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Microwave-assisted alkylation of *p-tert*-butylcalix[4]arene lower rim: the effect of alkyl halides

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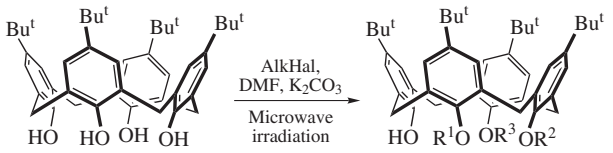
Alkylation of *p-tert*-butylcalix[4]arenes with alkyl bromides or iodides under microwave irradiation affords mostly the corresponding distal disubstituted ethers, whereas in case of alkyl chlorides reasonable yields of monoethers were achieved.

Calix[4]arenes[1,2] are generally obtained by condensation between formaldehyde and phenols. Their unique properties are due to their cavity and can be tuned by functionalization of their upper and lower rim.[3–8] Calix[4]arenes find use in supramolecular chemistry as macrocyclic receptors, sensors and components of molecular devices.[9–13] One of the main problems in calixarene functionalization is a long reaction time and low yields of products. Microwave irradiation is widely used to accelerate reactions,[14–19] which seems reasonable to be extended into calixarene chemistry.

In the present work, O-alkylation of *p-tert*-butylcalix[4]arene **1** with haloalkanes under microwave irradiation (Scheme 1) was studied, halogen, length of alkyl chain and nature of phase-transfer catalyst having been varied.



1

Hal = Cl, Br, I

2 R^1 = Alk, R^2 = R^3 = H
3 R^1 = R^2 = Alk, R^3 = H
4 R^1 = R^3 = Alk, R^2 = H

Scheme 1

Firstly, halogen nature influence on the etherification outcome was tested using BuHal (Hal = Cl, Br, I) as a model reactant. Reaction course was controlled by TLC, MALDI-TOF spectrometry and ^{1}H NMR spectroscopy. In all cases formation of three products was established, which were monosubstituted (**2**), proximal (**3**) and distal (**4**) disubstituted derivatives (Table 1). Neither tri- nor tetra-substituted ones were detected. The presence of mono- and diethers (**2**–**4**) in the reaction mixture can be easily observed in ^{1}H NMR spectra, in which signals of OH protons are very characteristic. Such protons of proximal and distal disubstituted derivatives appear as singlet at 8.95[20] and 7.81[21] ppm, respectively, whereas two singlets at 9.61 and 10.20 ppm are assigned to OH groups of monoether.[22]

Reaction of compound **1** (0.47 mmol) with BuCl (1.2 mmol) in the presence of K_2CO_3 (2.4 mmol) in DMF (1 ml) after 10 min of MW irradiation (400 W) afforded 40% of monoether **2** as a major product.† Processing under conventional heating provided 44% yield of monoether after 18 h.[23] The content of distal diether **4** in reaction mixture was small at the beginning and became

Table 1 Ratios of reagents, conditions and products of reaction of *p-tert*-butylcalix[4]arene **1** with alkyl halides.

Entry	AlkHal	Time of reaction/ min	Monosubstituted ether **2**[a] (%)	Proximal disubstituted ether **3**[a] (%)	Distal disubstituted ether **4**[a] (%)	**1**:AlkHal ratio	TBAB
1	BuCl	10	40	0	6	1:2.5	–
2	BuCl	20	41	6	32	1:2.5	–
3	BuCl	40	33	5	33	1:2.5	–
4	BuCl	40	52	0	11	1:2.5	+
5	BuCl	80	22	7	48	1:2.5	–
6	BuCl	100	24	6	44	1:2.5	–
7	BuCl	120	45	3	22	1:4.5	–
8	BuCl	120	51	2	22	1:4.5	+
9	BuBr	10	15	10	67	1:2.5	–
10	BuBr	20	14	10	71	1:2.5	–
11	BuBr	40	7	7	75	1:2.5	–
12	BuBr	40	4	7	76	1:2.5	+
13	BuBr	80	5	2	90	1:2.5	–
14	BuBr	100	5	2	89	1:2.5	–
15	BuBr	120	2	8	84	1:4.5	+
16	BuBr	120	3	9	85	1:4.5	–
17	BuI	10	12	13	73	1:2.5	–
18	BuI	20	23	5	65	1:2.5	–
19	BuI	40	27	4	66	1:2.5	–
20	BuI	40	9	11	77	1:2.5	+
21	BuI	80	4	4	89	1:2.5	–
22	BuI	100	17	4	69	1:2.5	–
23	BuI	120	14	5	76	1:2.5	–
24	BuI	120	1	5	93	1:4.5	+
25	BuI	120	5	5	89	1:4.5	–
26	*n*-C_6H_{13}Br	40	5	10	81	1:2.5	–
27	*n*-C_8H_{17}Br	40	5	11	82	1:2.5	–
28	*n*-$C_{10}H_{21}$Br	40	14	9	74	1:2.5	–
29	*n*-$C_{12}H_{25}$Br	40	3	10	85	1:2.5	–
30	*n*-$C_{14}H_{29}$Br	40	3	9	87	1:2.5	–
31	*n*-$C_{16}H_{33}$Br	40	7	8	81	1:2.5	–

[a] Content in the reaction mixture determined with ^{1}H NMR spectrometry.

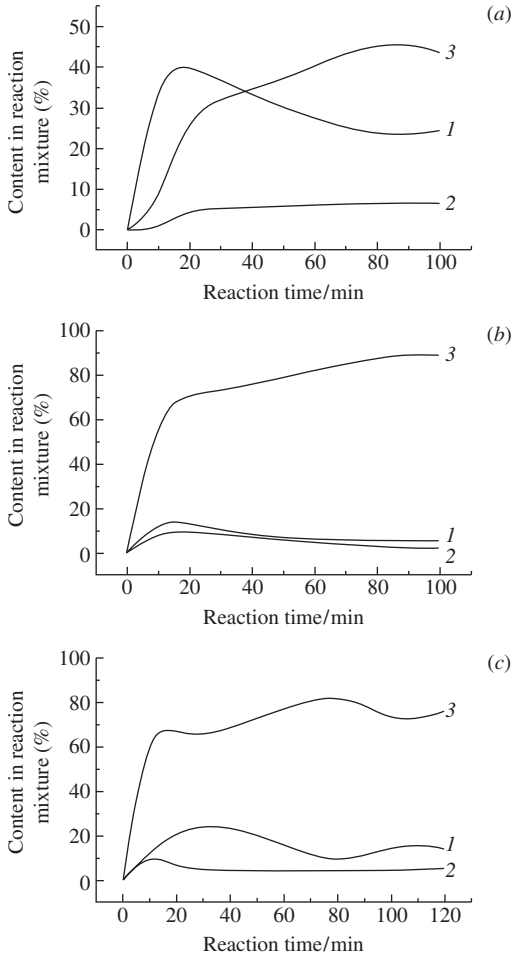


Figure 1 Dependence of (*1*) monosubstituted (**2**), (*2*) proximal disubstituted (**3**) and (*3*) distal disubstituted (**4**) ether formation on the reaction time; AlkHal is (*a*) BuCl; (*b*) BuBr and (*c*) BuI.

to dominate only after 60 min [Figure 1(*a*)]. This result is very important for calixarene chemistry, because an easy access to monoethers can further provide availability of non-symmetrically substituted calix[4]arenes derivatives.

In the case of BuBr under the same experimental conditions, different results were obtained [Figure 1(*b*)]. Thus, 10 min of 400 W MW irradiation gave 67% of distal diether **4**, time prolongation to 40 min raised this content to 75%, while fractions of mono- **2** and proximal disubstituted **3** ethers were minor throughout the whole experiment. It is important to emphasize that alkylation with BuBr under classical heating reaction proceeds within 18 h giving 45% of distal disubstituted ether.[24]

In the case of BuI [Figure 1(*c*)], unusual regularities were established. After 10 min of processing, content of distal diether **4** was 73% along with other alkylated products (25%) and small amount of unreacted calixarene (2%) (Table 1, entry 17). Within the next 20–30 min its content diminished with an increase in the fraction of monosubstituted ether **2**. Such behaviour can be explained by the reversibility of etherification reaction of calix[4]arene with alkyl iodide under MW irradiation. Apparently, iodide anion formed during the reaction is more nucleophilic than chloride and bromide and for this reason the reverse reaction can occur. It seems likely that the presence of phase-transfer catalyst [tetrabutylammonium bromide (TBAB)] should accelerate the forward reaction and consequently diethers content can be greater owing to additional amount of deprotonated calixarene species (nucleophiles). Data presented in Table 1 (entries 19 and 20) are in line with this suggestion.

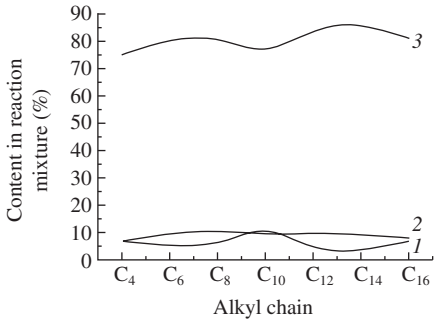


Figure 2 Dependence of (*1*) monosubstituted (**2**), (*2*) proximal disubstituted (**3**) and (*3*) distal disubstituted (**4**) ether formation on the alkyl length (BuBr, *n*-$C_6H_{13}Br$, *n*-$C_8H_{17}Br$, *n*-$C_{10}H_{21}Br$, *n*-$C_{12}H_{25}Br$, *n*-$C_{14}H_{29}Br$, *n*-$C_{16}H_{33}Br$).

Earlier[21] formation of *p-tert*-butylcalix[4]arene 1,3-dipropyl ether by the interaction between **1** and PrI in 80% yield after irradiation for 1.5 h was reported. This is consistent with our results (Table 1, entries 21 and 22), however, our study demonstrated that the close yield can be achieved in 10 min.

It is known that 1,3-alkylation of calix[4]arenes with short chain haloalkanes (Hal = Br, I) requires 10–20 h reflux for the completion, whereas such a time for longer homoloques (C_5 onward) grows up to 120–140 h.[25] To see the effect of alkyl chain length in case of MW, the number of C_4–C_{16} *n*-alkyl bromides were tested (40 min of MW irradiation, Table 1, entries 11, 26–31). In all cases despite the chain length of AlkBr, contents of distal dialkyl ethers **4** were as good as 74–87% (Figure 2).

To see the effect of phase-transfer catalyst on the selectivity of etherification of calixarenes under MW irradiation, TBAB was added to the reaction mixture. Obtained results are collected in Table 1 (entries 4, 8, 12, 15, 20, 24). Adding TBAB did not cause significant effect on the content of distal dialkyl ethers **4** for reactions with BuBr (Table 1, entries 11, 12 and 15, 16); for BuI content of distal dialkyl ethers **4** rose slightly with simultaneous decrease in monosubstituted ether **2** content (Table 1, entries 19, 20 and 24, 25). In the case of less reactive BuCl the content of monoalkylated product **2** increased upon TBAB addition.

In conclusion, a microwave-assisted procedure for the etherification of phenolic groups of calix[4]arene with AlkHal (Hal = = Br, I) to access distal dialkyl ethers in good to high yield has been elaborated. No effect of alkyl chain length on the product content was discovered. Important to note that in case of alkyl chlorides, monoethers are formed in reasonable content in mixture (35–50%). The results obtained can promote wider use of new amphiphilic macrocyclic compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.03.022.

† *p-tert*-Butylcalix[4]arene **1** *cone* was prepared as described.[2] All alkyl halides, DMF, $CHCl_3$ and TBAB were commercially available from Sigma-Aldrich.

Alkylation was performed using 'GlassChem' vessels (CEM® corporation) with fiber optic temperature control and magnet stirring in CEM Mars 5 microwave system with following parameters: 400 W power, 150 °C, for the reaction time see Table 1. Alkyl halide (1.2 mmol or 2.1 mmol) was added to a mixture of **1** (0.47 mmol) and K_2CO_3 (2.4 mmol) in absolute DMF (1 ml). In some cases TBAB (0.0094 mmol) was added. The reaction mixture was treated with 10 ml of $CHCl_3$, then with aqueous HCl, washed 3 times in separating funnel with distilled water, dried over $MgSO_4$ and then concentrated *in vacuo*. The solid residue was dried *in vacuo* for 24 h. The sample was then analyzed by ^{1}H NMR spectroscopy (Bruker Nanobay, 400 MHz). For ^{1}H NMR spectra, see Online Supplementary Materials.

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