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Synthesis of Macrocyclic Lactones Building on Double Calix[4]arenes

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Abstract: The macrocyclic lactones building on calix[4]arenes **3a-b** and double calix[4]arenes **4a-b** were synthesized by the reaction of *p-tert*-butylcalix[4]arene (**1a**) or calix[4]arene (**1b**) with glycol bis(2-chloroacetate) (**2**). The conditions to improve the yields of double calix[4]arenes have been discussed.

Keywords: Macrocyclic lactones, double calix[4]arenes, synthesis.

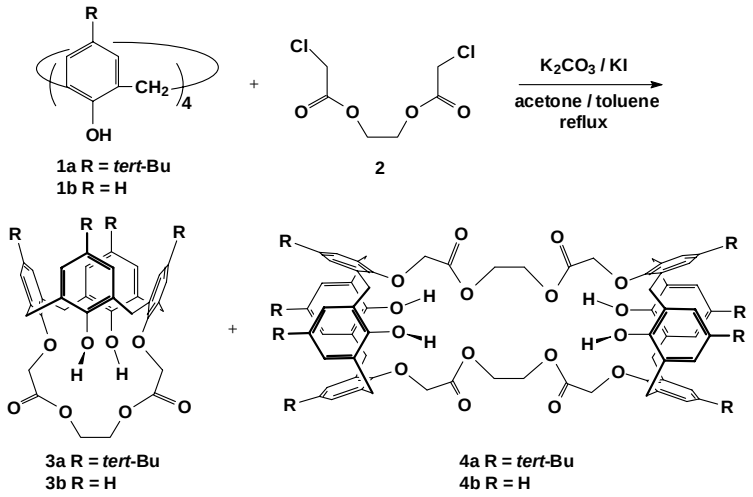
Natural macrocyclic lactones and lactams as the ionophores have absorbed extensive interests because of their very high selective recognition for alkali metals. For example, nactins[1] and valinomycin[2] have the highest selectivity for potassium among all the ionopohores. Artificial macrocyclic lactones also showed selectivity for cations, although the binding strength was lower than that of common crown ethers[3]. Calixarenes were a very important kind of artificial receptors, whose derivatives have showed the highest selectivity for Na^+, K^+ and Cs^+ among the synthesized macrocycles[4]. Here, we wish to report the method to synthesize the macrocyclic lactones building on double calix[4]arenes.

Recently, the method of synthesis of calix[4]crowns containing ester groups was reported and found that their nitrated products have the abilities of recognition for alkyl amines[5]. However, in the original procedure, the main products were those linked intramolecularly for the template of potassium and the products linked intermolecularly could be determined from TLC but not to be separated for very low yield. In order to improve the yield of intermolecular products, we have modified the procedure as follows:

a) Glycol bis(2-chloroacetate) and KI were mixed in acetone at first and stirred for 30 min to form glycol bis(2-iodioacetate). Then equivalent *p-tert*-calix[4]arenes **1a** or calix[4]arenes **1b**, K_2CO_3 were suspended in toluene and added into the solution.
b) The concentration of reaction mixtures was increased from about 1.5×10^{-2} mol/L to 4×10^{-2} mol/L (for the calixarene).

After refluxing for 8~10 h and work up, the intramolecular product **3a-b**[5] and intermolecular product **4a-b**[6] were obtained. (**Scheme 1**) Although the main product was **3a** (67 %) or **3b** (75 %), the yield of **4a** (18 %) or **4b** (15 %) was obviously higher than before and can be separated and their structures can be determined.

Scheme 1



The spectra and elemental analysis of **4a** and **4b** were very similar with **3a** and **3b**, except of mass spectra. We have determined that the conformations of these products were all in cone because the signals of protons of methylene between two phenol rings showed AB system.

References and notes

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6. **4a**: m.p. 178-180 °C. MS (maldi-TOF): 1604 (M^++Na). ^{1}H-NMR ($CDCl_3$) δ 1.00 (s, 36H, $C(CH_3)_3$),1.26 (s, 36H, $C(CH_3)_3$), 3.28 and 4.35 (ABq, J = 12.2 Hz, 16H, $ArCH_2Ar$), 4.65 (s, 8H, CO_2CH_2), 4.70 (s, 8H, $ArOCH_2$), 6.79 (s, 4H, OH), 6.84 (s, 8H, ArH), 6.99 (s, 8H, ArH). ^{13}C-NMR ($CDCl_3$) δ 31.02, 31.49 ($C(CH_3)_3$), 31.61 ($ArCH_2Ar$), 33.77, 33.92 ($C(CH_3)_3$), 62.76 (CO_2CH_2), 71.95 ($ArOCH_2$), 125.06, 125.69, 127.90, 132.72, 141.41, 147.23, 149.88, 150.22 (ArC), 168.95 (CO_2). IR (KBr) ν 3475, 1754 (CO), 1484 cm^{-1}; Anal. Calcd. for $C_{100}H_{124}O_{16}$: C, 75.92; H, 7.90. Found: C, 75.77; H, 7.81. **4b**: m.p. 159-161 °C. MS (maldi-TOF): 1155 (M^++Na). ^{1}H-NMR ($CDCl_3$) δ 3.33 and 4.36 (ABq, J = 12.8 Hz, 16H, $ArCH_2Ar$), 4.60 (br, 8H, CO_2CH_2), 4.69 (s, 8H, $ArOCH_2$), 6.64 (t, J = 7.6 Hz, 4H, ArH), 6.76 (t, J = 8.0 Hz, 4H, ArH), 6.91 (d, J = 7.6 Hz, 8H, ArH), 7.02 (d, J = 8.0 Hz, 8H, ArH), 7.74 (s, 4H, OH). ^{13}C-NMR ($CDCl_3$) δ 31.33 ($ArCH_2Ar$), 62.83 (CO_2CH_2), 72.04 ($ArOCH_2$), 119.25, 125.73, 128.12, 128.51, 129.11, 133.31, 151.70, 152.82 (ArC), 168.59 (CO_2). IR (KBr) ν 3424, 1750 (CO), 1466 cm^{-1}. Anal. Calcd. for $C_{68}H_{60}O_{16}$: C, 72.07; H, 5.34. Found: C, 71.50; H, 5.25.

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