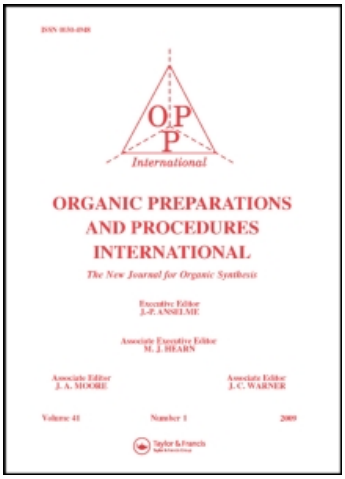

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NEW SYNTHESIS OF 1-AZABICYCLO[5.3.0]DECANE

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NEW SYNTHESIS OF 1-AZABICYCLO[5.3.0]DECANE

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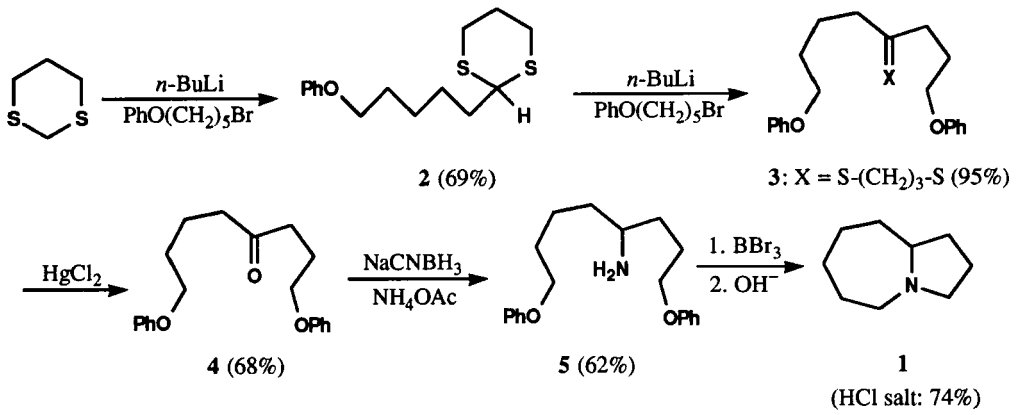
We have been interested in developing new conditions for the synthesis of 1-azabicyclo[5.3.0]decane (**1**). The synthesis of fused 7/5-heterobicyclic systems poses considerable difficulties, due in part to entropy losses upon cyclization which are not compensated by ring stability. Our approach to the synthesis of **1** is shown below.



Construction of the 9-carbon skeleton in **4** was performed using dithiane as a masked synthon for the carbonyl carbon.[1] The anion of dithiane was generated using *n*-BuLi. Alkylation with 5-bromo-1-phenoxypentane[2] furnished the dithioacetal **2** in 69% yield. The second alkylation with 3-bromo-1-phenoxypropane[3] yielded the desired dithioketal **3** very cleanly in 95% yield. Contrary to literature reports,[4] the one-pot sequential dialkylation of 1,3-dithiane with the above bromophenoxy-alkanes produced a mixture of dithioacetal **2**, dithioketal **3**, along with a number of volatile by-products, including thiols and phenol. The surprisingly different results between a one-pot and a stepwise dialkylation are difficult to explain, although a similar phenomenon has been observed

previously.[5] Desulfurization of **3** was achieved simply by refluxing with mercury(II) chloride in aqueous acetonitrile for 7.5 hrs, providing ketone **4** in 68% yield.

An alternate route, the synthesis of ketone **4**[6] *via* the Grignard reaction of $PhO(CH_2)_5MgBr$ and $PhO(CH_2)_3CN$, gave only poor yields of **4** (27%) and undesired by-products: 1-phenoxypentane, 1,10-diphenoxydecane and phenol. The low yield obtained in the Grignard reaction[7] was marginally improved (40%) using Canonne's conditions.[8] The conversion to amine **5** was carried out directly using sodium cyanoborohydride in the presence of ammonium acetate in methanol (62% yield). Cleavage of the phenoxy groups was achieved by treatment of a solution of **5** in dichloromethane with boron tribromide at 0°. The resulting dibromoamine **6** was converted into its hydrochloride salt in 83% yield. Cyclization to the final bicyclic product occurred by addition of a dilute aqueous solution of this hydrochloride salt, over a period of 6 hrs, to a stirred solution of 0.1N sodium hydroxide at 50° (74%).

The above route to 1-azabicyclo[5.3.0]decane **1** proceeds in reasonable yield and can be utilized in large scale preparations.

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 or a Pye-Unicam SP 1050 spectrophotometer. Samples were run either as nujol mulls (solids) or as liquid films. NMR spectra were recorded on a Perkin-Elmer R12B spectrometer (^1H at 60 MHz, ^{19}F at 56.4 MHz) or on a Perkin-Elmer R14 instrument (^1H at 100.1 MHz). Unless noted the solvent used was $CDCl_3$; TMS was used as the internal standard. All mass spectra were obtained on a Kratos MS 80 mass spectrometer using a DS 55 data processing unit; only selected ions are reported. TLC was carried out using Kieselgel 60 F_{254} (Merck) silica-gel precoated 0.25 mm plates. Column chromatography was carried out on either activated alumina 100 mesh or silica-gel Kieselgel 60, 70-230 mesh, type 7734 (Merck). Solutions of organic compounds isolated by extraction were dried over anhydrous magnesium sulfate and concentrated at reduced pressure on a rotary evaporator. All solvents were dried and distilled using standard procedures. All nonaqueous reactions were carried out under anhydrous conditions and N_2 atmosphere.

2-(5-Pentoxybenzene)-1,3-dithiane (2).- To a solution of freshly sublimed 1,3-dithiane (35.3 g, 0.294 mol) in tetrahydrofuran (THF) (600 mL), cooled to -40° was added dropwise *n*-BuLi (0.303 mol) in THF. The resulting mixture was stirred and allowed to warm up to -20° over a period of 1.5 hr. It was then recooled to -78° before 5-bromo-1-phenoxypentane[2] (70.7 g, 0.291 mol) in THF (200 mL) was added dropwise over 40 min. The reaction was then allowed to warm up to room temperature and the solvents were removed under reduced pressure. The residual oil was mixed with water (1.2 L) and extracted with dichloromethane (3 x 350 mL). The organic layer was then washed with brine (250 mL), dried and concentrated to give a yellow oil (85.9 g) which crystallized on standing and was recrystallized from petroleum ether (40-60°). The mother liquors were treated as follows: distillation *in vacuo* at 0.1 mmHg separated the volatile impurities (14 g). The residual oil was then recrystallized from petroleum ether (40-60°). The combined crystalline fractions (57 g, 69%

yield) consisted of pure **2**, mp. 50.5-51.5°. IR: 1600, 1580, and 1490 cm^{-1}; MS (m/z): 282 (12, M^+), 189 (10), 119 (100), 94 (43), 77 (20); ^1H NMR δ 1.10-2.25 (10H, m, CH_2'), 2.6-3.0 (4H, m, CH_2S), 3.93 (3H, m, CH_2O, CH), 6.7-7.5 (5H, m, aromatic H).

Anal. Calcd for $C_{15}H_{22}OS_2$: C, 63.78; H, 7.85; S, 22.70. Found: C, 64.10; H, 7.80; S, 23.00

2-(5-Pentoxybenzene)-2-(3-propoxybenzene)-1,3-dithiane (3).- The above procedure was applied to the preparation of **3**. The anion of **2** (25.14 g, 0.089 mol), generated by treatment with *n*-BuLi (0.092 mol) in THF (175 mL) was reacted with 3-bromo-1-phenoxy propane[3] (19.4 g, 0.090 mol) in THF (65 mL). After workup, purification by column chromatography (silica gel, 1:1 CH_2Cl_2 -CCl_4), afforded **3** (35.2 g, 95% yield) as a colorless oil. IR: 1600, 1580 and 1490 cm^{-1}; ^1H NMR δ 1.2-2.3 (14H, m, CH_2), 2.8 (4H, t, J = 6 Hz, CH_2S), 3.94 (2H, t, J = 6 Hz, CH_2O), 3.97 (2H, t, J = 6 Hz, CH_2O), 6.7-7.5 (10H, m, aromatic H).

Anal. Calcd for $C_{24}H_{32}O_2S_2$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.10; H, 7.75; S, 15.70

1,9-Diphenoxy-4-nonanone (4).- A mixture of $HgCl_2$ (48.7 g, 0.179 mol), water (100 mL), and **3** (33.9 g, 0.0815 mol) in acetonitrile (400 mL) was refluxed for 7.5 hrs with vigorous stirring. It was then left to stir overnight at room temperature and the white solid filtered. After washing with dichloromethane /hexane (1/1, 350 mL), the filtrate separated in two layers. The top layer was then washed with 5M ammonium acetate (100 mL), dried and concentrated. Recrystallization from hexane furnished **4** (13.1 g, 68% yield) as white platelets, mp. 66-68°. IR: 1705 cm^{-1}; ^1H NMR δ 1.2-2.8 (12H, m, CH_2), 3.93 (4H, t, J = 6 Hz, CH_2O), 6.7-7.5 (10H, m, aromatic H).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.20; H, 8.15

1,9-Diphenoxy-4-nonanamine (5).- A solution of sodium cyanoborohydride (0.7 g, 0.009 mol), ammonium acetate (12.0 g, 0.156 mol) and methanol (150 mL) was mechanically stirred while 1,9-diphenoxy-4-nonanone **4** (5.0 g, 0.015 mol) in dichloromethane (40 mL) was added dropwise. Stirring was continued for 68 hrs. at room temperature before the slow addition of conc. hydrochloric acid (20 mL). The solvents were removed *in vacuo* and the residual white solid was mixed with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The bottom layer was separated and its pH brought to 10 with potassium hydroxide. The aqueous solution was then saturated with sodium chloride and extracted with diethyl ether (3 x 80 mL). The ethereal extracts were dried and concentrated to yield **5** (3.1 g, 62% yield). An analytical sample was prepared by recrystallization from water followed by a second recrystallization from acetonitrile. The white crystals obtained had a mp. 108-110°. IR: 3400-3260, 1600, 1588, 1495 cm^{-1}; ^1H NMR: δ 1.15-2.15 (14H, m, CH_2), 2.45-3.00 (1H, m, CH), 3.95 (4H, t, J = 6 Hz, CH_2O), 6.75-7.5 (10H, m, aromatic H).

Anal. Calcd for $C_{21}H_{30}ClNO_2$: C, 69.31; H, 8.31; N, 3.85; Cl, 9.74

Found: C, 69.50; H, 8.30; N, 4.15; Cl, 9.40

1,9-Dibromo-4-nonanaminium Chloride (6•HCl).- Boron tribromide (2.5 mL, 26 mmol) in dry dichloromethane (16 mL) was added *via* a syringe into a solution of 1,9-diphenoxy-4-nonanamine **5** (5.6 g, 17 mmol) in dichloromethane (50 mL) at 0°. The resulting mixture was allowed to warm up

to room temperature overnight and was quenched by the cautious addition of water (60 mL). The organic layer was then separated and concentrated. Water (5 mL) was added to it and the viscous mixture was washed with diethyl ether (3 x 30 mL) to remove phenol. Finally, the aqueous suspension was mixed with dichloromethane (100 mL). The organic phase was dried, filtered and saturated with dry hydrogen chloride, after concentration, (**6•HCl**) (4.8 g, 83% yield) was obtained as a viscous oil. IR: 3000, 2600, 2000 cm^{-1}; ^1H NMR: δ 1.3-2.8 (12H, m, CH_2), 3.15-3.70 (5H, m, CH_2Br, CH), 8.2 (3H, br s, NH_3).

1-Azabicyclo[5.3.0]decane (1).- A solution of 1,9-dibromo-4-nonanaminium chloride (**6•HCl**) (1.1 g, 3.3 mmol) in water (187 mL) was added dropwise to a stirred solution of 0.1N sodium hydroxide (1 L) at 50°, over a period of 6 hrs. When the addition was complete, the mixture was acidified with 4N hydrochloric acid (50 mL) and concentrated to approximately 10% of its initial volume. It was turned alkaline by addition of 1.5N sodium hydroxide (50 mL) and was extracted with diethyl ether (3 x 50 mL). After drying, the ethereal extracts were saturated with dry hydrogen chloride, and concentrated to yield **1** as its hydrochloride salt (430 mg, 74% yield). An aliquot corresponding to the free amine (82 mg, 0.59 mmol), a colorless liquid with a characteristic odor, was dissolved in ethanol (2 mL) and added dropwise to a saturated solution of picric acid (115 mg, 0.50 mmol) in ethanol at 30°. A yellow precipitate formed, which was then recrystallized twice from ethanol, furnishing the corresponding picrate salt as yellow needles (155 mg), mp. 205-208° (dec.), lit.[9] mp. 213° (dec.). IR: 3500-3200 cm^{-1} (R_3N^+H); ^1H NMR: δ 1.3-2.1 (12H, m, CH_2), 2.1-2.7 (3H, m, CH-N, CH), 2.9-3.3 (2H, m, CH-N).

Anal. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.60; H, 5.20; N, 14.90

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