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Selective Synthesis of Functionalized Thia- and Oxacalix[2]arene[2]pyrimidines

Wouter Maes, Wim Van Rossom, Kristof Van Hecke,[†] Luc Van Meervelt,[†] and Wim Dehaen*

Molecular Design and Synthesis and Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

wim.dehaen@chem.kuleuven.be

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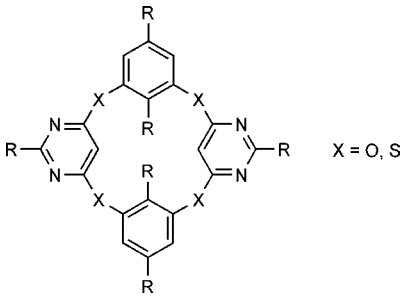
ABSTRACT



Functionalized oxacalix[*m*]arene[*n*]pyrimidines have been synthesized by S_NAr on 4,6-dihalopyrimidine building blocks. Depending on the S_NAr conditions, either a mixture of oxacalix[*n*]arenes, ranging from oxacalix[4]- up to oxacalix[12]arene, could be prepared or the oxacalix[4]-arene could be synthesized selectively in a high yield. The electrophilic (pyrimidine) and the nucleophilic components could both be varied, allowing the preparation of functionalized oxacalix[4]arenes. Moreover, the procedure also gives access to the analogous thiacalix[4]arenes.

Calix[*n*]arenes are [1$_n$]metacyclophanes that are quite easy to prepare and functionalize and therefore play an important part in supramolecular chemistry.[1] Heterocalixarenes, in which the carbon linkages between the aromatic units are replaced by heteroatoms, are far less prevalent in the chemical literature.[2] Lately, thiacalixarenes have been studied extensively due to the discovery that they can be prepared directly from phenols and elemental sulfur.[3] Azacalix[*n*]-arenes (and *N*-methylazacalixarenes) have recently been obtained by Pd-catalyzed amination reactions.[4] Oxacalix-arenes were already prepared in 1966, but up until a few years ago it has been very quiet in this field.[5,6] An important breakthrough in oxacalixarene chemistry was achieved by Katz in 2005.[6f] He was able to prepare functionalized oxacalix[4]arenes in a single step in very high yields through

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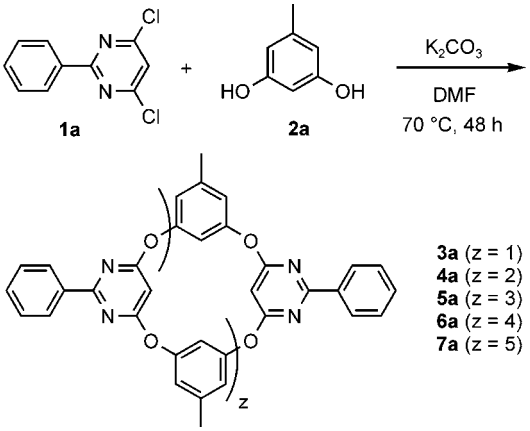
nucleophilic aromatic substitution (S_NAr) reactions of substituted 1,3-dihydroxybenzenes with 1,5-difluoro-2,4-dinitrobenzene. Variation of the nucleophilic component was possible in this strategy, allowing the preparation of oxacalix[4]arenes with more favorable solubility characteristics compared to the previously reported structures. Vicente further varied the nucleophilic component by introducing the dihydroxybenzene moiety on a porphyrin macrocycle.[6h]

Synthetic pyrimidine chemistry is a very well-studied part of organic chemistry since the versatile pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides, and herbicides.[7a] Dihalopyrimidines have been used extensively for the synthesis of multitopic ligands suitable for the generation of grid-type metal ion architectures.[7b] In previous work, we have been studying the synthesis and reactivity of 4,6-dichloropyrimidines as structural components of *meso*-pyrimidinyl-substituted porphyrinoids and pyrimidine dendrimers.[8,9] With this background in pyrimidine chemistry (and S_NAr on heteroaromatic systems), we now envisaged to prepare functional oxacalixarenes by S_NAr on diverse 4,6-dihalopyrimidine building blocks.

Initially, 4,6-dichloro-2-phenylpyrimidine (**1a**)[10] and orcinol (**2a**) were mixed in equimolar amounts with an excess of K_2CO_3 (2.5 equiv)[11] in DMF at 70 °C (Scheme 1), since

Scheme 1. Synthesis of Oxacalix[*m*]arene[*n*]pyrimidines



these conditions had been used before for efficient S_NAr on dichloropyrimidines.[8,9] The reaction was run for 48 h, and the crude reaction mixture was analyzed by MS.[12] The mass spectrum revealed, besides the expected oxacalix[4]arene **3a**, the presence of larger macrocyclic species, ranging from oxacalix[6]arene **4a** up to oxacalix[12]arene **7a**. Chromatographic separation of the obtained mixture afforded pure oxacalix[8]arene **5a** (10%), oxacalix[10]arene **6a** (8%), oxacalix[6]arene **4a** (8%), oxacalix[12]arene **7a** (8%), and oxacalix[4]arene **3a** (30%), respectively. Such formation of larger macrocycles (in modest yield) in the S_NAr-based macrocyclization was also observed by Vicente[6h] and very recently by Katz.[6j] However, to the best of our knowledge, an oxacalix[12]arene has never been successfully prepared and isolated so far. The obtained yields for the larger oxacalix[*n*]arenes are quite good, but the yield for oxacalix[4]arene is very modest compared to the yields reported by Katz (86−92%).[6f]

All oxacalix[*m*]arene[*n*]pyrimidines **3**−**7a** showed reasonable to good solubility in a variety of organic solvents, and they were completely characterized by ^1H and ^{13}C NMR spectroscopy. On comparison of the ^1H NMR spectra of the oxacalix[*n*]arenes, a clear shift is observed for certain protons of the smaller macrocycles. The signal corresponding to the proton on the C_5-position of the pyrimidine moiety (positions 25 and 27 when considering the calix[4]arene numbering scheme[1]) is considerably shifted upfield (5.36 ppm) for oxacalix[4]arene **3a** compared to the same signal for the larger oxacalix[*n*]arenes (e.g., 6.16 ppm for oxacalix[8]arene **5a**). This upfield shift for the interior protons of the electrophilic component of oxacalix[4]arenes has been observed before and can be attributed to anisotropic effects and conjugation of the O-bridging atoms into the electrophilic aromatic ring.[6] The signals for the *o*-protons of the phenyl substituent on the pyrimidine C_2-position also show a distinct chemical shift depending on the macrocycle size. For **3a** a signal is observed at 8.48 ppm, with a clear downfield chemical shift compared to the larger oxacalix[*n*]arenes (e.g., 8.07 ppm for **5a**).

To observe the conformation of oxacalix[4]arene **3a** in the solid state, suitable crystals were grown by vapor diffusion of pentane into a $CHCl_3$ solution of **3a**. The single-crystal X-ray structure of **3a** adopts a 1,3-alternate conformation (Figure 1). The nucleophilic (benzene) as well as the electrophilic (pyrimidine) component aromatic rings are positioned almost perpendicular to each other and the angles between the planes through the aromatic rings are 86.1° and 86.7°, respectively, resulting in a highly symmetrical cavity. This observation is somewhat different from previously reported X-ray structures for similar oxacalix[4]arenes, in which the nucleophilic component rings are eclipsing and nearly parallel, while the electrophilic aromatic rings approach planarity or are oriented to maintain conjugation to the bridging O-atoms.[6b,e,f] For **3a**, the average bond distance between the bridging O-atom and the electrophilic and nucleophilic rings is 1.36 and 1.39 Å, respectively. This difference is less pronounced in comparison with the previously reported structures, but still indicates that the

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(11) Finely ground, as described by Katz (ref 6f).

(12) After 24 h, a number of oligomers (e.g., the 1/1 adduct) could still be observed by MS.

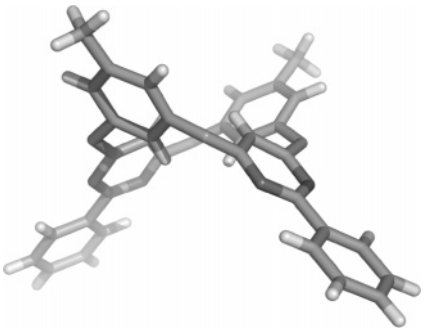

Figure 1. Single-crystal X-ray molecular structure for **3a**.

electrons of the bridging O-atoms mainly conjugate to the pyrimidine rings. The crystal lattice shows the formation of columns due to $\pi-\pi$ stacking of the molecules of **3a** (see the Supporting Information).

Although the described procedure gives access to a number of expanded oxacalix[*n*]arenes in reasonable yields, a more ring-size selective synthesis was pursued, more in particular toward oxacalix[4]arene **3a**, which is probably the most promising one in terms of future applications (due to its semirigid structure). A search for the optimum conditions to obtain a maximum amount of **3a** was pursued (Table 1).

Table 1. Optimization of the Yield for Oxacalix[4]arene **3a**

entry	pyrim	base	solvent	cat.	*T* (°C)	time (h)	**3a**[a] (%)
1	**1a**	K_2CO_3	DMF	–	70	48	34
2	**1a**	K_2CO_3	CH_3CN	–	70	48	18
3	**1b**	K_2CO_3	DMF	–	70	48	65
4	**1b**	Na_2CO_3	DMF	–	70	48	43
5	**1b**	K_2CO_3	DMF	–	20	48	46
6	**1b**	K_2CO_3	DMF	–	150	24	35
7	**1b**	K_2CO_3	DMSO	–	20	0.2[b]	16
8	**1b**	K_2CO_3	DMSO	–	70	48	49
9	**1b**	K_2CO_3	DMF	18C6	70	48	82
10	**1b**	**K_2CO_3**	**DMF**	**18C6**	**70**	**24**	**80**
11	**1b**	K_2CO_3	DMF	18C6	70	2	50
12	**1a**	K_2CO_3	DMF	18C6	70	24	55

[a] Based on NMR analysis of the oxacalix[*n*]arene mixture. [b] 12 min.

The oxacalixarene ring size selectivity in the S_NAr reaction could easily be checked by ^1H NMR analysis of the crude reaction mixture, since the signal for the interior pyrimidine C_5-proton is reasonably shifted upfield for the smaller oxacalix[4]arene macrocycle compared to the larger oxacalix[*n*]arenes (and the noncyclic oligomers, polymer). On analyzing the ^1H NMR spectrum for the crude reaction mixture obtained for the reaction described in Scheme 1, the yield for **3a** was estimated to be 34%, which is in close agreement with the isolated yield of 30% (entry 1). Changing the solvent from DMF to acetonitrile, which was shown to be effective for the construction of dendrimers through S_NAr,[9a] caused a drop in the estimated yield to 18% (entry 2). A very effective modification to achieve a higher selectivity for oxacalix[4]arene **3a** was the use of 4,6-difluoro-2-phenylpyrimidine (**1b**)[13] as the electrophilic partner. This difluoropyrimidine is clearly more reactive toward S_NAr and could easily be obtained by reaction of **1a** with KF under the conditions described by Plé.[14] When **1b** was reacted with orcinol, under similar conditions as used for **1a**, **3a** could be obtained in a yield of 65% (entry 3), which is almost the double of the yield obtained with **1a**. After chromatographic purification, **3a** was obtained in 60% yield, while the larger oxacalix[*n*]arenes were only isolated in very small quantities (2% **4a**, 3% **5a**, 1% **6a**, and 1% **7a**). Changing the base to Na_2CO_3 caused a drop in the yield to 43% (entry 4). Changing the concentration of the reagents did not really affect the obtained yield, as was reported before.[6] On performing the reaction at rt or at 150 °C, the oxacalix[4]arene amount again decreased (entries 5 and 6). After repeating the reaction under the conditions optimized by Katz (entry 7),[6f] **3a** was formed in only 16% yield, and on increasing the temperature to 70 °C, **3a** was formed in 49% yield (entry 8), which is still 16% less than was obtained in DMF. Another important improvement of reaction selectivity was obtained on adding 18-crown-6 (18C6) to the reaction mixture. The amount of **3a** could now be estimated at 82% (entry 9). On decreasing the reaction time to 24 h (entry 10), no significant drop in the yield was observed, and after chromatographic purification 78% of pure oxacalix[4]arene **3a** was obtained. Although larger cyclooligomers were still observed in the crude mixture by MS, they could only be obtained in negligible amounts under these conditions. A further decrease in the reaction time to 2 h caused a drop in the yield to 50% (entry 11). When the reaction was now repeated with 4,6-dichloro-2-phenylpyrimidine (**1a**), under the optimized conditions, **3a** was obtained in 55% yield (entry 12), which means that the yield was increased by 21% on adding 18C6 to the reaction mixture.

Hence, on optimizing the S_NAr conditions, the yield for **3a** was increased to ~80%. The crucial parameter to obtain the oxacalix[4]arene macrocycle with high yield and selectivity seems to be the enhancement of the reactivity of both reaction partners in the S_NAr (by fluorination and addition of 18C6).

Besides the control of oxacalix[*n*]arene ring size, the major advantage of the introduction of pyrimidine units in the oxacalixarene skeleton is the fact that 4,6-dihalopyrimidines can easily be obtained with a diverse substitution pattern.[7] A number of 4,6-dihalopyrimidines **1a**−**f** were reacted with orcinol under the conditions as optimized for oxacalix[4]arene **3a** (Table 2).

The introduction of a substituent on the pyrimidine C_2-position results in the formation of oxacalix[2]arene[2]pyrimidines with two substituents on the upper rim (extraannular). First of all, 4,6-dichloropyrimidine (**1c**) was used as the electrophilic partner and oxacalix[4]arene **3b** was ob-

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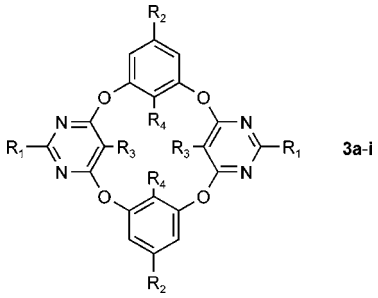
Table 2. Overview of Synthesized Oxacalix[4]arenes **3a**−**i**



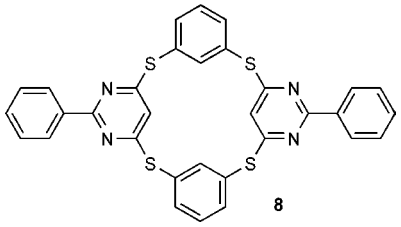
3a-i

entry	pyrimidine **1** (X^a/R_1/R_3)	nucleophile **2** (R_2/R_4)	[4]	yield[b] (%)
1	**1a** (X = Cl, R_1 = Ph, R_3 = H)	**2a** (R_2 = Me, R_4 = H)	**3a**	51
2	**1b** (X = F, R_1 = Ph, R_3 = H)	**2a**	**3a**	78
3	**1c** (X = Cl, R_1 = H, R_3 = H)	**2a**	**3b**	75[c]
4	**1d** (X = Cl, R_1 = SMe, R_3 = H)	**2a**	**3c**	65[c]
5	1/1 mixture of **1c** and **1d**	**2a**	**3d**	43[c,d]
6	**1e** (X = Cl, R_1 = H, R_3 = CHO)	**2a**	**3e**	–
7	**1f** (X = Cl, R_1 = H, R_3 = NO_2)	**2a**	**3f**	–
8	**1b**	**2b** (R_2 = H, R_4 = H)	**3g**	80
9	**1b**	**2c** (R_2 = H, R_4 = OH)	**3h**	31
10	**1c**	**2d** (R_2 = H, R_4 = Me)	**3i**	15

[a] X = halogen on $C_{4,6}$. [b] Isolated yield. [c] 48 h. [d] Based on % **2a** consumed.

tained in 75% yield (entry 3), despite the usage of the dichloropyrimidine instead of the fluorinated derivative.[15] An increase of 24% was hence observed on removing the phenyl substituent on the pyrimidine component. On introducing a thiomethyl group at the pyrimidine C_2-position, the corresponding oxacalix[4]arene **3c** was obtained in 65% yield (entry 4). On using an equimolar mixture of pyrimidines **1c** and **1d**, 3 oxacalix[4]arenes **3b**−**d** were isolated (91% global yield) of which the monosubstituted "mixed" oxacalix[4]arene **3d** was obtained in a remarkable 43% yield (entry 5). Such monosubstituted oxacalix[4]arenes are important in view of potential applications, e.g., attachment to fluorophores (sensors) and all kinds of supports (e.g., dendrimers) or the construction of monolayers. We have also tried to introduce substituents on the pyrimidine C_5-position, since these substituents would end up at the lower rim of the oxacalix[4]arenes (intraannular). However, reaction of 4,6-dichloropyrimidine-5-carbaldehyde (**1e**)[16] (entry 6) or 4,6-dichloro-5-nitropyrimidine (**1f**)[17] (entry 7) with orcinol did not result in the formation of the desired oxacalixarenes. The nucleophilic component of the oxacalix[*m*]arene[*n*]pyrimidines could also be varied. Reaction of **1b** with resorcinol (**2b**) resulted in the formation of **3g** in a high yield of 80% (entry 8). Lower rim functionalized oxacalix[4]arenes can be obtained by using 2-substituted *m*-dihydroxybenzenes. Reaction of **1b** with pyrogallol (**2c**) afforded **3h** in 31% yield (entry 9), while reaction of **1c** with 2-methylresorcinol (**2d**) resulted in the formation of **3i** in 15% yield (entry 10). Oxacalix[4]arenes with substituents on the lower rim are hence accessible, but the obtained yields are much lower.

Thiacalixarenes have already been prepared through S_NAr-based procedures.[5d,6a,18] We have also tried to synthesize a thiacalix[2]arene[2]pyrimidine through the same (optimized) S_NAr procedure. Reaction of 4,6-difluoro-2-phenylpyrimidine and 1,3-benzenedithiol (**2e**) afforded thiacalix[4]arene **8** in a (isolated) yield of 69%.



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In conclusion, novel oxacalix[*m*]arene[*n*]pyrimidines have been synthesized by S_NAr reactions on halogenated pyrimidine building blocks. Depending on the S_NAr conditions, either a mixture of oxacalix[*n*]arenes, ranging from oxacalix[4]- up to oxacalix[12]arene, could be prepared or the oxacalix[4]arene could be synthesized selectively in a high yield (up to 80%). Some parameters controlling the ring size selectivity were clarified. A high reactivity of both reaction partners in the S_NAr seems to be crucial to obtain the oxacalix[4]arene macrocycle with a high yield and selectivity. The pyrimidine and the nucleophilic component were both varied, allowing us to prepare some functionalized oxacalix[4]arenes. Moreover, the procedure also allows the preparation of analogous thiacalix[4]arenes. The ease of elaboration of the substitution pattern, the remarkably symmetrical cavity of oxacalix[4]arene **3a**, the tunable macrocycle size and their good solubility make the presented heterocalix[*n*]arenes versatile platforms for further exploration of selective recognition processes of various guest molecules (cations, anions, and neutral species, depending on the substituents).

Acknowledgment. We gratefully acknowledge financial support by K. U. Leuven.

Supporting Information Available: Experimental procedures and characterization data (and spectra) for heterocalix[*m*]arene[*n*]pyrimidines **3**−**7a**, **3b**−**i**, and **8**. X-ray structure for **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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