1,4-Bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines in Synthesis. Intramolecular Alkylation Reactions and Stereoselective Synthesis of Anti-2,6-Disubstituted Piperidines

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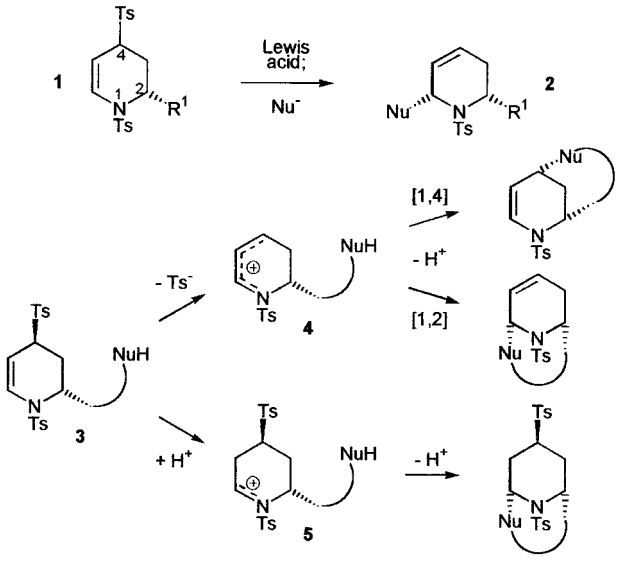
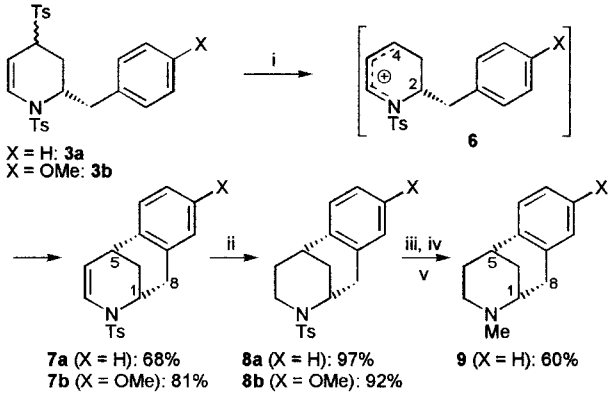
Abstract: 1,4-Bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **1** having R^1 containing aromatic groups undergo intramolecular electrophilic aromatic substitution reactions to give benzo-fused bicyclo[3.3.1] systems with chemoselectivities which depend on the nature of the acidic reagent used. Cationic hydrogenation of the C-5–C-6 double bond in substrates **1** substituted at C-6 provides an entry to anti-2,6-disubstituted piperidines upon desulfonylation.

In the preceding communication[1] we described the Lewis acid-assisted S_N1' reactions of 2-alkyl 1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines **1**, which give syn-2,6-disubstituted 1,2,5,6-tetrahydropyridines **2** in excellent yields and with complete regio- and stereoselectivity. As a natural development of this study, we became interested in the intramolecular reactions of the analogous compounds **3** possessing nucleophilic R^1 groups. It was anticipated that ionisation of **3** would immediately be followed by cyclisation to give bicyclic products. Compounds **3** may in principle form two distinct cationic species **4** and **5** by loss of tolylsulfinate ion and protonation respectively, and we wished to assess the extent to which these competing pathways could be controlled (Scheme 1). This Letter reports the results of these investigations, and describes new chemistry for the synthesis of anti-2,6-disubstituted piperidines.



Scheme 1

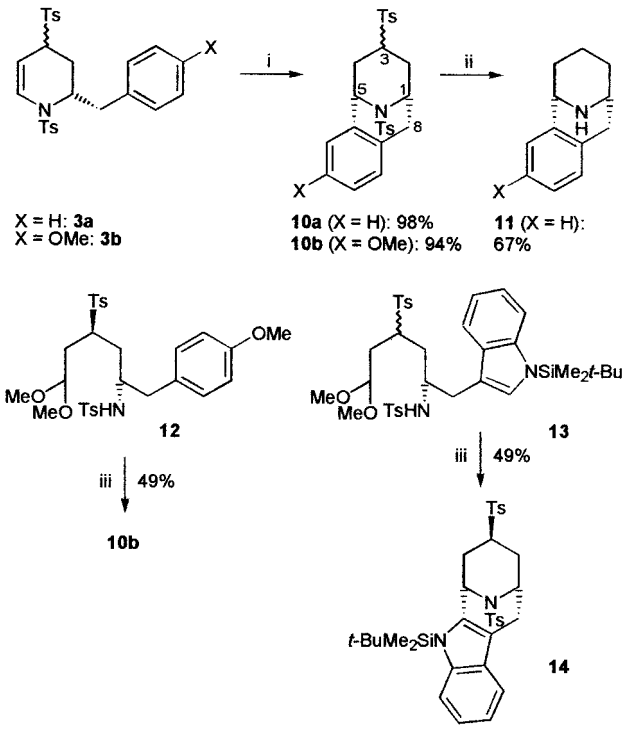
Compounds **3a**,**b** were made from 1,1-dimethoxy-3-(4-tolylsulfonyl)propane and respectively (*S*)-2-benzyl-1-(4-tolylsulfonyl)aziridine and (*S*)-2-[(4-methoxyphenyl)methyl]-1-(4-tolylsulfonyl)aziridine[2] in two steps as described in the preceding communication. Treatment of **3a** with $SnCl_4$ in dichloromethane gave exclusively and in good yield the tricycle **7a**, the product of interception of the putative cation **6** at the 4-position. The analogous substrate **3b** (X = OMe) similarly gave **7b** in high yield. The identities of **7a**,**b** were firmly established by the appearance in their ^1H nmr spectra of the methine signals characteristic of the enamide double bond. Both **7a** and **7b** were reduced by the action of triethylsilane and trifluoroacetic acid[3] to give tricycles **8a** and **8b**; **8a** was further elaborated by sequential desulfonylation[4] and two-step methylation to give 2-methyl-6,7-benzomorphan **9**[5] (Scheme 2).



Scheme 2: (i) $SnCl_4$ (2.2 eq), CH_2Cl_2 (0.05M), -78°C→rt, 1 h; (ii) Et_3SiH (2 eq), CF_3CO_2H (2 eq), CH_2Cl_2 (0.15M), rt, 1 h; (iii) 6% Na(Hg) (5 eq), 1:1 THF–MeOH (0.04M), reflux, 12 h; (iv) EtOCOCl (3 eq), Et_3N (1.5 eq), CH_2Cl_2 (0.22M); (v) $LiAlH_4$ (3 eq), Et_2O (0.1M).

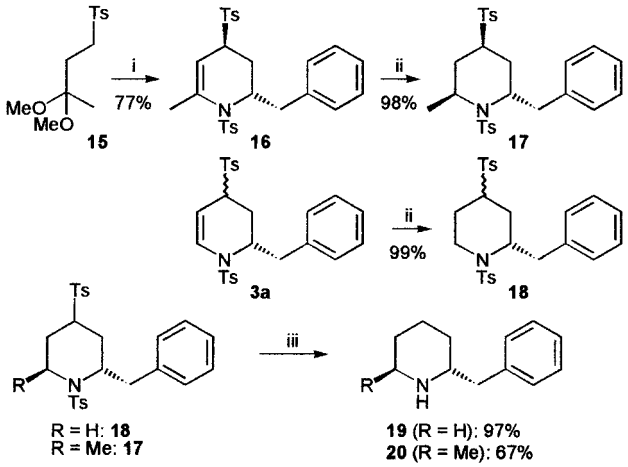
We next looked at the Brønsted acid-catalysed cyclisation reactions of **3**. Exposure of **3a** and **3b** to catalytic sulfuric acid in dichloromethane effected rapid, clean cyclisation to the tropane analogues **10a** and **10b** respectively. Tropane **10a** was cleanly desulfonylated using the standard Na(Hg) conditions. The facility with which the acid-mediated cyclisations occurred was such that during the formation of **3b** from its acyclic precursor **12**, compound **10b** was formed to a significant extent if larger quantities of acid and/or longer reaction times were employed. This tandem cyclisation was also observed when the tryptophan-derived compound **13** was treated with TMS-I according to one of the two standard tetrahydropyridine-forming methods described in the preceding paper; compound **14** was formed as a single diastereomer in moderate yield.[6] The acid-mediated cyclisation reactions of tetrahydropyridines **3a** and **3b**, and of the acyclic substrates **12** and **13** are depicted in Scheme 3.

The last part of this phase of our study was directed towards the development of a route to anti-2,6-disubstituted piperidines using the Brønsted acid-catalysed reactions described above. We reasoned that in*ter*molecular interception of iminium ions such as **5** (Scheme 1) with a hydride source would take place on the α-face of C-6 along an axial trajectory, such that any substituent at C-6 in the substrate would be oriented β in the product piperidine. Substrate **16**, bearing a methyl group at C-6 was readily assembled using the method used previously. Thus, reaction of the lithio-anion of sulfonylacetal **15**[7] with (*S*)-1-(4-tolylsulfonyl)-2-benzylaziridine, and brief treatment of the product with catalytic sulfuric acid in dichloromethane gave **16** essentially as a single stereoisomer.[8] Treatment of **16** with triethylsilane in the presence of trifluoroacetic acid in dichloromethane gave piperidine **17** as a single,



Scheme 3: (i) H_2SO_4 (cat.), CH_2Cl_2 (0.21M), rt, 30 min; (ii) 6% Na(Hg) (5 eq), 1:1 THF–MeOH (0.03M), reflux, 12 h; (iii) TMSI (6 eq), MeCN (0.1M), rt, 20 min.

2,6-anti diastereomer, as evidenced by X-ray crystallographic analysis (Figure).[9] Similarly, exposure of cyclisation substrate **3a** to the same reagents gave the piperidine **18**. Both **18** and **17** were cleanly desulfonylated using Na(Hg), giving respectively piperidines **19** and **20** (Scheme 4).[10]



Scheme 4: (i) *n*-BuLi (1 eq), THF–TMEDA (3:1, 0.4M), -78°C, add (*S*)-2-benzyl-1-(4-tolylsulfonyl)aziridine (0.9 eq), -78°C→rt, 12 h, then AcOH–THF (1 eq); H_2SO_4 (cat.), CH_2Cl_2 (0.2M), rt, 20 min; (ii) Et_3SiH (2 eq), CF_3CO_2H (2 eq), CH_2Cl_2 (0.15M), rt, 1 h; (iii) 6% Na(Hg) (5 eq), 1:1 THF–MeOH (0.03M), reflux, 12 h.

In summary, we have shown that 1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines containing aryl side-chains are useful intermediates both for the enantiospecific synthesis of 2-substituted and anti-2,6-disubstituted piperidines, and for the efficient assembly of structurally more complex, polycyclic frameworks with high stereoselectivities. Future contributions from this laboratory will describe the applications of these and related reactions to the synthesis of naturally occurring alkaloids.

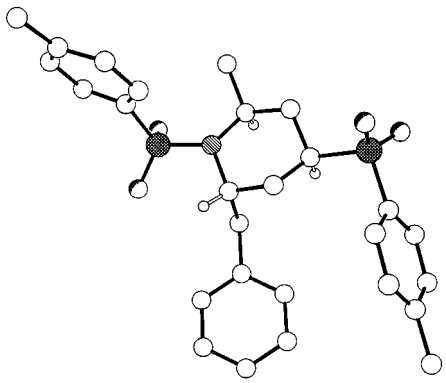


Figure: X-Ray structure of **17**

Acknowledgements

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References and Notes

1. Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett*, **1998**, 55.
2. (*S*)-2-[(4-Methoxyphenyl)methyl]-1-(4-tolylsulfonyl)aziridine was prepared from *O*-methyltyrosine (Aldrich Chemical Co.) by reduction to *O*-methyltyrosinol followed by one-pot *N*,*O*-ditosylation and cyclisation. All yields cited herein are of isolated, purified materials which gave satisfactory ^1H, ^{13}C nmr and ir spectra, and which showed low-resolution ms and either elemental combustion analysis or high-resolution ms characteristics in accord with the assigned structures.
3. For a review of ionic hydrogenation, see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633-651.
4. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477-3478.
5. For other syntheses, see: Takeda, M.; Jacobson, A. E.; Kanematsu, K.; May, E. L. *J. Org. Chem.* **1969**, *34*, 4154-4157; Stella, L.; Raynier, B.; Surzur, J. M. *Tetrahedron* **1981**, *37*, 2843-2854.
6. Compound **14** contains four of the five rings present in the naturally occurring indole alkaloid alstonerine. See: Peterson, A. C.; Cook, J. M. *J. Org. Chem.* **1995**, *60*, 120-129, and references cited therein.
7. Bonete, P.; Nájera, C. *Tetrahedron* **1995**, *51*, 2763-2776.
8. We speculate that under the acidic conditions used for the cyclisation reaction to form **16**, the minor diastereomer undergoes epimerisation via an ionisation–recombination mechanism.
9. We thank Professor David J. Williams and Dr Andrew J. P. White of this department for these determinations.
Crystal data for **17**: $C_{27}H_{31}NO_4S_2$, M = 497.7, monoclinic, space group $P2_1$ (no. 4), a = 11.124(1), b = 8.649(1), c = 13.236(1) Å, β = 90.40(1)°, V = 1273.5(2) Å^3, Z = 2, D_c = 1.298 g cm^{-3}, μ(Cu-K$_\alpha$) = 2.16 mm^{-1}, F(000) = 528, T = 293 K. A clear hexagonal blocky needle of dimensions 0.40 x 0.23 x 0.13 mm was used. 2266 Independent reflections were measured on a Siemens P4/PC diffractometer with Cu-K$_\alpha$ radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give R_1 = 0.040, wR_2 = 0.097 for 2080 independent observed absorption corrected reflections

[$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 128°$] and 296 parameters. The absolute chirality was determined unambiguously by use of the Flack parameter which refined to a value of –0.06(6). Computations were carried out using the SHELXTL PC program system version 5.03.10.

10. Experimental procedure for preparation of **7a**.
To a solution of **3a** (45.9 mg, 0.095 mmol) in dry CH_2Cl_2 (3 ml) at -78°C was added $SnCl_4$ (210 µl of a 1M solution in CH_2Cl_2, 0.21 mmol, 2.2 eq) and the mixture allowed to warm to rt. After 1 h the reaction was quenched with satd. aq. $NaHCO_3$ (3 ml), the layers separated and the aqueous layer extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (5 ml) and dried ($MgSO_4$). Chromatography (SiO_2, 70% ether–petrol) yielded **7a** (21 mg, 68%) as a colourless solid, mp 104-106°C; $[\alpha]_D^{26}$ +401.9 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2928, 1642, 1597, 1498, 1451, 1398, 1362, 1341, 1253, 1163, 1110, 1099, 1022, 938, 892, 745, 717, 684 cm^{-1}; δ_H (500 MHz) 7.72 (2H, d, J 8.5 Hz, H-2 and H-6 of Ts), 7.32 (2H, d, J 8.5 Hz, H-3 and H-5 of Ts), 7.25-7.23 (3H, m, Ph), 7.10-7.07 (3H, m, Ar), 7.05-7.03 (1H, m, Ar), 6.71 (1H, d, J 8 Hz, H-3), 5.27 (1H, td, J 7, 1.5 Hz, H-4), 4.52-4.50 (1H, m, H-1), 3.27 (1H, dd, J 18.5, 6 Hz, H-8), 3.30-3.24 (1H, m, H-5), 3.12 (1H, d, J 18.5 Hz, H-8), 2.44 (3H, s, CH_3 of Ts), 1.81 (1H, ddd, J 12.5, 4, 2.5 Hz, CHC*H*$_2$CH), 1.43 (1H, br d, J 12.5 Hz, CHC*H*$_2$CH); δ_C (75 MHz) 142.6, 140.5, 136.4, 132.9, 129.8, 129.6, 127.3, 126.8, 126.1, 125.9, 123.0, 112.3, 48.3, 37.9, 31.4, 30.3, 29.7, 25.9, 21.6; *m/z* (CI) 326 $[M+H]^+$, 172 (Found: $[M+H]^+$, 326.1197. $C_{19}H_{19}NO_2S$ requires $[M+H]^+$, 326.1215).
Experimental procedure for preparation of **10b**.
To a solution of **3b** (69.5 mg, 0.1358 mmol) in dry CH_2Cl_2 (3 ml) were added 2 drops of conc. H_2SO_4 giving a yellow-brown solution. After 30 min at rt the reaction was quenched with satd. aq. $NaHCO_3$ (3 ml), and diluted with water and CH_2Cl_2. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organics were washed with brine and dried ($MgSO_4$). Chromatography (20→30% EtOAc–petrol) yielded a mixture of diastereomers of **10b** (68.1 mg, 98%) as a colourless solid; υ_{max} (film) 2958, 2926, 1613, 1592, 1504, 1446, 1341, 1319, 1270, 1240, 1160, 1050, 813, 674 cm^{-1}; δ_H (400 MHz, major isomer) 7.61 (2H, d, J 8.5 Hz, H-2 and H-6 of Ts), 7.44 (2H, d, J 8.5 Hz, H-2 and H-6 of Ts), 7.33 (2H, d, J 8 Hz, H-3 and H-5 of Ts), 7.01 (2H, d, J 8 Hz, H-3 and H-5 of Ts), 6.67 (1H, d, J 8.5 Hz, aromatic CHC(OCH_3)CHC*H*), 6.63 (1H, dd, J 8.5, 2.5 Hz, aromatic CHC(OCH_3)C*H*CH), 6.48 (1H, d, J 2.5 Hz, aromatic C*H*C(OCH_3)CHCH), 5.13 (1H, br s, H-5), 4.44 (1H, m, H-1), 3.76 (3H, s, OCH_3), 3.04 (1H, tt, J 13, 4.0 Hz, H-3), 2.74 (1H, dd, J 17.5, 8.0 Hz, H-8), 2.46 (3H, s, CH_3 of Ts), 2.34 (1H, d, J 17.5 Hz, H-8), 2.29 (3H, s, CH_3 of Ts), 2.12 (1H, br d, J 12.5 Hz) and 2.02-1.87 (3H, m, H-2 and H-4); δ_C (100 MHz) 158.1, 145.2, 143.3, 136.6, 134.8, 132.7, 129.9, 129.3, 129.2, 129.2, 127.0, 124.8, 113.9, 110.8, 60.4, 55.3, 55.3, 52.1, 47.2, 32.7, 29.8, 21.7, 21.4; *m/z* (CI) 529 $[M+NH_4]^+$, 512 $[M+H]^+$, 358, 202 (Found: $[M+H]^+$, 512.1580. $C_{27}H_{29}NO_5S_2$ requires $[M+H]^+$, 512.1565).
Experimental procedure for preparation of **18**.
To a solution of **3a** (84 mg, 0.17 mmol) in dry CH_2Cl_2 (3 ml) was added triethylsilane (31 µl, 0.19 mmol, 1.1 eq) and trifluoroacetic acid (27 µl, 0.35 mmol, 2 eq). The reaction mixture was stirred at rt for 30 min and then quenched with satd. aq. $NaHCO_3$ (3 ml). The layers were separated and the aqueous layer extracted with ether (3 x 10 ml). The combined organic layers were washed with satd. aq. $NaHCO_3$ (5 ml), brine (5 ml) and dried ($MgSO_4$). Chromatography (SiO_2, 80→90% ether–petrol) yielded a mixture of diastereomers of **18** (84 mg, 99%) as a colourless solid, mp 179-190°C; ν_{max} (film) 2951, 2925, 2855, 1597, 1455, 1315, 1145, 1098, 938, 670, 603 cm^{-1}; δ_H (300 MHz, major isomer) 7.65 (2H, d, J 8 Hz, H-2 and H-6 of Ts), 7.55 (2H, d, J 8.5 Hz, H-2 and H-6 of Ts), 7.33 (2H, d, J 8 Hz, H-3 and H-5 of Ts), 7.21 (2H, d, J 8 Hz, H-3 and H-5 of Ts), 7.16-7.11 (3H, m, Ph), 6.91-6.88 (2H, m, Ph), 4.39-4.32 (1H, m, H-2), 3.93 (1H, dd with additional fine splitting, J 14, 2.5 Hz, H-6), 3.25 (1H, tt, 12.5, 3 Hz, H-4), 3.08 (1H, td, J 13.5, 2 Hz, H-6), 2.75-2.60 (2H, m, C*H*$_2$Ph), 2.45 (3H, s, CH_3 of Ts), 2.39 (3H, s, CH_3 of Ts), 2.10 (1H, br d, J 13 Hz, equatorial H-3 or equatorial H-5), 1.77 (1H, br d, J 12 Hz, equatorial H-5 or equatorial H-3), 1.68-1.45 (2H, m, axial H-3 and axial H-5); δ_C (75 MHz) 145.1, 143.5, 137.5, 137.1, 133.2, 129.9, 129.8, 129.1, 128.9, 128.7, 126.9, 126.7, 57.2, 53.6, 39.5, 36.1, 26.2, 24.2, 21.7, 21.5; *m/z* (CI) 501 $[M+NH_4]^+$, 484 $[M+H]^+$, 392 $[M-C_7H_7]^+$, 330, 238, 172, 108, 82 (Found: C, 64.34; H, 5.79; N, 2.83. $C_{26}H_{29}NO_4S_2$ requires C, 64.57; H, 6.04; N, 2.90%).