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New synthetic route to homooxacalix[*n*]arenes via reductive coupling of diformylphenols

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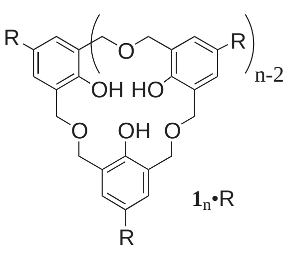
Abstract—Reductive homocoupling of 4-substituted-2,6-diformylphenols with Et_3SiH in the presence of Me_3SiOTf gave homooxacalix[*n*]arenes ($\mathbf{1}_n\cdot R$, $n=3$, 4) in moderate yields. Heterocoupling reaction of 4-substituted-2,6-diformylphenols with tris(trimethylsilyl) ether of 4-substituted-2,6-bis(hydroxymethyl)phenols afforded homooxacalix[*n*]arenes ($\mathbf{2}_3\cdot R^1\cdot R^2\cdot R^m$ and $\mathbf{2}_4\cdot R^1\cdot R^2\cdot R^1\cdot R^m$, $m=1$, 2) with different substituents in a one-pot fashion. © 2001 Elsevier Science Ltd. All rights reserved.

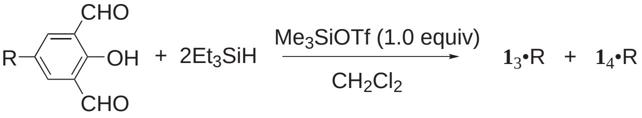
Hexahomotrioxacalix[3]arenes ($\mathbf{1}_3$) and their derivatives have gained increasing attention as ligands for transition metals,[1] and receptors for metal cations,[2] ammonium ions[2g,h,3] and buckminsterfullerene, C_{60}.[4] Quite recently, they were applied to the construction of biological models[5] and supramolecular capsules.[6] However, their synthesis has been limited to the following two routes; (1) direct synthesis of $\mathbf{1}_n$ ($n=3$, 4) by dehydration of bis(hydroxymethyl)phenols in the presence or absence of Brønsted acid at high temperature[7,8] and (2) stepwise synthesis of hexahomotrioxacalix[3]arenes with different substituents via acid-catalyzed cyclization of linear trimers.[9] Herein is reported an alternative route to homooxacalix[*n*]arenes ($\mathbf{1}_n$, $n=3$, 4) by reductive homocoupling (Scheme 1) and a one-pot way to homooxacalix[*n*]arenes with different substituents ($\mathbf{2}_n$, $n=3$, 4) by reductive heterocoupling (Scheme 2). Preliminary results of the inclusion property for fullerenes are also described.



$\mathbf{1}_n$•R

The homocoupling reaction was carried out in the following procedure based on the reported one:[10] to a stirred solution of 4-substituted-2,6-diformylphenol[11] and Me_3SiOTf (1 equiv.) in dry dichloromethane was added a dichloromethane solution of triethylsilane (2.2 equiv.) using a syringe pump over 1–2 h under an argon atmosphere. After stirring for several hours, the mixture was poured into aqueous $NaHCO_3$ and extracted three times with dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The white solid insoluble in ethyl acetate was filtered off and assigned as $\mathbf{1}_4$ from the ^1H NMR and MALDI-TOF-MS spectra. The crude $\mathbf{1}_3$ in the filtrate was subjected to flash column chromatography on silica gel (1/50–1/5 ethyl acetate/hexane). In the case of *t*-butylhomooxacalixarene ($\mathbf{1}_n\cdot t$-Bu, run 1 in Table 1), the crude residue was directly submitted to a flash column chromatography (1/50–1/20 ethyl acetate/hexane) to give both $\mathbf{1}_3$ and $\mathbf{1}_4$ in pure forms.

Yields and reaction conditions for the homocoupling reaction are summarized in Table 1. Reaction conditions depend largely on the nature of the substituent (R) at the 4-position of substrates. The highest yield for each halogenophenol was obtained at 0°C (runs 5–8), while lower temperature (−78 to −45°C) and higher concentration were the conditions of choice for the other phenols (runs 1–4). The macrocycles, $\mathbf{1}_3$ and $\mathbf{1}_4$,



Scheme 1.

Keywords: calixarene; coupling reactions.

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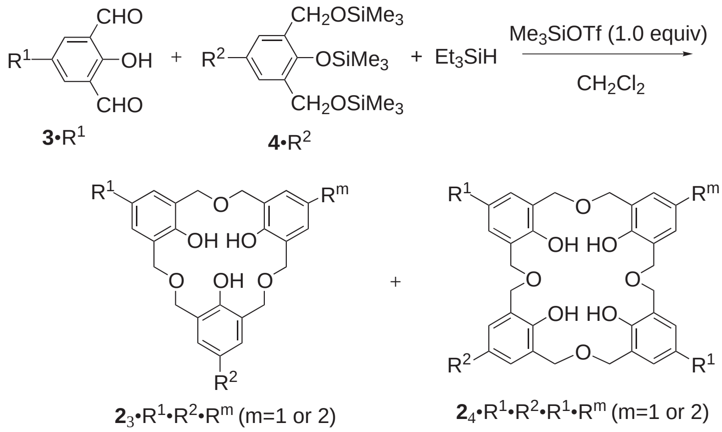
Table 1. Synthesis of homooxacalix[*n*]arenes ($\mathbf{1}_n$; $n=3$, 4) by reductive homocoupling

Run	R	Conc. (M)	React. time (h)	Temp. (°C)	Yield (%)[a]	
					$\mathbf{1}_3$	$\mathbf{1}_4$[b]
1	*t*-Bu	0.05	8	−78	38	22
2	Me	0.05	7.5	−78	35	12
3	CH_2Ph	0.05	7.5	−78	32	14
4	Ph	0.05	9.5	−45	11	18
5	F	0.01	9	0	29	24
6	Cl	0.01	7	0	29	22
7	Br	0.01	7.5	0	28	26
8	I	0.01	9	0	13	0

[a] Isolated yield.

[b] Separated as a white solid insoluble in ethyl acetate except for $\mathbf{1}_4$·*t*-Bu in run 1.



Scheme 2.

Table 2. Synthesis of homooxacalix[*n*]arenes ($\mathbf{2}_3$·R^1·R^2·R^m and $\mathbf{2}_4$·R^1·R^2·R^1·R^m, $m=1$, 2) by reductive heterocoupling at −78°C

Run	R^1 (mmol)[a]	R^2 (mmol)[a]	React. time (h)	Yield (%)[b]			
				$\mathbf{2}_3$·R^1·R^2·R^1	$\mathbf{2}_3$·R^1·R^2·R^2	$\mathbf{2}_4$·R^1·R^2·R^1·R^1	$\mathbf{2}_4$·R^1·R^2·R^1·R^2[c]
1	*t*-Bu (0.20)	Me (0.19)	8	8	5	0	28
2	Me (0.21)	*t*-Bu (0.20)	8	19	12	0	32
3	$PhCH_2$ (0.20)	*t*-Bu (0.20)	8	15	8	0	26
4	*t*-Bu (0.20)	*t*-Bu (0.21)	8	26 ($\mathbf{1}_3$·*t*-Bu)	26	42 ($\mathbf{1}_4$·*t*-Bu)	42
5	Cl (0.20)	*t*-Bu (0.20)	11.5	5	7	0	20
6	Br (0.20)	*t*-Bu (0.20)	11.5	8	6	0	13
7	F (0.20)	*t*-Bu (0.20)	10	3	1	0	26
8	F (0.42)	*t*-Bu (0.20)	7.5	24	0	12	3
9	F (0.32)	*t*-Bu (0.11)	7	15	Trace	20	0
10[d]	*t*-Bu (0.43)	F (0.22)	7	22	0	13	8

[a] Amounts of $\mathbf{3}$·R^1 and $\mathbf{4}$·R^2 used are indicated in parentheses.

[b] Isolated yield.

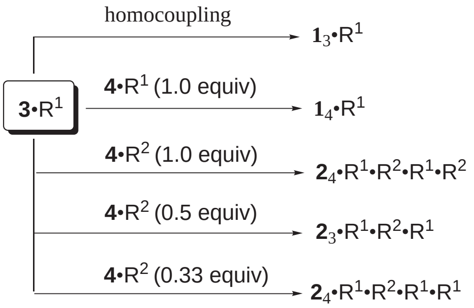
[c] Separated as a white solid insoluble in ethyl acetate except for $\mathbf{1}_4$·*t*-Bu in run 4 and $\mathbf{2}_4$·R^1·R^2·R^1·R^2 in runs 1–3.

[d] $\mathbf{1}_3$·*t*-Bu was obtained in 13% yield.

were obtained in around 50% yields except for runs 4 and 8. Larger macrocycles than $\mathbf{1}_4$ were not detected at all on the ^1H NMR spectra of the crude mixtures. These results indicate that the hydrogen bonding network in the linear trimer and tetramer worked well as a template for cyclization, while linear precursor larger than tetramer could not take a suitable conformation for cyclization. Compared to the methods reported previously,[4e,7] this procedure gave the products, $\mathbf{1}_3$ and $\mathbf{1}_4$, in better yields under milder reaction conditions using Lewis acid at lower temperature after a more facile way of product separation by simple filtration (runs 2–8) or column chromatography (run 1).

The results of the heterocoupling reaction are summarized in Table 2. The stoichiometry of the substrates, $\mathbf{3}\cdot R^1$ and $\mathbf{4}\cdot R^2$, remarkably changed the distribution of the cyclization products, $\mathbf{2}_3\cdot R^1\cdot R^2\cdot R^m$ and $\mathbf{2}_4\cdot R^1\cdot R^2\cdot R^1\cdot R^m$ ($m=1$, 2), which were separated by filtration and column chromatography using a similar procedure to that of the homocoupling reaction. An equimolar reaction between **3** and **4** gave $\mathbf{2}_4$ preferentially (runs 1–7). When the *p*-substituents, R^1 and R^2, are the same, $\mathbf{1}_4$ was obtained as a major product (run 4). When the ratio of $\mathbf{3}\cdot$F and $\mathbf{4}\cdot t$-Bu was changed to 2:1 and 3:1 in runs 8 and 9, $\mathbf{2}_3\cdot\mathrm{F}\cdot t\text{-Bu}\cdot\mathrm{F}$ and $\mathbf{2}_4\cdot\mathrm{F}\cdot t\text{-Bu}\cdot\mathrm{F}\cdot\mathrm{F}$ were produced as the major products, respectively. Although $\mathbf{2}_3\cdot\mathrm{F}\cdot t\text{-Bu}\cdot t\text{-Bu}$ was not obtained in run 8, the substrates with the reversed substituents, $\mathbf{3}\cdot t$-Bu and $\mathbf{4}\cdot$F, in a 2:1 ratio provided $\mathbf{2}_3\cdot t\text{-Bu}\cdot\mathrm{F}\cdot t\text{-Bu}$ ($=\mathbf{2}_3\cdot\mathrm{F}\cdot t\text{-Bu}\cdot t\text{-Bu}$) as a major product (run 10). This method realized the preferential preparation of all the homooxacalix[*n*]arenes ($n=3$, 4) with one or two kinds of substituents, except one homooxacalix[4]arene ($\mathbf{2}_4\cdot R^1\cdot R^1\cdot R^2\cdot R^2$), by choosing the reaction mode, the substrates and their stoichiometry, as shown in Scheme 3.

As for the inclusion property, it was disclosed that *p*-iodohaxahomotrioxacalix[3]arene ($\mathbf{1}_3\cdot$I) precipitated C_{70}, while no black precipitates were formed from the mixture of C_{60} and $\mathbf{1}_3\cdot$I. Preferential precipitation of C_{70} over C_{60} was confirmed by the addition of $\mathbf{1}_3\cdot$I to the mixture of fullerenes; the ratio of C_{70}/C_{60} improved from 58/42 to 88/12. Other symmetric trimers ($\mathbf{1}_3$) precipitated neither C_{60} nor C_{70} under the reported conditions.[4e,g] Further studies are in progress and will be reported in due time.



Scheme 3.

In conclusion, the first efficient and flexible method for the synthesis of homooxacalix[*n*]arenes ($n=3$, 4) with different *p*-substituents has been devised. The utility of these compounds is also demonstrated in preferential C_{70} precipitation with $\mathbf{1}_3\cdot$I.

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