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A Convenient Synthesis of Octahydro-pyrazino[1,2-a]pyrazine

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ABSTRACT

Octahydro-pyrazino[1,2-a]pyrazine has been prepared by a new and efficient method starting from 1,3-dichloro-2-propanol and *N*-tosylated diethylenetriamine. The structure of title compound was determined by spectroscopy and x-ray diffraction technique.

Key Words: Piperazine; Pyrazine; Macrocycle; Condensation; Cyclization.

The piperazine structure is particularly attractive, since it is present in a large number of biologically active compounds, and there is considerable

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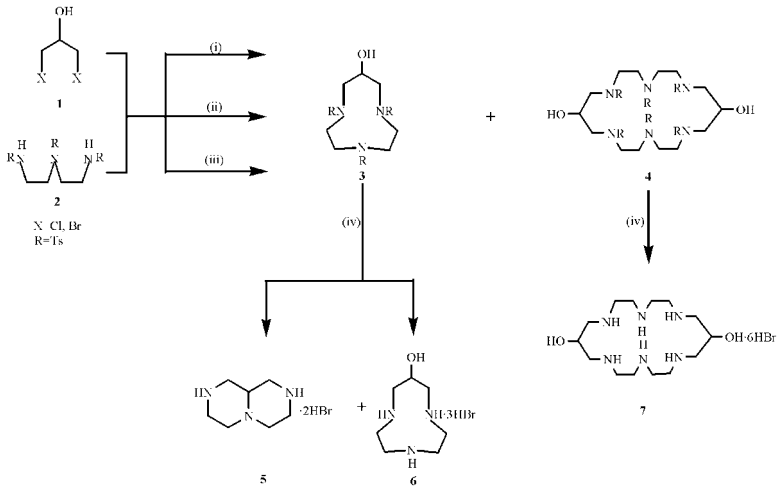
interest in the modification of the piperazine ring system.[1] The recent research results suggest a series of octahydro-pyrazino[1,2-a]pyrazines are useful as antiallergic agents.[2] Gubert et al. developed a route from 1,4-dibenzyl-2-ethoxycarbonylpiperazine for the synthesis of this ring system.[3] Under their conditions, this ring system was obtained with a low overall yield in six steps. Optimization of synthetic route to this ring system is still desirable.

Previously we have described a variety of interesting hydroxyl-substituted macrocyclic polyamines obtained by cyclization of 1,3-dichloro-2-propanol with di(poly)-*N*-tosylamides in the presence of sodium ethoxide in ethanol.[4,5] As an extension of this work, we employed three methods to synthesize macrocycle **3**. While we followed method (**i**), [2 + 2] condensation product **4** was isolated. However, the tosyl groups of macrocycle **3** were removed by treatment with 33% HBr/AcOH in the presence of a large excess of phenol to give octahydro-pyrazino[1,2-a]pyrazine **5** in high yield. The synthetic routes are outlined in Sch. 1. Table 1 shows that the best reaction condition is 48 hr for compound **5** formation.

The structure of compound **5** was established on the basis of spectroscopic data. The DEPT and gHSQC technique were employed to give us some important information (Fig. 1). From the structural formula, the high field signals at δ42.24 can be assigned to C5 and C7; signals at δ43.62 can be



Scheme 1. Reagents (yields): (i) NaOEt/EtOH (**3**, 45%; **4**, 10%); (ii) K_2CO_3/CH_3CN or K_2CO_3/EtOH (**3**, 21%); (iii) KF-Al_2O_3/EtOH (**3**, 30–45%); (iv) HBr/HOAc; PhOH (**5**, 10–63%; **6**, 30–85%; **7**, 90%).

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Table 1. The product distributions while the tosyl groups of macrocycle **3** were removed.

	Reaction time (hr)				
	24	36	48	72	96
Yield (%)					
Compound **5**	10	37	61	61	63
Compound **6**	85	55	31	33	30

assigned to C1 and C3; signals at δ49.51 can be assigned to C4 and C6; the low field signal at δ54.37 can be assigned to C2; and signal at δ54.47 can be assigned to DSS (as standard). The ^{1}H NMR spectra lines of H protons are complicated and hard to be assigned. In order to confirm the spectroscopic results, the structure of compound **5** was determined by x-ray crystallography showing one six-membered ring fused to the other six-membered ring in chair-chair conformation.[a] Figure 2 gives the ORTEP drawing of the crystal structure.

In conclusion, we have presented an efficient synthesis of octahydro-pyrazino[1,2-a]pyrazine that was carried out in good overall yield without any chromatography.

EXPERIMENTAL

General

Melting points were determined on an X4 microscope melting point apparatus and temperature uncorrected. The IR spectra were recorded on a

[a]X-ray crystallograph for **5**: $C_7H_{20}Br_3N_3O$, Mr = 401.99, crystal, 0.30 × 0.20 × 0.10 mm, monoclinic, Space group P2(1)/c, T = 293(2) K, a = 10.238(2) Å, b = 9.5959(19) Å, c = 14.020(3) Å, β = 91.04(3) Å, v = 1377.2(5) Å^3, Z = 4, $\lambda(MoK_\alpha)$ = 0.71073 Å, Dc = 1.924 Mg/m^3, μ = 8.767 mm^{-1}, F(000) = 784, 9573 intensities, collected $2.57^\circ < \theta < 27.48^\circ$, R1 ($I > 2\sigma(I)$) = 0.0457, wR2 = 0.0829, s = 0.849, largest diff. Peak and hole: 0.963 and −0.975 e Å^{-3}. Atomic coordinates, bond angles, bond lengths and thermal parameters assisted to this compound have been deposited at the Cambridge Crystallographic Data Centre in CIF file. CCDC number: 200701.

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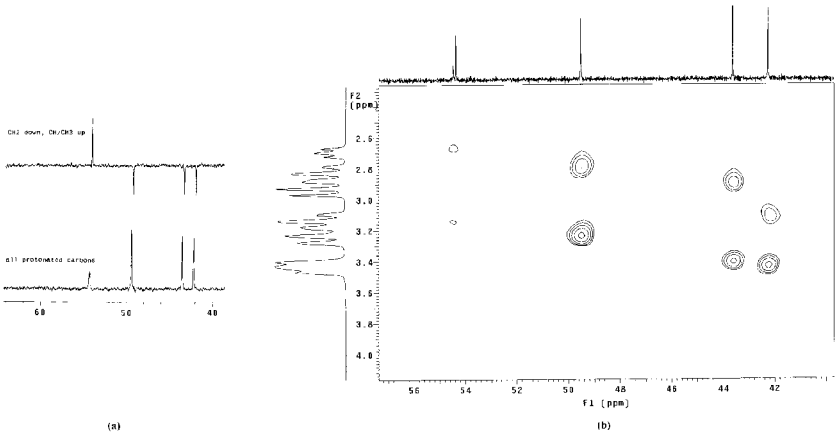

Figure 1. (a) The ^{13}C DEPT spectra for compound **5** (with DSS as standard) in D_2O solution; (b) the gHSQC spectra for compound **5** (with DSS as standard) in D_2O solution.

Nicolet Avatar 360 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury VX-300 MHz spectrometer using TMS as internal standard. The MS spectra were recorded on a ZAB 3F-HF spectrometer. Elemental analyses were conducted on a Perkin–Elmer 204B elemental analyzer.

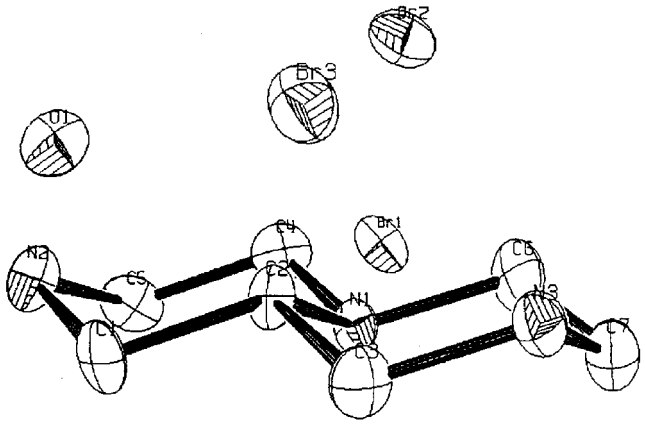

Figure 2. The structure of **5** crystal. Only nonhydrogen atoms are shown.

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Preparation of *N*-tosyl Macrocycles 3 and 4

Method (i)

Compounds **3** and **4** were obtained following the procedure described in Ref.[5]. **3**: (45% yield), M.p. 210–212°C. IR (KBr, ν, cm^{-1}): 3510, 1335, 1155, 1102. ^1H NMR ($CDCl_3$): δ2.42 (s, 9H, $ArCH_3$), 3.05–3.42 (m, 12H, NCH_2), 3.70 (s, 1H, OH), 4.46 (q, 1H, OCH), 7.20–7.81 (m, 12H, ArH). MS (FAB); m/z (%): 623 (62) $[M + 1]^+$. Anal. calcd. (%) for $C_{28}H_{35}N_3O_7S_3$, C 54.08, H 5.68, N 6.76; found: C 54.41, H 5.34, N 6.45. **4**: (10% yield), M.p. 280–282°C. IR (KBr, ν, cm^{-1}): 3521, 1331, 1150, 1096. ^1H NMR (DMSO): δ2.42 (s, 18H, $ArCH_3$), 3.02–3.20 (m, 24H, NCH_2), 3.75 (s, 2H, OH), 5.20 (q, 2H, OCH), 7.20–7.78 (m, 24H, ArH). MS (FAB); m/z (%): 1245 (18) $[M + 1]^+$. Anal. calcd. (%) for $C_{56}H_{70}N_6O_{14}S_6$, C 54.08, H 5.68, N 6.76; found: C 53.80, H 5.49, N 6.54.

Method (ii)

N-tosylated diethylenetriamine **2** (1.13 g, 2 mmol) and K_2CO_3 (0.69 g, 5 mmol) were suspended in CH_3CN (50 mL) under N_2. To this mixture, a solution of 1,3-dichloro-2-propanol **1** (0.26 g, 2 mmol) in CH_3CN (50 mL) was added at room temperature. The addition was completed over 2 hr after which the suspension was stirred for a further 20 hr then filtered. The solution was evaporated under vacuum and the residue was crystallized from EtOH giving **3** (0.25 g, 20.2% yield).

N-tosylated diethylenetriamine **2** and K_2CO_3 were suspended in refluxing EtOH under N_2. After the addition was complete, the suspension was refluxed for 20 hr then filtered. The solution was evaporated under vacuum and the residue was crystallized from EtOH giving **3** (21.1% yield).

Method (iii)

N-tosylated diethylenetriamine **2** (5.65 g, 10 mmol) and $KF-Al_2O_3$[6] (7.9 g) were suspended in refluxing EtOH (150 mL) under N_2. To this mixture, a solution of 1,3-dichloro-2-propanol **1** (1.30 g, 10 mmol) in EtOH (50 mL) was added. The addition was completed over 2 hr after which the suspension was refluxed for a further 20 hr then filtered. The solution was evaporated under vacuum and the residue was crystallized from EtOH giving **3** (1.87 g, 30.1% yield).

The yield improved when 1,3-dichloro-2-propanol was replaced with 1,3-dibromo-2-propanol (45.7% yield).

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Preparation of Compounds 5·2HBr and 6·3HBr

The *N*-tosyl macrocycle **3** (1.24 g, 2 mmol), 33%HBr/AcOH (30 mL) and phenol (2 g) were combined and stirred at 80–90°C for 48–96 hr. After being cooled to r.t., the solution was poured into dry Et_2O (200 mL) to give the red precipitate. **5**·2HBr and **6**·3HBr were separated by fractional crystallization from EtOH : H_2O (1 : 1 to 10 : 1) solutions. **5**·2HBr (0.49 g, 60.9% yield). M.p. >280°C (dec.). IR (KBr, ν, cm^{-1}): 3447, 3172, 1410, 1075. ^{1}H NMR (D_2O): δ2.61–3.40 (m, 13H, NCH_2, NCH). ^{13}C NMR (D_2O): δ42.24 (C5, C7), 43.62 (C1, C3), 49.51 (C4, C6), 54.37 (C2). Anal. calcd. (%) for $C_7H_{15}N_3 \cdot 3HBr \cdot H_2O$, C 20.02, H 5.29, N 10.01; found: C 20.22, H 5.41, N 10.14. **6**·3HBr (0.25 g, 31.1% yield). M.p. >280°C (dec.). IR (KBr, ν, cm^{-1}): 3435, 2932, 1457, 1137, 1044. ^{1}H NMR (D_2O): δ 3.01–3.40 (m, 12H, NCH_2), 4.21 (q, 1H, OCH). Anal. calcd. (%) for $C_7H_{17}N_3O \cdot 3HBr$, C 20.02, H 5.29, N 10.01; found: C 20.27, H 5.61, N 9.84.

Preparation of Compound 7·6HBr

The *N*-tosyl macrocycle **4** (1.24 g, 1 mmol), 33%HBr/AcOH (30 mL) and phenol (2 g) were combined and stirred at 80–90°C for 24 hr. After being cooled to r.t., the solution was poured into dry Et_2O (200 mL) and the red precipitate was recrystallized from EtOH to give **7**·6HBr (0.72 g, 89.6% yield). M.p. >280°C (dec.). IR (KBr, ν, cm^{-1}): 3422, 2999, 1443, 1127, 1023. ^{1}H NMR (D_2O): δ3.21–3.62 (m, 24H, NCH_2), 4.88 (q, 2H, OCH). Anal. calcd. (%) for $C_{14}H_{34}N_6O_2 \cdot 6HBr$, C 20.92, H 5.02, N 10.45; found: C 20.73, H 4.91, N 10.29.

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