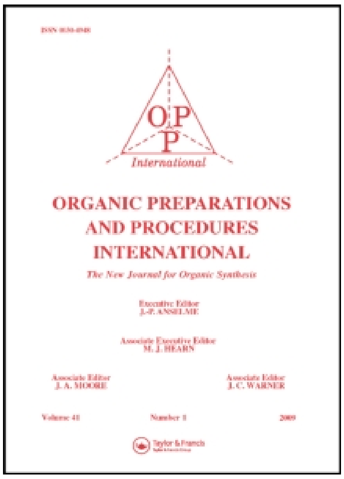

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THE ONE-STEP SYNTHESIS OF *p-tert*-BUTYLCALIX[5]ARENE

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THE ONE-STEP SYNTHESIS OF *p-tert*-BUTYLCALIX[5]ARENE

Submitted by (08/11/92)

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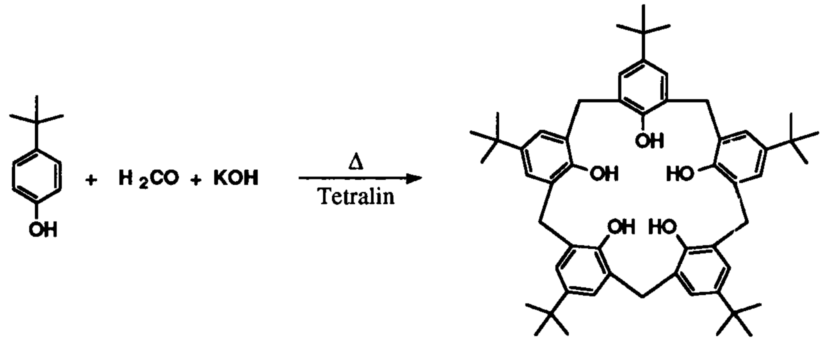
The one-step synthesis of *p-tert*-butylcalix[5]arene (**1**) from *p-tert*-butylphenol and formaldehyde was first reported in 1982 by Ninagawa and Matsuda[1], who isolated it in *ca* 6% yield. Regen and co-workers[2] repeated the synthesis in 1986 and, although using a different work-up procedure, obtained a similar yield. With the recent escalation in research in calixarene chemistry this less accessible member of the calixarene family is assuming increasing importance. The present communication provides details whereby it can be prepared in yields up to 15% which, while still low, nevertheless allows the easy accumulation of workable amounts of this potentially useful compound.



1

EXPERIMENTAL SECTION

Caution: *The high temperature, the high flammability of the hot tetralin, and the large scale of the procedure described below make it a potentially dangerous preparation. Be certain to perform it in a fire-resistant fume hood with apparatus that has been carefully set up and checked before each stage of heating.*

A slurry of 112.5 g (0.748 mol) of *p-tert*-butylphenol,[3] 75.0 g (2.5 mol) of paraformaldehyde, 13.5 g (0.207 mol) of 86% pure KOH in 50 mL of water, and 1.5 L of tetralin was stirred in a 3 L, 3 necked, round-bottomed flask equipped with a mechanical stirrer, a Dean- Stark water trap fitted with a condenser, a nitrogen inlet,[4] and a thermometer.[5] The mixture was heated to 80-85° and held at that temperature for 1.5 hr under a small positive pressure of nitrogen. During this time the reaction mixture became turbid and changed to a lemon-yellow color. The heat was increased to rapidly bring the temperature to 180-185°, and the nitrogen flow was increased to facilitate the removal of water.[6] During this heating period, the color of the reaction mixture changed from a bright, lemon-yellow to a light yellow and finally to a dark, red-brown, as 80-100 mL of formalin was collected. Once a temperature of 180-185° was reached, the reaction mixture was held at that temperature for 10 min, and the heating mantle was then removed to quickly reduce the temperature to 160-165°. The reaction mixture was held within this range for 3 hrs and then allowed to cool to room temperature. When cooled, the reaction mixture was filtered and the precipitate was washed with toluene to leave 70-90 g of an off-white powder.[7] The filtrate was evaporated to dryness *in vacuo*[8] and the residual dark-brown, gummy residue was stirred vigorously with 400 mL of chloroform and 200 mL of 1N HCl for 15 min. This biphasic solution was filtered under vacuum[9] to give *ca* 4.5 g of a white powder.[10] The chloroform layer was washed with water, dried, and removed *in vacuo*. The residue was triturated by refluxing for 0.5 hr with 400 mL of acetone and filtered hot to leave *ca* 7 g of white powder.[11] The filtrate was concentrated to 250-300 mL and allowed to cool to room temperature. After a few hours at room temperature, a small amount of white powder sometimes formed and was removed by filtration.[12] The filtrate was placed in a freezer at -15°, and after *ca* 3-12 hrs, 12-17 g (10-15%) of *p-tert*-butylcalix[5]arene (1) was collected as large, diamond-shaped crystals,[13] mp 310-312°, lit.[1] mp 310°. Concentration[14] and cooling of the mother liquor to -15° yielded an additional 1-2 g of slightly impure **1**.[15,16]

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2. M. A. Markowitz, V. Janout, D. G. Castner and S. L. Regen, *J. Am. Chem. Soc.*, **111**, 8192 (1989).

3. Reagent grade *p-tert*-butylphenol (mp. 98-101°), paraformaldehyde, tetralin, and KOH were obtained from Aldrich Chemical Co., Inc.

4. Since the reaction mixture is not refluxed, a modest flow of nitrogen over the reaction mixture and exiting through the condenser on top of the Dean and Stark water trap was used to facilitate the removal of water and formaldehyde during the second heating stage. It is necessary to insulate the water trap and the top of the reaction vessel; otherwise, water may not be efficiently trapped, and it must be removed for the reaction to proceed properly and reach the target temper-

atures. Also, with a modest flow of nitrogen throughout the heating period, the reaction mixture does not turn as dark as when only a small, positive pressure of nitrogen is used.

5. Ace Glass Co. flask inlet adapter (catalog # 5031) accommodates a thermometer and a nitrogen inlet.

6. Refluxing the reaction mixture may dramatically reduce the yield of the **1**. For instance, when refluxing mesitylene (bp 163-166°) was used in place of tetralin, less than 1% of **1** was found. Possibly, a small amount of water and/or formaldehyde is necessary for **1** to be formed in significant yield.

7. This precipitate consists of *p-tert*-butylcalix[6] and [8]arenes in roughly equal amounts along with a smaller amount of *p-tert*-butylcalix[4]arene.

8. Tetralin can be conveniently removed at 95° and *ca* 1 torr on a rotary evaporator in which the distillation path is insulated. The recovered tetralin can be used in subsequent preparations of **1**.

9. The use of a filtering agent such as *Celite* is often necessary.

10. This powder is usually *p-tert*-butylcalix[4]arene (> 95% pure).

11. This white powder is usually a mixture of *p-tert*-butylcalix[4], [6], and [8]arenes. Sometimes it contained a significant amount of **1** and should, therefore, be checked by TLC (See Ref 16).

12. This is a mixture of even-membered calixarenes.

13. These crystals often measure 4-5 mm on a side and have been found as large as 10-15 mm on a side.

14. If the mother liquor is concentrated too much, increasing amounts of a white powder may be formed that contains a substantial amount (6-70%) of *p-tert*-butylcalix[7]arene.

15. *p-tert*-Butylcalix[5]arene is soluble at room temperature in acetone. Upon cooling to -15° large crystals form. Any other compounds that precipitate appear as powders, allowing the large crystals of **1** to be separated manually.

16. TLC analysis can be carried out on two silica gel plates with the two eluants shown below, allowing the various calixarenes to be detected as separate spots. The bracketed numbers represent the calix[n]arenes with n = 4-8.

    A. R_f values with CH_2Cl_2 / Pet. Ether (1:1): [4] = 0.54 [5] = 0.60, [6] = 0.66, [7] = 0.62, [8] = 0.83.

    B. R_f values with Acetone / Pet Ether (1:9): [4] = 0.48, [5] = 0.68, [6] = 0.36], [7] = 0.20, [8] = 0.46.