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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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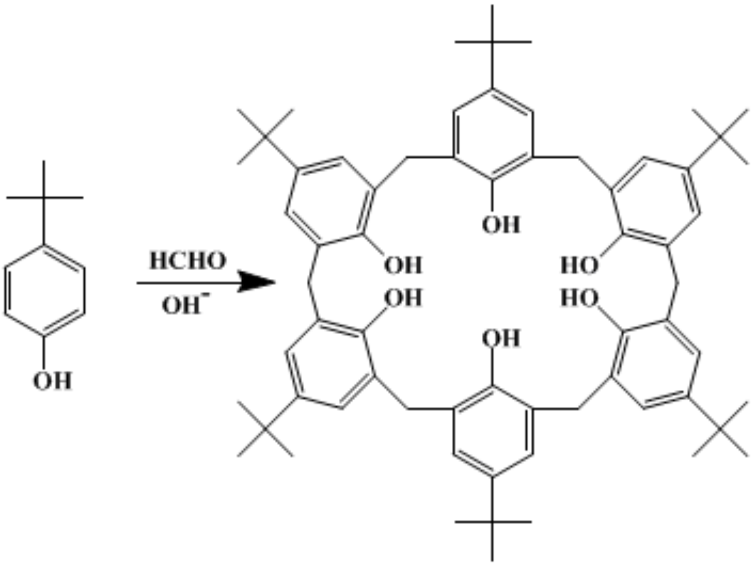
p-tert-BUTYLCALIX[6]ARENE



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Checked by Roger J. Butlin and James D. White.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a nitrogen inlet, a mechanical stirrer, and a Dean–Stark trap and condenser (Note 1) is placed in a Glas-Col heating mantle. To the flask are added 100 g (0.665 mol) of *p-tert*-butylphenol, 135 mL of 37% formalin solution (1.8 mol of HCHO), and 15 g (0.227 mol) of potassium hydroxide pellets (corresponding to 0.34 equiv of the phenol) (Note 2) and (Note 3). Heating and stirring are begun, and after 15 min nitrogen is blown across the reaction mixture at a brisk rate and out through the condenser on top of the Dean–Stark trap (Note 4); the reaction mixture is heated and stirred for 2 hr (Note 5). As the reaction progresses, the originally clear solution turns bright lemon yellow and, as water is removed, the reaction mixture eventually changes to a thick, golden-yellow mass of taffylike consistency (Note 6). During this period some frothing occurs, and the reaction mixture expands somewhat before shrinking to the original volume. Xylene (1 L) is now added to the flask to dissolve the semisolid mass and give a yellow solution that is brought quickly to reflux by increasing the temperature of the heating mantle (Note 7). After 30 min a precipitate begins to form, and the color of the reaction mixture changes from yellow to orange. Refluxing is continued for 3 hr, the heating mantle is removed, and the mixture is allowed to cool to room temperature. The mixture is filtered, and the precipitate is washed with xylene and dried on a Büchner funnel to yield 105–110 g of crude, almost colorless product. This material is powdered, placed in an Erlenmeyer flask, dissolved in 2.5 L of chloroform (not completely soluble), and treated with 800 mL of 1 *N* hydrochloric acid. After 10–15 min the stirred solution turns yellow to light orange; stirring is continued for an additional 10 min, and the mixture is transferred to a separatory funnel. The chloroform layer is drawn off, the aqueous layer is extracted with an additional 250 mL of chloroform, and the combined chloroform extracts are washed once with water and dried over magnesium sulfate. Magnesium sulfate is removed by filtration, the chloroform solution is concentrated to ca. 1 L by boiling, and 1 L of hot acetone is added to the boiling chloroform solution. The mixture is allowed to cool and is then filtered to give 90–95 g (83–88%) of product as a white powder: mp 372–374°C (Note 8),(Note 9),(Note 10).

2. Notes

1. It is not essential that a Dean–Stark trap be used. However, it provides a convenient way for monitoring this stage of the reaction and for collecting the aqueous formaldehyde mixture that is

evolved.

2. *p-tert*-Butylphenol from Aldrich Chemical Company, Inc., mp 98–101°C, and 37% formaldehyde solution from Fisher Chemical Company, Certified ACS grade, were used. The potassium hydroxide (KOH) pellets are ca. 85% KOH and 15% water. When sodium hydroxide or lithium hydroxide is used instead of potassium hydroxide the yield of product is considerably lower.

3. Sometimes the reaction between the phenol and formaldehyde proceeds with sufficient speed after mixing that considerable warming takes place. The ultimate outcome of the reaction is the same regardless of whether spontaneous warming occurs.

4. Typically, the rate of nitrogen flow is ca. 200 bubbles per minute, as measured by a bubbler attached to the condenser outlet. Although a rapid flow of nitrogen is not essential, it facilitates the removal of water and formaldehyde from the reaction mixture; this should amount to ca. 85 mL in the lower layer of the Dean–Stark trap.

5. Stirring is not absolutely necessary, but it accelerates the rate of removal of water. In unstirred reaction mixtures the frothing contents may fill the entire flask. Stirring reduces the amount of frothing.

6. As the reaction mixture becomes more viscous it is necessary to increase the torque on the stirring motor to keep the taffylike mass in motion while heating is continued. It is important to remove as much of the water as possible in this first stage of the reaction by continuing the stirring as long as possible (see (Note 7)). When stirring becomes very difficult or when the yellow mass no longer sticks to the sides of the flask, xylene is added. Care should be taken not to scorch the reaction mixture at this point. As a further aid to rapid removal of water it is recommended that the upper portion of the reaction flask as well as the Dean–Stark trap be covered with insulating material such as cotton or glass wool.

7. Incomplete removal of water and/or too slow removal of water can result in the formation of a significant amount of cyclic octamer, which is difficult to separate from the cyclic hexamer. It is important, therefore, to bring the reaction mixture to reflux (10–15 min) and to remove all the water. In addition to the ca. 85 mL of H_2O/HCHO removed in the first phase of the reaction, an additional ca 10 mL (as a cloudy, lower layer in the Dean–Stark trap) is removed in the second phase.

8. HPLC analysis of this product usually shows it to contain less than 1% of other calixarenes. If these are present in greater amounts (usually the cyclic tetramer, cyclic heptamer, or cyclic octamer), their content can be reduced to less than 1% by triturating the product with hot acetone. The purity of the product can be qualitatively checked with TLC using a petroleum ether (30–60°C)/methylene chloride mixture (1 : 1) as eluant. The R_f of the cyclic hexamer is ca. 0.65, and the appearance of any spots with $R_f > 0.1$ indicates the presence of other calixarenes.

9. The melting point is measured in an evacuated and sealed melting-point tube.

10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) δ: 1.29 (s, 54 H), 3.90 (s, 12 H), 7.16 (s, 12 H), 10.42 (s, 6 H).

3. Discussion

p-tert-Butylcalix[6]arene was first prepared by Gutsche et al.[2] by the reaction of *p-tert*-butylphenol and paraformaldehyde in the presence of rubidium hydroxide (RbOH). A few other *p*-substituted calix[6]arenes have been prepared, including *p*-phenylcalix[6]arene[3] and *p*-isopropylcalix[6]arene.[4]

References and Notes

1. Department of Chemistry, Washington University, St. Louis, MO 63130.
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3. Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795.
4. Dhawan, B.; Chen, S. I.; Gutsche, C. D. *Macromol. Chem.* **1987**, *188*, 921.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

petroleum ether

HCHO

p-tert-Butylcalix[6]arene

H_2O/HCHO

p-phenylcalix[6]arene

p-isopropylcalix[6]arene

hydrochloric acid (7647-01-0)

sodium hydroxide (1310-73-2)

formaldehyde,
formalin (50-00-0)

chloroform (67-66-3)

phenol (108-95-2)

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

xylene (106-42-3)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

lithium hydroxide (1310-65-2)

p-tert-butylphenol (98-54-4)

rubidium hydroxide (1310-82-3)

paraformaldehyde (30525-89-4)