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Microwave-assisted synthesis of 1,3-dialkyl ethers of calix[4]arenes: application to the synthesis of cesium selective calix[4]crown-6 ionophores

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ABSTRACT

Partial etherification of phenolic-OH groups of calix[4]arenes with various alkyl halides/tosylates and K_2CO_3 under microwave irradiation afforded 1,3-dialkoxycalix[4]arenes in their cone conformation only as predominant/sole product in good yields (71–85%). The protocol was found to be much superior to conventional heating both in terms of yield and reaction time. Some of the 1,3-dialkoxycalix[4]arenes were elaborated further to the syntheses of cesium selective calix[4]crown-6 ionophores.

The safe treatment and disposal of high level radioactive waste (HLW) have been the subject of intense research in nuclear industry.[1,2] Among the various metal ions present in HLW, ions having long half life (20–30 years) such as ^{90}Sr and ^{137}Cs, constitute a major source of heat in these wastes. Therefore, their removal from an acidic aqueous solution would greatly simplify handling, storage and ultimate disposal. Accordingly, intense efforts have been made for the synthesis of ionophores for selective extraction of ^{137}Cs in the presence of large concentration of sodium ions present in nuclear waste.

In recent years, calix[4]arenes have been used as three dimensional molecular building block for the construction of more elaborate host molecules with desired properties.[3–18] Among them calix[4]crowns possess preorganized structures and more rigid binding sites in comparison with calix[4]arene and crown ethers. They exhibit superior recognition ability toward alkali metal ions by the cooperative effects of calixarene and crown moieties.[19–24] Moreover, their complexing ability not only depends on the length of the crown ether chain but also on their conformation.[19]

Earlier, Reinhoudt and co-workers have reported that 1,3-di(1-octyloxy)-2,4-crown-6-calix[4]arene 1,3-alternate (**4a**) is highly efficient for selective extraction of ^{137}Cs ion in the presence of large quantity of Na^+ from highly concentrated nitric acid solution present in active nuclear waste.[19] In continuation of our quest for the design and synthesis of ionophores for selective extraction of useful metal ions from nuclear waste, it was of interest to synthesize **4a** in larger quantities for the selective separation of cesium from high level nuclear waste.

Compound **4a** was conventionally prepared by the 1,3-distal dialkylation of phenolic groups of calix[4]arene (**1a**) to 1,3-dioctyloxycalix[4]arene-cone (**3a**) in the first step followed by the introduction of a suitable polyether bridges on the two remaining OH groups using Cs_2CO_3 which acts as a template for assuming 1,3-alternate conformation.[19] In contrast to the 1,3-dialkylation of calix[4]arene with reactive electrophlies ($CH_3Br/I/OTs$, $BrCH_2CO_2R$, $BrCH_2Ph$, etc.) which usually take 8–12 h reflux for completion, the reactions with longer chain alkyl halides (C5 onwards), however, are very sluggish and the reaction time varies from 5–6 days. In fact, the reported procedure for the synthesis of **3a** needs 5 days refluxing to get moderate yield of the product.[19] Moreover, long time refluxing, necessary for 1,3-dialkylation of **1** with poorly reactive long chain alkyl halides, often lead to the formation of side products together with unreacted starting material and thus needs rigorous column chromatography for purification of the desired product. This poses a serious hurdle in their large scale synthesis.

Microwave irradiation (MWI) is known to be an important tool in organic synthesis to improve the selectivity, rate enhancement and reduction of thermal degradative byproducts.[25,26] Keeping this in view, etherification of calix[4]arene **1a** (2 mmol) using 1-iodooctane (6 mmol) and K_2CO_3 (5 mmol) in acetonitrile was investigated under MWI (400 W, 63–65 °C). Irradiation of the reaction mixture for 60 min led to complete consumption of **1a** and formation of two compounds (monitored by TLC). The compounds were separated by column chromatography and characterized as cone-calix[4]arene mono-octyl ether (**2a**, 36%) and cone-calix[4]arene 1,3-dioctyl ether (**3a**, 55%)[19] by their physical and spectral data

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(Table 1, entry 1). The ^{1}H NMR spectra of **2a** displayed three sets of doublets at δ 3.38, 4.20 and 4.29 with coupling constants J = 13.0, 13.7 and 13.7 Hz, respectively, for methylene bridged protons (ArCH_2Ar) while its ^{13}C NMR spectra displayed signals at around δ 31 ppm for the methylene bridge carbons (see the Supplementary data). This clearly indicates the formation of **2a** as cone conformation.[27] Similarly, ^{1}H NMR spectra of compound **3a** showed a pair of doublet at δ 3.30 (J = 12.9 Hz) and 4.25 (J = 12.9 Hz) and ^{13}C NMR spectra displayed signals at around δ 31 for the methylene bridge carbons confirming their cone conformation.[19] Irradiation of the reaction mixture for 90 min led to predominant formation of **3a** (74%) along with **2a** (11%) (Table 1, entry 2). Further increase in irradiation time (2.25 h) led to the formation of **3a** as sole product in an 81% yield (Table 1, entry 3). To see the effect of microwave irradiation, the same reaction was carried out under refluxing conditions (120 h) when **1a** was fully consumed and cone-**3a** was obtained as the sole product in a 51% yield (Table 1, entry 4).

To see the scope and generality of the microwave-assisted protocol for 1,3-dialkylation of calixarenes, etherifications of both **1a** and **1b** were carried out with a variety of electrophiles with K_2CO_3 as base (Scheme 1). As in the case of **1a**, the reaction of **1b** with 1-iodooctane (3.0 equiv) using K_2CO_3 (2.5 equiv) under MWI also yielded a mixture of both mono-octyl ether of 4-*tert*-butylcalix[4]arene (**2b**) and 1,3-dioctyl ether of 4-*tert*-butylcalix[4]arene (**3b**) in 10% and 72% yields, respectively, while **3b** was obtained as the sole product in a 79% yield after irradiation for 2.5 h (Table 1, entries 5 and 6). When the reaction was carried out under refluxing conditions (120 h), **3b** was obtained in a 49% yield (Table 1, entry 7). Both the compounds **2b** and **3b** were formed only in cone conformations; no other conformations were detected. Similarly, reaction of **1a** with methyl tosylate under MWI afforded the 1,3-dimethoxycalix[4]arene **3c** as the sole product in an 83% yield (Table 1, entry 9) while the same reaction under refluxing conditions (16 h) yielded **3c** in a 65% yield (Table 1, entry 10). Reaction of **1b** with methyl tosylate under MWI afforded the 1,3-dimethoxycalix[4]arene **3c** as the sole product in good yield (Table 1, entry 12). As expected, reaction of **1a** with 1-iodopropane yielded the corresponding 1,3-dialkylated product **3e** in good yield (Table 1, entry 14) while **3e** was obtained in a 66% yield under reflux for 24 h (Table 1, entry 15). Similarly reaction of **1b** with 1-iodopropane yielded the corresponding 1,3-dialkylated products **3f** in good yield (Table 1, entry 16). Importantly, with reactive electrophiles such as benzyl bromide, ethyl bromoacetate, and bromo acetonitrile, the reaction time under MWI were less and the reaction completed at a relatively lower power (300 W) to afford the cone conformer of 1,3-dialkylated ethers (**3g–l**) as sole product in good to high yields without the formation of any mono-alkylated products (Table 1, entries 17–22). Furthermore, alkylation of **1a** with 2′-(2-bromoethoxy)acetophenone afforded 1,3-dialkyl ether (**3m**) as sole product in 74% yield (Table 1, entry 23) while the reaction of **1b** with 2′-(2-bromoethoxy)acetophenone afforded a mixture of monoalkylated (**2f**) and 1,3-dialkylated product (**3n**) in 4% and 72% yields, respectively, which on further irradiation yielded **3n** as sole product in a 74% yield (Table 1, entries 24 and 25). The cone conformation of all the synthesized calix[4]arene ethers was established on the basis of their ^{1}H NMR and ^{13}C NMR data.

To see the role of bases on the selective etherification of calixarenes under MWI, Cs_2CO_3 was used in the place of K_2CO_3. Accordingly, reaction of **1a** (1 mmol) with 1-iodooctane (3 mmol) using Cs_2CO_3 (2.5 mmol) led to the formation of cone conformer of **3a** as the sole product albeit in moderate yield (44%) along with unreacted **1a** (28%). However, no mono-alkylated product **2a** was detected (Table 1, entry 26). Similarly, reaction of **1a** with ethyl bromoacetate/Cs_2CO_3 afforded the cone conformer of **3i** as a major product (53%) along with small amount of other alkylated products (~5%) and unreacted **1a** (16%) (Table 1, entry 27). Thus K_2CO_3 was

Table 1

Phenolic alkylation of calix[4]arene (**1a**)/4-*tert*-butyl calix[4]arene (**1b**) with alkyl halides/tosylates under microwave irradiation[a]

Entry	Calix[4]arene	R^1X	Power (W)	Time (h)	Product/s[ref][b] (% yield)	
1	**1a**	$C_8H_{17}I$	400	1.0	**2a** (36)	**3a**[19] (55)
2	**1a**	$C_8H_{17}I$	400	1.5	**2a** (11)	**3a** (74)
3	**1a**	$\mathbf{C_8H_{17}I}$	**400**	**2.25**	–	**3a (81)**
4	**1a**	$C_8H_{17}I$	Reflux	120.0	–	**3a** (51)
5	**1b**	$C_8H_{17}I$	400	1.5	**2b**[27] (10)	**3b** (72)
6	**1b**	$\mathbf{C_8H_{17}I}$	**400**	**2.5**	–	**3b** (79)
7	**1b**	$C_8H_{17}I$	Reflux	120.0	–	**3b** (49)
8	**1a**	CH_3OTs	400	1.5	**2c**[28] (12)	**3c**[29] (76)
9	**1a**	CH_3OTs	400	2.5	–	**3c** (83)
10	**1a**	CH_3OTs	Reflux	16.0	–	**3c** (65)
11	**1b**	CH_3OTs	400	1.5	**2d** (14)	**3d**[29] (71)
12	**1b**	$\mathbf{CH_3OTs}$	**400**	**2.5**	–	**3d** (77)
13	**1a**	C_3H_7I	400	1.5	**2e**[28] (8)	**3e**[19] (78)
14	1a	$\mathbf{C_3H_7I}$	**400**	**2.0**	–	**3e** (81)
15	**1a**	C_3H_7I	Reflux	24.0	–	**3e** (66)
16	**1b**	C_3H_7I	400	1.5	–	**3f**[30] (80)
17	**1a**	$C_6H_5CH_2Br$	300	0.5	–	**3g**[29] (78)
18	**1b**	$C_6H_5CH_2Br$	300	0.5	**–**	**3h**[31](83)
19	**1a**	$BrCH_2CO_2C_2H_5$	300	0.5	**–**	**3i**[32] (81)
20	**1b**	$BrCH_2CO_2C_2H_5$	300	0.5	**–**	**3j**[33] (85)
21	**1a**	$BrCH_2CN$	300	0.75	**–**	**3k**[34] **(**76)
22	**1b**	$BrCH_2CN$	300	0.75	**–**	**3l**[33] (72)
23	**1a**	2-(O-C_2H_4Br)$C_6H_4COCH_3$	400	1.0	–	**3m** (74)
24	**1b**	2-(O-C_2H_4Br)$C_6H_4COCH_3$	400	1.5	**2f** (4)	**3n** (72)
25	**1b**	2-(O-C_2H_4Br)$C_6H_4COCH_3$	400	2.0	**–**	**3n** (74)
26[c]	**1a**	$C_8H_{17}I$	400	1.5	**–**	**3a** (44)[d]
27[c]	**1a**	$BrCH_2CO_2C_2H_5$	300	0.5	**–**	**3i** (53)[d,e]

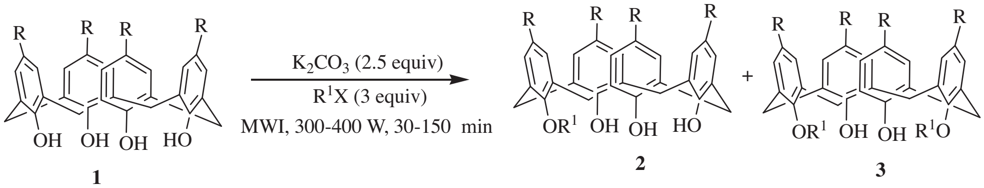
[a] Reaction conditions: calix[4]arene/4-*tert*-butyl calix[4]arene (2.0 mmol), K_2CO_3 (5.0 mmol), alkyl halide/tosylate (6.0 mmol), acetonitrile (4 ml) under MWI.

[b] Isolated as cone conformers only, no other conformer/s was detected.

[c] Cs_2CO_3 (2.5 equiv) was used in place of K_2CO_3 (2.5 equiv).

[d] Unreacted **1a** was isolated.

[e] Isolated mainly as a cone conformer along with small amount of other conformers (by ^{1}H NMR data).

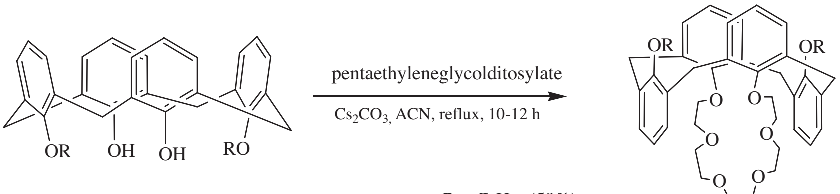


a: R = H
b: R = *t*-Bu

2a: R = H; $R^1 = C_8H_{17}$
2b: R = *t*-Bu; $R^1 = C_8H_{17}$
2c: R = H; $R^1 = CH_3$
2d: R = *t*-Bu; $R^1 = CH_3$
2e: R = H; $R^1 = C_3H_7$
2f: R = *t*-Bu; $R^1 = CH_2CH_2O\text{-}(2\text{-}COCH_3)C_6H_4$

3a: R = H; $R^1 = C_8H_{17}$
3b: R = t-Bu; $R^1 = C_8H_{17}$
3c: R = H; $R^1 = CH_3$
3d: R = t-Bu; $R^1 = CH_3$
3e: R = H; $R^1 = C_3H_7$
3f: R = t-Bu; $R^1 = C_3H_7$
3g: R = H; $R^1 = CH_2Ph$
3h: R = t-Bu; $R^1 = CH_2Ph$
3i R = H; $R^1 = CH_2CO_2C_2H_5$
3j: R = t-Bu; $R^1 = CH_2CO_2C_2H_5$
3k: R = H; $R^1 = CH_2CN$
3l: R = t-Bu; $R^1 = CH_2CN$
3m: R = H; $R^1 = CH_2CH_2O\text{-}(2\text{-}COCH_3)C_6H_4$
3n: R = t-Bu; $R^1 = CH_2CH_2O\text{-}(2\text{-}COCH_3)C_6H_4$

Scheme 1. Synthesis of mono- and 1,3-dialkyl ethers of calix[4]arenes under microwave irradiation.



a: R = C_8H_{17} (58%)
b: R = C_3H_7 (79%)

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1,3-alternate

Scheme 2. Synthesis of cesium ion selective calix[4]crown-6 1,3-alternate ionophores from 1,3-dialkoxy calix[4]arene.

found to be the base of choice for cone-selective 1,3-dietherification of calix[4]arenes under MWI.

Finally, both 1,3-di-*n*-octyloxycalix[4]arene (**3a**) and 1,3-di-*n*-propyloxy calix[4]arene (**3e**) were converted into 1,3-di-*n*-octyloxycalix[4]arene-crown-6[19] (**4a**) and 1,3-di-*n*-propyloxycalix[4]arene-crown-6[19] (**4b**), respectively, in 1,3-alternate conformations using Cs_2CO_3/pentaethyleneglycol ditosylate/acetonitrile (Scheme 2).

In conclusion, we have developed a microwave-assisted protocol for the etherification of phenolic groups of calix[4]arene/4-*tert*-butylcalix[4]arene with a variety of elctrophiles (2.5 equiv) to afford 1,3-dialkoxycalix[4]arenes as major/sole product in good to high yields. The reaction times were found to be much shorter (30–150 min) when compared to conventional refluxing conditions which required several hours to days for completion. Moreover there is no need for anhydrous reaction conditions and calix[4]arene ethers were formed only in cone conformations. Thus the present protocol will be very useful in the multi-step synthesis of complex calix[4]arene derivatives as most of those involve 1,3-dietherification in the very first step.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.142.

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