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SELECTIVE ETHERIFICATION OF CALIX[4]ARENES

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Abstract: Calix[4]arenes **1** or **2** react with alkyl halides and aqueous potassium hydroxide in the presence of PEG as phase transfer catalyst at room temperature to give the selectively *distally* dietherified product **3** or **4** in excellent yields. While at the same reaction conditions, calix[8]arene **5** give the fully etherified product **6**.

Calixarenes are cavity containing macrocyclic compounds, and they attract more interests because of their potential for forming host-guest complexes and acting as enzyme mimics,[1,2] if appropriately functionalized. The hydroxyl groups of the lower rim of calixarenes provide obvious sites for the attachment of other functional groups *via* ether and ester formation. Etherification, as well as esterification, usually engages all of the hydroxyl groups of a calixarene regardless of ring size if a sufficiently reagent is used. However, the selectively functionalized calix[4]arenes, especially the *distally* 1,3-dialkylated calix[4]arenes, are useful intermediates.

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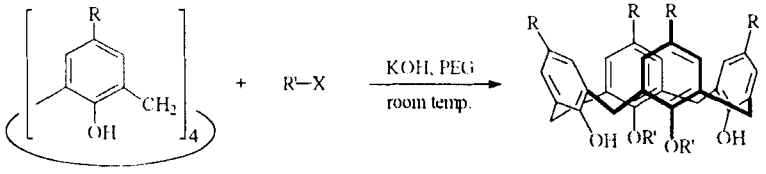
Some selective etherification of calix[4]arenes has been reported by reaction with two equivalents of an alkylating agent in the presence of same equivalent of potassium carbonate in refluxing acetonitrile or other solvents.[3-15] Herein, we wish to report a new synthetic method of *distally* 1,3-dialkylated calix[4]arenes in a very mild condition at room temperature in the presence of polyethylene glycol (PEG) as phase transfer catalyst in excellent yields.

When calix[4]arene (**1**) and tetra-*p*-*t*-butylcalix[4]arene (**2**) react with methyl iodide, ethyl iodide, allyl bromide or benzyl bromide and aqueous potassium hydroxide in chloroform in the presence of PEG as phase transfer catalyst at room temperature, the *distally* 1,3-dialkylated calix[4]arenes **3** or **4** are easily obtained in excellent yields. The structure of **3** or **4** with *distal* substitution are confirmed by a pair of doublet of the methylene protons between aromatic rings in the ^{1}H NMR spectra, and this also shows that the **3** or **4** are in cone conformation.

The advantages of this method for synthesis of *distally* dialkylated calix[4]arenes are: unnecessary to control the reagent equivalent, even large excess of alkylated



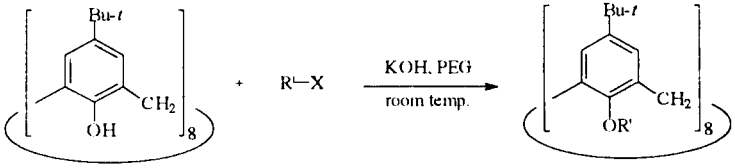
1, R = H
2, R = *t*- Bu

3, R = H
4, R = *t*- Bu

3, **4**	**a**	**b**	**c**	**d**
R'	CH_3	C_2H_5	$CH_2CH{=}CH_2$	$CH_2C_6H_5$

agent being used, only dialkylated product is formed; the reaction conditions are very mild (room temperature); simple work-up procedure to obtain pure product; and the excellent yields.

When calix[8]arene **5** react with alkyl halides at the same conditions mentioned above, the octaethers of calix[8]arene **6** are obtained in excellent yields. The structure of **6** are also confirmed by spectroscopic data. The alkylation of calix[6]arenes at the same conditions result to give a hardly separated reaction product mixture. This situation is very similar to the esterification of calixarenes with acyl chlorides in the presence of triethylamine at room temperature.[16]



5 **6**

6	**a**	**b**	**c**	**d**
R'	CH_3	C_2H_5	$CH_2CH{=}CH_2$	$CH_2C_6H_5$

Experimental

Melting point are uncorrected. ^1H NMR spectra were recorded with a Varian Unity 200 spectrometer using $CDCl_3$ as solvent. Mass spectra were measured on a Biflex III instrument. Elemental analyses were performed by the Analytical Laboratory of the Institute.

Synthesis of 3 and 4, General Procedure:

A mixture of 2.5 mmol of **1** or **2**, 1.12 g (20 mmol) of potassium hydroxide in 20

ml of water, 30 mmol of alkyl halide and 5 g of PEG 400 in 30 ml of chloroform was stirred at room temperature for 20 h. Then the mixture was neutralized with hydrochloric acid, the chloroform layer was separated, and the water layer was extracted with chloroform. Combine the chloroform solution and dried. After removal of most of the solvent, methanol was added to the residue, the product **3** or **4** was obtained in white powder.

25,27-Dimethoxy-26,28-dihydroxycalix[4]arene (3a): [4,7,14,15]

Yield: 89%. M. p > 300 °C. ^{1}H NMR: δ = 7.67 (s, 2H, O*H*), 6.50-7.15 (m, 12H, Ar-*H*), 4.31 (d, 4H), 3.39 (d, 4H) (ArCH_2Ar), 3.97 (s, 6H, CH_3).

25,27-Diethoxy-26,28-dihydroxycalix[4]arene (3b): [20]

Yield: 94%. M. p > 260 °C. ^{1}H NMR: δ = 7.69 (s, 2H, O*H*), 6.90-7.15 (m, 12H, Ar-*H*), 4.31 (d, 4H), 3.38 (d, 4H) (ArCH_2Ar), 4.14 (q, 4H, CH_2CH$_3$), 1.74 (t, 6H, CH$_2$CH_3).

25,27-Diallyloxy-26,28-dihydroxycalix[4]arene (3c): [4,7]

Yield: 91%. M. p. 145-147 °C. ^{1}H NMR: δ = 7.90 (s, 2H, O*H*), 6.60-7.05 (m, 12H, Ar-*H*), 4.30 (d, 4H), 3.37 (d, 4H) (ArCH_2Ar), 6.15-6.35 (m, 2H, C*H*=CH$_2$), 5.77 (dd, 2H), 5.39 (dd, 2H) (CH=CH_2), 4.52 (d, 4H, CH_2-CH=CH$_2$).

25,27-Dibenzyloxy-26,28-dihydroxycalix[4]arene (3d): [4,7,14]

Yield: 87%. M. p. 219-221 °C. ^{1}H NMR: δ = 7.74 (s, 2H, O*H*), 6.65-7.70 (m, 22H, Ar-*H*), 4.32 (d, 4H), 3.32 (d, 4H) (ArCH_2Ar), 5.05 (s, 4H, CH_2C$_6$H$_5$).

5,11,17,23-Tetra-tert-butyl-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (4a): [3,7,14]

Yield: 92%. M. p. > 300 °C. ^{1}H NMR: δ = 7.16 (s, 2H, O*H*), 7.02 (s, 4H), 6.72 (s, 4H) (Ar-*H*), 4.27 (d, 4H), 3.30 (d, 4H) (ArCH_2Ar), 1.30 (s, 18H), 0.92 (s, 18H), (C(CH_3)$_3$), 3.90 (s, 6H, CH_3).

5,11,17,23-Tetra-tert-butyl-25,27-diethoxy-26,28-dihydroxycalix[4]arene ***(4b)***: [4,7,14]

Yield: 95%. M. p. 273-275 °C. ^{1}H NMR: δ = 7.56 (s, 2H, O*H*), 7.02 (s, 4H), 6.83 (s, 4H) (Ar-*H*), 4.33 (d, 4H), 3.30 (d, 4H) (ArCH_2Ar), 1.32 (s, 18H), 0.97 (s, 18H), (C(CH_3)$_3$), 4.08 (q, 4H, CH_2CH$_3$), 1.60 (t, 6H, CH$_2$CH_3).

5,11,17,23-Tetra-tert-butyl-25,27-diallyloxy-26,28-dihydroxycalix[4]arene ***(4c)***:

Yield: 94%. M. p. 180-182 °C. ^{1}H NMR: δ = 7.47 (s, 2H, O*H*), 7.04 (s, 4H), 6.82 (s, 4H) (Ar-*H*), 4.28 (d, 4H), 3.30 (d, 4H) (ArCH_2Ar), 1.28 (s, 18H), 0.96 (s, 18H), (C(CH_3)$_3$), 6.16-6.36 (m, 2H, C*H*=CH$_2$), 5.72 (dd, 2H), 5.37 (dd, 2H) (CH=CH_2), 4.54 (d, 4H, CH_2-CH=CH$_2$). MS (MALDI-TOF): *m/z* = 750.37 ([M-1]$^+$+Na$^+$). Anal. cacld. for $C_{50}H_{64}O_4$: C, 82.37; H, 8.85. Found: C, 82.35; H, 8.78.

5,11,17,23-Tetra-tert-butyl-25,27-diallyloxy-26,28-dihydroxycalix[4]arene ***(4d)***: [11,12,14]

Yield: 90%. M. p. 214-216 °C. ^{1}H NMR: δ = 7.19 (s, 2H, O*H*), 7.03 (s, 4H), 6.77 (s, 4H) (Ar-*H*), 4.28 (d, 4H), 3.41 (d, 4H) (ArCH_2Ar), 1.29 (s, 18H), 0.94 (s, 18H), (C(CH_3)$_3$), 6.90-7.35 (m, 10H, CH$_2$C$_6$*H*$_5$), 5.05 (s, 4H, CH_2C$_6$H$_5$).

Synthesis of ***6****, General Procedure:*

A mixture of 1.30 g (1 mmol) of **5** in 20 ml of chloroform, 0.67 g (12 mmol) of potassium hydroxide in 20 ml of water, 5 g of PEG 400 and 24 mmol of alkyl

halide was stirred at room temperature for 20 h, and worked up as above-mentioned procedure.

5,11,17,23,29,35,41,47-Octa-tert-butyl-49,50,51,52,53,54,55,56-octamethoxy-calix[8]arene (6a): [16,17]

Yield: 92%. M. p. 274-276 °C. ^{1}H NMR: δ = 6.85 (s, 16H, Ar-*H*), 3.94 (s, 16H, ArC*H*$_2$Ar), 1.13 (s, 72H, C(C*H*$_3$)$_3$), 3.40 (s, 24H, C*H*$_3$).

5,11,17,23,29,35,41,47-Octa-tert-butyl-49,50,51,52,53,54,55,56-octaethoxy-calix[8]arene (6b): [21]

Yield: 94%. M. p. > 260 °C. ^{1}H NMR: δ = 6.85 (s, 16H, Ar-*H*), 3.96 (s, 16H, ArC*H*$_2$Ar), 1.14 (s, 72H, C(C*H*$_3$)$_3$), 3.48 (q, 16H, C*H*$_2$CH$_3$), 1.70 (t, 24H, CH$_2$C*H*$_3$).

5,11,17,23,29,35,41,47-Octa-tert-butyl-49,50,51,52,53,54,55,56-octaallyloxy-calix[8]arene (6c):

Yield: 89%. M. p. 215-217 °C. ^{1}H NMR: δ = 6.85 (s, 16H, Ar-*H*), 4.00 (s, 16H, ArC*H*$_2$Ar), 1.08 (s, 72H, C(C*H*$_3$)$_3$), 5.65-5.85 (m, 8H, C*H*=CH$_2$), 5.03 (dd, 8H), 4.85 (dd, 8H) (CH=C*H*$_2$), 3.95 (d, 16H, C*H*$_2$-CH=CH$_2$). MS (MALDI-TOF): *m/z* = 1656.9 (M^++K^+). Anal. cacld. for $C_{112}H_{144}O_8$: C, 83.12; H, 8.97. Found: C, 82.98; H, 8.95.

5,11,17,23,29,35,41,47-Octa-tert-butyl-49,50,51,52,53,54,55,56-octabenzyloxy-calix[8]arene (6d): [18,19]

Yield: 91%. M. p. 216-218 °C. ^{1}H NMR: δ = 6.80-7.20 (m, 56H, Ar-*H*), 4.06 (s, 16H, ArC*H*$_2$Ar), 1.01 (s, 72H, C(C*H*$_3$)$_3$), 4.46 (s, 16H, C*H*$_2$C$_6$H$_5$).

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