Regioselective synthesis of *distal*-bisalkoxytetrathiacalix[4]arenes by a protection–deprotection method using benzyl groups

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Regioselective synthesis of *distal*-bisalkoxytetrathiacalix[4]arenes is accomplished by a protection–deprotection method using benzyl groups as a protecting group. The deprotection of benzyl group was succeeded in the presence of $AlCl_3$ or solid superacid (Nafion-H) under refluxing benzene.

Keywords: thiacalix[4]arene, *O*-benzylation, protecting group, conformation, deprotection, solid superacid, Nafion-H

The introduction of larger alkyl groups on the phenolic oxygens of calix[4]arenes led to a situation where the OR groups within a cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation.[1] There exist four possible conformational isomers in calix[4]arenes; *i.e.* cone, partial-cone, 1,2-alternate and 1,3-alternate.[1] Similarly, four conformational isomers are possible in the case of tetrathiacalix[4]arene. The inhibition of interconversion between conformers derived from tetrathiacalix[4]arene **1** by *O*-substitution differs from that of the calix[4]arenes. On the other hand, the regioselective *O*-alkylation of hydroxy groups in calixarenes is important for many purposes, in particular, for the construction of multiple binding receptors or larger molecules starting from several calixarene building units.[2] Shinkai *et al*. reported the specific synthesis of calix [4]arene derivatives in a certain conformation using benzyl residues as protecting groups.[3]

The different intramolecular hydrogen bondings among the hydroxy groups between the diarylsulfide units are expected to affect the regioselectivity of the *O*-alkylations of tetrathiacalix[4]arenes.[4] Furthermore, regioselective synthesis of internally *O*-alkyl substituted tetrathiacalix[4]arenes has not yet been established.[5,6] Recently, Miyano *et al.* reported the *O*-benzylation of the flexible tetrahydroxytetrathiacalix[4]-arene to afford *distal*-di-*O*-benzylated tetrathiacalix[4]arene.[7] This compound afforded convenient starting material for the attempted preparation of *distal*-*O*-substituted tetrathiacalix[4]arenes. We now report on the possibility for application to the regioselective synthesis of *O*-substituted tetrathiacalix-[4]arenes using benzyl residues as protecting groups.

Results and discussion

O-Benzylation of tetrathiacalix[4]arene **1** carried out with 10 equiv. of benzyl bromide in the presence of Na_2CO_3 according to the reported procedure furnished exclusively the formation of the disubstituted product *distal*-**2** in spite of the use of a large excess of benzyl bromide. The reaction of bisbenzylated compound *distal*-**2** with methyl iodide in acetone in the presence of Cs_2CO_3 as base under reflux for 17 h yielded **3a** in 92% yield. Similarly, *O*-alkylation of *distal*-**2** with alkyl iodides in the presence of Cs_2CO_3 afforded the disubstitution products **3b–3d** in 72–74% yields.

Attempted removal of the benzyl group in **3a** with Me_3SiBr[8,9] in $CHCl_3$ at room temperature for 3 h or hydrogenation in the presence of Pd–C[10] at room temperature for 3 h to afford the desired dimethoxy derivative **4a** was unsuccessful. Only the recovery of the starting compound was obtained which is different from the results affording the debenzylated products in quantitative yield in the case of calix[4]arenes.[8] It is possible that the sulfur atoms in the thiacalix[4]arene might deactivate the catalytic activity of Pd–C. Finally, we succeeded in the debenzylation of **3a** in the presence of $AlCl_3$ in toluene at room temperature for 5 h to give the desired diol **4a** in 72%. The maximum yield was obtained in the presence of 5 equivalents of $AlCl_3$. The ring cleavage of the S–C bond in the thiacalixarene moiety as well as trans-*tert*-butylation was not observed under the conditions used. However, a large excess of $AlCl_3$ was required to complete the present debenzylation.

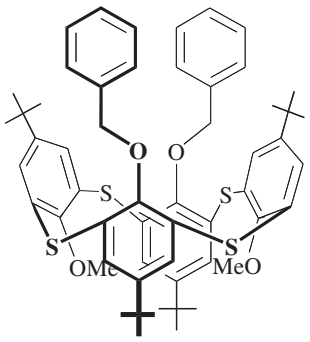

Figure 1 Structure of 1,3-*alternate*-**3a**.

On the other hand, recently, we have found that the Nafion-H catalyst, a perfluorinated sulfonic acid resin,[11] is effective in a wide range of liquid and gas phase reactions, including electrophilic substitutions on aromatic nuclei, transalkylations, condensations and so on.[12] Debenzylation of **3a** in the presence of Nafion-H (100 wt%) as a catalyst, was carried out in boiling benzene for 24 h to afford the desired dimethoxy derivative **4a** in 85% yield along with diphenylmethane. Depending on the amount of Nafion-H and an acceptor for benzyl group, *i.e.* benzene and toluene, selective debenzylation was found to be possible. Similar results were obtained for the dialkoxy derivatives (**4b–d**) *via* the alkylation of diol *distal*-**2** followed by the deprotection in the presence of Nafion-H in benzene. These results indicate that the protection–deprotection method is recommended as a useful strategy for the synthesis of these regioisomers. Furthermore, the presently developed procedure provides excellent yield, easy isolation of the products, and ready regeneration of the catalyst without the loss of activity.[11]

The ^{1}H NMR spectra of **3a–d** show two singlets for the *tert*-butyl protons at δ 0.85–0.90 ppm and δ 1.26–1.30 ppm, in which the former peak can be observed at a higher field due to the ring current effect arising from the two benzyl benzene rings introduced. A singlet signal of the methoxy protons in **3a** was also observed at higher field (δ 3.55 ppm) due to the ring current effect arising from the two inverted calix benzene rings. Similar upfields of alkoxy protons were observed in **3b**–**d**. These observations strongly suggest **3a–d** adopt 1,3-alternate conformation.

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The calixarenes show concentration-independent hydroxyl stretching bands in the 3200 cm^{-1} region of the IR spectrum and a signal at δ 9–10 ppm in the ^1H NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes.[1] The IR (KBr) spectrum of **4a** shows the absorption for the hydroxyl stretching vibration around 3373 cm^{-1}. The ^1H NMR signal for hydroxyl group was observed at δ 7.77 ppm. Similar findings are observed in **4b–d**. These observations suggest the intramolecular hydrogen bonding does exist in di-*O*-alkylated derivatives **4a–d**. Furthermore, the previously noted upfield shift for the methyl protons in the alkoxy groups in the ^1H NMR spectra of **3a–d** has not been observed. Therefore, the dialkoxy derivatives **4a–d** might adopt the *cone*-conformation due to the intramolecular hydrogen bonding between two hydroxy groups and alkoxy groups. Thus hydroxy groups and alkoxy groups of dialkoxytetrathiacalix[4]arenes have a tendency to orientate in the same direction and therefore favoured the adoption of the "cone" conformation.

Conclusions

We have demonstrated for the first time that the regioselective synthesis of *distal*-dialkoxy-tetrathiacalix[4]arene (*distal*-**4a–d**) are accomplished by a protection–deprotection method using benzyl groups as a protecting group. Solid superacid (Nafion-H) was found to be a good catalyst for the present deprotection of benzyl group. Further studies on the possibility for application to the regioselective synthesis of *O*-substituted tetrathiacalix[4]arenes using benzyl residues as protecting groups are now in progress.

Experiment

All melting points are uncorrected ^1H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system.

Materials. *Distal*-26,28-Bis(benzyloxy)-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,27-diol, *distal*-**2** was prepared in 93% yield from 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** according to the reported procedure.[7]

*Methylation of distal-***2** *with methyl iodide in the presence of* Cs_2CO_3
A mixture of *distal*-**2** (200 mg, 0.222 mmol) and Cs_2CO_3 (342 mg, 1.78 mmol) in acetone (10 cm^3) was heated at reflux for 1 h. Methyl iodide (250 mg, 1.78 mmol) was then added and the mixture heated at reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 $cm^3 \times 2$) and washed with water (50 $cm^3 \times 2$), and dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was washed with methanol to give **3a** (190 mg, 92%) as a colourless solid.

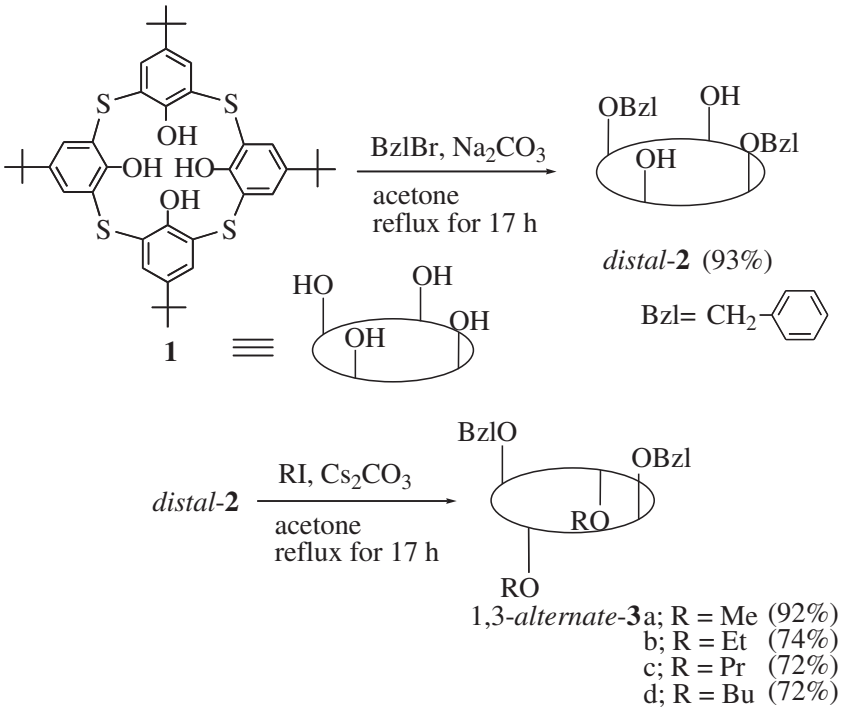
1,3-alternate-25,27-Bis(benzyloxy)-26,28-dimethoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**3a**): Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 278–280 °C. IR (KBr) ν_{max}: 2962, 2870, 1771, 1455, 1435, 1264, 966, 877; ^1H NMR ($CDCl_3$) δ 0.90 (18H, s, *t*Bu), 1.26 (18H, s, *t*Bu), 3.55 (6H, s, O*Me*), 4.95 (4H, s, OCH_2), 7.12–7.22 (10H, m, Ar–*H*), 7.17 (4H, s, Ar–*H*), 7.49 (4H, m, Ar–*H*); *m/z*: 928 (M^+); Found: C 72.29, H 6.85. Calcd. for $C_{56}H_{64}O_4S_4$ (929.37): C 72.37, H 6.94%.

Similarly, the compounds (**3b**–**3d**) were synthesised in the same manner as described above for **3a** and the yields are compiled in Scheme 1.

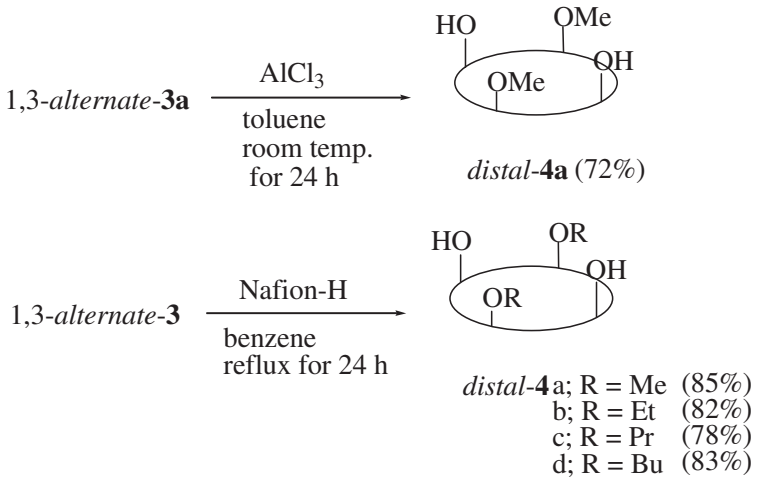
1,3-alternate-25,27-Bis(benzyloxy)-26,28-diethoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**3b**): Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 243–244 °C. ^1H NMR ($CDCl_3$) δ 0.70 (6H, t, *J*=7.2, OCH_2CH_3), 0.85 (18H, s, *t*Bu), 1.30 (18H, s, *t*Bu), 3.96 (4H, q, *J*=7.2, OCH_2CH_3), 5.06 (4H, s, OCH_2), 6.94–7.15 (10H, m, Ar–*H*), 7.05 (4H, s, Ar–*H*), 7.46 (4H, m, Ar–*H*); *m/z*: 956 (M^+); Found: C 72.92, H 7.35. Calcd. for $C_{58}H_{68}O_4S_4$ (957.43): C 72.76, H 7.16%.

1,3-alternate-25,27-Bis(benzyloxy)-26,28-dipropoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**3c**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 274–275 °C. ^1H NMR ($CDCl_3$) δ 0.70 (6H, t, *J*=7.2, $OCH_2CH_2CH_3$), 0.85 (18H, s, *t*Bu), 1.07–1.14 (4H, m, $OCH_2CH_2CH_3$), 1.30 (18H, s, *t*Bu), 3.83 (4H, m, $OCH_2CH_2CH_3$), 5.06 (4H, s, OCH_2Ph), 6.94–7.15 (10H, m, Ar–*H*), 7.05 (4H, s, Ar–*H*), 7.41 (4H, m, Ar–*H*); *m/z*: 984 (M^+). Found: C 73.29, H 7.53. Anal. calcd. for $C_{60}H_{72}O_4S_4$ (985.48): C 73.13, H 7.36%.

1,3-alternate-25,27-Bis(benzyloxy)-26,28-dibutoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (**3d**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 276–277 °C. ^1H NMR ($CDCl_3$) δ 0.85 (6H, t, *J*=7.2, $OCH_2CH_2CH_2CH_3$), 0.85 (18H, s, *t*Bu), 1.10–1.20 (8H, m, $OCH_2CH_2CH_2CH_3$), 1.30 (18H, s, *t*Bu), 3.85 (4H,



Scheme 1



Scheme 2

q, *J*=7.2, O*CH*$_2$CH$_2$CH$_2$CH$_3$), 5.06 (4H, s, O*CH*$_2$Ph), 6.95–7.17 (10H, m, Ar–*H*), 7.06 (s, 4H, Ar–*H*), 7.40 (4H, m, Ar–*H*); *m/z*: 1012 (M^+); Found: C 73.62, H 7.63. Calcd. for $C_{62}H_{76}O_4S_4$ (1013.53): C 73.47, H 7.56%.

$AlCl_3$ catalysed debenzylation of **3a** *in benzene*

A mixture of $AlCl_3$ (246 mg, 1.85 mmol) in dry CH_2Cl_2 (1.5 cm^3) was stirred at room temperature for 30 min and then **3a** (350 mg, 0.37 mmol) dissolved in toluene (10 cm^3) was added. The reaction was vigorously stirred at room temperature for 5 h and then quenched with 1 N HCl, extracted with CH_2Cl_2. The organic layer was separated, washed twice with brine, dried with $MgSO_4$ and evaporated to dryness to obtain crude product **4a** (199 mg, 72%) as a colourless solid. Recrystallisation from MeOH–$CHCl_3$ (3:1) yielded pure **4a** as colourless prisms.

Distal-26,28-dimethoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene-25,27-diol (**4a**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 265–267 °C. IR (KBr) ν_{max}: 3373 (OH). ^{1}H NMR ($CDCl_3$) δ 0.93 (18H, s, *t*Bu), 1.34 (18H, s, *t*Bu), 4.02 (6H, s, O*Me*), 7.19 (4H, s, Ar–*H*), 7.61 (4H, s, Ar–*H*), 7.77 (2H, s, O*H*); *m/z*: 748 (M^+); Found: C 67.49, H 6.96. Calcd. for $C_{42}H_{52}O_4S_4$ (749.12): C 67.34, H 7.0%.

Nafion-H catalysed debenzylation of **3a** *in benzene*

A mixture of **3a** (200 mg, 0.215 mmol) and Nafion-H (200 mg) in benzene (6 cm^3) was heated at 100 °C for 24 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a yellow oil, which was washed with hexane to give **4a** (142 mg, 85%) as a colourless solid.

Similarly, compounds (**4b**–**4d**) were synthesised in the same manner as described above for **4a** and yields are compiled in Scheme 2.

Distal-26,28-diethoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene-25,27-diol (**4b**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 272–274 °C. ^{1}H NMR ($CDCl_3$) δ 0.73 (6H, t, *J*=7.2, OCH$_2$*CH*$_3$), 0.80 (18H, s, *t*Bu), 1.31 (18H, s, *t*Bu), 3.88 (4H, q, *J*=7.2, O*CH*$_2$CH$_3$), 6.98 (4H, s, Ar–*H*), 7.62 (4H, s, Ar–*H*), 7.92 (2H, s, O*H*); *m/z*: 776 (M^+); Found: C 67.84, H 7.39. Calcd. for $C_{44}H_{56}O_4S_4$ (777.17): C 68.00, H 7.26%.

Distal-26,28-dipropoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene-25,27-diol (**4c**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)), m.p. 275–279 °C. ^{1}H NMR ($CDCl_3$) δ 0.80 (18H, s, *t*Bu), 1.15 (6H, t, *J*=7.2, OCH$_2$CH$_2$*CH*$_3$), 1.32 (18H, s, *t*Bu), 1.99 (4H, m, OCH$_2$*CH*$_2$CH$_3$), 4.44 (4H, m, O*CH*$_2$CH$_2$CH$_3$), 6.96 (4H, s, Ar–*H*), 7.64 (4H, s, Ar–*H*), 7.98 (2H, s, O*H*); *m/z*: 804 (M^+); Found: C 68.83, H 7.46. Calcd. for $C_{46}H_{60}O_4S_4$ (805.23): C 68.62, H 7.51%.

Distal-26,28-dibutoxy-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene-25,27-diol (**4d**)*:* Colourless prisms (MeOH–$CHCl_3$ (3:1)); m.p. 268–271 °C. ^{1}H NMR ($CDCl_3$) δ 0.80 (18H, s, *t*Bu), 1.02 (6H, t, *J*=7.2, OCH$_2$CH$_2$CH$_2$*CH*$_3$), 1.33 (18H, s, *t*Bu), 1.61 (4H, m, OCH$_2$CH$_2$*CH*$_2$CH$_3$), 1.98 (4H, m, OCH$_2$*CH*$_2$CH$_2$CH$_3$), 4.49 (4H, m, O*CH*$_2$CH$_2$CH$_2$CH$_3$), 6.95 (4H, s, Ar–*H*), 7.64 (4H, s, Ar–*H*), 7.94 (2H, s, O*H*); *m/z*: 832 (M^+); Found: C 69.33, H 7.86. Calcd. for $C_{48}H_{64}O_4S_4$ (833.28): C 69.19, H 7.74%.

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