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A CONVENIENT SYNTHESIS OF MACROCYCLIC PARACYCLOPHANES

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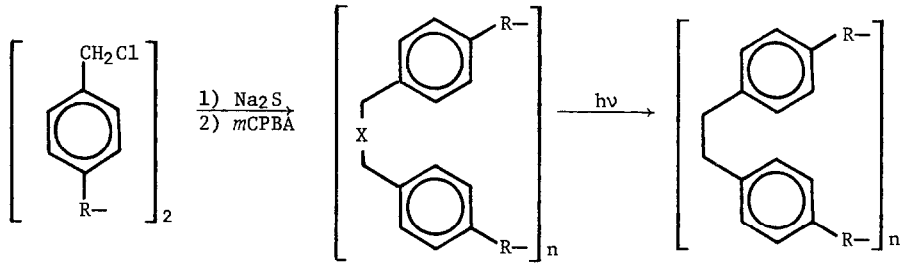
Abstract: *[2.n]-paracyclophanes are made from 1,n-bis-[4-chloromethylphenyl]-alkanes.*

Frustrated in our attempts to synthesize macrocyclic paracyclophanes via Würtz[1] coupling, but needing a series of macrocyclic rings to serve as standards in HPLC analysis, we turned our attention to alternative means of achieving this end. Photoextrusion of SO_2 has been used in the synthesis of [2.2]-paracyclophane and a variety of analogous compounds.[2] Since oligomers with three and five repeat units are especially interesting where knots are concerned, Na_2S was used to link the ends of 1,n-*bis*-[4-chloromethylphenyl]-alkanes in a single step. Treatment of a hot, saturated ethanol solution of 1,12-*bis*-[4-chloromethylphenyl]-dodecane[3] with a stoichiometric quantity of Na_2S results in the formation of a mixture of thioparacyclophanes. Oxidation of the sulfur and photoextrusion of SO_2 proceed in very high yield.

Scheme



1 (2a) X = S (2b) X = SO_2 3

R = $(CH_2)_6$; n = 1, 2, 3

A. 2-thia-[3.12]-paracyclophane (2a): 1,12-*bis*-[4-chloromethylphenyl]-dodecane (1) (2 g, 4.77 mmole) is dissolved in 95% ethanol (850 mL) and heated to boiling. A solution of Na_2S (1.14 g, 4.22 mmole) in 25 mL of water is added in one portion with vigorous stirring. The flask is fitted with a condenser and the milk-white solution is refluxed overnight, and filtered hot. The solid residue contains a mixture of the dimer and higher oligomers; the filtrate contains the monomer which crystallizes on cooling. The crude 2,thia-[3.12]-paracyclophane residue is dissolved in hot methanol (150 mL), cooled to ambient temperature and

filtered. The combined filtrates are treated with water (~40 mL), and the pure monomer which precipitates is collected, and the procedure repeated until a precipitate no longer forms upon the addition of water. The residue is dried in air to give 0.86 g (47% yield) of 2-thia-[3.12]-paracyclophane (2a) which is sufficiently pure for use in the next step. Recrystallization from methanol/water gives white crystals (m.p. = 67°C).

B. 2-dioxothia-[3.12]-paracyclophane (2b): A 250 mL Erlenmeyer flask equipped with a magnetic stirrer is charged with 1.235 g (7.15 mmol) of 85% *m*-chloroperbenzoic acid,[4] 25 mL of dichloromethane, and 0.86 g (2.26 mmol) of 2-thia-[3.12]-paracyclophane (2a) in 50 mL of dichloromethane. The mixture is stirred vigorously for 30 min, then poured into 100 mL of 5% aqueous $NaHSO_3$. The layers are separated and the organic phase is washed with 50 mL of 5% $NaHSO_3$, and 25 mL portions of 5% $NaHCO_3$, two 25 mL portions of water, and dried over anhydrous $MgSO_4$. The dichloromethane is removed by rotary evaporation leaving the crude sulfone (2b) as a white solid (m.p. = 173°C), 0.90 g, 96.6% yield which is sufficiently pure for use in the next step.

C. [2.12]-paracyclophane (3): A 1-L pyrex photolysis vessel[5] equipped with a magnetic stirrer, a capillary for introducing N_2, a bubbler, and a medium pressure Hg lamp in a Vycor cooling jacket is charged with 0.47 g of crude sulfone (2b) from the preceding section in 1 L of benzene. The solution is N_2 purged with stirring for 20 min and irradiated 16-20 hr.[6] The yellow solution is concentrated using rotary evaporation and purified by flash chromatography to give a water white oil which could be distilled under reduced pressure (Kugelrohr) to give analytically pure 3.[7]

The procedure outlined above can be successfully applied to each of the other oligomers to obtain pure samples of the macrocycles. The synthesis of unknotted macrocyclic paracyclophanes lays the basis for detecting and characterizing knotted paracyclophanes.

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4. 2-thia-[3.12]-paracyclophane (2). ^{1}H nmr ($CDCl_3$) δ: 6.95 and 6.85 (8H,AB), 3.62(4H,s), 2.53(4H,t), 1.56(4H,bm), 1.21(16H,s). ^{13}C nmr ($CDCl_3$) δ: 141.14, 136.37, 128.89, 128.52, 36.35, 34.84, 30.50, 28.17, 27.96, 27.69. ir (CCl_4) cm^{-1}: 2922, 2847, 1507. Anal. Calc'd for $C_{26}H_{36}S$ C: 82.04%; H: 9.53%. Found C: 82.19%; H: 9.32%.

5. 2-dioxothia-[3.12]-paracyclophane (3): ^{1}H nmr ($CDCl_3$) δ: 7.05 and 6.95 (8H,ab), 4.19 (4H,s), 2.61(4H,t), 1.61(4H,bm), 1.23(16H,s). ^{13}C nmr ($CDCl_3$) δ: 143.31, 130.41, 128.95, 125.32, 59.65, 34.62, 30.02, 27.96, 27.79, 27.42. ir (CCl_4) cm^{-1}: 2932, 1330. Anal. Calc'd for $C_{26}H_{36}SO_2$ C: 75.68%; H: 8.79%. Found C: 75.67%; H: 8.71%.

6. [2.12]-paracyclophane (4). ^{1}H nmr ($CDCl_3$) δ: 6.90 and 6.75 (8H,ab), 2.90(4H,s), 2.52 (4H,t), 1.55(4H,bm), 1.25(16H,s). ^{13}C nmr ($CDCl_3$) δ: 139.68, 137.78, 128.95, 127.98, 36.41, 34.40, 30.34, 28.01, 27.58. ir (CCl_4) cm^{-1}: 2931, 2845, 1520. Anal. Calc'd for $C_{26}H_{36}$ C: 89.59%; H: 10.41%. Found C: 89.76%; H: 10.42%.

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