Investigation of macrocyclisation routes to 1,4,7-triazacyclononanes: Efficient syntheses from 1,2-ditosylamides

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Instrumentation

Melting points were determined on a Reichert 7905 hot stage and are uncorrected. Specific rotations were measured at 20 ˚C in a 1 cm^3 cell with a pathlength of 10 cm using a Perkin-Elmer 341 polarimeter . The [α]$_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g/100 cm^3. ^{1}H-nmr spectra were recorded on Bruker WM-250, Jeol 270, or Bruker AMX-400 spectrometers in the indicated solvents operating at 250, 270 or 400 MHz, respectively. ^{13}C-NMR spectra were obtained on the same instruments operating at 62.89, 67.80, and 100 MHz, respectively. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dq, doublet of quartets; sep, septet. Coupling constants were recorded in Hz. Infra-red (IR) spectra were recorded on a Nicolet Impact 400D FTIR spectrometer either as liquid films, KBr discs or as a 1–2% solution (CCl_4). Mass spectra were recorded on a Jeol JMS AX505 spectrometer at Strathclyde or at the EPSRC National Mass Spectrometry service, Swansea. UV-visible spectra were recorded using a Perkin-Elmer Lambda 2 spectrophotometer using quartz cells with a 1 cm pathlenghth with far UV acetonitrile as the solvent. Microanalyses were performed by the microanalytical service at Strathclyde University. Chiral hplc was carried out using an ACS 351 isocratic pump, Jasco UV-975 uv/vis detector set at 254 nm, Jasco OR-2090plus chiral monitor and data handling was carried out using AZUR software. The determination of the ees of aziridine **25** was carried out using a Chiralcel OJ chiral column (0.46 × 25 cm) and guard column (0.46 × 5 cm) with isopropanol-hexane (1:1, 1 cm^3 min^{-1}) as the eluant.

General methods

Anhydrous reactions were carried out under an atmosphere of nitrogen in oven dried glassware (140 ˚C). Anhydrous solvents were obtained using standard procedures: ethanol ($Mg(OEt)_2$), pyridine (predried over KOH, distilled from CaH_2), THF (K metal), toluene (Na metal) and triethylamine (CaH_2). All other reagents were used as supplied. Flash column chromatography was performed according to the procedure of Still *et al.*[1] using silica gel (230–400 mesh).

Experimental procedures

Synthesis *via* Route B

(±)-*N*-(2-Aminocyclohexyl)-4-methylbenzenesulfonamide 10

To a solution of (±)-*trans*-1,2-cyclohexanediamine **9** (4.0 g, 35 mmol) in dichloromethane (30 cm^3) at 0 ˚C was added a solution of *p*-toluenesulfonyl chloride (2.2 g, 11 mmol) dropwise over 30 min. The reaction was allowed to attain room temperature and stirred overnight. The resulting solution was extracted with 2M HCl (× 3, 50 cm^3). The organic layer was rejected and the aqueous phase was basified with 2M NaOH. The aqueous phase was extracted with dichloromethane (× 3, 25 ml) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to form a gum (2.6 g, 9.6 mmol, 83% (27% based on (±)-**9**)). Found: MH^+ 269.1323. Calculated for $C_{13}H_{20}N_2O_2S$: 269.1319. υ_{max} (KBr, cm^{-1}) 3361 (w, NH_2), 3297 (w, NHTs), 3046 (w, C_6H_4), 2921 (m, CH), 1319 (s, SO_2NH), 1155 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 1.11 (m, 4H, CH_3), 1.59 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.36 (m, 1H, C*H*), 2.42 (s, 3H, $C_6H_4CH_3$), 3.48 (m, 1H, C*H*), 7.29 (d, J 8.0, 2H, $C_6H_4CH_3$), 7.78 (d, J 8.0, 2H, $C_6H_4CH_3$); δ_C (100 MHz, $CDCl_3$) 21.7 ($C_6H_4CH_3$), 25.0 (CH_2), 25.1 (CH_2), 32.8 (CH_2), 35.9 (CH_2), 55.1 (*C*H), 60.68 (*C*H), 127.2 (2× Ar*C*H), 129.9 (2× Ar*C*H), 138.1 (Ar*C*), 143.0 (Ar*C*).

1-[(4-Methylphenyl)sulfonyl]aziridine 12[2]

The title compound was prepared from ethanolamine **11** *via* a modification of the two step procedure of Bulkowski and co-workers.[2] Ditosylation according to Bulkowski and co-workers gave 2-{[(4-methylphenyl)sulfonyl]amino}ethyl-4-methylbenzenesulfonate (73%).

A solution of the foregoing 2-{[(4-methylphenyl)sulfonyl]amino}ethyl-4-methylbenzenesulfonate (2.5 g, 6.7 mmol) in THF (30 cm^3) was added to a suspension of hexane-washed NaH (60% in oil, 178 mg, 7.4 mmol) in THF (30 cm^3) at room temperature over 15 min. The resulting mixture was stirred for 2 h and upon completion was quenched by slow addition of brine (50 cm^3). The aqueous solution was extracted with ether (× 3, 25 cm^3) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to form the title compound as an off white solid (1.2 g, 6.4 mmol, 96%); mp 62-64 ˚C; (lit.[2] mp 64.2-64.4 ˚C). Found: C, 54.6; H, 5.6; N, 6.9; S, 16.3; MH^+ 198.0589. Calculated for $C_9H_{11}NO_2S$: C, 54.8; H, 5.6; N, 7.1; S, 16.3; MH^+ 198.0587. υ_{max} (KBr, cm^{-1}) 1322 (s, SO_2NH), 1157 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 2.37 (s, 4H, CH_2), 2.45 (s, 3H, CH_3), 7.34 (d, J 8.0, 2H, $C_6H_4CH_3$), 7.84 (d, J 8.0, 2H, - $C_6H_4CH_3$); δ□ (100 MHz, $CDCl_3$) 21.8 ($C_6H_4CH_3$), 27.6 (2 × CH_2), 128.2 (2 × Ar*C*H), 129.9 (2 × Ar*C*H), 135.0 (Ar*C*), 144.9 (Ar*C*).

(±)-4-Methyl-*N*-{2-[(2-{[(4-methylphenyl)sulfonyl]amino}ethyl)amino] cyclohexyl}benzenesulfonamide 13

A solution of (±)-*N*-(2-aminocyclohexyl)-4-methylbenzenesulfonamide **10** (340 mg, 1.27 mmol) in anhydrous toluene (7 cm^3) was heated to reflux under an inert atmosphere. To this solution was added a solution of 1-[(4-methylphenyl)sulfonyl]aziridine **12** (250 mg, 1.27 mmol) in toluene (4 cm^3) dropwise over a 2 h period. The reaction mixture was continued at reflux temperature for an additional 60 h. On completion, the toluene was removed under reduced pressure and the residue was purified by column chromatography on silica (hexane:EtOAc:CH_2Cl_2 2:3:5) which afforded a white solid (266 mg, 0.57 mmol, 44%); mp 52-54 ˚C. Found: C, 56.5; H, 6.7; N, 8.8; S, 13.7; MH^+ 466.1827. $C_{22}H_{31}O_4S_2N_3$ requires: C, 56.8; H, 6.7; N, 9.0; S, 13.8; MH^+ 466.1834. υ_{max} (KBr, cm^{-1}) 3272 (s, NHTs), 3062 (w, C_6H_4), 2930 (m, CH), 2856 (m, CH), 1326 (s, SO_2NH), 1159 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 0.88 (m, 1H, CH_2), 1.11 (m, 3H, CH_2), 1.61 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 2.14 (m, 1H, C*H*), 2.42 (s, 6H, $C_6H_4CH_3$), 2.53 (m, 1H, C*H*), 2.68 (m, 2H, CH_2NH), 2.94 (m, 2H, CH_2NTs), 7.29 (m, 4H, $C_6H_4CH_3$), 7.78 (m, 4H, $C_6H_4CH_3$); δ_C (100 MHz, $CDCl_3$) 21.7 ($C_6H_4CH_3$), 21.8 ($C_6H_4CH_3$), 24.6 (CH_2), 24.8 (CH_2), 31.7 (CH_2), 33.0 (CH_2), 43.4 (CH_2NH), 45.0 (CH_2NTs), 57.7 (*C*HNH), 60.5 (*C*HNTs), 127.3 (Ar*C*H), 127.4 (Ar*C*H) 129.9 (Ar*C*H), 130.0 (Ar*C*H), 137.1 (Ar*C*), 137.9 (Ar*C*), 143.5 (2 × Ar*C*), 143.6 (Ar*C*).

(±)-4-Methyl-*N*-{2[[4-methylphenyl)sulfonyl](2-[[(4-methylphenyl)sulfonyl]amino}ethylamino]cyclohexyl}benzenesulfonamide 6

To a solution of 4-methyl-*N*-{2-[(2-{[(4-methylphenyl)sulfonyl]amino}ethyl)amino] cyclohexyl}benzenesulfonamide **13** (200 mg, 0.43 mmol) in pyridine (20 cm^3) at 0 ˚C under a nitrogen atmosphere was added *p*-toluenesulfonyl chloride (81 mg, 0.43 mmol) in batches over 30 min. The orange solution was allowed to come to room temperature and stirred for a further 6 h, whereby the colour changed from orange to red. The reaction was quenched with ice (~100 g) and conc. HCl (25 cm^3). This mixture was extracted with dichloromethane (× 2, 25 cm^3), and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford a crude dark brown oil. Purification by column chromatography on silica (hexane:EtOAc:CH_2Cl_2 4:1:5) afforded a yellow solid (192 mg, 0.31 mmol, 72%); mp 77-79 ˚C. Found: MH^+ 466.1827. $C_{22}H_{31}O_4S_2N_3$ requires: 466.1834. υ□□□ (KBr, cm^{-1}) 3281 (s, NHTs), 3062 (w, C_6H_4), 2936 (s, CH), 2856 (m, CH), 1598 (s), 1453 (s) 1331 (s, SO_2NH), 1160 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 1.11 (m, 2H, *CH*$_2$), 1.25 (m, 1H, *CH*$_2$), 1.33 (m, 1H, *CH*$_2$), 1.61 (m, 1H, *CH*$_2$), 1.93 (m, 1H, *CH*$_2$), 2.42 (s, 3H, $C_6H_4CH_3$), 2.43 (s, 3H, $C_6H_4CH_3$), 2.44 (s, 3H, $C_6H_4CH_3$), 3.02-3.11 (m, 6H, 2 × C*H*$_2$NTs + C*H*$_2$), 3.22 (m, 1H, C*H*NTs), 3.37 (m, 1H, C*H*NTs), 5.20 (d, 1H, CHN*H*Ts), 5.31 (m, 1H, CHN*H*Ts), 7.31 (m, 6H, $C_6H_4CH_3$), 7.65 (d, J 8.3, 2H, $C_6H_4CH_3$) 7.77 (m, 4H, $C_6H_4CH_3$); δ_C (100 MHz, $CDCl_3$) 21.7 (3 × $C_6H_4CH_3$), 24.3 (*C*H$_2$), 25.5 (*C*H$_2$), 30.4 (*C*H$_2$NTs), 34.8 (*C*H$_2$NTs), 43.9 (*C*HNTs), 54.9 (*C*HNTs), 127.1 (2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 130.0 (2 × Ar*C*H), 130.2 (2 × Ar*C*H), 136.9 (Ar*C*), 137.2 (Ar*C*), 138.9 (Ar*C*), 143.6 (Ar*C*), 143.7 (Ar*C*), 144.2 (Ar*C*).

(±)-1,4,7-Tris[(4-methylphenyl)sulfonyl]dodecahydro-1*H*-1,4,7-benzotriazonine 3

Hexane-washed NaH (60% in oil, 12 mg, 0.48 mmol) in DMF (1 cm^3) was added to a solution of the 4-methyl-*N*-{2[[4-methylphenyl)sulfonyl](2-[[(4-methylphenyl)sulfonyl] amino}ethylamino]cyclohexyl}benzenesulfonamide **6** (150 mg, 0.24 mmol) in DMF (5 cm^3) at room temperature. The resulting solution was heated to 80 ˚C and a solution of ethyleneglycol ditosylate **7** (90 mg, 0.24 mmol) in DMF (1 cm^3) was added dropwise over 1h. During this period

the colour of the solution became dark brown. The reaction was stirred overnight at 80 ˚C and at completion was quenched by addition of water (10 cm^3). The volatiles were removed under reduced pressure (12 mm Hg) and the residue was dissolved in dichloromethane (15 cm^3). The organic layer was washed with water (× 2, 20 cm^3), dried (Na_2SO_4), filtered and evaporated to give a brown solid. Purification by column chromatography on silica (hexane:EtOAc:CH_2Cl_2 4:1:5) afforded a white solid (103 mg, 0.16 mmol, 67%); mp 260-262 ˚C. Found: C, 57.7; H, 5.9; N, 6.2; S, 14.9; MH^+ 646.2093. $C_{31}H_{39}O_6S_3N_3$ requires: C, 57.7; H, 6.1; N, 6.5; S, 14.9; MH^+ 646.2079. υ_{max} (KBr, cm^{-1}) 3065 (w, C_6H_4), 2928 (m, CH), 2865 (m, CH), 1326 (s, SO_2NH), 1153 (s, SO_2NH); δ_H (400 MHz, $CDCl_3$) 1.14 (m, 2H, CH_2), 1.27 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.79 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.35 (s, 3H, $C_6H_4CH_3$), 2.42 (s, 6H, $C_6H_4CH_3$), 2.62 (m, 1H, CH_2NTs), 3.07 (m, 1H, CH_2NTs), 3.28 (m, 3H, CH_2NTs), 3.48 (m, 3H, CH_2NTs), 3.75 (m, 1H, C*H*NTs), 4.89 (m, 1H, C*H*NTs), 7.29 (m, 6H, $C_6H_4CH_3$), 7.61 (d, J 8.3, 2H, $C_6H_4CH_3$), 7.76 (m, 2H, $C_6H_4CH_3$), 8.00 (m, 2H, $C_6H_4CH_3$); δ_C (100 MHz, $CDCl_3$) 21.7 (3 × $C_6H_4CH_3$), 24.7 (*C*H_2), 26.1 (*C*H_2), 29.0 (*C*H_2), 30.3 (*C*H_2), 47.1 (*C*H_2NTs), 52.4 (*C*H_2NTs), 55.0 (*C*H_2NTs), 55.8 (*C*H_2NTs), 60.2 (*C*HNTs), 68.2 (*C*HNTs), 127.3 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 129.9 (4 × Ar*C*H), 130.1 (2 × Ar*C*), 135.1 (Ar*C*), 137.5 (Ar*C*), 143.6 (Ar*C*), 144.2 (Ar*C*).

Notes and references

1 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.,* 1978, **43,** 2923–2925.

2 A. E. Martin, T. M. Ford and J. E. Bulkowski, *J. Org. Chem.,* 1982, **47**, 412-418.