ORGANIC LETTERS

2005
Vol. 7, No. 1
91−94

Synthesis of Functionalized Oxacalix[4]arenes

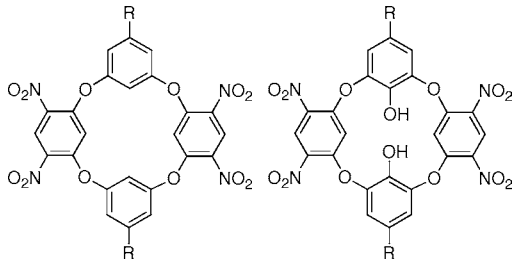
Jeffrey L. Katz,* Michael B. Feldman, and Rebecca R. Conry

Department of Chemistry, Colby College, 5754 Mayflower Hill, Waterville, Maine 04901

jlkatz@colby.edu

Received October 19, 2004

ABSTRACT



Tetranitrooxacalix[4]arenes are generated in high yield by the room-temperature S_NAr reaction of 1,3-dihydroxybenzenes with 1,5-difluoro-2,4-dinitrobenzene. The reaction is tolerant to a range of functionality on the nucleophilic component, including hydroxyl-substitution at the 2- and 5-positions, which yields previously unknown 26,28- and 5,17-dihydroxyoxacalix[4]arenes.

Calixarenes, [1$_n$]metacyclophanes with bridging carbon atoms, have been the subject of intensive study for decades and are a staple of modern supramolecular chemistry.[1] Although modulating the calixarene skeleton by linking the aromatic rings with atoms other than carbon has the potential to impart new physical and chemical properties on this class of compounds, these heterocalixarenes are far less prevalent in the chemical literature. Investigations into sulfur-bridged calixarenes have increased dramatically since their formation by condensation of phenols with elemental sulfur was reported in 1997.[2] Routes to nitrogen-bridged calixarenes are rare, although *N*-methyl azacalixarenes have recently been synthesized by palladium-catalyzed amination.[3] There have also been reports of silicon- and germanium-linked calixarenes, as well as related structures bridging heteroaromatic subunits.[4]

Oxygen-bridged calixarenes (hereafter referred to as oxacalixarenes) are all but absent from the chemical literature. Formation of an oxacalix[4]arene in modest yield was first reported in 1966[5] followed by several manuscripts from 1974 to 1976,[6] all of which utilized nucleophilic aromatic substitution (S_NAr) to form the macrocycles. Although these S_NAr-based strategies were reported to be efficient for oxacalix[4]arene formation, most of the resulting compounds displayed very low solubility in all solvents, hindering purification and preventing complete characterization. Several groups have since investigated the synthesis of related compounds,[7] but over the past 28 years only one group has reported the synthesis of new oxacalixarenes.[8]

The flexibility of S_NAr-based routes is attractive for the efficient formation of highly functionalized oxacalixarenes, and we envisioned that substitution on the nucleophilic component could impart more favorable solubility charac-

(1) See: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: London, 2000 and references therein. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745 and references therein.

(2) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971−3972.

(3) (a) Ito, A.; Ono, Y.; Tanaka, K. *New J. Chem.* **1998**, *22*, 779. (b) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236−8241. (c) Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945−7948. (d) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838−842.

(4) See: König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303−2310 and references therein.

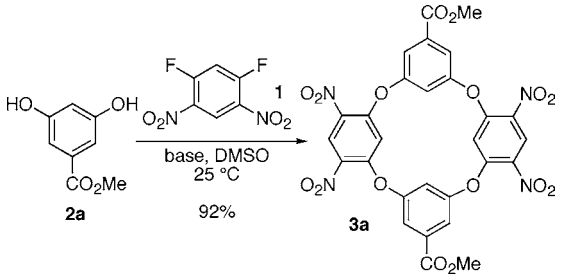
(5) Sommer, N.; Staab, H. A. *Tetrahedron Lett.* **1966**, *25*, 2837−2841.

(6) (a) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727−733. (b) Gilbert, E. E. *J. Heterocycl. Chem.* **1974**, *11*, 899−904. (c) Bottino, F.; Foti, S.; Papalardo, S. *Tetrahedron* **1976**, *32*, 2567−2570.

10.1021/ol047840t CCC: $30.25
Published on Web 12/08/2004

teristics upon the product macrocycles. Methyl 3,5-dihydroxybenzoate **2a** was chosen as the nucleophilic coupling partner for optimization of calixarene formation by condensation with 1,5-difluoro-2,4-dinitrobenzene **1** (Scheme 1).

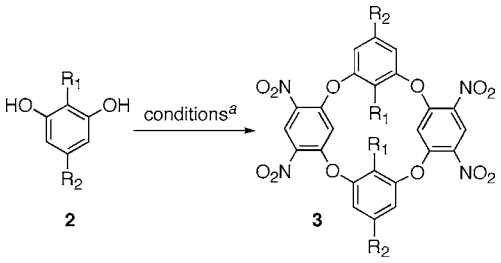
Scheme 1



Previous oxacalix[4]arene formations were reported to proceed at or near reflux in DMF,[5,6] or in refluxing monoglyme over several days.[8] These are rather vigorous conditions, especially considering the reactivity of electrophile **1**. DMSO has been shown to be superior to DMF for the S_NAr reaction of phenols in the formation of diaryl ethers,[9] and use of either anhydrous Cs_2CO_3 or K_2CO_3[10] base in DMSO promoted cyclization of **1** and **2a** to oxacalix[4]arene **3a** *in under 10 min at 25 °C*.[11] The use of Na_2CO_3 or KF led to an equally high-yielding yet substantially slower reaction (4−8 h). Oxacalixarene **3a** proved soluble in a variety of organic solvents and was isolated in 92% yield following purification on silica gel. Diminished yields and slower reaction rates were observed using DMF as solvent, although room-temperature reaction was still observed. Larger oxacalixarenes were not detected under any of the conditions screened. The cyclizations were run under ambient atmosphere using air-dried glassware. High dilution is not necessary to suppress linear oligomer formation, as yields are not diminished even at 0.5 M in **2a**.[12]

With an optimized procedure for the formation of **3a**,[13] the reaction scope was then investigated with respect to the functional group tolerance on nucleophilic component **2** (Table 1). Alkyl substitution at the 5-position is well tolerated, as oxacalix[4]arenes **3b** (entry 2) and **3c** (entry 3) derived from orcinol (**2b**) and olivetol (**2c**) were isolated in excellent yield. These alkylated oxacalix[4]arenes showed good solubility in organic solvents and were purified on silica. Efficient cyclization was also observed with 3,5-dihydroxybenzaldehyde (**2d**) to furnish oxacalix[4]arene **3d** (entry 4), although this oxacalixarene displayed extremely low solubility in all solvents. Fortunately, **3d** could still be obtained in high purity by precipitation and washing with methanol.

Table 1. Scope of Oxacalix[4]arenes **3** Synthesized



entry	substitution	nucleophile	product	yield[b]
1	$R_1 = H$, $R_2 = CO_2Me$	**2a**	**3a**	92%
2	$R_1 = H$, $R_2 = Me$	**2b**	**3b**	87%
3	$R_1 = H$, $R_2 = n$-pentyl	**2c**	**3c**	91%
4	$R_1 = H$, $R_2 = CHO$	**2d**	**3d**	(75%)
5	$R_1 = OH$, $R_2 = H$	**2e**	**3e**	88%
6	$R_1 = OH$, $R_2 = C(CH_3)_3$	**2f**	**3f**	89%
7	$R_1 = OH$, $R_2 = CO_2Et$	**2g**	**3g**	86%
8	$R_1 = H$, $R_2 = OH$	**2h**	**3h**	90%

[a] All reactions were run under the general reaction conditions as described in ref 13. [b] Isolated yield following chromatographic purification. Parentheses indicate isolated yield following precipitation and washing with methanol.

The successful formation of oxacalix[4]arenes using resorcinol derivatives led us to examine 1,2,3-triphenols for the synthesis of 26,28-dihydroxyoxacalix[4]arenes.[14] Thus, in addition to avoiding oligomer formation, high-yielding cyclizations would require selective reaction at the 1- and 3-positions of the nucleophilic component. We reasoned that the increased steric hindrance of the central phenol would partially insulate it from reaction, obviating any need for protection during the cyclization. This selectivity was observed, as pyrogallol **2e** smoothly formed "lower-rim" dihydroxylated oxacalix[4]arene **3e** in 88% yield (Table 1, entry 5). Additional functionality can also be present on the nucleophilic component, as 4-*tert*-butylpyrogallol **2f** (entry 6) and ethyl gallate **2g** (entry 7) cyclized with equal efficiency, providing 26,28-dihydroxyoxacalix[4]arenes **3f** and **3g** in 89% and 86% yield, respectively.

(7) (a) Boros, E. F.; Andrews, C. W.; Davis, A. O. *J. Org. Chem.* **1996**, *61*, 2553−2555. (b) Abd-El-Aziz, A. S.; de Denus, C. R.; Zaworotko, M. J.; Sharma, C. V. K. *Chem. Commun.* **1998**, 265−266.

(8) (a) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137−2147. (b) Chambers, R. D.; Hoskin, P. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *J. Fluorine Chem.* **2002**, *116*, 19−22.

(9) Evans, D. A.; Watson, P. S. *Tetrahedron Lett.* **1996**, *37*, 3251−3254.

(10) Well-ground (with a mortar and pestle) K_2CO_3 is critical for short reaction times. Use of granular K_2CO_3 led to a very sluggish reaction, requiring 6−12 h for complete conversion.

(11) Rebek and co-workers have reported that the S_NAr-based formation of tetranitroresorcinarenes using electrophile **1** proceeds at room temperature in DMF: Shivanyuk, A.; Far, A. R.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 1555−1558.

(12) Gilbert[6b] reported similar observations regarding reaction tolerance with respect to moisture, atmospheric oxygen, and concentration.

(13) **General Reaction Conditions.** Under ambient atmosphere, 200 mg of 1,5-difluoro-2,4-dinitrobenzene (0.98 mmol, 1 equiv), 1,3-dihydroxybenzene derivative (0.98 mmol, 1 equiv), and 338 mg of finely ground anhydrous K_2CO_3 (2.45 mmol, 2.5 equiv) are combined. DMSO (10 mL) is added, and the reaction is stirred vigorously for 15 min. The reaction mixture is then partitioned between EtOAc (50 mL) and 1 M HCl (40 mL), the resulting mixture is separated, and the aqueous layer is extracted twice with EtOAc (20 mL). The combined organics are washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification is effected as described in Supporting Information.

(14) For a discussion of the calixarene numbering scheme, see ref 1, section 1.4.

Unlike triphenols **2e**−**2g**, phloroglucinol **2h** bears three identical alcohol moieties. We were pleased to find that under the general reaction conditions phloroglucinol, absent of steric or electronic differentiation among its hydroxyls, smoothly formed "upper-rim" 5,17-dihydroxylated oxacalix[4]arene **3h** in 90% yield (Table 1, entry 8). This clearly indicates that steric differentiation between nucleophilic sites is not required for efficient ring formation. In accord with a study on S_NAr-based routes to thiacalixarenes,[15] the remarkably high yields obtained for the formation of **3a**−**3h** over other potentially accessible linear or cyclic structures suggest that ring opening and closing may be reversible under the reaction conditions and that the oxacalix[4]arene architecture may be the thermodynamic product of these cyclizations. Investigations into the mechanistic details of this unusual selectivity are currently underway.

As a result of limited published spectral data for oxacalix[4]arenes, the lack of NMR-active nuclei on the bridging atoms, and only one reported X-ray structure,[16] ambiguities still exist with regard to oxacalix[4]arene conformation. A 1,3-alternate conformation[1a] (Figure 1) was originally

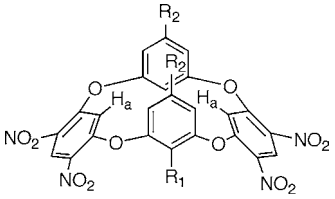


Figure 1. Three-dimensional representation of oxacalix[4]arenes **3** in a 1,3-alternate conformation conformation. Some substituents have been removed for clarity. The interior electrophilic aromatic ring protons are labeled H_a.

proposed[6a] for unhydroxylated oxacalix[4]arenes, primarily on the basis of the unusual high-field chemical shifts observed for the interior protons on the electrophilic component aromatic rings (H_a in Figure 1). It has been suggested that in this conformation H_a lies inside the anisotropic shielding cone of the adjacent aromatic rings.[5,6,11,17]

Crystals of **3b** and **3e** suitable for X-ray diffraction analysis were obtained by vapor diffusion of acetonitrile into acetone (for **3b**) or ethyl acetate (for **3e**). Oxacalixarene **3b** adopts a highly distorted 1,3-alternate conformation in the solid state (Figure 2a). The electrophilic component aromatic rings approach coplanarity (168.9° angle between ring planes), while the nucleophilic component rings are eclipsing and nearly parallel (18.0° angle between ring planes with the methyl groups pointing toward each other, presumably due

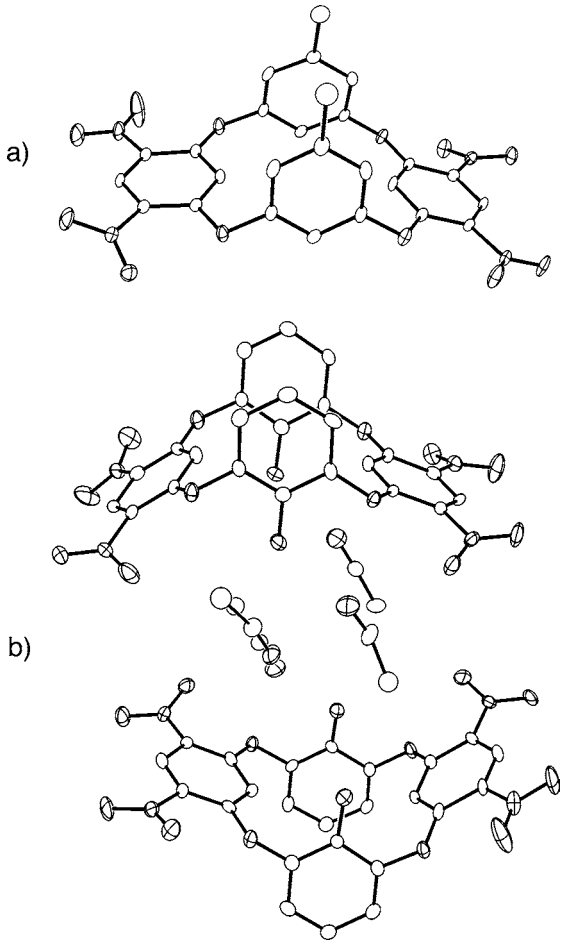


Figure 2. Thermal ellipsoid depictions of the asymmetric units for (a) **3b** and (b) **3e**·2CH_3CN. The hydrogen atoms have been omitted for clarity. Carbon atoms are shown with only boundary ellipsoids; heteroatoms are shown with boundary ellipsoids and principals.

to crystal packing forces). Oxacalixarene **3e** adopts a less distorted 1,3-alternate conformation in the solid state and crystallizes as a solvate of acetonitrile (Figure 2b). Four acetonitrile molecules align in a parallel array between each pair of oxacalixarene molecules in the asymmetric unit, which serves to fill the voids between adjacent molecules of **3e**. Each acetonitrile also forms one hydrogen bond to a phenol. As seen for **3b**, the nucleophilic component aromatic rings are eclipsed and nearly parallel (9.6° average angle between ring planes). However, in **3e** the electrophilic component aromatic rings are oriented to maintain conjugation to the bridging oxygen atoms (124.6° average angle between ring planes).

Carbon-bridged calixarenes lacking two or more hydroxyl groups are reported to have highly mobile solution conformations.[18] In the solid state, deshydroxycalix[4]arenes adopt

(15) Freund, T.; Kübel, C.; Baumgarten, M.; Enkelmann, V.; Gherghel, L.; Reuter, R.; Müllen, K. *Eur. J. Org. Chem.* **1998**, *555*, 5−564.

(16) The oxacalixarene X-ray structure reported by Chambers (ref 8) bore nitrogen atoms at the interior positions of the electrophilic component aromatic rings and adopted a 1,3-alternate conformation in the solid-state.

(17) The 1,3-alternate conformation was also proposed for analogous thiacalix[4]arenes: Montaudo, G.; Bottino, F.; Trivellone, E. *J. Org. Chem.* **1972**, *37*, 504−505.

(18) (a) Grynszpan, F.; Goren, Z.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 532−536. (b) McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, *32*, 5665−5668. (c) Goren, Z.; Biali, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1484−1487. (d) Rajca, A.; Padmakumar, R.; Smithhisler, D. J.; Desai, S. R.; Ross, C. R.; Stezowski, J. J. *J. Org. Chem.* **1994**, *59*, 7701−7703.

Table 2. Chemical Shift (ppm) of H_a for Oxacalix[4]arenes **3** at 298 K

solvent	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
DMSO-d_6	7.23	6.82	6.48	7.47	5.64	5.66	6.09	6.74

a flattened 1,2-alternate conformation described by the authors as a "chair",[18b,d] whereas 26,28-dihydroxycalix[4]-arenes adopt a 1,2-alternate conformation.[18a] In contrast, both the X-ray data (Figure 2b) and ^{1}H NMR data (Table 2) suggest that 26,28-dihydroxyoxacalix[4]arenes **3e**−**3g** prefer the 1,3-alternate conformation, apparently enforced by maintenance of conjugation between the bridging oxygen atoms and the nitro-bearing aromatic rings. As a result of both anisotropic effects and this conjugation, the electron-rich adjacent aromatic rings cause the unusual high-field chemical shifts (δ 5.64 and 5.66 for **3e** and **3f**) of the interior electrophilic aromatic ring protons (H_a) as compared to the other oxacalixarenes **3** or analogous acyclic compounds.[6a] The shielding is somewhat mitigated if an electron-withdrawing group is also appended to the nucleophilic component ring (δ 6.09 for **3g**). The chemical shift for H_a observed in the ^{1}H NMR spectrum of **3b** (δ 6.82) is also in accord with its solid-state conformation (Figure 2a), as the 168.9° angle between electrophilic component ring planes does not place H_a inside the anisotropic shielding cone of the adjacent rings. Variable-temperature NMR experiments show that the ^{1}H signals of **3a**, **3b**, and **3e** remain sharp and consistent over the temperature range 193−298 K, indicating either that these macrocycles exist in a single conformation or that conformational interconversion is rapid on the NMR time scale even at low temperature. The similarity in chemical shifts observed for H_a in **3b**, **3c**, and **3h** suggest that these oxacalix[4]arenes all adopt a distorted 1,3-alternate conformation in solution. The lower-field shift of H_a seen in **3a** and **3d** may be a consequence of the pendant electron-withdrawing groups or may indicate a different conformational preference for these macrocycles.

In conclusion, tetranitrooxacalix[4]arenes are readily synthesized in a single step by room-temperature S_NAr reactions. Full characterization of this class of compounds including two solid-state structures is reported. Our continued work toward the synthesis and conformational analysis of these molecules will be reported in due course.

Acknowledgment. The authors are grateful for financial support of this work by a Research Corporation Cottrell College Science Award and a Colby College Natural Sciences Division Grant. The National Science Foundation is acknowledged for funding of the X-ray and NMR facilities.

Supporting Information Available: Characterization data for compounds **3a**−**3h** and X-ray crystallographic data for **3b** and **3e** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047840T