Acid-catalysed Synthesis of a New Class of Calix[4]arenes

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Reaction of formaldehyde with 2,2'-dihydroxytriphenylmethanes **3** in acidic media gives calix[4]-arenes **4** bearing two aryl groups on the diametrical methylene bridges.

Cyclic condensation products from *para*-substituted phenols and formaldehyde (calix[*n*]arenes) are of current interest in host–guest chemistry because of their three dimensional structure which allows their use as receptors for neutral molecules as well as cations.[1] Moreover, the possibility of selectively introducing different functionalities at both rims of the calix[4]arene skeleton has endowed these molecules with a rich chemistry.[2] Therefore, the preparation of such cyclic ligands has attracted the interest of an increasing number of research groups.

Commonly, calixarenes are synthesized in a 'one-step' process by direct condensation of convenient *para*-substituted phenols with formaldehyde under basic catalysis,[3] whereas the acid-catalysed process is usually unsuccessful. Multi-step non-convergent as well as convergent syntheses were also developed from phenolic building blocks.[1b-d] Recently Tabatabai *et al.*, have reported on the use of triphenylmethane moieties as fragments in acid catalysed synthesis of calix[4]arenes containing resorcinol units.[4] Nevertheless, little effort has been directed towards the construction of calix[4]arenes bearing functional groups at the methylene bridges starting from a phenolic precursor and formaldehyde.[5] We were recently involved in developing general methods in which our experience on the regioselective phenol–aldehyde condensation[6] might be exploited for the synthesis of new calix[4]arenes **4** as depicted in Scheme 1.

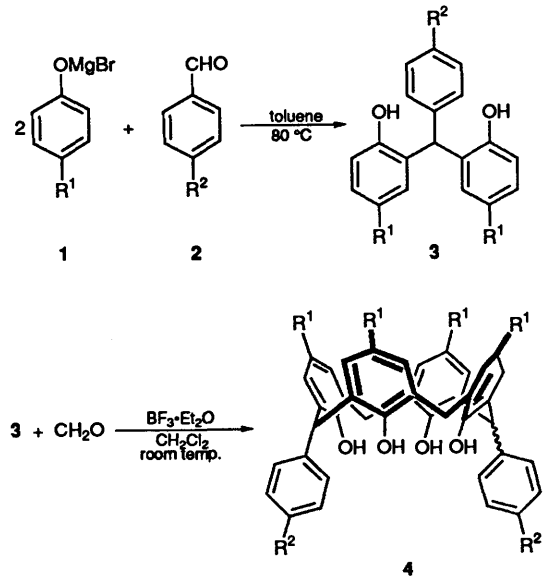
We now report a facile assembly of calix[4]arenes bearing aryl groups on the methylene bridges in diametrical positions *via* an acid promoted condensation of triphenylmethanes **3** and formaldehyde.

The phenolic precursors of calix[4]arenes **4a**, **b** are the 2,2'-dihydroxytriphenylmethanes **3a**, **b** which are easily synthesized by 'metal-template' *ortho*-regioselective alkylation of bromomagnesium phenolates **1** with different aromatic aldehydes **2** (yield 40–90%).[7]

Treatment of **3a** (R^1 = H, R^2 = Bu^t) with an equimolecular amount of paraformaldehyde in dry CH_2Cl_2 under an inert atmosphere in the presence of BF_3·Et_2O afforded the macrocycle **4a** in 27% yield as a mixture of the *cis* and *trans* isomers (molar ratio ~1:1) easily separated by flash chromatography.†

These compounds manifest the conformational mobility peculiar to the parent *p-tert*-butylcalix[4]arene. This was confirmed by their ^{1}H NMR spectra under variable temperature conditions. In fact, the spectra of the *trans* isomer in $CDCl_3$ show in the methylene bridge region (δ 3.1–4.5) a pair of doublets at −20 °C (δ 3.55 and 4.25) which coalesce giving rise to a sharp singlet at 60 °C (δ 3.91), while those of the *cis* isomer exhibit two pairs of doublets at −20 °C (δ 3.53, 3.60 and 4.19, 4.32) which coalesce giving rise to a sharp singlet at 60 °C (δ 3.94).[8]

The reaction of precursor **3** with different R^1 and R^2 groups was then tried and some significant results are reported in Table 1.



Scheme 1

Table 1

Entry	R^1	R^2	Yield[a] **4** (%)
a	Bu^t	H	27 (*cis* + *trans*)
b	Bu^t	NO_2	18 (*trans*)
c	Me	H	0

[a] Yields, not optimized, refer to isolated products and are based on amount of compound **3** added.

Thus, the reaction of **3b**, easily prepared from *p-tert*-butylphenol and *p*-nitrobenzaldehyde, with paraformaldehyde under the reaction conditions used for **4a**, afforded the *trans* isomer **4b** in 18% yield while the *cis* isomer, if present, could not be isolated. It is worthy of note that the *p*-nitrophenyl group inserted at the methylene bridge allows the introduction of a rich number of different functional groups without changing the nature of the macrocycle.

Finally, these preliminary results seem to confirm the crucial role of the *p-tert*-butyl group in promoting macrocyclization.[1] In fact, the intermediate **3c**, where the *tert*-butyl group was replaced by the methyl group, produced a resinous mixture of telomers when treated with paraformaldehyde in the presence of various acidic promoters.

Experimental

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were

† Small amounts of calix[6]arenes were also recovered.

recorded on a Bruker AC300 spectrometer at 300 MHz and on a Bruker AMX 400 spectrometer at 400 MHz. Chemical shifts are expressed in ppm relative to TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Mass spectra were obtained on a Finnigan SSQ 710 instrument in 'E.I. mode'. Microanalyses were carried out by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy. All compounds **4** gave satisfactory elemental analyses.

Synthesis of Calix[4]*arenes* **4**: *General Procedure*.—To a solution of the selected compound **3** (0.01 mol), prepared as described in the literature,[7] in dry CH_2Cl_2 (150 cm^3) in the presence of BF_3·Et_2O (4.5 × 10^{-4} g, 0.40 cm^3, 3.1 × 10^{-6} mol) was added under nitrogen a solution of paraformaldehyde (0.3 g, 0.01 mol) in dry CH_2Cl_2 (150 cm^3) and the reaction mixture was stirred for 2 h. The reaction was quenched with aqueous 10% HCl (200 cm^3) and then extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic phases were dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on silica gel plates with hexane–ethyl acetate mixtures (25–30%) to give the products.

Compound **4a** (trans *isomer*) White solid, m.p. 215–217 °C (from toluene); ν_{max}(KBr)/cm^{-1} 3195 (OH); δ_H(300 MHz; $CDCl_3$) 1.18 and 1.25 [36 H, 2 s, $(CH_3)_3C$], 3.6 (2 H, br s, CH_2 eq), 4.2 (2 H, br s, CH_2 ax), 5.3 (1 H, br s, CH eq), 6.1 (1 H, br s, CH ax), 6.8–7.5 (18 H, m, ArH) and 10.04 (4 H, s, OH); *m*/*z* 802 (M + 1, 100%).

Compound **4a** (cis *isomer*). White solid, m.p. 234–237 °C (from toluene); ν_{max}(KBr)/cm^{-1} 3205 (OH); δ_H(300 MHz; $CDCl_3$) 1.18 and 1.22 [36 H, 2 s, $(CH_3)_3C$], 3.6 (2 H, br s, CH_2 eq), 4.3 (2 H, br s, CH_2 ax), 5.3 and 6.2 (2 H, 2 br s, CH eq and CH ax), 6.8–7.5 (18 H, m, ArH) and 10.04 (4 H, s, OH); *m*/*z* 802 (M + 1, 100%).

Compound **4b** (trans *isomer*). White solid, decomp. before melting (from toluene); ν_{max}(KBr)/cm^{-1} 3200 (OH); δ_H(400 MHz; $CDCl_3$; 293 K) 1.16 and 1.27 [36 H, 2 s, $(CH_3)_3C$], 3.6 (2 H, br s, CH_2 eq), 4.2 (2 H, br s, CH_2 ax), 5.4 (1 H, br s, CH eq), 6.1 (1 H, br s, CH ax), 6.8–8.3 (16 H, m, ArH) and 10.04 (4 H, s, OH); δ_H(400 MHz; $CDCl_3$; 273 K) 1.14 and 1.29 [36 H, 2 s, $(CH_3)_3C$], 3.61 (2 H, d, CH_2 eq, *J* 14.0), 4.24 (2 H, d, CH_2 ax, *J* 14.0), 5.41 (1 H, s, CH eq), 6.09 (1 H, s, CH ax), 6.94, 7.08, 7.17 and 7.30 (8 H, 4 d, *J* 1.9, ArH), 7.39, 7.50, 8.16 and 8.20 (8 H, 4 d, *J* 8.7, ArH) and 10.09 (4 H, s, OH); *m*/*z* 892 (M + 1, 30%).

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