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(1+1) or (2+2) Coupling for bis(tosyloxyethoxy)benzenes with calix[4]arene and thiacalix[4]arene

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Abstract—As bifunctional reagents, bis(tosyloxyethoxy)benzenes can react with *p-tert*-butylcalix[4]arene or *p-tert*-butylthiacalix[4]arene to afford intramolecularly bridged (1+1) or intermolecularly bridged (2+2) products. It was found that the bridging pattern strongly depended on the structure of bis(tosyloxyethoxy)benzene and the kind of calixarene. For the *ortho*-isomer of bis(tosyloxyethoxy)benzene, intramolecularly bridged calix[4]arene and thiacalix[4]arene were the main products. For the *para*-isomer, the bridging reaction was in a (2+2) fashion. As for the *meta*-isomer, double thiacalix[4]arene and intramolecularly bridged calix[4]crown were synthesized.

It is well known that bifunctional reagents can react with calix[4]arene to afford intermolecularly or intramolecularly bridged products depending on the structure of the reactants and the reaction conditions. In a few cases, both kinds of products can be obtained, although one of them is always a by-product. In general, *p*-dihalomethylarene, *m*-dihalomethylarene and short, rigid reagents such as ethylene ditosylate are preferable to form intermolecularly bridged products; *o*-dihalomethylarene, long and flexible reagents such as oligoethylene glycol ditosylates are preferable to afford intramolecularly bridged ones, although exceptions sometimes do occur.[1]

Thiacalixarene (TCA) is a new member of the calixarene family, and its potential applications are based on replacing traditional methyl bridges with sulfur atoms.[2,3] However, its conformation is rather mobile which inhibits its application as a host molecule. Intra- or inter-bridging is an effective route to inhibit its flexibility or even immobilize its conformation. A number of bridged thiacalix[4]arenes have been synthesized from thiacalix[4]arene directly[4–13] or indirectly,[14–16] by the traditional base promoted synthesis[4–8,10–12] or Mitsunobu protocol using the DEAD/TPP system.[9] In most cases, intramolecularly bridged products were the main resultants from thiacalix[4]arene itself. The first representatives of 1,3-alternate thiacalix[4]monocrown-5 and -6 were reported in 2002,[7] and 1,3-conic thiacalix[4]monocrown-4 and -5 were prepared by the cyclocondensation of thiacalix[4]arene with corresponding oligoethylene glycol under Mitsunobu protocol.[9a] Other intramolecularly bridged products including 1,2-crowned thiacalix[4]arenes were also reported.[5,9] However, the (2+2) coupling was rather rare. Under the Mitsunobu protocol, two thiacalix[4]arenes reacted with two diethylene glycols to give a (2+2) cyclocondensation product, wherein two thiacalix subunits were connected by diethylene glycol chains,[9a] and the Mitsunobu reaction of TCA with thiodiethylene glycol (TDEG) or *N*-phenyl-iminodiethanol also gave intermolecular products.[9c] Another (2+2) cyclocondensation product was obtained from thiacalix[4]arene and 1,3-propanediol.[9b] Very recently, we have synthesized a new double thiacalix[4]arene by the reaction of thiacalix[4]arene with 2,6-bis(bromomethyl)-4-methylanisole, a novel type of intermolecularly coupled product.[17] Bis(tosyloxyethoxy)benzenes are an interesting type of bridging reagents, which contain a rigid arene nuclei and two flexible oxyethylene arms. It is interesting to see what happens when they are used as bridging reagents to react with thiacalix[4]arene and calix[4]arene.

The reaction of *p-tert*-butylcalix[4]arene or *p-tert*-butylthiacalix[4]arene with bis(tosyloxyethoxy)benzene in

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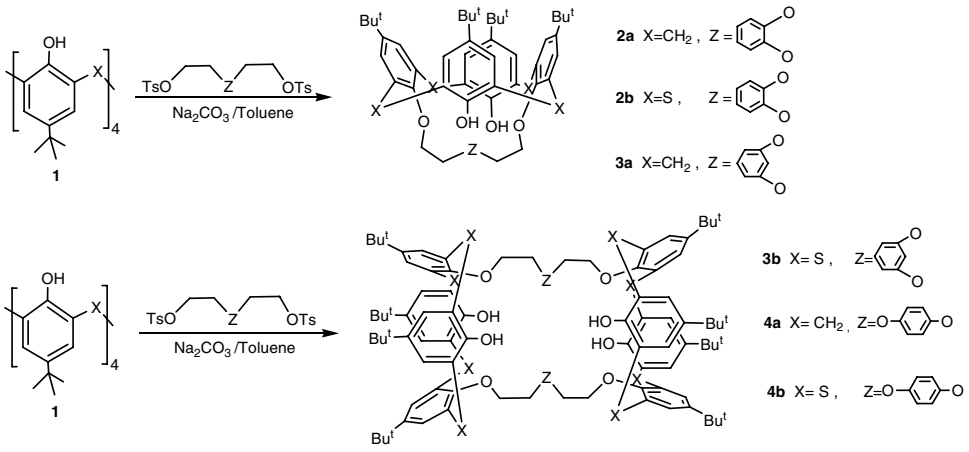

Figure 1. (1+1) coupling or (2+2) coupling for *p-tert*-butylcalix[4]arene and *p-tert*-butylthiacalix[4]arene with bis(tosyloxyethoxy)benzenes.

Na_2CO_3/toluene afforded intramolecularly bridged (1+1) or intermolecularly bridged (2+2) products. The synthetic route was depicted in Figure 1. When 1,2-bis(tosyloxyethoxy)benzene was used as the bridging reagent, intramolecularly bridged (1+1) calix[4]crown **2a** and thiacalix[4]crown **2b** were afforded. For 1,3-bis(tosyloxyethoxy)benzene, intramolecularly bridged (1+1) calix[4]crown **3a** and intermolecularly bridged (2+2) double thiacalixarene **3b** were obtained. When 1,4-bis(tosyloxyethoxy)benzene was used as bridging reagent, intermolecularly bridged (2+2) products were obtained; at least, only double *p-tert*-butylcalix[4]arenes **4a** and double thiacalix[4]arenes **4b** were separated. Their structures were characterized by ESI MS, elemental analyses, and ^{1}H NMR spectra.[18]

Compounds **2a** and **2b** were synthesized in the yields of 25% and 34%, respectively. The ESI-MS data proved **2a** and **2b** to be (1+1) intramolecularly coupled derivatives. Their ^{1}H NMR spectra showed two singlets in a ratio of 1:1 for the *tert*-butyl protons, which indicated clearly that they were 1,3-bridged products. The signals of methylene protons of **2a** appeared as a pair of doublets, suggesting that it existed in a conic conformation. In the ^{1}H NMR spectrum of **2b**, the signals of *tert*-butyl protons appeared at δ 0.91 and 1.30 ppm, which were similar to that of 1,3-conic monocrown thiacalix[4]arene (δ 0.93 and 1.36 ppm).[9a]

Compounds **3a** and **3b** were similarly obtained in the yields of 35% and 13%, respectively. The ^{1}H NMR spectra of **3a** and **3b** showed two singlets in a ratio of 1:1 for the *tert*-butyl protons as well as the aromatic protons on the skeleton of **3a** and **3b**, which obviously indicated that they were 1,3-bridged products. Their ESI-MS spectra showed that **3a** was an (1+1) intramolecular ring-closure product and **3b** was an (2+2) intermolecularly bridged *p-tert*-butylthiacalix[4]arene. Furthermore, in the ^{1}H NMR spectrum of **3a**, a pair of doublets was assigned for the methylene-bridged protons, which indicated that **3a** was locked in a conic conformation. The signals of *tert*-butyl protons of **3b** at δ 0.82 and 1.33 ppm were so similar to those of the conic double thiacalix[4]arenes reported by Bitter and co-workers[9b,c] and Beer and co-workers,[15] it was suggested that the conformation of **3b** should be conic.

The ESI-MS data showed that **4a** and **4b** were (2+2) coupled resultants. In their ^{1}H NMR spectra, their highly symmetric structures were reflected by the presence of two *tert*-butyl signals of equal intensity and two resonances for phenyl protons in a 1:1 ratio, which indicated that they were 1,3-bridged products. The signals the of methylene protons of **4a** split as a pair of doublets, which suggested that it adopted a conic conformation. Because the spectrum of **4b** was so similar to its analogues of conic double thiacalix[4]arenes reported by Bitter and co-workers[9b,c] and Beer and co-workers,[15] it was suggested that **4b** existed in a conic conformation too.

The model of the bridging reaction affected the yield of the product. The yields of (2+2) coupling were lower than that of the (1+1) coupled resultants. When two kinds of products were obtained at the same time, (1+1) bridging resultant was usually preferable. The similar observation was also reported by Vicens and co-workers in their investigation for the reaction of *p-tert*-butylcalix[4]arene with triethylene glycol ditosylate, they found that the intramolecular and intermolecular bridged products were in the yields of 52% and 15%, respectively.[19] In addition, the types of reaction products depend on the kinds of bis(tosyloxyethoxy)benzenes, but not calixarenes when 1,2-bis(tosyloxyethoxy)benzene and 1,4-bis(tosyloxyethoxy)benzene were used. In such cases, intramolecular coupled products and intermolecular coupled products were obtained, respectively. When 1,3-bis(tosyloxyethoxy)benzene was used as the bridging reagent, the bridging pattern was determined by the type of calixarene being used, and double thiacalix[4]arene derivative and calix[4]crown were obtained, respectively.

The shape of bis(tosyloxyethoxy)benzene affected the model of the bridging reaction. 1,4-Isomer is a linear molecule, and the angle between the two oxyethylene arms is 180 degree, and it is beneficial to form an intermolecular bridged product. On the other hand, the 1,2-

isomer is a bent molecule, and the angle of two oxyethylene is 60 degree; obviously, this would favor an intramolecular coupling. Similarly, Csokai et al. also reported that the reaction of thiacalix[4]arene with 1,2-dihydroxyethoxyethoxybenzene afforded thiacalix[4]-crown in a yield of 50% under the Mitsunobu protocol.[9a] 1,3-Isomer situates at the boundary, both coupling patterns might occur, intra versus intermolecular reaction pathway is determined by the size complementarity between reagent and substrate. The reaction pattern of bis(tosyloxyethoxy)benzenes is different from that of the dihalomethylbenzenes to some extent, because the former possess a rigid core and two flexible oxyethylene arms, while the latter possess a rigid core with two rigid methylene groups.

In conclusion, bis(tosyloxyethoxy)benzenes are a new type of bridging reagents for calixarenes. They possess a rigid phenylene core with two flexible oxyethylene arms. 1,2-Bis(tosyloxyethoxy)benzene tends to form intramolecularly bridged products with calix[4]arene and thiacalix[4]arene, while 1,4-isomer is preferable to form the intermolecularly bridged ones. For 1,3-isomer, the bridging pattern is dependent on the nature of calixarene being used.

Acknowledgments

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18. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$ at 300 MHz and 75 MHz, respectively, on a Varian Mercury-VX300 spectrometer. The chemical shifts were recorded in parts per million (ppm) with TMS as the internal reference. ESI mass spectra were determined using Finnigan LCQ Advantage mass spectrometer. Elemental analyses were performed with Yanaco MT-5. *General procedure for the synthesis of* **2a**, **3a**, **4a**, **2b**, **3b**, **4b**: To the stirred mixture of *p-tert*-butylcalix[4]arene (2 mmol) or *p-tert*-butylthiacalix[4]arene (2 mmol) in 250 mL toluene, 1,2-bis(tosyloxyethoxy)benzene or its isomer (2 mmol) and Na_2CO_3 (10 mmol) were added and allowed to react under refluxing temperature for 3 days, and then the solvent was evaporated under reduced pressure, 50 mL of HCl (1 mol/L) and 50 mL of $CHCl_3$ were added. The organic phase was washed with purified water (2×100 mL), dried over anhydrous $MgSO_4$, and concentrated. The resulting residue was passed through a silica column using CH_2Cl_2/acetate mixed solvent as eluent. Evaporation of the solvent obtained crude product. The recrystallization from methanol gave a white powder **2a**, **3a**, **4a**, **2b**, **3b**, **4b**.
Compound **2a**. Yield: 25%; mp >260 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (s, 18H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$), 3.35 (d, 4H, $J = 12.3$ Hz, ArCH_2Ar), 4.43 (d, 4H, $J = 12.3$ Hz, ArCH_2Ar), 4.52 (t, 4H, $J = 5.4$ Hz, ArOCH_2CH_2), 4.64 (t, 4H, $J = 5.4$ Hz, ArOCH_2CH_2), 6.97 (s, 4H, ArH), 7.00–7.03 (m, 4H, ArH), 7.10 (s, 4H, ArH), 8.76 (s, 2H, ArOH); MS m/z: 833.6 [M+Na]$^+$; Anal. Calcd for $C_{54}H_{66}O_6$: C, 79.96; H, 8.20; found: C, 79.90; H, 8.17.
Compound **2b**. Yield: 34%; mp >260 °C; ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (s, 18H, C(CH_3)$_3$), 1.30 (s, 18H, $C(CH_3)_3$), 4.80 (t, 4H, $J = 5.1$ Hz, ArOCH_2CH$_2$), 5.01 (t, 4H, $J = 5.1$ Hz, ArOCH$_2$CH_2), 6.95–6.97 (m, 2H, ArH), 7.08–7.10 (m, 2H, ArH), 7.13 (s, 4H, ArH), 7.60 (s, 4H, ArH), 8.37 (s, 2H, ArOH); ^{13}C NMR ($CDCl_3$): $\delta = 31.0$ (C(CH_3)$_3$), 31.7 (C(CH_3)$_3$), 34.3 (C(CH$_3$)$_3$), 34.4 (C(CH$_3$)$_3$), 70.5, 74.6 (OCH_2), 117.7, 122.3, 122.9,129.0, 134.3, 134.9, 142.8, 148.2, 150.4, 156.6, 157.9 (Ar); MS m/z: 905.2[M+Na]$^+$; Anal. Calcd for $C_{50}H_{58}O_6S_4$: C, 67.99; H, 6.62; found: C, 67.95; H, 6.53.
Compound **3a**. Yield: 35%; mp >260 °C; ^{1}H NMR ($CDCl_3$): $\delta = 0.94$ (s, 18H, C(CH_3)$_3$), 1.29 (s, 18H, C(CH_3)$_3$), 3.32 (d, 4H, $J = 13.2$ Hz, ArCH_2Ar), 4.25 (d, 4H, $J = 13.2$ Hz, ArCH_2Ar), 4.27 (t, 4H, $J = 4.7$ Hz, ArOCH_2CH_2), 4.62 (t, 4H, $J = 4.7$ Hz, ArOCH_2CH_2), 6.67 (d, 2H, $J = 8.0$ Hz, ArH), 6.80 (s, 4H, ArH), 7.05 (s, 4H, ArH), 7.15 (t, 1H, $J = 8.0$ Hz, ArH), 7.29 (s, 1H, ArH); 7.76 (s, 2H, ArOH); MS m/z: 833.3 [M+Na]$^+$; Anal. Calcd for $C_{54}H_{66}O_6$: C, 79.96; H, 8.20; found: C, 79.88; H, 8.22.
Compound **3b**. Yield: 13%; mp >250 °C; ^{1}H NMR ($CDCl_3$): $\delta = 0.77$ (s, 36H, C(CH_3)$_3$), 1.34 (s, 36H, C(CH_3)$_3$), 4.04 (t, 8H, $J = 4.5$ Hz, ArOCH_2CH_2), 4.86 (t, 8H, $J = 4.5$ Hz, ArOCH_2CH_2), 6.52 (d, 4H, $J = 8.4$ Hz, ArH), 6.66 (s, 2H, ArH), 6.93 (s, 8H, ArH), 7.23 (t, 2H,

$J = 8.4$ Hz, Ar*H*), 7.69 (s, 8H, Ar*H*), 8.26 (s, 4H, ArO*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.7$ (C(*C*H_3)$_3$), 30.5 (C(*C*H_3)$_3$), 33.0 (*C*(CH_3)$_3$), 33.2 (*C*(CH_3)$_3$), 66.5, 71.4 (O*C*H_2), 100.5, 106.3, 121.2, 128.4, 128.5, 131.6, 133.7, 141.5, 147.0, 154.6, 155.0, 158.9 (Ar); MS *m*/*z*: 1782.3 [M+H_2O]$^+$; Anal. Calcd for $C_{100}H_{116}O_{12}S_8$: C, 67.99; H, 6.62; found: C, 67.92; H, 6.58.

Compound **4a**. Yield: 10%; mp >250 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (s, 36H, C(C*H*$_3$)$_3$), 1.26 (s, 36H, C(C*H*$_3$)$_3$), 3.30 (d, 8H, $J = 13.2$ Hz, ArC*H*$_2$Ar), 4.22 (t, 8H, $J = 4.5$ Hz, ArOC*H*$_2$CH$_2$), 4.25 (t, 8H, $J = 4.5$ Hz, ArOCH$_2$C*H*$_2$), 4.38 (d, 8H, $J = 13.2$ Hz, ArC*H*$_2$Ar), 6.68 (d, 4H, $J = 8.7$ Hz, Ar*H*); 6.84 (d, 4H, $J = 8.7$ Hz, Ar*H*), 6.87 (s, 8H, Ar*H*), 7.03 (s, 8H, Ar*H*), 7.61 (s, 4H, ArO*H*); MS *m*/*z*: 1622.3 [M]$^+$; Anal. Calcd for $C_{108}H_{132}O_{12}$: C, 79.96; H, 8.20; found: C, 79.90; H, 8.17.

Compound **4b**. Yield: 15%; mp >250 °C; ^{1}H NMR ($CDCl_3$): δ: 0.77 (s, 36H, C(C*H*$_3$)$_3$), 1.36 (s, 36H, C(C*H*$_3$)$_3$), 3.98 (t, 8H, $J = 4.7$ Hz, ArOC*H*$_2$CH$_2$), 4.88 (t, 8H, $J = 4.7$ Hz, ArOCH$_2$C*H*$_2$), 6.94 (s, 8H, Ar*H*), 7.71 (s, 8H, Ar*H*), 8.35 (s, 4H, ArO*H*); ^{13}C NMR ($CDCl_3$): $\delta = 29.7$ (C(*C*H_3)$_3$), 30.5 (C(*C*H_3)$_3$), 33.0 (*C*(CH_3)$_3$), 33.1 (*C*(CH_3)$_3$), 66.2, 71.8 (O*C*H_2), 113.8, 121.3, 128.4, 131.5, 133.8, 141.6, 147.0, 152.0, 154.6, 155.0 (Ar); MS *m*/*z*: 1788.1 [M+Na]$^+$; Anal. Calcd for $C_{100}H_{116}O_{12}S_8$: C, 67.99; H, 6.62; found: C, 67.94; H, 6.56.

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