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Multiply Bridged Acetylenic Thiacyclophanes

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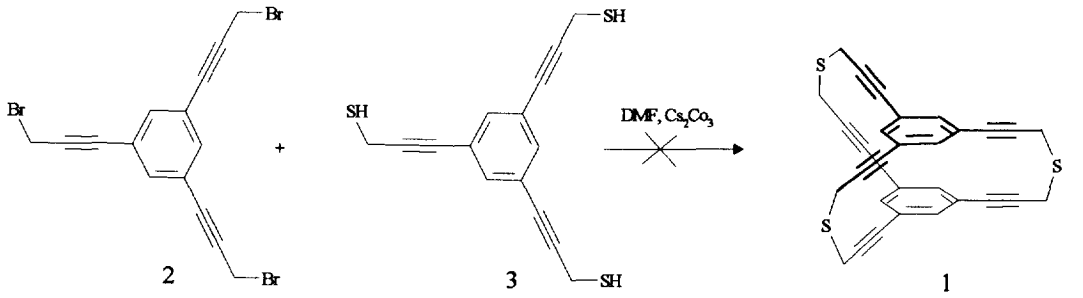
Abstract: The 4,17,30-trithia-[7_3](1,3,5)cyclophane (**1**) has been prepared by a two-stage, palladium assisted coupling of propargylOTHP with 1,3,5-tribromobenzene, followed by sulfide ring closure. The intermediate (**8**) on deprotection, followed by bromination and reaction with Na_2S gives **1** in 58% yield.

Interest in high carbon containing macromolecules has led us to investigate synthetic routes to thiacyclophanes containing multiple acetylenic bridges. The 1,3,5-cyclophane **1** (7,19,28-trithiatetracyclo-[11.11.7.$1^{3,23}$.$1^{11,15}$]tritriaconta-1,3(32),11,13,15(33),23-hexaene-4,9,16,21,25,30-hexayne) is appealing not only due to its symmetry, but because it contains a C_{30} skeleton possessing two sets of 18 conjugated π electrons. Extrusion of sulfur from **1** could produce a $C_{30}H_6$ hydrocarbon spheroid having no sp^3 carbon atoms.[1] Utilizing the palladium and copper(I) mediated coupling of acetylenes and aryl halides,[2] compound **1** can be prepared in good yield. The attempted six fold coupling of hexaiodobenzene with acetylenes is also discussed.

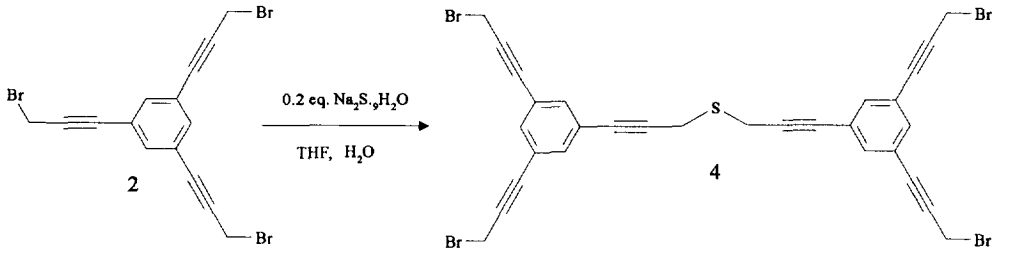
The reaction of alkyl halides and mercaptans in the presence of cesium ion has been extensively employed in the preparation of various thiacyclophanes.[3] This process involves the addition of the two reactants into a suspension of cesium carbonate under high dilution conditions. The three fold coupling of 1,3,5-tribromobenzene with the tetrahydropyranyl ether of propargyl alcohol (propargylOTHP) in the presence of cuprous iodide (6.5 mole %), bistriphenylphosphine palladium chloride (1.7 mole %), and DBU (4 eq.) in refluxing benzene is complete in 4 hours to give the symmetrical triacetylenic derivative (96% yield), which on deprotection followed by bromination yielded the tribromide **2** in an overall yield of 78%.

Treatment of **2** with excess potassium thioacetate (in methanol) and acid catalyzed hydrolysis gave the trithiol **3**. The reaction of **2** with **3**, however proved inapplicable to the synthesis of **1** due to the instability of **3** under conditions required for the cyclization. Treatment of **2** with 1.5 eq. of sodium sulfide (in THF:H_2O; 2:1) under high dilution conditions yielded less than 1% of **1**, with the rest of the material forming a polymeric mixture of sulfides. Reaction of **2** with 0.2 eq. of sodium sulfide (in THF:H_2O; 2:1), on the other hand,



produced compound **4** in 89% yield based on recovered starting material, and only small amounts of oligomeric products. In addition, unreacted starting material could be recovered and reused for the same transformation. Further treatment of **4** with 2 equivalents of sodium sulfide (THF : H_2O; 2:1) under high dilution conditions gave the desired cyclophane **1** in a yield of 80%.

While this methodology was effective in the synthesis of **1**, complete conversion of the tribromide to **4** is impossible and the purification of the reaction mixture is tedious on a large scale. Because of these

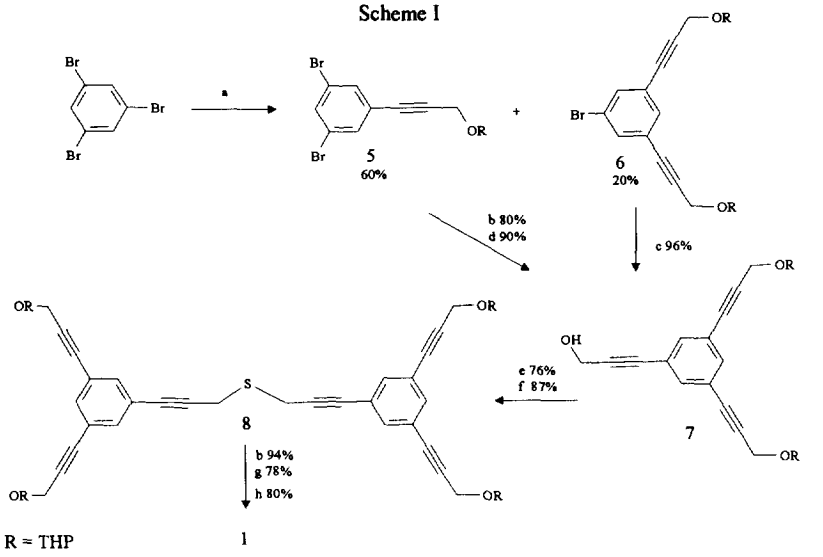


drawbacks, a different approach involving the sequential introduction of the acetylenic substituents was undertaken. The reaction of 1,3,5-tribromobenzene with one equivalent of propargylOTHP (1 hr) gives an easily separable mixture of compounds **5** and **6** (60 and 20% yields, respectively), Scheme I. The successively slower rates of coupling of **5** and **6** with respect to tribromobenzene are in accordance with earlier observations that electron withdrawing groups assist the reaction while electron donating groups retard the coupling process.[4]

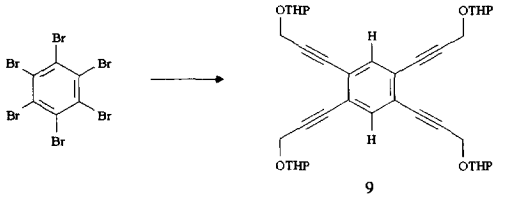
Hydrolysis of the THP protecting group of **5**, followed by further coupling of the dihalide with propargylOTHP gave **7**. Compound **7** was also obtained by the palladium catalyzed coupling of **6** with propargyl alcohol. Tosylation of **7** followed by treatment with sodium sulfide produces **8** in high yields. The trithiacyclophane **1** is obtained in a yield of 58% after deprotection of the hydroxyl groups, bromination of the resulting free alcohols, and nucleophilic displacement by sulfide. The structure of **1** has been confirmed by X-ray crystallography.[5]

The sixfold coupling of hexabromobenzene and acetylenes in poor to fair yields has been reported.[6] Several attempts to couple hexabromobenzene with propargylOTHP failed and the only isolable product, albeit in 15% yield was **9**, resulting from reduction at the para positions of the aromatic ring.[4b, 6b]

Scheme I

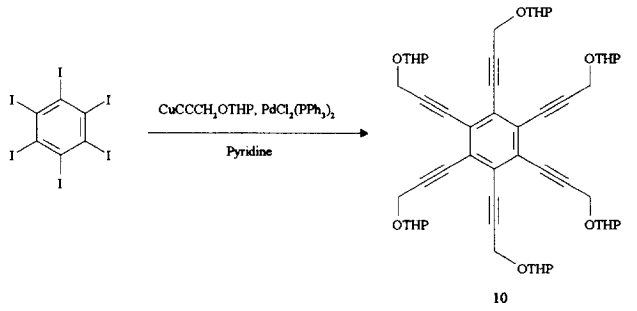


a) 1eq. propargylOTHP, $PdCl_2(PPh_3)_2$ (0.5 mole%), CuI (3.3 mole%), DBU, C_6H_6, reflux, 30 min. b) CSA (cat.)/MeOH. c) excess propargyl alcohol, $PdCl_2P(Ph_3)_2$ (0.8 mole%), CuI (7.7 mole%), DBU, C_6H_6, reflux, 60 hr. d) excess propargylOTHP, $PdCl_2P(Ph_3)_2$ (1.6 mole%), CuI (15 mole%), DBU, C_6H_6, reflux, 10 hr. e) NaH, TsCl, THF. f) $Na_2S{\cdot}9H_2O$, THF/H_2O. g) PBr_3, THF. h) 2eq. $Na_2S{\cdot}9H_2O$, THF/MeOH.



Increasing the quantity of copper iodide in such cross coupling reactions has been found to improve yields in cases where the aromatic ring has electron donating substituents. This has been rationalized by the more efficient displacement of the halide in the oxidative adduct $(PPh_3)_2PdAr(X)$, due to the greater concentrations of the cuprous acetylide present in the reaction mixture.[7] While copper acetylides are known to substitute aryl halides at temperatures greater than 100°C, this process is greatly facilitated in the presence of palladium and proceeds smoothly at room temperature.[4a,8]

When hexabromobenzene is treated with the cuprous acetylide of propargylOTHP (CAUTION![9]) in pyridine in the presence of bistriphenylphosphine palladium chloride, the desired hexaacetylene is obtained in a 10% yield, this is greatly improved with hexaiodobenzene and **10** is obtained in a yield of 70%. The reaction may be performed using a slight excess of the acetylide as opposed to those where the free acetylene is used, and the absence of viscous byproducts[6b] greatly simplifies isolation of the reaction product. A typical experiment is as follows: 5 g hexaiodobenzene (5.99 mmole), 8.5 g of the cuprous acetylide (42 mmole, 7eq.), and 300 mg bistriphenylphosphine palladium dichloride (7.1 mole %) are placed in a 200 mL, 2 neck round bottomed flask. The system is placed under a nitrogen atmosphere and 100 mL anhydrous, degassed pyridine



10

is added with vigorous stirring. On completion of the reaction, all the solvent is evaporated at reduced pressures, and the mixture dissolved in methanol and filtered to separate the inorganic material present. Evaporation of the methanol and flash chromatography gave **10** as colorless crystals, 3.12 g (57%).[10]

References and notes.

1. Boekelheide, V; Hollins, R.A. *Angew. Chem. Int. Ed. Eng.* **1969**, *8*, 274; Boekelheide, V. *Top. Curr. Chem.* **1983**, *113*, 87.
2. Sonogashira, K; Tohda, Y; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467; Alami, M; Ferri, F; Linstrumelle, G., *ibid.*, **1993**, *34*, 6403; Paley, R.S; Lafontaine, J.A; Ventura, M.P., *ibid.* **1993**, *34*, 3663.
3. Voglte, F; Klieser, B. *Synthesis* **1982**, 294; Klieser, B; Vogtle, F. *Angew. Chem. Int. Ed. Eng.* **1982**, *21*, 618.
4. a. Stephens, R.D; Castro, C.E. *J. Org. Chem.* **1963**, *28*, 3313. b. Neenan, T.X; Whitesides, G.M., *ibid.* **1988**, *53*, 2489.
5. Mague, J.T; Ensley, H.E; Mahadevan, S. *Acta. Cryst.* **1995**, *C51*, 2595.
6. a. Diercks, R; Armstrong, J.C; Boese, R; Volhardt, K.P.C. *Angew. Chem. Int. Ed. Eng.* **1986**, *25*, 268; Boese, R; Green, J.R; Mittendorf, J; Mohler, D.J; Volhardt, K.P.C. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 1643. b. Tao, W; Nesbitt, S; Heck, R.F. *J. Org. Chem.* **1990**, *55*, 63.
7. Zhou, Q; Carrol, P.J; Swager, T.J. *J. Org. Chem.* **1984**, *59*, 1294.
8. Beletskaya, I.P. *J. Organomet. Chem.* **1983**, *250*, 551.
9. The cuprous acetylide of propargylOTHP is relatively stable but caution should be used with less stable cuprous acetylides.
10. All new compounds gave satisfactory physical/spectral data. For **1**: mp. 170°C (decomp); IR (KBr) 3057, 2934, 2894, 2222, 1585, 1400; ^{1}H NMR ($CDCl_3$): δ 3.61 (12H, s, CH_2), 7.14 (6H, s, ArH); ^{13}C NMR ($CDCl_3$): δ 23.07, 82.66, 86.79, 123.52, 134.02. For **2**: mp. 109-112°C; IR (KBr) 3058, 2924, 2222, 1596; ^{1}H NMR ($CDCl_3$): δ 4.12 (6H, s, CH_2), 7.46 (3H, s, ArH); ^{13}C NMR ($CDCl_3$): δ 14.56, 84.48, 85.75, 122.98, 135.04. For **4**: IR (neat) 3065, 2999, 2951, 2231, 1583; ^{1}H NMR ($CDCl_3$): δ 3.66 (4H, s, CH_2S), 4.12 (8H, s, CH_2Br), 7.42-7.43 (6H, m, ArH); ^{13}C NMR ($CDCl_3$): δ 14.72, 20.21, 81.56, 84.67, 85.64, 86.42, 122.87, 123.68, 134.54, 135.04. For **5**: IR (CCl_4) 3066, 2942, 2869, 2231, 1593, 1562; MS m/z(%) 290(66), 209(40), 181(40), 130(27), 102(100); ^{1}H NMR ($CDCl_3$): δ 1.40-1.90 (6H, m, CH_2), 3.53-3.58 (1H, m), 3.82-3.88 (1H,m), 4.42 (1H, d, J=16Hz, CH_2OTHP), 4.48(1H, J=16Hz, CH_2OTHP), 4.85 (1H, t, J=3.2Hz, CH), 7.50 (2H, d, J=2Hz, ArH), 7.59 (1H, t, J=2Hz, ArH); ^{13}C NMR ($CDCl_3$): δ 18.96, 25.34, 30.21, 54.46, 61.97, 82.83, 88.08, 96.93, 123.37, 126.11, 133.23, 134.13. For **7**: IR (CCl_4) 3448, 2944, 2852, 2229, 1600; MS m/z(%) 408(M+, 2), 324(8), 240(75), 223(70), 207(30), 165(45), 85(55), 55(100); ^{1}H NMR ($CDCl_3$): δ 1.45-1.90 (12H, m, CH_2), 3.49-3.59 (2H, m), 3.82-3.86 (2H,m), 4.40 (2H, d, J=16Hz, CH_2OTHP), 4.44 (2H, s, CH_2OH), 4.47(2H, J=16Hz, CH_2OTHP), 4.85 (2H, t, J=3.2Hz, CH), 7.40 (2H, s, ArH), 7.42 (1H, s, ArH); ^{13}C NMR ($CDCl_3$): δ 18.98, 25.31, 30.21, 51.32, 54.58, 62.02, 83.95, 84.04, 86.43, 87.97, 96.87, 123.21, 123.34, 134.47, 134.68. For **8**: IR (neat) 3063, 2943, 2870, 2227, 1583; ^{1}H NMR ($CDCl_3$): δ 1.45-1.90 (24H, m, CH_2), 3.50-3.55 (4H, m), 3.64(4H, s, CH_2S), 3.81-3.87 (4H,m), 4.38 (4H, d, J=16Hz, CH_2OTHP), 4.46 (4H, J=16Hz, CH_2OTHP), 4.84 (4H, t, J=3.2Hz, CH), 7.41 (6H, s, ArH); ^{13}C NMR ($CDCl_3$): δ 19.00, 19.98, 25.32, 30.22, 54.53, 61.97, 81.76, 84.04, 85.85, 86.47, 96.80, 123.31, 123.40, 134.52, 134.62.

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