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Single Step Synthesis of Acetylene-Substituted Oxacalix[4]arenes

Jay Wm. Wackerly,[‡] Mengfei Zhang,[†] Stephen T. Nodder,[†] Stephen M. Carlin,[†] and Jeffrey L. Katz^{*,†}

[†]Department of Chemistry, Colby College, 5754 Mayflower Hill, Waterville, Maine 04901, United States

 ‡ Department of Chemistry, Central College, 812 University Street, Pella, Iowa 50219, United States

Supporting Information

ABSTRACT: Oxacalixarenes bearing acetylene groups are synthesized in a single step by nucleophilic aromatic substitution reactions of orcinol with various 1,5-diethynyl-2,4-difluorobenzenes. Thermodynamic equilibration of the cyclooligomer mixtures was accomplished for arylethynyl activating groups, leading to increased yields of the corresponding oxacalix[4]arenes. A 1,3-alternate macrocycle conformation is observed in the solid state, presenting a large V-shaped π -surface.

O xacalixarenes remain a heavily investigated and compelling platform for the design of molecular receptors.¹ Since early publications on their synthesis via nucleophilic aromatic substitution (S_NAr) methods,^{2,3} researchers continue to diversify the accessible oxacalixarene architectures through modification of the nucleophilic and electrophilic aromatic starting materials.^{4,5} The nucleophilic coupling partner, typically a resorcinol, is the most extensively varied reactant; oxacalixarenes have been constructed using dihydroxy-benzenes, naphthalenes, tryptycenes, and biphenylenes, terphenylenes, and related extended aromatic systems.^{4,5}

Alterations of the electrophilic component in S_NAr -based oxacalixarene formation have so far proven more limited in scope. Most commonly constructed using 2,4,6-trichloro-1,3,5-triazine^{3a} or 1,5-difluoro-2,4-dinitrobenzene,^{3b} successful macrocyclizations have also been reported using alternative nitrogen heterocycles including pyridines, pyrazines, pyrimidines, quinazolines, quinoxalines, and naphthyridines.^{4,5} Frameworks composed of all-carbon arenes, however, continue to depend on 1,5-difluoro-2,4-dinitrobenzene as the electrophile, and this restricts the accessible functional group profiles of oxacalixarenes bearing all-carbon aromatic rings.

Our laboratory recently reported that ethynyl groups are sufficiently electron-withdrawing to activate fluorobenzenes for nucleophilic aromatic substitution.⁶ In addition to simple 4fluoroethynylbenzenes, 1,5-diethynyl-2,4-difluorobenzenes 1 were effectively substituted by oxygen and aniline nucleophiles with displacement of both fluorine atoms. Phenols were shown to be competent nucleophiles for this process, with 1,5diethynyl-2,4-difluorobenzenes 1a and 1b reacting with *p*-cresol at 60 °C to produce disubstitution products 2 in 89–93% yields with negligible alkyne addition side reactions (Scheme 1). Alkyne-substituted oxacalixarenes have not yet been reported in the literature, although such systems are compelling scaffolds for further expansion of the oxacalixarene functional group profile, and for the electronic properties imparted by the arylethynyl moieties. The efficiency of aryl ether formation







using 1,5-diethynyl-2,4-difluorobenzenes 1 prompted us to investigate such systems as viable electrophiles for the single-step construction of acetylene-substituted oxacalixarenes.

We initially attempted oxacalixarene formation by reacting 1,5-di(trimethylsilylethynyl)-2,4-difluorobenzene 1c with orcinol 3 using Cs₂CO₃ or CsF base in DMSO (120 °C, 18 h; see Table 1). With Cs_2CO_3 base we observed the formation of a complex mixture of side products resulting from degradation of the pendant ethynyl groups, along with only small amounts of oxacalix[4] arene 4a. A change to CsF base mitigated but did not eliminate alkyne degradation. Using either Cs₂CO₃ or CsF, it was evident that the TMS groups are rapidly removed in situ, prior to aromatic substitution. Optimizing time and temperature with CsF base (125 °C, 24 h) allowed us to raise the isolated yield of oxacalix[4] arene 4a to 32%. Along with 4a, oxacalix[6]arene 5a and oxacalix[8]arene 6a were also isolated in 17% and 13% yield, respectively (Table 1, entry 1). Extending the reaction time beyond 24 h or raising the temperature of the reaction resulted only in increased alkyne decomposition and lower isolated quantities of oxacalixarenes 4a-6a.

The high yields observed for many oxacalix[4] arene formations are often attributed to thermodynamic equilibration of the initially formed linear and cyclooligomeric mixture to the thermodynamically preferred oxacalix[4] arene.^{4b} The modest isolated yield of oxacalixarene **4a**, along with appreciable quantities of higher cyclooligomers, appeared to result from a

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kinetic ring formation without significant macrocycle equilibration. Reversible C–O bond formation with only alkyne activating groups was not effective at 125 $^{\circ}$ C, and the use of higher temperatures for that system was precluded due to the sensitivity of the ethynyl groups.

We next investigated the use of 1,5-di(phenylethynyl)-2,4difluorobenzene 1b, an electrophile bearing phenylethynyl groups that are more resistant to anionic side reactions in alkyne-activated S_NAr reactions than the *in situ* revealed ethynyl groups using 1c.⁶ Reaction of 1b with orcinol 3 (CsF, DMSO, 125 °C, 24 h) provided a mixture of oxacalixarene cyclooligomers similar to that seen using 1c, but without appreciable alkyne decomposition or side reactions. Extending the reaction time and temperature to 130 °C for 4 d furnished a separable mixture of oxacalixarenes more strongly favoring oxacalix[4]arene 4b (43%) but still containing oxacalix[6]arene 5b (22%), oxacalix[8] arene 6b, 10%, as well as smaller quantities of higher cyclooligomers (Table 1, entry 2). Although electrophile 1b reacts completely with phenol and alcohol nucleophiles at relatively mild temperatures (see Scheme 1),⁶ equilibration of aryloxy substituents on the diethynylbenzene electrophile was found to be remarkably sluggish. Higher temperatures and extended reaction times using 1b promoted slow but continued equilibration of cyclooligomers to oxacalix[4] arene 4b along with only minor alkyne decomposition, and our optimized yield of 4b (54%) was obtained after 4 days at 160 °C (Table 1, entry 3).

With an optimized procedure for oxacalix[4]arene **4b**, we turned to investigating modifications to the arylethynyl substituents on electrophiles **1**. Difluorides **1d** and **1e** bearing 3-pyridyl and 4-trifluoromethylphenyl groups, respectively, were accessed via Sonogashira coupling of 1,5-dibromo-2,4-difluorobenzene⁷ with the appropriately functionalized acety-lene. Both **1d** and **1e** condense effectively with orcinol **3** to furnish tetraethynyloxacalix[4]arenes **4d** and **4e** (Scheme 2). The added electron-withdrawing capacity of the arylethynyl groups on **1d** and **1e** also served to modestly increase the rate of equilibration over that observed for **1b**. The 3-pyridylethynyl

Scheme 2. Synthesis of Oxacalix[4]arenes 4d and 4e

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groups were found to be resistant to decomposition at high temperature, and optimal isolated yields of 4d were obtained at 160 °C over 2 d (66% yield). The 4-trifluoromethyl(phenyl-ethynyl) groups were more sensitive to degradation, and the highest yields of 4e were obtained at slightly lower temperatures (150 °C, 2 d, 49% yield) in order to minimize decomposition under the strongly anionic conditions.

X-ray quality crystals of 4b were obtained by vapor diffusion of hexanes into CH_2Cl_2 (Figure 1). As is common with



Figure 1. Solid state structure of oxacalix[4]arene 4b, two views. Atoms modeled at partial occupancy have been depicted in single positions for clarity.

oxacalixarenes derived from alternative electrophiles, macrocycle **4b** adopts a distorted 1,3-alternate conformation in the solid state. The nucleophile-derived rings are nearly eclipsed, with a 4.3° angle between ring planes. The electronwithdrawing capacity of the phenylethynyl groups is evident from inspection of the C–O bond lengths. As seen in oxacalix[4] arene structures bearing 2,4-dinitrobenzenes,^{3a,4b} bond lengths from the bridging oxygen atoms to the

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electrophile-derived rings are significantly shorter (1.38 Å average for 4b) when compared to the equivalent bonds to the nucleophile-derived rings (1.40 Å average). The rigid phenylethynyl groups on the electrophile-derived aromatic rings of 4b extend the macrocyclic topology and create a large V-shaped cavity. The dimensions, as measured from the most distant carbon atoms in the solid state structure (Figure 1), are an average of 14.5 Å along the *meta*-phenylene (electrophilic ring) portion and an average of 12.6 Å between aryl acetylenes across the nucleophile-derived bridge.

In conclusion, 1,5-diethynyl-2,4-difluorobenzenes are effective electrophiles for the single step construction of oxacalixarenes, permitting the synthesis of the first examples of acetylene-substituted oxacalixarenes. Investigations to further expand the scope of acetylene-activated electrophiles for oxacalixarene formation, and of the supramolecular interactions of oxacalix[4] arenes 4 are ongoing.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for compounds 1c-e, 4-6, and X-ray crystallographic data for compound 4b (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jlkatz@colby.edu.

Notes

The authors declare no competing financial interest.

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