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Improved Synthesis of Cavitands

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Introduction

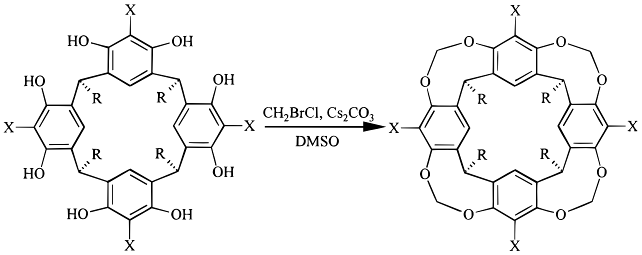
Methylene-bridged resorcin[4]arene cavitands have been used for a variety of purposes because of their rigid structures, bowl-shaped cavities, and synthetic accessibility. Cavitands have served as precursors to carcerands and hemicarcerands,[1] which are usually prepared in rather low yields with high dilution techniques. Therefore, the efficient synthesis of cavitands is an important goal in the development of the chemistry of these hosts and their complexes, which are often kinetically stable and, thus, provide a unique chemical environment for the incarcerated guest.

Our group is particularly interested in the electrochemical behavior of redox active guests encapsulated inside hemicarcerand hosts.[2] This work requires the solubilization of hemicarcerands and their inclusion complexes in polar solvents, suitable for electrochemical experiments. Recently, Cram and co-workers have reported the preparation of a water-soluble hemicarcerand,[3] which would be ideal for electrochemical experimentation. A key step in the preparation of this hemicarcerand is the synthesis of cavitand **2**. Here, we report a considerably improved procedure for the synthesis of **2** and related cavitands.

Results and Discussion

The reported procedure[4] for the preparation of **2** involves the reaction of octol **1** with CH_2BrCl at 60−70 °C for 24 h (see Scheme 1). After column chromatography, necessary to separate **2** from partially bridged cavitands[5] and other byproducts, the pure cavitand was isolated in 55% yield. The key difficulty with this procedure is the low normal boiling point of CH_2BrCl (68 °C), which limits the reaction temperature. We solved this problem by heating the reaction mixture at 88 °C in a sealed tube. (CAUTION: The reaction vessel must be able to withstand an internal pressure of several atmospheres.) The higher temperature leads to a much shorter reaction time (3 h) and substantially increased yield (95%). Furthermore, the almost quantitative yield greatly simplifies the workup, eliminating the need for any chromatographic separations. We have also investigated similar reaction conditions for the preparation of another three commonly utilized cavitands (**4**, **6**, and **8**) and found that the procedure reported here leads to vastly improved yields after shorter reaction times for two of them (**4** and **8**, see Table 1). The yield of the fourth cavitand (**6**) is already quite high using the previously reported method. Therefore, our reaction conditions only lead to shortened reaction times in this particular case.

Scheme 1. The Preparation of Cavitands from Octols



1, R=CH_3, X=Br
3, R=$(CH_2)_4CH_3$, X=Br
5, R=$(CH_2)_4CH_3$, X=CH_3
7, R=CH_2CH_2Ph, X=Br

2, R=CH_3, X=Br
4, R=$(CH_2)_4CH_3$, X=Br
6, R=$(CH_2)_4CH_3$, X=CH_3
8, R=CH_2CH_2Ph, X=Br

Table 1. Yields for the Preparation of Cavitands from the Corresponding Octols

cavitand	reported yield, %	reference	yield (this work), %
2	55	4	95
4	56	6	88
6	92	7	92
8	52	8	94[a]

[a] The reaction was carried out in DMF.

In summary, we have found a simple procedure for the preparation of cavitands **2**, **4**, **6**, and **8** in higher yield, shorter reaction times, and significantly easier workup as compared to the previously reported methods.

Experimental Section

All solvents and reagents were commercially available and used without further purification. The four octols used in his work were prepared according to literature procedures.[4,6−8] NMR spectra were recorded in a 400 MHz spectrometer. MS spectra were recorded in FAB mode. Combustion analyses were performed by Atlantic Microlab (Atlanta, GA).

General Procedure for the Synthesis of Cavitands. A mixture of the corresponding octol (1.00 g), Cs_2CO_3 (3.00 g, 9.21 mmol), and CH_2BrCl (3.0 mL, 46 mmol) in dry DMSO (20 mL) (15 mL of DMF and 0.80 g of octol for the synthesis of **8**) was stirred in a sealed tube (Ace pressure tube, Aldrich) at 88 °C for 3 h. (Caution: Changes in the reaction conditions may result in much larger internal pressures.) After cooling, the mixture was poured into 2% HCl (200 mL), and the solid formed was filtered and dried at 100 °C under high vacuum to yield the corresponding cavitand. All cavitands were suitable for use in subsequent reactions. A small sample of every cavitand was recrystallized from chloroform and dried to give samples with

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satisfactory combustion analyses. The ^{1}H NMR (400 MHz) spectra of the cavitands corresponded exactly to those previously reported.[4,6−8] Molecular peaks were detected in FAB MS experiments.

^{13}C NMR (100 MHz, CDCl$_3$). Cavitand **2**: δ 15.9, 32.1, 98.4, 113.5, 118.5, 140.1, 151.7. Cavitand **4**: δ 14.0, 22.6, 27.4, 29.9, 31.9, 37.7, 98.5, 113.5, 119.1, 139.3, 152.1. Cavitand **8**: δ 32.3, 34.3, 37.8, 98.5, 113.9, 118.9, 126.3, 128.4, 128.7, 139.1, 141.1, 152.3. The ^{13}C NMR spectrum of cavitand **6** has been reported.[7]

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