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SYNTHESIS OF 6,16,22,32-TETRAHYDROXY[3.3.3.3]META-CYCLOPHANE WITH THE AID OF A NEW COPPER CATALYST

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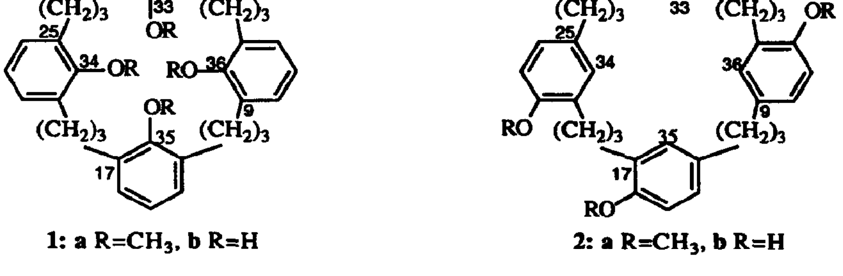
Abstract: Metacyclophane 2 has been prepared in 4 steps starting from 2-bromoanisole with the aid of a new copper catalyst. The catalyst was prepared by mixing CuBr-SMe_2 with LiSPh and LiBr in THF.

Because of their potential in host-guest chemistry and usefulness in the study of noncovalent binding, cyclophanes have attracted much attention.[1] As part of our program to develop efficient pathways for the preparation of [n.n.n.n]metacyclophanes, n>1, and to study their potential as synthetic receptors, we recently reported the 5-step synthesis and characterization of [3.3.3.3]metacyclophane 1, where the methylene bridges are all oriented ortho to the four phenolic oxygens.[2] Recent reports have documented that receptors capable of both arene-arene interactions and hydrogen bonding can function in a polar solvent or even an aqueous environment.[3] We felt that metacyclophane 2 might prove an interesting first generation target for this kind of receptor because of its potential hydrogen bonding capability from convergent phenolic oxygens in the "bow" and "stem" of the boat-like orientation of the phenolic rings (the structure predicted by molecular mechanics calculations[4]). The phenolic rings, in turn, are capable of π-stacking interactions.[5] We now wish to report the 4-step synthesis of [3.3.3.3]metacyclophane 2 where the methylenes are oriented in an ortho-para-ortho-para fashion with respect to their phenolic oxygens. The 4-step synthesis is an improvement over the protocol reported previously, due to the use of a novel copper catalyst made from mixing CuBr-SMe_2 with LiSPh and LiBr in THF.

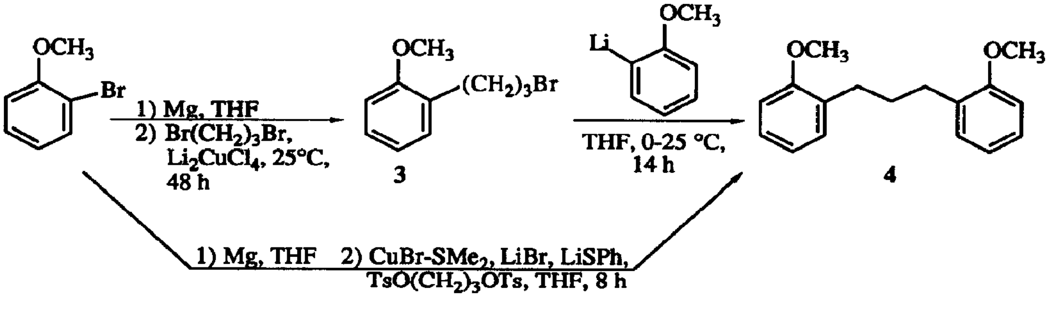


1: **a** R=CH_3, **b** R=H

2: **a** R=CH_3, **b** R=H

Fig. 1

In our previous protocol, compound 4 (Scheme 1) was prepared in two steps by coupling 2-(1-methoxy)phenylmagnesium bromide with 1,3-dibromopropane using catalytic amounts of Li_2CuCl_4 (6 mole %, THF, rt, 48 h), followed by addition of lithiated anisole (THF, 0-25 °C, 12 h), with an overall yield of 50-55% over the two reaction sequence. In the first step less than 5% of 4 was produced even when excess Grignard was present. While Li_2CuCl_4 has been shown by others to be effective when coupling alkyl Grignards to primary alkyl bromides[6] and to exhibit moderate activity when coupling aromatic Grignards with primary alkyl bromides,[7] the coupling of primary alkyl bromides with a stabilized aromatic Grignard reagent is apparently less efficient. Interestingly, it was observed that the soluble Li_2CuCl_4 catalyst exhibited two distinct rates of reaction during the coupling reaction that furnished 3 (as followed by ^1H NMR). After 0.5 hours the rate quickly slowed 5-fold to a second rate that held constant for several hours. In the hope that different ligands would stabilize the more active species, the Cu(II) catalyst was modified by exchanging the Cl^- ligands with Br^-, I^-, and/or ^-SPh, since these ligands stabilize Cu(I),[8] the active coupling agent in the reaction mixture[9] (however, several kinds of Cu(I) species may exist in the reaction mixture[10]).



Scheme 1

Mixtures of $CuBr_2$ and two equivalents of LiBr or LiI remained soluble in THF (1M solution), presumably forming $Li_2CuX_2Y_2$ (X=Y=Br; X=Br, Y=I), and when used as catalysts furnished 4 directly in 8-10% yield. When $CuBr_2$ was mixed with two equivalents of LiSPh in THF at room temperature, however, a yellow suspension formed over the course of 30-45 minutes. The yellow solid, after filtration and washing with THF followed by vacuum drying, produced the ^1H NMR spectrum shown in Figure 2a. The sharp peak widths strongly suggested that paramagnetic Cu(II) had been reduced to diamagnetic Cu(I),[11] and indeed the yellow solid became bright blue upon exposure to air. The ^1H NMR spectrum partially elucidated the copper complex's structure, exhibiting resonance peaks corresponding to thiophenoxide and THF ligands (3:2 ratio, respectively). The THF supernatant was concentrated to a solid and produced an ^1H NMR spectrum that suggested a soluble Cu(I) species was present. The THF supernatant and the solid each coupled the Grignard reagent with 1,3-dibromopropane, and it was found convenient to use the suspension as the catalyst. When 6 mole percent of this catalyst was used with two equivalents of Grignard reagent, 4 was formed in 15-20% yield over a period of 8-12 hours. Under the same reaction conditions the yield of 4 increased to 65% with little or no Wurtz product formation when 1,3-propanediol di-*p*-tosylate was used instead of 1,3-dibromopropane. However, when the bis-tosylate was used along with the soluble catalyst Li_2CuCl_4, Wurtz product was produced in 5-10% yield, along with only small amounts of compound 4. The major products consisted of a mixture of 3 due to bromide-tosylate exchange (bromide from RMgBr) and 1-(*para*-toluenesulfonyl)-3-(2-methoxyphenyl)propane.

For a comparison to the above system, a Cu(I) species, $CuBr\text{-}SMe_2$, was mixed with LiBr and LiSPh in THF, and again a yellow suspension formed over a 30-45 minute time period.[12] The ^1H NMR spectrum

(Figure 2b) of the solid, prepared as before, exhibited resonance peaks corresponding to thiophenoxide, dimethylsulfide, and THF ligands (3:2:2 ratio, respectively). As before, the solid turned blue upon exposure to air. When this suspension was used as the catalyst, the coupling of 2-(1-methoxy)phenylmagnesium bromide with 1,3-propanediol di-*p*-tosylate (THF, 6 mole %, rt, 8 h) furnished 4 in 75% yield and no Wurtz product was formed. On the other hand, 4 was produced in only 40% yield (with respect to the Grignard reagent) when the reaction mixture contained the typical[10,13] 10-25% CuBr and excess Grignard reagent in a refluxing solution of THF and HMPA. The CuBr-SMe$_2$/ LiBr/ LiSPh mixture avoided the waste of excess Grignard reagent needed with lower order Grignard copper reagents and less reactive catalysts, and furnished the desired product in good yield.

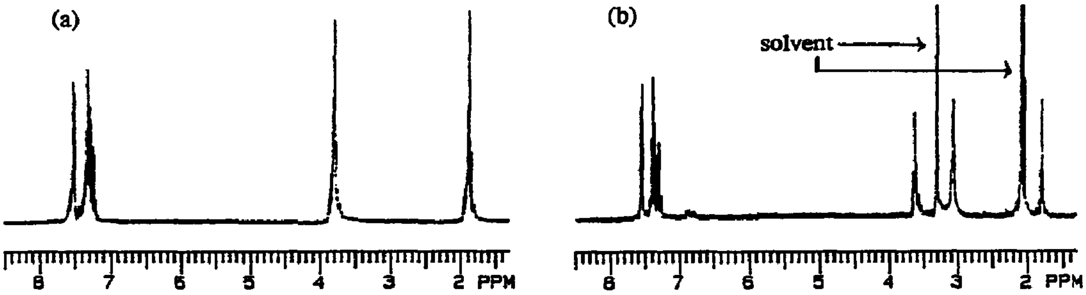
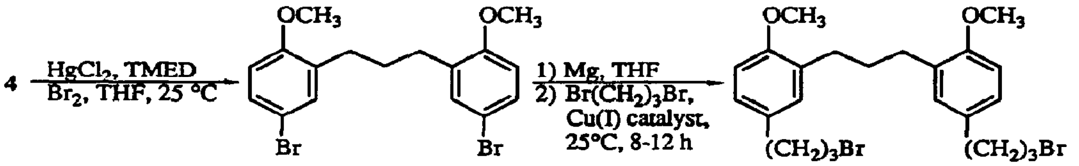


Fig. 2. (a) ^{1}H NMR (300 MHz, acetone-d$_6$) of solid formed when CuBr$_2$ was mixed with LiSPh in THF. (b) ^{1}H NMR of solid formed when CuBr-SMe$_2$ was mixed with LiSPh and LiBr in THF.

Compound 4 was then brominated with Br$_2$ in Et$_2$O/THF utilizing HgCl$_2$ /TMED as a Lewis acid,[14] furnishing *para*-dibromo 5 in 70-75% yield after recrystallization, while no *ortho*-bromination was observed (Scheme 2).[15] Formation of the bis-Grignard of 5 (5, Mg, THF, reflux, 12 h) and elaboration with 1,3-dibromopropane utilizing the CuBr-SMe$_2$/ LiBr/ LiSPh mixture as the catalyst produced compound 6 in 60% yield. Although 1,3-propanediol di-*p*-tosylate was the reagent of choice for the synthesis of 4, when this reagent was used for the elaboration of 5 the reaction produced mixtures of 6 (bromide-tosylate exchange) and 1-[4-(3-bromopropyl) -2-methoxyphenyl] -3- [4-(3-*para*-toluenesulfonylpropyl) -2-methoxyphenyl]propane. The bis-Grignard of 5 was again prepared as above, and the Grignard solution and a second solution of 6 in THF were then added over a period of 3 hours to a refluxing solution of CuBr-SMe$_2$ (50 mole %) in THF/HMPA, and the reaction mixture was allowed to stir at reflux for 20 hours. The reaction furnished 2a[16] in 25% yield, along with linear products, and was easily purified by chromatography using a Chromatotron.[17]



5

6

Scheme 2

The one methoxy resonance (3.78 ppm) in the ^{1}H NMR spectrum of **2a** demonstrates the symmetry of the macrocycle and indicates the methoxy groups are not shielded by the aromatic rings, i.e., they are directed outside of the rings, exhibiting a normal anisole resonance, and therefore suggests a structure consistent with that predicted by force field calculations (unlike **1a** and its homologs, whose upfield methoxy resonance (3.45 ppm) suggests shielding from the aromatic rings[2]). Cyclophane **2a** was subjected to BBr$_3$ in dichloromethane resulting in cyclophane **2b**[15] in 92% yield. It was not possible to determine the existence of internal hydrogen bonding between the phenolic hydrogens by ^{1}H NMR because **2b** was only soluble in solvents such as acetone or DMSO, but IR spectroscopy (KBr) exhibited no detectable hydrogen bonding (in comparison to demethylated **4**[2]). Binding studies of **2** (and its homologs) with aromatic and non-aromatic amines, along with studies to further characterize the copper catalyst, are currently under investigation.

REFERENCES AND NOTES

1. (a) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362-386.
   (b) Gutsche, C.D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J.F., Ed.; The Royal Society of Chemistry: Cambridge, 1989.
2. Burns, D. H.; Miller, J. D.; Santana, J. *J. Org. Chem.* *1993*, *58*, 6526-6528.
3. (a) Rotello, V. M.; Viani, E. A.; Deslongchamps, G.; Murray, B. A.; Rebek, J. *J. Am. Chem. Soc.* **1993**, *115*, 797-798.
   (b) Kearney, P. C.; Mizoue, L.S.; Kumpf, R. A.; Forman, J. E.; McCurdy, A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907-9919.
4. ALCHEMY III, TRIPOS Associates, Inc., 1699 South Hanley Road, Suite 303, St. Louis, Missouri, 63144.
5. Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 9701-9702.
6. Freidman, L.; Shani, A. *J. Am. Chem. Soc.* **1974**, *96*, 7101-7103.
7. Kadkhodayan, M.; Singleton, T.; Heldrich, F. O. *Syn. Commun.* **1984**, *14*, 707-712.
8 (a) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788-7800.
   (b) Hathaway, B. J. Copper. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, Vol 5; 1987; pp. 536-538.
9. Tamura, M.; Kochi, J. K. *J. Organometal. Chem.* **1972**, *14*, 205-228.
10. Lipshutz, B.; Sengupta, S. Organocopper Reagents: Substitution, Conjugate Addition, Carbo/Metallocupration, and Other Reactions. In *Organic Reactions*; Paquette, L. A. *et al*, Eds.; John Wiley and Sons, Inc.: New York, Vol 41, 1992; pp. 149-184.
11. Presumably the reduction of Cu(II) to Cu(I) results from the oxidation of the thiophenoxide to the disulfide, which is found in the product mixture. Additionally, many Cu(I) thiolates form insoluble complexes; see Knotter, D. M.; van Maanen, H. L.; Grove, D. M.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1991**, *30*, 3309-3317.
12. Mixing of CuBr-SMe$_2$ and LiSPh in THF produces a suspension within five minutes, with a ^{1}H NMR different than the other mixtures. For LiBr effects on stoichiometric copper and Grignard coupling reactions, see Carpita, A.; Rossi, R. *Synthesis* **1982**, 469-471.
13. Yamato, T.; Matsumoto, J.; Tokuhisa, K.; Kajihara, M.; Suehiro, K.; Tashiro, M. *Chem. Ber.* **1992**, *125*, 2443-2454.
14. Yields of **5** are drastically reduced without the presence of TMED, a phenomena currently under investigation.
15. All new compounds gave satisfactory spectroscopic and elemental analysis.
16. Cyclophane **2a**. m.p. (uncorrected): 119-120° C. ^{1}H NMR (300 MHz, CDCL$_3$): δ 6.94-6.92 (m, 8H), 6.73 (d, 4H, J=8.1 Hz), 3.78 (s, 12H), 2.65 (t, 8H, J=8.0 Hz), 2.56 (t, 8H, J=8.1 Hz), 1.77-1.88 (m, 8H). Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 81.04; H, 8.11.
17. Harrison Research, 840 Moana Court, Palo Alto, California.

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