Sterically hindered fluorinated and brominated Tröger bases: synthesis and X-ray diffraction analysis†

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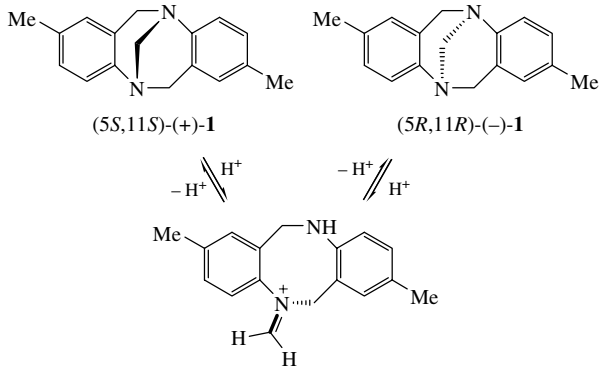
Two bis-*ortho*-substituted Tröger bases, bis(*ortho*-, *para*-trifluoromethyl) 2 and bis(*ortho-tert*-butyl, *para*-bromo) 3 were synthesised. The crystal structure investigation of 2 is presented.

Tröger bases (TBs) are readily available prime stereochemistry objects with chirality due to bridgehead nitrogen atoms. Various TBs have been synthesised, and the synthesis was optimised; the libraries of TBs are currently available.[2] One of their interesting applications is the use of TBs as DNA drugs.[3]

A complication in the enantioselective chemistry of TBs is the easy racemization in acidic media *via* an iminium intermediate (Scheme 1).[4] Thus, bis-*ortho*-substitution by methyl groups increases the barrier of racemization by ~30 kJ mol^{-1}.[4(d)] Bulky substitution at *ortho* positions may further increase this barrier. For instance, CF_3 groups with a high steric volume[5] also could provide interesting electronic properties to the TB core. Here, we describe the synthesis of two bis-*ortho*-substituted TBs: bis(*ortho*-, *para*-trifluoromethyl) **2** and bis(*ortho-tert*-butyl, *para*-bromo) **3**.

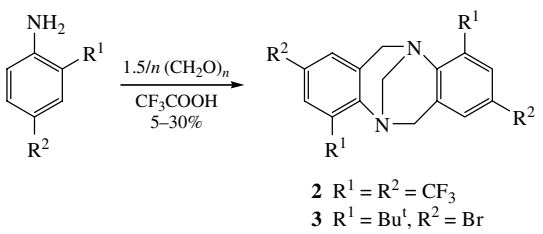


Scheme 1 Formation of the methyleneiminium intermediate during racemization of TB **1**.

TBs with *para*-, *ortho*- and *meta*-F substitution were synthesized previously.[6] Compound **2** is the first TB with CF_3 functionality. Compound **2** was isolated as a free base by crystallization of the reaction mixture from HCl/MeOH. Recrystallization from hexane gave crystals suitable for X-ray diffraction analysis. Compound **3** was isolated by chromatography on silica (EtOAc–petroleum ether, bp 70–100 °C).‡

Compound **2** crystallises in centrosymmetric space group *C*2/*c* (the molecule occupies a special position on a twofold axis). The crystal structure of **2** is similar to previously studied TBs in terms of conformation and bond angles.[7] The dihedral angle between the root mean square planes of phenyl rings is equal to 105.8°. The analysis of intermolecular contacts revealed that molecules in a crystal are assembled into chains by weak C–H···π bonds [C(9)–H(9A)···C(8) (1 – *x*, 1 + *y*, 1/2 – *z*)] with the pronounced directionality [H(9A)···C(8) 2.70 Å, C(9)–H(9A)–C(8) 174°].§

The analytical enantioseparation of compound **3** was achieved on commercial Chiralcel OD-H and Chiralpak AD columns (0.1% Pr^{i}OH–hexane); however, preparative separation was impossible because of solubility problems.



2 $R^1 = R^2 = CF_3$
3 $R^1 = Bu^t$, $R^2 = Br$

Scheme 2 Synthesis of sterically hindered compounds **2** and **3**.

† Asymmetric nitrogen, part 96. For part 95, see ref. 1.

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‡ The synthesis was carried out in trifluoroacetic acid as a solvent using 1 mol of aniline (aniline hydrochloride in the case of **3**) and 1.5 mol of paraformaldehyde. The reaction mixtures were kept at room temperature for 24 h; the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and shaken with aqueous Na_2CO_3; the solvent was evaporated, and the residue was purified.

(±)-**2**: yield 5%; colourless needles; mp 145–150 °C. ^{1}H NMR (400 MHz, [$^2H_6$]acetone) δ: 4.47 (s, 2H, NCH_2N), 4.75 (m, 4H, $2CH_2N$, AB spectrum, $\Delta\nu$ 160 Hz, $^2J_{ab}$ –18 Hz) 7.79 (s, 2H) 7.87 (s, 2H). ^{19}F NMR (188 MHz, [$^2H_6$]acetone) δ: –59.31 (s, 6F), –62.03 (s, 6F) (referred to $CFCl_3$). ^{13}C NMR (50 MHz, [$^2H_6$]acetone) δ: 57.45, 65.58, 121.55, 121.75, 123.54 (sept., *J* 4.7 Hz), 126.71, (q, *J* 27.0 Hz), 126.83 (q, *J* 29.5 Hz), 129.58 (br. s), 133.12, 151.32.

(±)-**3**: synthesised from 4-bromo-2-*tert*-butylaniline hydrochloride;[8] plates; yield 30%; mp 217–223 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 18H, Bu^t), 4.11 (s, 2H, NCH_2N), 4.13 (m, 4H, $2CH_2N$, AB spectrum, $\Delta\nu$ 244 Hz, $^2J_{ab}$ –17.4 Hz), 6.83 (d, 2H, ^4J 2.0 Hz), 7.26 (d, 2H, ^4J 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.35, 35.98, 58.15, 65.24, 118.08, 127.36, 128.70, 132.69, 147.61, 147.83. ESI-MS [M + H]$^+$: found, 491.06920; calc. for $C_{23}H_{29}N_2Br_2^+$, 491.06924.

§ *Crystallographic data*. Crystals of **2** ($C_{19}H_{10}F_{12}N_2$, M = 494.29) are monoclinic, space group *C*2/*c*, at 298 K, a = 16.209(3), b = 5.2843(11), c = 23.200(5) Å, β = 107.53(3)°, V = 1894.9(7) Å^3, Z = 4 (Z' = 0.5), d_{calc} = 1.733 g cm^{-3}, μ(MoKα) = 1.86 cm^{-1}, F(000) = 984. Intensities of 5494 reflections were measured with a Syntex P21 diffractometer [λ(MoKα) = 0.71072 Å, $\theta/2\theta$-scans, $2\theta < 60°$], 2752 independent reflections [R_{int} = 0.0400] were used in the further refinement. The structures were solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. For **1** the refinement converged to wR_2 = = 0.0932 and GOF = 0.947 for all independent reflections [R_1 = 0.0498 was calculated against F for 1546 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0 on IBM PC AT.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 610119. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.

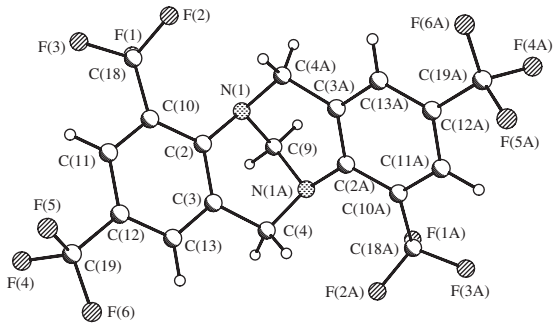

Figure 1 General view of **2**. Selected bond lengths (Å): N(1)–C(2) 1.421(2), N(1)–C(9) 1.463(2), N(1)–C(4A) 1.477(2), C(2)–C(3) 1.398(2), C(2)–C(10) 1.408(2), C(3)–C(13) 1.3859(2), C(3)–C(4) 1.514(2), C(10)–C(11) 1.378(2), C(10)–C(18) 1.509(2), C(11)–C(12) 1.392(2), C(12)–C(13) 1.3779(19), C(12)–C(19) 1.490(2); selected bond angles (°): C(2)–N(1)–C(9) 110.7(1), C(2)–N(1)–C(4A) 114.0(1), C(9)–N(1)–C(4A) 107.97(9), C(3)–C(2)–C(10) 119.0(1), C(3)–C(2)–N(1) 120.3(1), C(10)–C(2)–N(1) 120.6(1), C(13)–C(3)–C(2) 119.9(1), C(13)–C(3)–C(4) 118.7(1), C(2)–C(3)–C(4) 121.4(1), N(1A)–C(4)–C(3) 113.4(1), N(1A)–C(9)–N(1) 112.3(2).

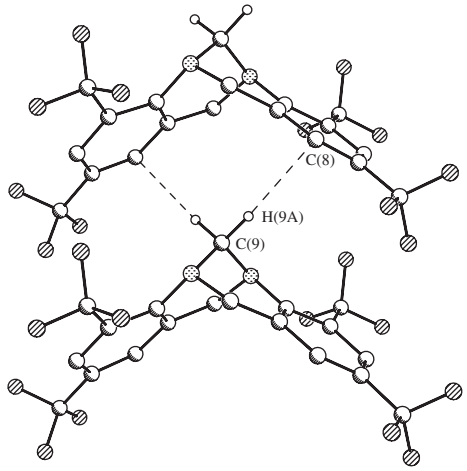

Figure 2 Fragment of a C–H···π bonded chain in the crystal of **2**.

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