Protection-deprotection method in synthesis of calixarene derivatives

LU, Guo-Yuan*(陆国元) LI, Qian(李倩) LIU, Fang(刘芳) WAN, Xiao-Bin(万小宾)
Department of Chemistry, Nanjing University, Nanjing, Jiangsu 210093, China

The debenzylation and selective de-*tert*-butylation of *p-tert*-calix[4]arene derivatives were studied and 11,17,23-tri-*tert*-butyl-25,26,27-tri-*O*-etherated calix[4]arenes were synthesized by a simultaneous debenzylation and selective de-*tert*-butylation process.

Keywords Debenzylation, de-*tert*-butylation, calixarene derivatives

Calixarenes are a class of macrocyclic compounds which are attracting increasing interest owing to their potential for forming host-guest complexes and acting as enzyme mimic, especially if appropriately functionalized.[1]

For the synthesis of functionalized calixarenes, it is important to use a protection-deprotection method.[2] So far as *p-tert*-butylcalixarene is concerned, the *tert*-butyl usually acts as protecting group for the *para*-position of the starting phenol OH. For example, *p-tert*-butylcalix[4]arene (**1**) can be easily prepared by the base-induced condensation of *p-tert*-butylphenol with formaldehyde.[3] The full de-*tert*-butylation of **1** and selective de-*tert*-butylation of 5,11,17,23-tetra-*tert*-butyl-26,28-di-*O*-alkylated calix[4]arenes have been reported. The reactions were carried out in the presence of anhydrous aluminium chloride at 0℃ or at room temperature.[4] In our experiments, however, it was only at higher temperature that the de-*tert*-butylation took place. For example, **2a** was selectively de-*tert*-butylated in the presence of $AlCl_3$ at 60℃ to give product **3** in good yield. The X-ray diffraction demonstrated that **3** existed in the form of cone conformation in the complex with acetone (Fig. 1).

As to the protection-deprotection method for the phenol OH of *p-tert*-calix[4]arene, Shinkai *et al.*[2] reported that benzyl group was used as protecting group, and debenzylation could be achieved in the presence of Me_3SiBr or Me_3SiCl. However, the simultaneous de-*tert*-butylation and debenzylation have not been reported so far. Recently, we found that the simultaneous de-*tert*-butylation and debenzylation of **2b** and **2c** could be realized in the presence of anhydrous $AlCl_3$ in toluene at 60℃. The clathrate of **4** with acetone (3:1) (recrystallized from acetone) was obtained in excellent yield. Our reaction procedure described above is useful for preparing some functionalized calixarenes, such as 11,17,23-tri-*tert*-butyl-25,26,27-tri-*O*-alkylated calix[4]arenes (**8** and **9**) which have cone conformation.

Although tri-*O*-alkylation of *p-tert*-butylcalix[4]-arene has been realized in the presence of $Ba(OH)_2$ as a base, the alkyl groups are only simple methyl,[5] ethyl,[6] propyl,[2] *n*-butyl[6] *etc*. We found that the direct tri-*O*-alkylation of the *p-tert*-calix[4]arenes was very difficult when the bromides such as $C_6H_5CH_2NHCOCH_2Br$, $CH_3OCH_2OCH_2CH_2Br$ were used as alkylating agents. Therefore, we took a new synthetic pathway, in which **1** was mono-*O*-benzylated[2] to give **6**, then thoroughly *O*-alkylated with the bromides in the presence of NaH to give **6** and **7**, followed by simultaneous de-*tert*-butylation and de-benzylation to give **8** and **9**.

In the ^1H NMR spectra, the peaks of $ArCH_2Ar$ protons of all new compounds **2a**, **2b**, **3**, **6**, **7**—**9** appeared as doublet or quadruplet at 3.21—3.56 (H_{exo}) and 4.23—4.68 (H_{endo}) and the chemical shift difference of H_{exo} and H_{endo} was about 1.0. Obviously they

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were consistent with the cone conformation.[1a,1b,2b,7,8]

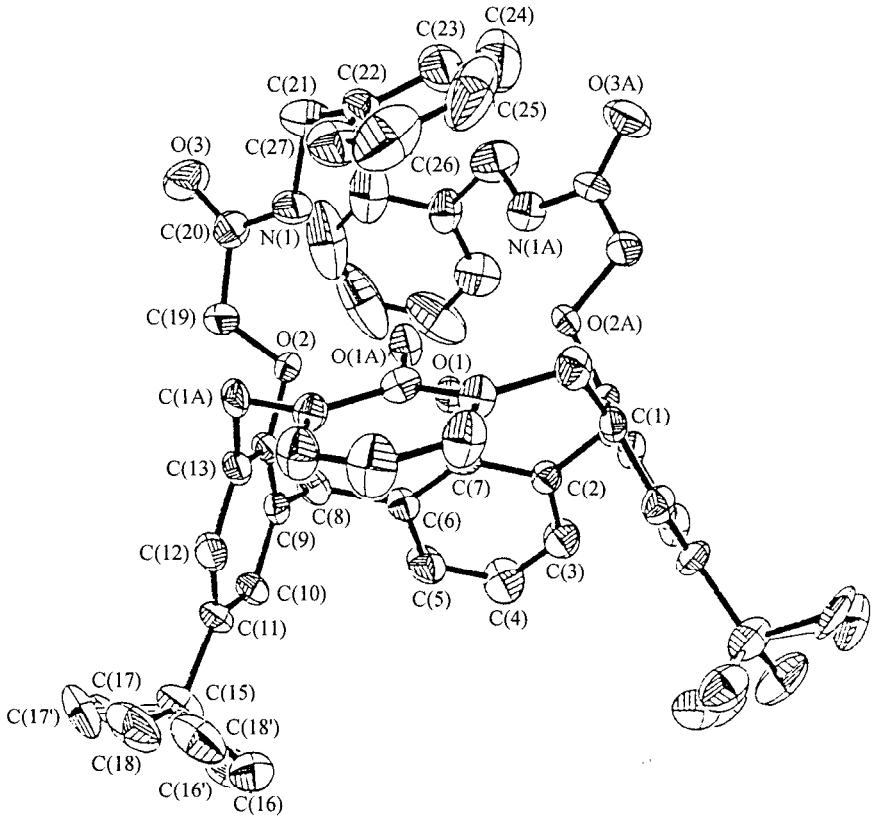


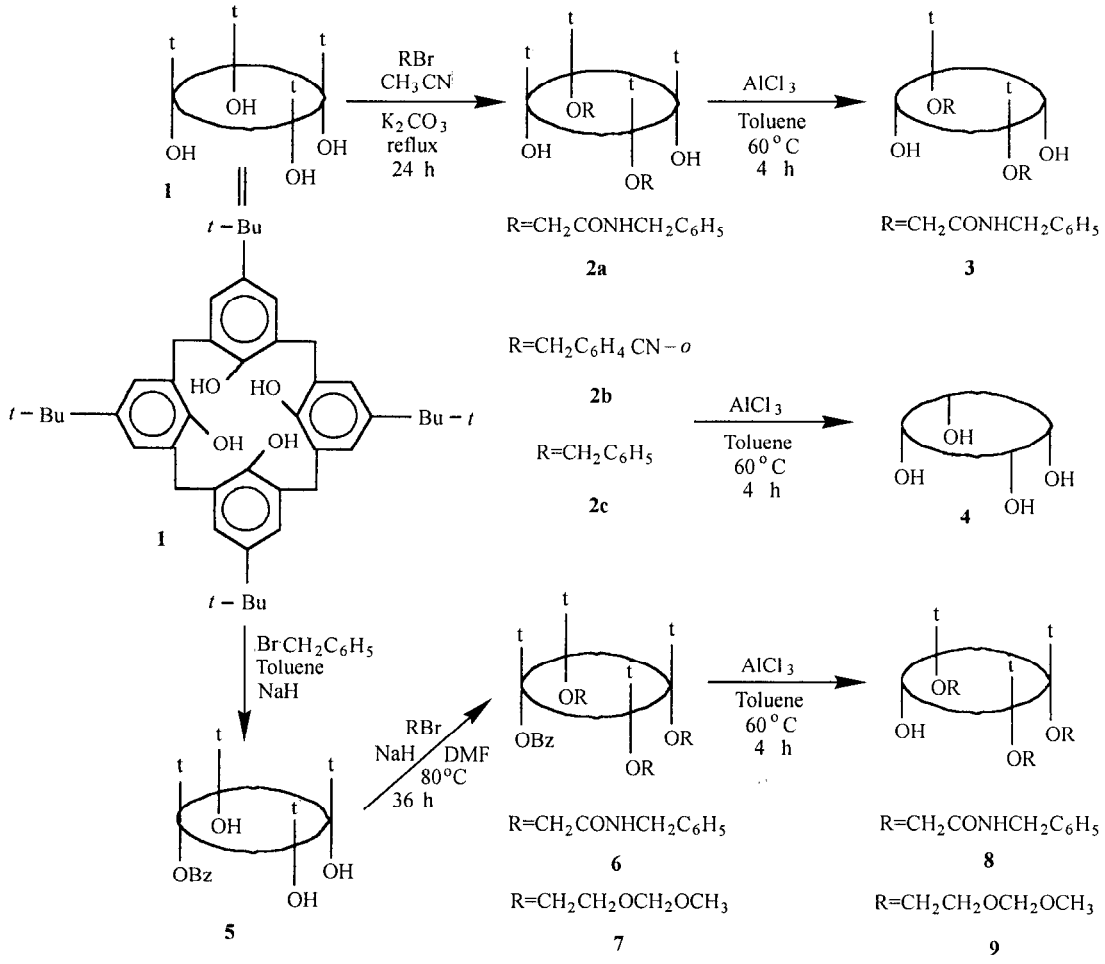
Fig.1 The X-ray structure of compound **3**.

Experimental

The ^1H NMR spectra of all compounds in $CDCl_3$ solution were recorded on a Bruker WP 500 MHz spectrometer with TMS as internal standard. The mass spectra were obtained using FAB technique on ZABHS apparatus. IR was recorded on a Nicolet FT-170/SAX apparatus with pressed KBr pellet. Elemental analyses were performed on a Perkin-Elmer 240C apparatus. The crystallographic data were collected on a Siemens P4 four-circle diffractometer.

Compounds **2a—2c**

2a—2b were synthesized according to the method described by Reinhoudt.[9] The *p-tert*-butylcalix[4]arene (**1**) (toluene complex,[3b] 2.0 g, 2.7 mmol) and bromoacetyl benzylamide $C_6H_5CH_2NHCOCH_2Br$ (1.23 g, 5.4 mmol) were dissolved in acetonitrile (50 mL), and the solution was refluxed for 24 h in the presence of K_2CO_3 (0.414 g, 3.0 mmol). The solvent was evaporated *in vacuo*. The residue was washed with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 solution was washed with 1.0 mol/L hydrochloride solution (2 × 20 mL) and water (3 × 20 mL) respectively, dried over $MgSO_4$ and evaporated to dryness. The residue was re crystallized from acetone, dried at 60℃ to give **2a** (2.14 g, 84.1%), mp 268—270℃. υ_{max} (cm^{-1}): 1680 (strong, C = O). δ_H: 0.90 (s, 18H, 2 × $(CH_3)_3C$), 1.20(s,18H, 2 × $(CH_3)_3C$), 3.22(d, J = 13.1 Hz, 4 × *exo*-ArCHAr), 3.80(d, J = 7.2 Hz, 4H, 2 × $C_6H_5CH_2N$), 4.33(s, 4H, 2 × OCH_2CO), 4.43(d, J = 13.1 Hz, 4H, 4 × *endo*-ArCHAr), 6.77 (s, 4H, ArH), 6.90(s, 2H, 2 × NH), 7.00(s, 4H, ArH), 7.13—7.30(m, 10 H, Ar'H), 8.83 (s, 2H, 2 × OH). *m/z*: 944 (M^+ + 2), 796 (M^+ + 2 − $C_6H_5CH_2NHCOCH_2$). Anal. $C_{62}H_{74}N_2O_6$. Calcd: C, 78.95; H, 7.91; N, 2.97. Found: C, 79.02; H, 7.70; N, 3.30.



2b (0.88 g) was obtained by the similar procedure from **1** (1.0 g, 1.35 mmol) and *o*-bromomethylbenzonitrile *o*-NC-C_6H_4-CH_2Br (0.534 g, 2.8 mmol), yield 74%, mp 276—278℃. υ_{max}(cm^{-1}): 2228(CN). δ_H: 0.95(s, 18H, 2 × $(CH_3)_3C$), 1.17(s, 18H, 2 × $(CH_3)_3C$), 3.52(d, J = 14.0 Hz, 4H, 4 × *exo*-ArCHAr), 4.38(d, J = 14.0 Hz, 4H, 4 × *endo*-ArCHAr), 5.40(s, 4H, 2 × $ArOCH_2Ar'$), 6.86(s, 4H, ArH), 7.20(s, 4H, ArH), 7.26—7.60(m, 8H, Ar' H), 8.36(s, 2H, 2 × OH). *m/z*: 880(M^+ + 2), 764(M^+ + 2 − $CH_2C_6H_4CN$), 648(M^+ + 2 − $2CH_2C_6H_4CN$). Anal. $C_{60}H_{66}N_2O_4$. Calcd: C, 81.97; H, 7.57; N, 3.19. Found: C, 81.87; H, 7.80; N, 3.21.

2c was synthesized according to the procedure described by Shinkai *et al*.[2b]

General procedure for de-tert-butylation/de-tert-butylation and debenzylation

The calixarene (1.0 mmol) (**2a**, **2b**, **2c**, **6**, **7** respectively) was added to the suspension of $AlCl_3$ in dry toluene (5.0 mmol, 80 mL) under N_2. The mixture was stirred at 60℃ for 4 h. After cooling, 1.0 mol/L HCl solution (50 mL) was slowly added under vigorous stirring. The organic layer was washed with H_2O until neutrality and evaporated to dryness *in vacuo*. The resulting residue was recrystallized from acetone or purified with silica gel column chromatography.

Compound **3** From **2a** (0.94 g, 1.0 mmol), **3** was afforded (0.67 g, 80.1%, recrystallized from acetone, dried at 80℃), mp 318—320℃. υ_{max}(cm^{-1}): 1682(strong, C = O). δ_H: 0.90 (s, 18H, 2 × $(CH_3)_3C$), 3.30(d, J = 13.8 Hz, 4H, 4 × *exo*-ArCHAr), 3.81(d, J = 6.8 Hz, 4H, 2 × $C_6H_5CH_2N$), 4.36(d, J = 13.8 Hz, 4H, 4 × *endo*-ArCHAr), 4.57

(s, 4H, 2 × OCH_2CO), 6.76—6.83(m, 6H, ArH, 2 × NH), 6.99(s, 6H, ArH), 7.07—7.21(m, 10H, 2 × Ar'H), 8.67—8.90(br. s, 2H, 2 × OH). *m/z*: 832(M^+ + 2), 684(M^+ + 2 − $C_6H_5CH_2NHCOCH_2$). Anal. $C_{54}H_{58}N_2O_6$. Calcd: C, 78.04; H, 7.04; N, 3.37. Found: C, 77.82; H, 7.13; N, 3.58.

The inclusion complex of **3** *with acetone* (1:3, [($C_{54}H_{58}N_2O_6$ · CH_3COCH_3) · $2CH_3COCH_3$]) The colorless crystals were obtained by slow evaporation of an acetone solution of **3**. The crystals rapidly faded on contact with the air to lose acetone, so they were sealed in a capillary and instantly subjected to the X-ray analysis. Crystal system: monoclinic; space group: *C2/c*; empirical formula: $C_{31.50}H_{38}NO_{4.50}$; unit cell dimensions: *a* = 2.6277(8) nm, *b* = 1.2967(5) nm, *c* = 2.0355 (4) nm, α = 90°, β = 124.8°, γ = 90°. **3** existed in form of a cone conformation, which was stabilized by the intramolecular hydrogen bonds between the phenol OH and the ether oxygen atoms (-O-H···O-) and between N-H of the amide groups and the oxygen atoms of phenol hydroxyl groups (-N-H···O-)(Fig. 1).

The clathrate of **4** *with acetone* (3:1) The product obtained from **2b** or **2c** according to the general procedure was recrystallized from acetone to give colorless hexagonal crystals (yield 93—95%), mp > 320℃. It was not soluble in any solvent. X-ray structure analysis indicated that it was a clathrate of calix[4]-arene **4** with acetone (3:1), empirical formula $C_{29}H_{26}O_{4.33}$; space group *P63/m*; *a* = *b* = 1.4584(2) nm, *c* = 1.8277(1) nm, α = β = 90°, γ = 120°. Bond distances, bond angles and molecular packing were consistent with those reported by Ungaro.[10] υ_{max}(cm^{-1}): 1710 (C = O). Anal. $C_{84}H_{72}O_{12}$ · CH_3COCH_3. Calcd. C, 78.46; H, 5.91. Found: C, 78.11; H, 5.99.

Compound **8** **8** (0.78 g, 75.1%) was obtained from **6** (1.18 g, 1.0 mmol) through silica gel column (ethyl acetate-hexane, 1:8 *V/V*), mp > 320℃. υ_{max}(cm^{-1}): 1682(strong, C = O). δ_H: 0.90 (s, 27H, 3 × $(CH_3)_3C$), 3.32(q, *J* = 13.1 Hz, 4H, 4 × *exo*-ArCHAr), 3.82(d, *J* = 6.8 Hz, 6H, 3 × $C_6H_5CH_2N$), 4.31(s, 6H, 3 × OCH_2CO), 4.43(d, *J* = 13.1 Hz, 2H, 2 × *endo*-ArCHAr), 4.62(d, *J* = 13.8 Hz, 2H, 2 × endo-ArCHAr), 5.80(s, 3H, 3 × NH, if added D_2O, disappeared); 6.75—7.03(m, 8H, ArH), 7.10—7.20(m, 5H, Ar'H), 7.85(s, 1H, OH). *m/z*: 1035(M^+ + 2), 887(M^+ + 2 − $C_6H_5CH_2NHCOCH_2$). Anal. $C_{67}H_{75}N_3O_7$. Calcd: C, 77.79; H, 7.31; N, 4.06. Found: C, 77.51; H, 7.24; N, 3.78.

Compound **9** **9** (0.58 g, 68.7%) was obtained from **7** (1.0 g, 1.0 mmol) through silica gel column (ethyl acetate-hexane, 1:5 *V/V*), mp 158—160℃. δ_H: 0.95(s, 27H, 3 × $(CH_3)_3C$), 3.41(q, *J* = 12.6 Hz, 4H, 4 × *exo*-ArCHAr), 3.50(s, 9H, 3 × OCH_3), 4.03—4.23(m, 12H, 3 × OCH_2CH_2O), 4.36 (d, *J* = 13.2 Hz, 2H, 2 × *endo*-ArCHAr), 4.54(d, *J* = 13.9 Hz, 2 × *endo*-ArCHAr), 4.86(s, 6H, 3 × OCH_2O), 6.78—6.93(m, 8H, ArH), 7.93(s, 1H, OH). *m/z*: 858(M^+ + 2). Anal. $C_{52}H_{72}O_{10}$. Calcd: C, 72.87; H, 8.47. Found: C, 72.55; H, 8.58.

Compound **6** Compound **5** was prepared according to the procedure described by Shinkai.[2b] **5**(1.0 g, 1.38 mmol) and $C_6H_5CH_2NHCOCH_2Br$(1.94 g, 8.5 mmol) were dissolved in DMF (80 mL) and the solution was stirred in the presence of NaH (0.24 g, 10.0 mmol) at 80 ~ 85℃ under N_2. After 36 h, DMF was removed *in vacuo*, and the residue was extracted with CH_2Cl_2(3 × 100 mL). The combined organic layer was washed with water (3 × 50 mL), dried over $MgSO_4$. Then solvent was evaporated to dryness, and the residue was purified with silica gel column (ethyl acetate-hexane, 3:10 *V/V*) to give **6** (1.32 g, 81.2 %), mp 309—311℃. υ_{max}(cm^{-1}): 1680(strong, C = O). δ_H: 0.86 (s, 27H, 3 × $(CH_3)_3C$), 0.97 (s, 9H, $(CH_3)_3C$), 3.35(q, *J* = 12.5 Hz, 4H, 4 × *exo*-ArCHAr), 3.85(d, *J* = 6.7 Hz, 6H, 3 × $C_6H_5CH_2N$), 4.32(s, 6H, 3 × OCH_2CO), 4.41(d, *J* = 13.2 Hz, 2H, 2 × *endo*-ArCHAr), 4.58(d, *J* = 13.9 Hz, 2H, 2 × *endo*-ArCHAr), 4.78(s, 2H, $C_6H_5CH_2O$), 6.76—6.98(m, 8H, ArH), 7.12—7.20(m, 15H, Ar'H), 7.31—7.50(m, 5H, Ar'H). *m/z*: 1181(M^+ + 2), 1090(M^+ + 2 − $C_6H_5CH_2$). Anal. $C_{78}H_{89}N_3O_7$. Calcd: C, 79.36; H, 7.60; N 3.56. Found: C, 79.09; H, 7.47; N, 3.25.

Compound **7** Compound **7** (0.93 g, 67.2%) was obtained from **5** (1.0 g, 1.38 mmol) and $BrCH_2CH_2OCH_2OCH_3$(1.44 g, 8.5 mmol), mp 134—136℃. δ_H: 0.93(s, 27H, 3 × $(CH_3)_3C$), 1.02(s, 9H, $(CH_3)_3C$), 3.28(q, *J* = 12.4 Hz, 4H, 4 × *exo*-ArCHAr), 3.52(s, 9H, 3 × OCH_3), 4.09—4.29(m, 12H, 3 × OCH_2CH_2O), 4.40(d, *J* = 13.1 Hz, 2H, 2 × *endo*-ArCHAr), 4.58(d, *J* = 13.8 Hz, 2H, 2 × *endo*-ArCHAr), 4.75(s, 2H, $C_6H_5CH_2O$), 4.87(s,

6H, 3 × OCH_2O), 6.79—7.02(m, 8H, ArH), 7.28—7.47(m, 5H, Ar'H). *m/z*: 1004($M^+ + 2$), 913($M^+ + 2 - C_6H_5CH_2$). Anal. $C_{63}H_{86}O_{10}$. Calcd: C, 75.40; H, 8.64. Found: C, 75.22; H, 8.48.

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