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The Nucleophilic Substitution Route. A Facile Method for the Fourfold Functionalization of the Methylene Bridges of Calix[4]arene

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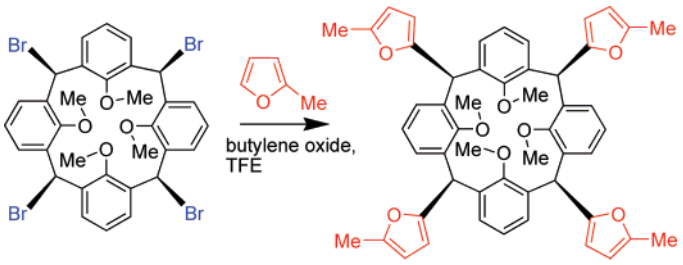
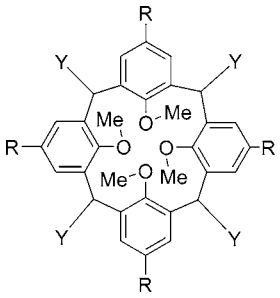
ABSTRACT



The radical bromination of *p-tert*-butylcalixarene tetramethyl ether was reinvestigated and the product (2b) characterized by X-ray crystallography. The tetrabromo calixarene derivatives 2a or 2b react with alcohols (TFE, EtOH), azide, and 2-methylfuran under solvolytic conditions affording calixarene derivatives functionalized at the four bridges. The reaction with alcohols and the aromatic compound proceeds in stereoselective fashion and affords the *rccc* isomer of the tetrasubstituted product.

The calixarenes have emerged as one of the most versatile building blocks for the construction of molecular hosts.[1] Although a plethora of synthetic methods have been developed for the modification of the aromatic rings of the calixarene scaffold, a general method for the introduction of substituents at *all* the methylene groups has remained an elusive goal.[2] At present only a handful of "classical" calix[4]arene derivatives[3] have been described in the literature with all four methylene bridges monofunctionalized.[2e,4] Here we report a general and surprisingly simple route for the preparation of the systems. Key intermediates are the tetrabromo calixarene derivatives **2a** and **2b**.[4] As exemplified in this paper, C−O, C−N, and even C−C bonds can be readily formed at the four bridges under mild solvolytic conditions.



1a R = Y = H
1b R = *t*-Bu, Y = H
2a R = H, Y = Br *(rccc)*
2b R = *t*-Bu, Y = Br *(rccc)*
3 R = *t*-Bu, Y = OCH_2CF_3 *(rccc)*
4 R = *t*-Bu, Y = OEt *(rccc)*
5 R = *t*-Bu, Y = N_3

The calixarenes **2a** and **2b** were prepared by reaction of the corresponding tetramethoxy derivatives **1a** and **1b** with

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(1) For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, UK, 1998. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001. (c) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2003; Chapter 19.

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NBS under irradiation, using a minor modification of the reported literature procedures.[5] Since compound **2b** possessed a ^{1}H NMR spectrum different from that reported in the literature,[6] a single crystal was grown from chloroform/hexane and submitted to X-ray crystallography. The crystal structure of **2b** is very similar to that reported for the *de-tert*-butylated analogue **2a**.[4a] The calixarene exists in a cone conformation with all bromine atoms located at equatorial positions (i.e., the *rccc* isomer, Figure 1).

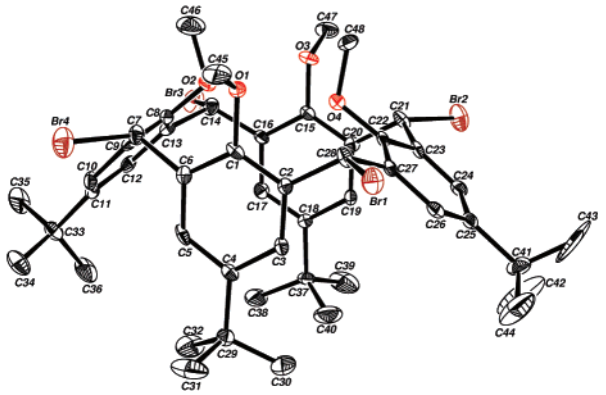

Figure 1. X-ray structure of the tetrabromo derivative **2b**. Solvent molecules that cocrystallized are omitted for clarity.

Calixarenes **2a** and **2b** are potential synthetic intermediates for the preparation of calix[4]arenes with all four bridges monofunctionalized provided that the bromine atoms can be readily replaced by another group. We examined the solvolysis of **2b** under S_N1 conditions. Trifluoroethanol (TFE) was initially chosen as the solvent due to its high ionizing power. The solvolysis was conducted in the absence of an additional nucleophile or a Lewis acid, yielding the tetrasubstituted product **3**. Several configurational isomers are possible for a tetrafunctionalized product (*rccc*, *rcct*, *rctt*, and *rtct* forms). The major product obtained is ascribed to the *rccc* isomer on the basis of its NMR spectrum (displaying single trifluoroethoxy, methoxy, methine, and *tert*-butyl signals) that strongly resembled that of the starting material **2b**.

We examined the solvolysis of **2b** in EtOH/TFE mixtures as a possible route to replace the bromines by ethoxy groups. Our expectation was that TFE should provide the ionizing medium while the more nucleophilic EtOH should react preferentially with the carbocations formed by dissociation of the C−Br bonds. Initial experiments were conducted by refluxing a 1:10 mixture of EtOH and TFE containing **2b**. The ^{1}H NMR spectrum of the product displayed two signals in the methine region in a 63:37 ratio assigned to C*H*OCH_2-CF_3 and C*H*OEt groups, respectively.[7] The crude reaction product displayed six singlets in the proton decoupled ^{19}F NMR spectrum (Figure 2), consistent with the formation of

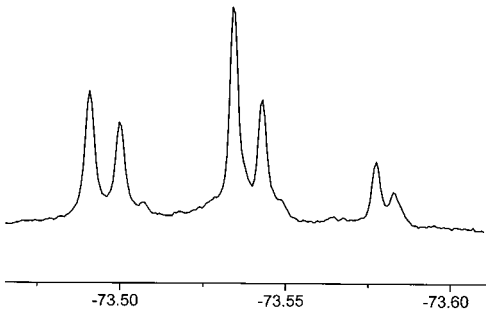

Figure 2. ^{19}F NMR spectrum of the product mixture obtained by using a 1:10 mixture of EtOH and TFE. From left to right, the three pairs of signals are assigned to groups flanked with two CF_3-CH_2O groups, a CF_3CH_2O/ethoxy pair, and a pair of ethoxy groups, respectively.

different *rccc* products possessing one to four OCH_2CF_3 groups.[8] Apparently, the higher nucleophilicity of EtOH is not sufficient to successfully compete with the TFE that is present in a larger concentration. However, when the reaction was conducted with a larger concentration of EtOH (i.e., an ca. 1:1 v/v TFE:EtOH mixture) the major product was the tetraethoxy derivative **4**. According to the NMR data, a single isomer (*rccc*) is formed preferentially.

The azide nucleophile is one of the first choices in selectivity studies involving carbocations.[9] It could be expected that if carbocations are generated from **2b**, the azide should successfully trap the carbocationic intermediate, resulting in the formation of tetraazido derivatives. Reaction of **2b** in TFE or hexafluoroisopropanol in the presence of NaN_3 yielded the tetraazido derivative, **5**, but in contrast to the reaction with alcohols, a mixture of the *rcct* (major product), *rctt*, and *rccc* isomers was obtained.[10]

After several recrystallizations from $CHCl_3$/MeOH a single crystal of the major isomer of **5** was obtained. X-ray analysis

(3) We use the term "classical" to designate calixarenes possessing methylene groups as opposed to "thiacalixarenes" (sulfur bridges) and "azacalixarenes" (nitrogen atoms). For an example of an azacalixarene substituted at the four nitrogen bridges see: Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165.

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(6) ^{1}H NMR of **2b** (400 MHz, $CDCl_3$): δ 7.27 (s, 8H), 6.71 (s, 4H), 3.99 (s, 12H), 1.11 (s, 36H) ppm. Reported (ref 4b): δ 8.06−7.41 (m, 8H), 6.5−4.96 (m, 4H), 3.97−3.02 (m, 12H), 1.33 (s, 36H).

(7) This does not indicate that only two products were formed (possessing four identical substituents: OEt or OCH_2CF_3) but rather that the chemical shift of the methine protons is mainly sensitive to the nature of the alkoxy group attached.

(8) There are six different *rccc* derivatives resulting from the different combinations of ethoxy and trifluoroethoxy groups at the bridges. Obviously, the tetraethoxy derivative is not detected in the ^{19}F spectrum while the tris-(trifluoroethoxy) monoethoxy derivative should display two signals. The rest of the products should display a single signal each.

(9) For a review on the synthetic uses of azides see: Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

(10) It may be possible that the absence of stereoselectivity is related to the small size of the azide ion as well as its high reactivity toward carbocations.

indicated that the molecule adopts in the crystal a partial cone conformation (Figure 3). The single azide group that

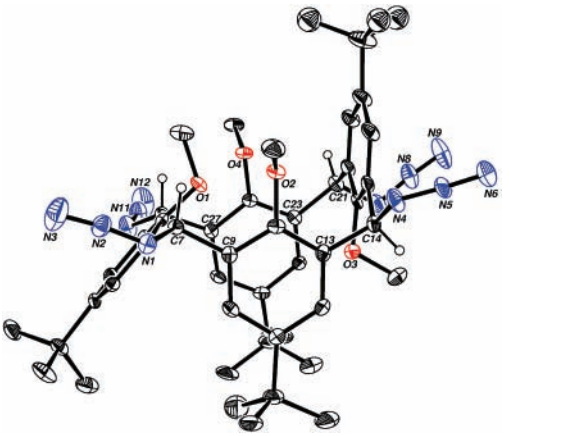
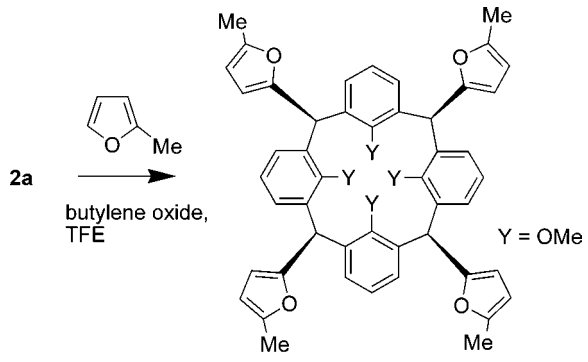


Figure 3. X-ray structure of the tetraazido derivative **5** (*rcct* form).

is *trans* to the rest (N4−N6) is located in an isoclinal position of the macrocycle.

Since oxygen- and nitrogen-containing groups can be readily attached to the methylene bridges using solvolytic conditions, we decided to examine whether C−C bonds can be formed by this route. The reaction was patterned based on the recent report by Mayr and co-workers that Friedel−Crafts (FC) alkylations can be conducted in alcoholic solutions in the absence of a Lewis acid catalyst.[11]

The solvolytic FC reaction was conducted with 2-methylfuran (MF), using 1,2-butylene oxide as a scavenger of HBr. MF was chosen as a substrate since it possesses a high Mayr nucleophilic parameter (N) (for π systems),[11] and since a furan ring can be easily transformed into arenes via Diels−



6

Alder reaction with a dienophile followed by deoxygenation.[12] Reflux of a solution of **2a** in TFE containing an excess of MF proceeded with high diastereoselectivity and afforded a major product (**6**) in good yield.

X-ray analysis of a single crystal of **6** grown from $CHCl_3$/MeOH indicated that the isomer *rccc* was obtained (Figure 4). The molecule adopts a pinched cone conformation with

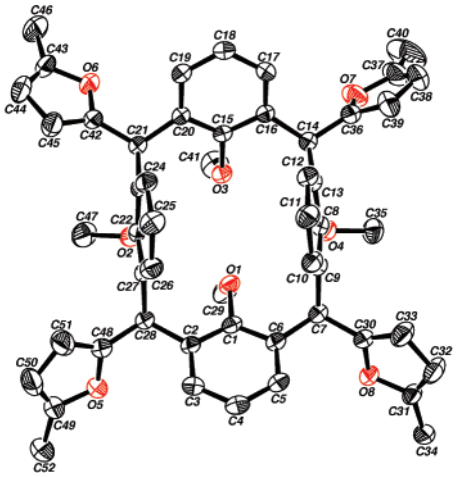


Figure 4. X-ray structure of the tetramethylfuranyl derivative **6**.

all the furanyl substituents located at equatorial positions of the macrocycle. The furanyl oxygens are pointing to the lower rim of the calix skeleton.

In conclusion, the tetrabromo derivatives can be used as starting materials for the preparation of calixarenes monosubstituted at the four bridges. With use of S_N1 reaction conditions, C−O, C−N, and C−C bonds can be readily formed under mild conditions.

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Supporting Information Available: Experimental procedures and spectroscopic data for **2b** and **3**−**6** and crystal data for **2b**, **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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