ORGANIC LETTERS

2009
Vol. 11, No. 8
1681−1684

Efficient Fragment Coupling Approaches toward Large Oxacalix[*n*]arenes (*n* = 6, 8)

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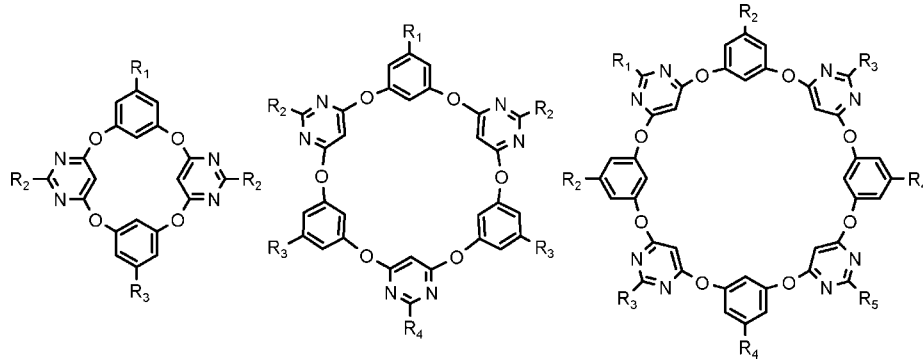
Received January 19, 2009

ABSTRACT



The first rational, stepwise synthesis of enlarged oxacalix[*n*]arenes (*n* > 4) is described. Variously substituted oxacalix[3]arene[3]pyrimidines were prepared rather selectively by a straightforward [3 + 3] fragment coupling approach after a thorough search for the optimum nucleophilic aromatic substitution conditions. Similar procedures also allowed facile synthesis of unsymmetrical oxacalix[4]- and oxacalix[8]arenes.

Heteracalixarenes, reassessed members of the calixarene family in which the classical methylene bridges are replaced by heteroatoms, are currently being studied intensively for the high promise they hold within diverse domains in supramolecular chemistry.[1−5] As a result of the difference in bridging units, heteracalixarenes inherently possess distinct physical and chemical properties, e.g., macrocycle and cavity size, conformational behavior, and molecular recognition ability. The lack of synthetic availability and versatility has severely hampered a detailed analysis of their supramolecular properties in the past, but nowadays, straightforward proce-

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10.1021/ol900116h CCC: $40.75
Published on Web 03/19/2009

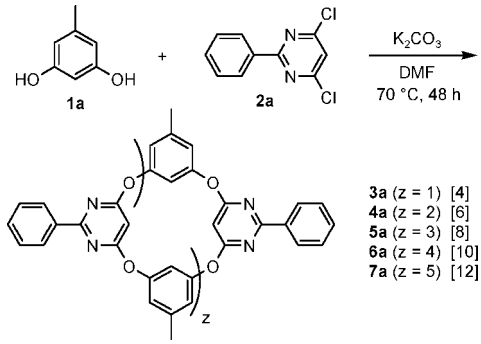
dures toward novel heteracalixarenes (mostly S,[2] N,[3,4] O[4,5]) and postmacrocyclization functionalizations of the heteracalixarene skeleton are frequently appearing in the literature.

The synthetic chemistry involving oxacalixarenes has been overlooked for many years but has now reached a more mature state due to an increasing amount of effort in recent years.[4−6] Virtually all procedures toward oxacalix[*n*]arenes reported to date focus on the preparation of oxacalix[4]arenes, [1_4]metacyclophanes composed of four O-bridged aryl moieties, either directly starting from monomeric precursors or via a stepwise approach. The majority of oxacalix[4](het)arenes have been synthesized by nucleophilic aromatic substitution (S_NAr) procedures involving a nucleophilic *m*-dihydroxybenzene component and an electrophilic 1,3-dihalogenated (hetero)aromatic building block. Careful optimization of the S_NAr reaction conditions has often afforded the oxacalix[4]arene rather selectively over other (larger) cyclooligomers and noncyclic materials by thermodynamic control.[5,6]

Larger oxacalix[*n*](het)arenes ($n = 6-12$, mostly 6) have been reported as being formed in modest yield upon usage of more "kinetic" S_NAr conditions, and (chromatographic) separation of these larger homologues is often not trivial.[6e,g−i,m,7,8] Hence, one of today's main challenges within the oxacalixarene field involves the selective synthesis of such large oxacalix[*n*]arenes, preferably by straightforward S_NAr procedures, to enable them to develop from rare examples into useful molecular probes for selective recognition studies. Herein, we present the first rational design of "expanded" oxacalix[*n*]arenes ($n = 6$, 8) via a fragment coupling protocol. Unsymmetrically substituted oxacalix[6]- and oxacalix[8]arenes were prepared in a selective way by limiting thermodynamic equilibration to the cyclotetramer.

In previous work, we have reported that a mixture of oxacalix[*m*]arene[*m*]pyrimidines ($m = 2-6$) can be obtained starting from orcinol (**1a**) and 4,6-dichloro-2-phenylpyrimidine (**2a**) under nonequilibrating conditions (Scheme 1).[6h]

Scheme 1. Synthesis of Oxacalix[*m*]arene[*m*]pyrimidines **3**−**7a**



Chromatographic separation afforded pure oxacalix[8] (10%), [10] (8%), [6] (8%), [12] (8%), and [4] (30%), respectively. On the other hand, on optimizing the S_NAr conditions, oxacalix[4]arene **3a** could be synthesized selectively in over 80% yield. Although large oxacalix[*n*]arenes are hence accessible starting from dichloropyrimidine precursors, a more selective synthesis (allowing easier purification) of these higher homologues is highly desirable if one wants to develop their supramolecular chemistry to a further extent.

Since (nontemplated) synthetic approaches starting from electrophilic and nucleophilic monomers are likely to afford the oxacalix[4]arene predominantly, we opted for a fragment coupling S_NAr strategy toward expanded oxacalix[*n*]arenes. A combination of triaryl building blocks carrying complementary functionality should allow us to obtain oxacalix[6]arenes selectively, at least if fragmentation and recombination of the building blocks affording the thermodynamic product (oxacalix[4]arene) can be limited. Bis(pyrimidine) electrophilic triaryl fragments could easily be synthesized on reacting (res)orcinol (**1a,b**) with a slight excess (~2.2 equiv) of an appropiately substituted 4,6-dihalopyrimidine **2b**−**e**. Among several conditions studied for monosubstitution of the dihalopyrimidine, best results were achieved in acetone at rt with K_2CO_3 base and 18-crown-6 (18C6) (Scheme 2,

Scheme 2. Synthesis of Triaryl Precursors **8a**−**f**/**9a**−**c**

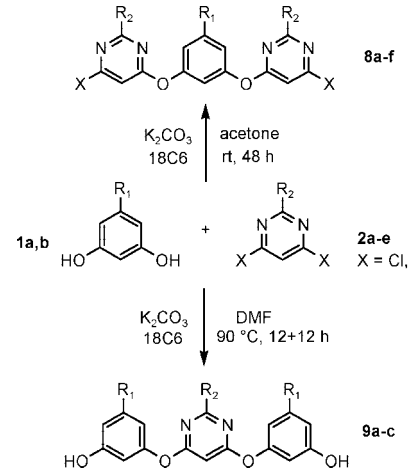


Table 1).[6k] A few substituent combinations were examined, affording triaryl precursors **8a**−**c** in high yield (90−96%). Upon reaction of two different dichloropyrimidines with orcinol, the unsymmetrical triaryl compound **8d** was prepared in 66% yield. This building block can be applied for the construction of oxacalix[*n*]arenes with a completely asymmetric substitution pattern.

The complementary linear precursors **9a**−**c** could be synthesized by dropwise addition of a dichloropyrimidine **2a**−**c** to a large excess (10 equiv) of a (res)orcinol derivative (DMF, K_2CO_3, 18C6, 90 °C, 12 + 12 h; 57−73%) (Scheme 2, Table 1).[9] The need for a large excess of (res)orcinol can

(7) You and co-workers obtained an oxacalix[6]arene in 25% yield through an Ullmann coupling protocol.[6f]

(8) A totally different approach was reported by Gibb et al.[6b] They demonstrated that functionalized oxacalix[8]arenes are accessible by removal of the resorcinarene template from their cavitand structures.

(9) A considerable part of the excess of (res)orcinol (~75%) can be recovered on chromatographic purification.

Table 1. Scope of Synthesized Triaryl Building Blocks.

electrophilic component	nucleophilic component	product (yield %)
1b (R_1 = H)	**2b** (R_2 = H, X = Cl)	**8a** (90)
1a (R_1 = Me)	**2c** (R_2 = SMe, X = Cl)	**8b** (95)
1b (R_1 = H)	**2d** (R_2 = Me, X = Cl)	**8c** (96)
1a (R_1 = Me)	**2b** (R_2 = H, X = Cl) **2c** (R_2 = SMe, X = Cl)	**8d** (66)[a]
1a (R_1 = Me)	**2e** (R_2 = SMe, X = F)	**8f** (84)
1b (R_1 = H)	**2b** (R_2 = H, X = Cl)	**9a** (73)
1b (R_1 = H)	**2c** (R_2 = SMe, X = Cl)	**9b** (57)
1a (R_1 = Me)	**2a** (R_2 = Ph, X = Cl)	**9c** (58)

[a] Concurrent formation of **8b** (37%)/**8e** (R_1 = Me, R_2 = H, X = Cl; 14%).

be circumvented by a two-step procedure involving substitution with 3-methoxyphenol and subsequent deprotection with boron tribromide (see Supporting Information).

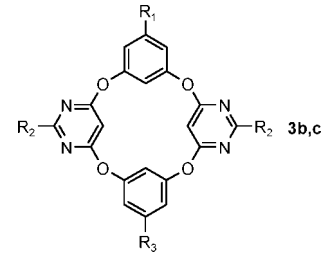
Before combination of both triaryl fragments was pursued, the ideal macrocyclization conditions were investigated using a [3 + 1] coupling strategy toward ABAC oxacalix[4]arenes.[6j,k,o] Oxacalix[4]arene synthesis is an ideal test case in the search for the requested kinetic S_NAr conditions, both from an economic (only one of the triaryls is consumed) and a practical (the reaction outcome can easily be monitored by ESI-MS and ^1H NMR analysis of the crude reaction mixture[10]) point of view. More thermodynamic conditions will induce scrambling, and hence, three different oxacalix[4]arenes will be obtained,[6j] whereas more kinetic conditions will afford the ABAC cyclotetramer predominantly. A thorough search for the optimum, most kinetic conditions (solvent, base, temp, reaction time, high dilution) was conducted, and the most illustrative examples are summarized in Table 2. The fragment coupling reaction of triaryl **8c** and orcinol in acetonitrile with K_2CO_3 base at 70 °C under high dilution conditions afforded 29% of the desired ABAC product **3b**.[11] Similar reactions in THF and DMF (for a short reaction time to limit equilibration) also afforded **3b** in 35% and 47% yield, respectively. All three approaches induced significant scrambling, and separation of the ABAC calixarene from both symmetrical oxacalix[4]arenes was difficult. An encouraging breakthrough was achieved on performing the reaction in 1,4-dioxane at reflux with K_2CO_3 base using high dilution techniques (simultaneous dropwise addition over 3 h and 3 additional h).[12] Under these conditions, scrambling could greatly be reduced and oxacalix[4]arene **3c** could be isolated in 55% yield. A longer reaction time resulted in a decreased yield (12 + 72 h; 17% **3b**). As observed before for the synthesis of oxacalix[2]arene[2]pyrimidines,[6h] the change of a dichloropyrimidine electrophilic (**8b**) building block for a difluoro

(10) Due to the distinct chemical shift for some intra-annular protons of oxacalix[4]arenes, e.g., the strongly shielded 5-pyrimidinyl signals.[6h]

(11) Alternatively, ABAC oxacalix[4]arenes were obtained via combination of orcinol with a mixture of dichloropyrimidines (43%).[6h]

(12) Too strong dilution has to be avoided; no (or very slow) reaction has been observed under such conditions.

Table 2. Scope of Synthesized Oxacalix[4]hetarenes



triaryl	diphenol	S_NAr conditions	oxacalix[4]arene
8c	**1a**	MeCN, K_2CO_3, 70 °C, 12 + 5 h[a]	**3b** (R_1 = H, R_2 = Me, R_3 = Me; 29%)[b]
8c	**1a**	THF, K_2CO_3, 18C6, reflux, 36 h	**3b** (R_1 = H, R_2 = Me, R_3 = Me; 35%)
8c	**1a**	DMF, K_2CO_3, 18C6, 150 °C, 2.5 h	**3b** (R_1 = H, R_2 = Me, R_3 = Me; 47%)[b]
8b (X = Cl)	**1b**	1,4-dioxane, K_2CO_3, 18C6, reflux, 3 + 3 h[a]	**3c** (R_1 = Me, R_2 = SMe, R_3 = H; 55%)
8f (X = F)	**1b**	1,4-dioxane, K_2CO_3, 18C6, reflux, 3 + 3 h[a]	**3c** (R_1 = Me, R_2 = SMe, R_3 = H; 76%)

[a] Time of simultaneous addition + extra time. [b] NMR yield.

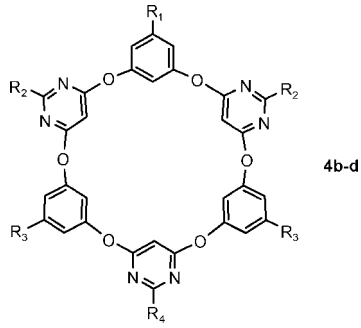
analogue (**8f**) resulted in a noticeable improvement (~20%) of the selectivity, affording **3c** in 76% yield. More reactive starting compounds and, hence, a short reaction time seem to be highly benefical for the reaction outcome.

When the optimized S_NAr procedure was applied to the [3 + 3] coupling, pure oxacalix[6]arenes **4b** and **4c** were isolated in 37% and 49% yield, respectively (Table 3). Again, the bis(fluoropyrimidine) precursor **8f** could beneficially be used to afford **4d** in an excellent 70% yield. During the purification of **4d**, oxacalix[12]arene analogue **7d** (see Supporting Information) could also be isolated in 9% yield. Under nonoptimized conditions (e.g., in MeCN or THF), the desired oxacalix[6]arenes were obtained in rather low yields after cumbersome purification from considerable amounts of calix[4]arenes. Reaction in DMF at 70 °C (K_2CO_3, 18C6, 12 + 12 h) resulted in a mixture of oxacalix[*n*]arenes (n = 4−12), whereas a similar reaction at 120 °C for 3 h afforded only the thermodynamically favored oxacalix[4]arenes.

The main advantage of oxacalix[*m*]arene[*m*]pyrimidines compared to their counterparts prepared from other (hetero)aromatic electrophilic building blocks is the ease and broad scope of modification of the oxacalixarene substitution pattern. Functionalization can be achieved via the use of (easily accessible) substituted pyrimidine building blocks or by unique postmacrocyclization modifications. It has been shown that oxacalix[2]arene[2]pyrimidines can easily be functionalized by Liebeskind−Srogl or S_NAr procedures.[6p] These functionalizations can now be extended to oxacalix[6]arenes, and depending on the number of thiomethyl groups, mono-, di-, and trifunctionalized oxacalixarenes can be prepared. As a proof-of-principle, a postmacrocyclization functionalization strategy was performed on **4d**. The methylsulfanyl moieties were first oxidized to methylsulfonyl groups (affording **4e** in 83% yield), after which S_NAr with

4-*tert*-butylphenol (at 70 °C in 1,4-dioxane) afforded oxacalix[6]arene **4f** (R_1 = Me, R_2 = R_4 = 4-*t*BuPhO, R_3 = H; 57%).[13]

Table 3. Scope of Synthesized Oxacalix[6]hetarenes



triaryls	oxacalix[6]arene[a]
8c and **9b**	**4b** (R_1 = H, R_2 = Me, R_3 = H, R_4 = SMe; 37%)
8b and **9a**	**4c** (R_1 = Me, R_2 = SMe, R_3 = H, R_4 = H; 49%)
8f and **9b**	**4d** (R_1 = Me, R_2 = SMe, R_3 = H, R_4 = SMe; 70%)

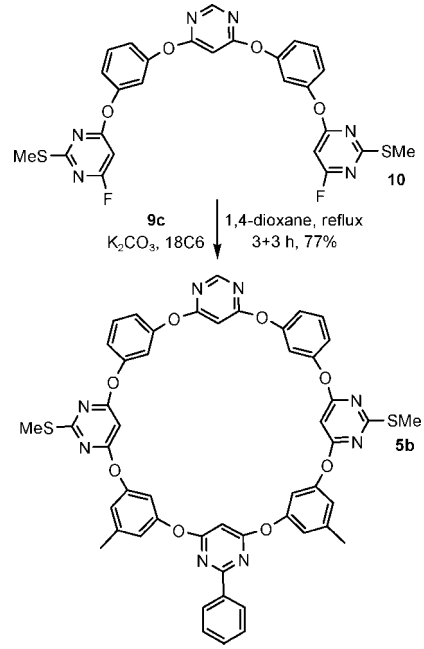
[a] General S_NAr conditions: 1,4-dioxane, K_2CO_3, 18C6, reflux, 3 + 3 h.

A logical extension to oxacalix[8]arenes involves combination of a penta- and triaryl building block. Since the synthesis of the bis(pyrimidine) fragments **8a**−**f** proceeded smoothly, tris(pyrimidine) pentaaryl precursor **10** was prepared by a similar strategy (triaryl **9a** and pyrimidine **2e** in acetone at rt, 95% yield) (Scheme 3).[14] A difluoro fragment was again preferred for formation of the oxacalix[8]arene due to its beneficial effect on the reaction yield. Under the previously optimized conditions, pentaaryl moiety **10** and triaryl **9c** were combined to afford **5b** in an exceptional 77% yield (Scheme 3).

Diffraction-quality crystals of an oxacalix[8]arene were obtained by vapor diffusion of pentane in a $CHCl_3$ solution of **5a**.[15,16] This example represents the first X-ray structure reported in literature of an enlarged oxacalix[*n*]arene ($n \neq 4$) (more details in Supporting Information).[17,18]

In summary, we have established conditions that allow the synthesis of variously functionalized large oxacalix[*n*]arenes (n = 6, 8) with unprecedentedly high selectivity by convenient stepwise S_NAr strategies, enabling further supramolecular research on these attractive macrocycles.

Scheme 3. Synthesis of Oxacalix[4]arene[4]pyrimidine **5b**



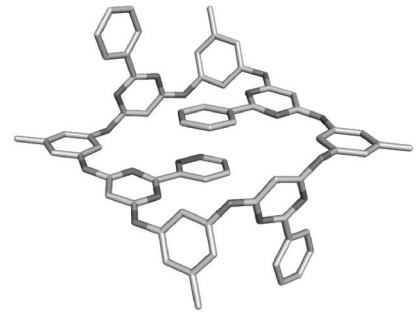


Figure 1. Single-crystal X-ray structure for oxacalix[8]arene **5a**.

Acknowledgment. The authors thank the FWO for financial support and a postdoctoral fellowship to W.M. and the KU Leuven and the Ministerie voor Wetenschapsbeleid for continuing financial support.

Supporting Information Available: Experimental procedures and data, and ^1H and ^{13}C NMR spectra for all novel building blocks and oxacalix[*n*]arenes. X-ray structure for **5a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The failure of the S_NAr functionalization in DMF at 90 °C (the conditions optimized for the oxacalix[4]arene) and the reduced yield seem to reflect the lower stability of larger oxacalix[*n*]arenes.

(14) For the opposite combination, the conditions (DMF, 90 °C) required to prepare the pentaaryl are likely to induce scrambling.

(15) Full synthetic details for this compound can be found in ref 6h.

(16) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as suppl. publ. no. CCDC-718550. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(17) Katz reported the structure of an oxacalix[6]- and an oxacalix[8]arene at the Calix 2007 conference (College Park, MD).

(18) The structures of two *ortho*-linked [1_6]oxacyclophanes were very recently reported: Ma, M.; Wang, H.; Li, X.; Liu, L.; Jin, H.; Wen, K. *Tetrahedron* **2009**, *65*, 300.