperature, the reaction mixture was concentrated in a vacuum, H_2O (150 mL) and ethyl acetate (150 mL) were added and the aqueous layer treated with 2N NaOH until a pH of 10 was reached. The aqueous phase was then extracted with EtOAc (100 mL × 3), the combined organic layers were washed with sat. NaCl (150 mL), dried over anhyd. Na_2SO_4, filtered, concentrated and distilled to give a pale yellow oil **6** (7.67 g, 74.5 mmol, 87%), b.p. 45–48 °C (10 mm Hg). $[\alpha]_D^{20}$ = + 35.62 (c 1.0, acetone). [lit.[12] of (S)-3-aminothiolane. $[\alpha]_D^{22}$ = –37.77 (c 1.0, acetone) The optical rotation of (R)-3-aminothiolane was not quoted in the literature and hence the value of the (s)-enantiomer is given here]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75–3.73 (m, 1 H), 3.05–2.98 (m, 3 H), 2.85–2.78(m, 1 H), 2.09–2.01 (m, 1 H), 1.99 (br s, 2H), 1.92–1.88 (m, 1 H). MS-ESI(*m/z*): 104.2 $[M+H]^+$.

The authors are grateful to Zhejiang Hisoar Pharmaceutical Co., Ltd for financial support.

Received 15 November 2011; accepted 1 December 2011
Paper 1100984 doi: 10.3184/174751911X13237056070415
Published online: 27 December 2011

References

1 U. Baettig, I. Bruce and S.J. Watson, *WO* 2010063802.
2 J. Neil and J. Simon, *WO* 2008148790.
3 T.D. Ashton, K.M. Aumann, S.P. Baker, C.H. Schiesser and P.J. Scammells, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6779.
4 C. Hansch, A. Leo and C. Schmidt, *J. Med. Chem.*, 1980, **23**, 1095.
5 R.D. Elliott, J.R. Piper, C.R. Stringfellow and T.P. Johnston, *J. Med. Chem.*, 1972, **15**, 595.
6 B. Unterhalt and M. Moellers, *Archiv. Pharmazie*, 1990, 317.
7 P.E. Bender, C.D. Perchonock, W.G. Groves, R.C.J. Smith, O.D. Stringer, R. Sneed, J.H. Schlosser, L.S. Hostelley and B.Y.H. Hwang, *J. Med. Chem.*, 1983, **26**, 1218.
8 F. Duane, P.C. Morrow, H.T. Johnson, W. David and L. Donald, *J. Med. Chem.*, 1973, **16**, 736.
9 B.J. Broughton, P. Chaplen, W.A. Freeman, P.J. Warren, K.R.H. Wooldridge and D.E. Wright, *J. Chem. Soc., Perkin Trans1*, 1975, 857.
10 J. Jones and R. McElhinney, *Chem. Commun.*, 1984, 1501.
11 M.J. Fan, G.Q. Li and Y.M. Liang, *Tetrahedron*, 2006, **62**, 6782.
12 E. Dehmlow and R. Westerheide, *Synthesis*, 1992, 947.