

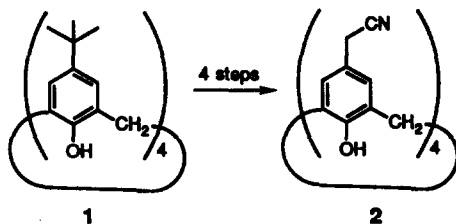
Synthesis of Calix[4]arenes Carrying Bulky Upper-rim Groups

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Abstract: NaH-induced arylmethylation of *p*-cyanomethylcalix[4]arene introduces arylmethyl groups on the phenolic oxygens and the carbons α to the cyano groups to give calixarenes carrying very bulky upper-rim substituents.

Upper-rim substituted calix[4]arenes are synthesized in many instances by replacing the *p*-*tert*-butyl groups of *p*-*tert*-butylcalix[4]arene (1) with a group that is generally less bulky and highly branched than *tert*-butyl. A typical example is *p*-cyanomethylcalix[4]arene (2), the starting compound for the present investigation, which is most readily prepared from 1 by de-*tert*-butylation followed by application of the quinonemethide procedure of Gutsche and Nam.¹

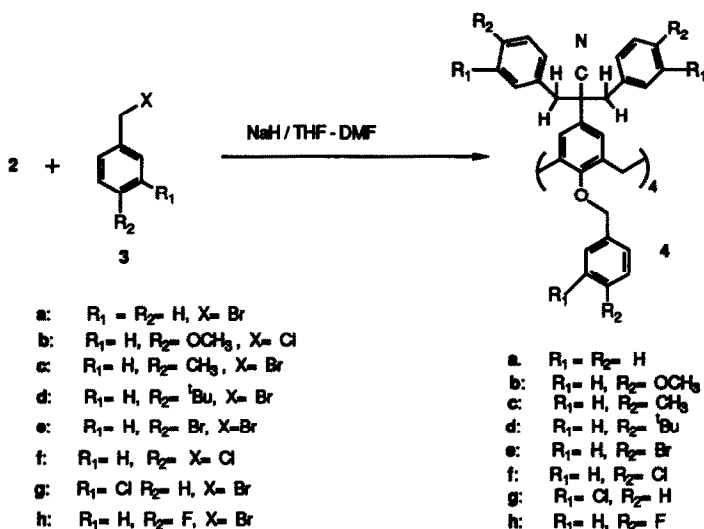


A standard method for converting calixarenes to calixarene ethers employs an alkyl halide with NaH in THF-DMF solution. When 2 is treated with an arylmethyl halide (3) under these conditions, however, not only does arylmethylation occur at the phenolic oxygens but at the carbons α to the cyano groups as well to produce 4 in which the upper rim substituents are even bulkier than the original

tert-butyls and which, moreover, include functional moieties.

Synthesis. To a 250 mL 3-necked, round-bottomed flask was added 1.0 g (25 equiv) of NaH (60% dispersion in oil) followed by a mixture of 60 mL of dry, freshly distilled THF-DMF (5:1). The air in the flask was replaced with N₂, the reaction mixture was maintained at 2-3° C in an ice bath, and 0.581 g (1 mmol) of 5, 11, 17, 23-tetracyanomethyl-25, 26, 27, 28-tetrahydrocalix[4]arene (2) was added. The flask was warmed to room temperature, and stirring was continued 30 min. A solution of 3.40 g (20 equiv) of benzyl bromide (3a) in 10 ml of dry THF was added dropwise over a period of 30 min, and the reaction mixture was refluxed for 8 h followed by stirring at room temperature overnight. The solvent was removed

under reduced pressure on a rotary evaporator, and the concentrated residue was neutralized with ice-cold 10 % HCl to produce a white precipitate. This was extracted into CH₂Cl₂ (100 ml, 3X) which was then removed under reduced pressure. The residue was triturated with 3 X 100 ml of MeOH and chromatographed on a 1" x 10" silica column (eluted with CHCl₃) followed by crystallization from CHCl₃/hexane to give 1.46 g (88 %) of 4a as colorless crystals²: m.p. 276-278° C.



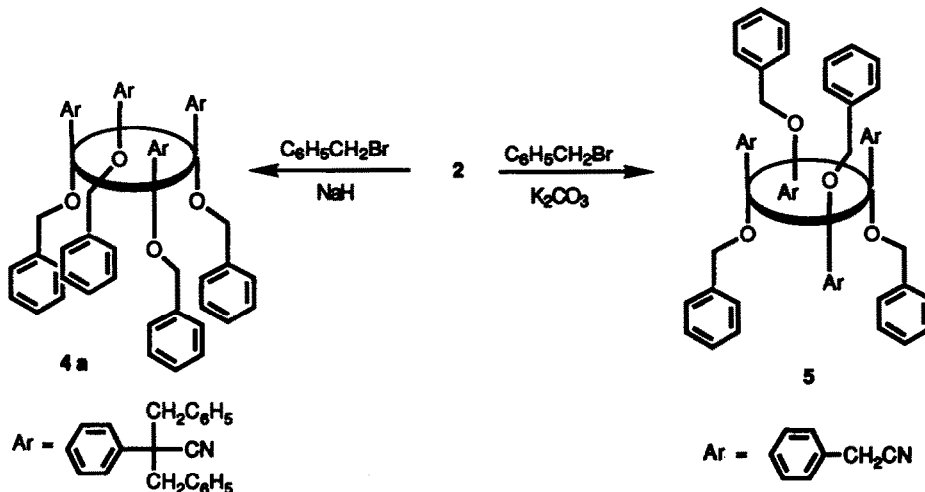
To explore the scope of this reaction a variety of arylmethyl halides, shown in Table 1, have been tested. In all but one case the yields are good, ranging from 75-92%, the exception being *p-tert*-butylbenzyl bromide

Arylmethyl Halide (Equivalents)	NaH (equiv)	THF/DMF (ratio) (ml)	Time, hrs	Product	Yield %	M.P., °C
3a (20)	25	5:1 (60)	8	4a	88	276-278
3b (20)	25	5:1 (60)	3	4b	92	136-138
3c (20)	30	5:1 (60)	3	4c	85	112-114
3d (25)	40	4:1 (50)	8	4d	34	216-218
3e (20)	30	4:1 (100)	13	4e	80	149-151
3f (20)	30	4:1 (50)	8	4f	75	135-138
3g (25)	30	5:1 (60)	18	4g	80	168-171
3h (25)	30	5:1 (60)	18	4h	83	124-127

Table 1. Reaction products from treatment of 2 with arylmethyl halides in the presence of NaH

which afforded only 34% of the product 4d.³ Other exceptions included several nitrobenzyl bromides which yielded only dark yellow, highly insoluble materials as uncharacterized products. All of the ethers shown in Table 1 exist in the cone conformation, as indicated by a pair of ¹H NMR doublets⁴ at δ 2.5-4 and a ¹³C NMR resonance at δ 29-30⁵ arising from the ArCH₂Ar groups.

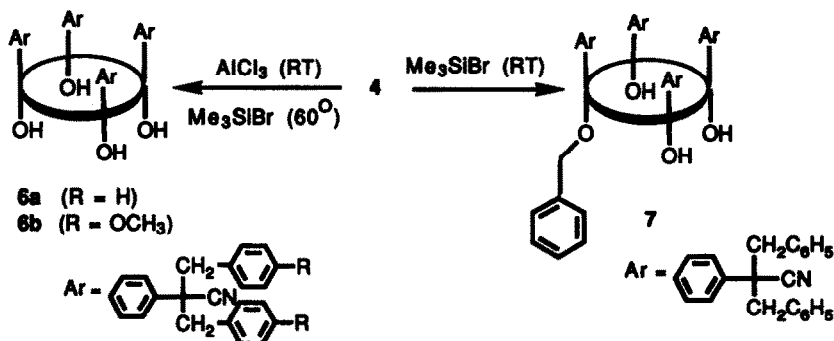
When the reaction of 2 with benzyl bromide was carried out in acetone solution containing KI, using K₂CO₃ as the base, only O-benylation occurred to produce the tetrabenzyl ether 5.⁶ In contrast to compounds 4a-h, which exist in the cone conformation, 5 exists in the 1,3-alternate conformation, as indicated by a singlet⁴ in the ¹H NMR at δ 3.65 and a ¹³C NMR resonance⁵ at δ 37.27 arising from the ArCH₂Ar groups. Subsequent treatment of 5 with benzyl bromide under the conditions used to synthesize 4a-h produced a compound structurally identical with 4a which, however, retains the 1,3-alternate conformation of the starting material. This indicates that NaH-induced arylmethylation leading to 4a-h proceeds by reaction at the carbon α to the cyano groups prior to reaction at the phenolic oxygen. Thus, it is another of the numerous examples in



which, in the simplest case, a dibasic acid treated with a strong base yields a dianion in which the more reactive center is at the site of the less acidic hydrogen. In the case of 2 the existence of a polyanion, possibly an octaanion, must be postulated as the reactive species.

Complete O-debenzylation of 4a was accomplished by treatment with AlCl₃ in toluene at room temperature or Me₃SiBr in refluxing CHCl₃, which yielded 6a in the cone conformation. With Me₃SiBr at room temperature for 7 days, however, the trihydroxy compound 7 was formed as the exclusive product, even when a large excess of Me₃SiBr was used. Interrupting the reaction after a shorter time yielded a mixture of the mono- and trihydroxy compounds, with no evidence for the dihydroxy compound. Debenzylation of 4b yielded

6b under all conditions investigated, and debenzoylation of **4d** with AlCl_3 in toluene produced **6a**, the result of debenzoylation as well as *de-tert*-butylation of the aryl groups at the top rim of the calixarene.



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References and Notes

- Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.*, **1988**, *110*, 6153.
- ¹H NMR (CDCl₃) δ 7.37 (m, 12 H, J= 7.1 Hz, ArH), 7.23 (m, 8 H, J= 6.5 Hz, ArH), 7.14 (m, 8 H, J= 7.1 Hz, ArH), 7.02 (t, 16 H, J=7.1 Hz, *m*-H of ArCH₂C), 6.92 (s, 8H, Calixarene ArH), 6.77 (d, 16 H, J= 7.5 Hz, *o*-H of ArCH₂C), 4.89 (s, 8 H, OCH₂Ar), 3.96 (d, 4 H, J= 12.36 Hz, ArCH₂Ar), 2.98 (d, 8 H, J= 13.56 Hz, NCCCH₂Ar), 2.76 (d, 8 H, J= 13.44 Hz, NCCCH₂Ar), 2.65 (d, 4 H, J= 12.36 Hz, ArCH₂Ar); ¹³C NMR (CDCl₃) δ 153.73 (COCH₂Ar), 137.19, 135.66, 135.22, 133.01, 130.46, 129.12, 128.12, 127.06, 126.36 (Ar), 121.24 (CN), 77.06 (OCH₂Ar), 50.14 (NCC [CH₂Ar]₂), 45.54 (NCC[CH₂Ar]), 30.59 (ArCH₂Ar); Anal. Calcd for C₁₂₀H₁₀₀N₄O₄ C, 86.71; H, 6.06; N, 3.37. Found C, 87.03; H, 5.90; N, 3.16.
- The major product of this reaction is a colorless, feathery crystalline material apparently formed in a reaction between *p-tert*-butylbenzyl bromide and the solvent. Its structure remains to be established.
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- Jaime, C.; deMendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.*, **1991**, *56*, 3372.
- It is interesting to note that *p-tert*-butylcalix[4]arene yields only the 1,3-dibenzyl ether under the same reaction conditions.

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