

## One-step Synthesis of *p*-tert-Butylcalix[6]-1,4-2,5- biscrown-4 and Its Tosyloxyethoxyethylate Derivative

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(Received: 24 November 2004; in final form: 25 March 2005)

**Key words:** bridging, calixcrown, HPLC, *p*-tert-butylcalix[6]arene, synthesis

### Abstract

*p*-tert-Butylcalix[6]-1,4-2,5-biscrown-4 (**2a**) is a typical member of the family of calix[6]biscrowns. In the literature, **2a** has been prepared in a two-step procedure, the total yield being less than 26.4% and the work-up was troublesome. Herein we wish to report an improved method to synthesize such a compound in one step with a yield of up to 63%. Furthermore, this method could provide a monosubstituted *p*-tert-butylcalix[6]-1,4-crown-4 (**2b**) as a by-product. Varying the reaction conditions, we could obtain **2b** as a main product with a 48% yield.

### Introduction

Following crown ethers and cyclodextrins, calixarenes and their derivatives have started playing a large role in host–guest and supramolecular chemistry [1, 2]. By incorporating crown ether segments into calixarene skeletons, calixcrowns were constructed. Calixcrowns possess well preorganized structures and more rigid binding sites in comparison with calixarenes and crown ethers and have demonstrated outstanding complexation ability towards alkali and other metal ions [3–5]. For example, the Na<sup>+</sup>/K<sup>+</sup> selectivity is 10<sup>3.1</sup> for crown ethers and 10<sup>5.1</sup> for diethoxycalix[4]-crown-4 in a partial cone conformation [6]. At present, calix[4]crowns chemistry approaches maturity [7–9] and calix[6]crowns become the next candidate for close scrutiny. First calix[6]crowns, *p*-tert-butylcalix[6]-1,4-crown-5 and calix[6]-1,4-crown-5, by selectively bridging the parent macrocycles with tetraethylene glycol ditosylate in the presence of *t*-BuOK in benzene [10], and *p*-tert-butylcalix[6]-1,4-crown-4 was obtained with its accompanying 1,3-isomer by reacting *p*-tert-butylcalix[6]arene with triethylene glycol ditosylate, using potassium carbonate as the base in acetonitrile with a 20% yield [11]. In 2000, two types of calix[6]biscrowns, which are 1,4-2,5 and 1,3-4,6 double bridged calix[6]biscrowns, were reported for the first time [12–14]. Since then, a number of other types of calix[6]biscrowns have been synthesized [15, 16]. However, to the best of our knowledge, little is known about the functionalization of them. As part of our ongoing investigation of functionalized *p*-tert-butylcalix[6]biscrowns, it is important to develop a convenient and simple method for the synthesis of calix[6]biscrowns.

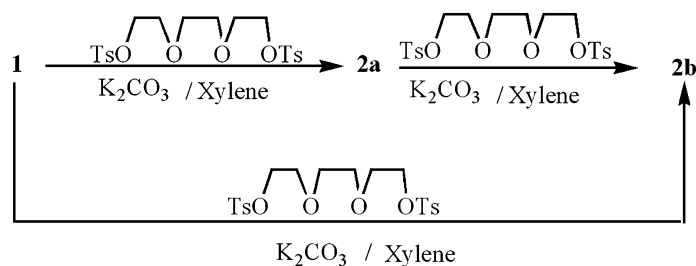
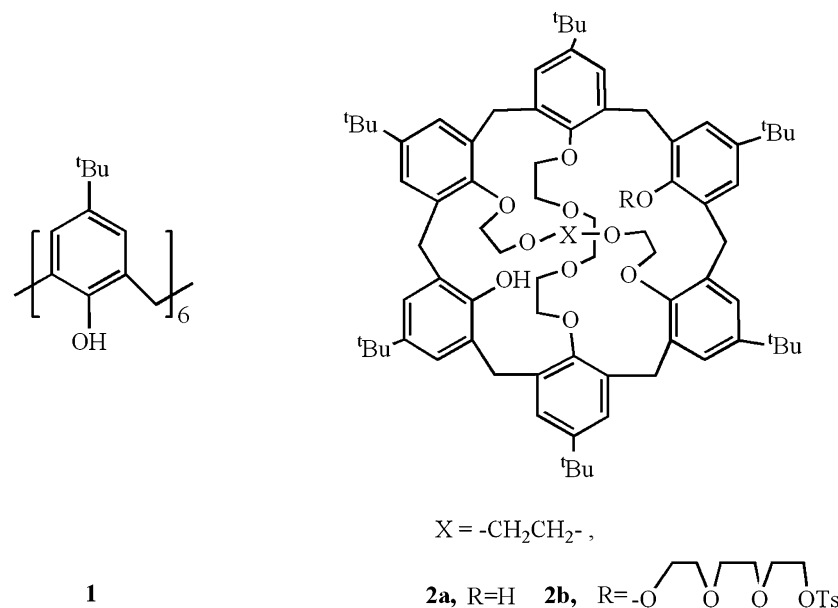
After much effort, a one-step method for preparing *p*-tert-butylcalix[6]-1,4-2,5-biscrown-4 was established. In comparison with the previous two-step method, the yield of *p*-tert-butylcalix[6]-1,4-2,5-biscrown-4 was increased from 26.4 (total yield of two steps) to 63%, while the reaction time was shortened considerably. Furthermore, we have had success by extending this method of synthesis to other calixbiscrowns and it will be reported later. Additionally, the improved method could provide a monosubstituted *p*-tert-butylcalix[6]-1,4-2,5-crown-4 (**2b**) all together. The latter could be obtained as a main product under appropriate conditions with 48% yield with 36% of **2a** as a by-product. At the same time, **2b** was also obtained by treating **2a** with triethylene glycol ditosylate in xylene, in the presence of anhydrous K<sub>2</sub>CO<sub>3</sub>. It is a very useful reagent for the preparation of more monosubstituted calix[6]biscrowns and calixarenebiscrown-containing polymer. The synthetic route is depicted in Scheme 1 below:

### Experimental

Melting points were recorded on a Gallenkamp melting point apparatus in open capillaries without correction. <sup>1</sup>H-NMR was recorded on a Varian Mercury VX300 instrument at ambient temperature with TMS as an internal standard. ESI-MS was recorded on Finnigan LCQ-Advantage instrument. All chemicals were in A.R. degree and purified by standard procedures.

The HPLC system consisted in a LC-10AD model pump (Shimadzu, Japan), SPD-10AV UV–Vis detector, shimpack SBC-ODS analytical column (5 μm,

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Scheme 1.

26 × 150 mm), C-R7A recorder and 5 μl injection loop. The HPLC separation that was developed employed a C18 stationary phase and a mobile phase comprising ethanol and water in a ratio of 8:2 (v/v). UV detection was set at 281 nm.

**General procedure:** A mixture of *p*-tert-butylcalix[6]arene, triethylene glycol ditosylate, anhydrous K<sub>2</sub>CO<sub>3</sub> and xylene was stirred at reflux temperature for 12 h. After removal of solvent under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with CHCl<sub>3</sub>. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated. All crude products were analyzed by HPLC and the results are shown in Table 1.

#### Synthesis of *p*-tert-butylcalix[6]-1,4-2,5-biscrown-4 (2a)

A mixture of 4.89 g (5.0 mmol) *p*-tert-butylcalix[6]arene, 5.02 g (10.0 mmol) triethylene glycol ditosylate, 2.11 g (15.2 mmol) anhydrous K<sub>2</sub>CO<sub>3</sub> and 500 ml xylene was stirred at reflux temperature for 12 h. After removal of

solvent under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with CHCl<sub>3</sub>. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and concentrated. After recrystallization from mixture of chloroform and ethanol (2:8, v/v), 3.13 g of **2a** was obtained as colorless crystals with 52% yield.

**2a**, m.p. > 270 °C; δH (CDCl<sub>3</sub>): 1.16 (36H, s, ArC(CH<sub>3</sub>)<sub>3</sub>), 1.33 (18H, s, ArC(CH<sub>3</sub>)<sub>3</sub>), 2.86 (4H, t, OCH<sub>2</sub>CH<sub>2</sub>), 3.25 (4H, q, OCH<sub>2</sub>CH<sub>2</sub>), 3.34–3.50 (16H, m, OCH<sub>2</sub>CH<sub>2</sub> and ArCH<sub>2</sub>Ar), 3.8 (4H, q, OCH<sub>2</sub>CH<sub>2</sub>), 4.07 (4H, s, ArCH<sub>2</sub>Ar), 4.39 (4H, d, ArCH<sub>2</sub>Ar), 6.91 (4H, s, ArH), 7.03 (2H, s, ArOH), 7.04 (4H, s, ArH), 7.11 (4H, s, ArH). FAB-MS: *m/z* 1200 (M<sup>+</sup>, 100%). Anal. Calcd. for C<sub>78</sub>H<sub>104</sub>O<sub>10</sub>(1200.76); C, 77.56; H, 8.72; Found: C, 78.10; H, 8.60.

#### Synthesis of tosyloxyethoxyethylated *p*-tert-butylcalix[6]-1,4-2,5-biscrown-4 (2b)

**Procedure 1:** A mixture of 4.89 g (5.0 mmol) *p*-tert-butylcalix[6]arene, 5.04 g (11.0 mmol) triethylene glycol

Table 1. Synthesis of *p*-tert-butylcalix[6]biscrown under various conditions\*

Amount of K <sub>2</sub> CO <sub>3</sub> , mmol	6	6	6	6	5	11	15	20	30	50	60	15 <sup>a</sup>	15 <sup>b</sup>
Amount of bridging reagent, mmol	5	10	14	50	10	10	10	10	10	10	10	10	10
Yield percentage of 2a	6.1	8.8	4.8	2.4	15.7	30.8	62.8	16.7	5.8	2.9	1.3	33.0	18.2

\*The amount of *p*-tert-butylcalix[6]arene was 5 mmol. The reactions were performed in 500 ml xylenes for 12 h under reflux.

<sup>a,b</sup>4.89 g (5 mmol) *p*-tert-butylcalix[6]arene, 5.02 g (10 mmol) triethylene glycol ditosylate, 2.11 g (15.2 mmol) anhydrous K<sub>2</sub>CO<sub>3</sub> and the amount of xylene used was 250 and 1000 ml respectively.

ditosylate, 2.09 g (15.2 mmol) anhydrous  $K_2CO_3$  and 250 ml xylene was stirred at reflux temperature for 18 h. After removal of solvent under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with  $CHCl_3$ . The organic layer was separated, dried over  $MgSO_4$  and filtered. The residue was purified by column chromatography on silica gel (100–200 mesh) with chloroform/cyclohexane (2:8, v/v) as mixed solvent. The white crystal **2b** was obtained at a yield of 31% (2.30 g).

**Procedure 2:** A mixture of 120 mg (0.10 mmol) *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4, 510 mg (0.11 mmol) triethylene glycol ditosylate, 300 mg (0.22 mmol) anhydrous  $K_2CO_3$  and 50 ml xylene was stirred at reflux temperature for 12 h. After removal of solvent under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with  $CHCl_3$ . The organic layer was separated, dried over  $MgSO_4$  and filtered. The residue was purified by column chromatography on silica gel (100–200 mesh) with chloroform/cyclohexane (1:9, v/v) as mixed solvent. The white crystal **2b** was obtained had a yield of 45% (68 mg).

**2b**, m.p. 173–175 °C;  $\delta H$  ( $CDCl_3$ ): 1.15 (9H, s,  $ArC(CH_3)_3$ ), 1.18 (9H, s,  $ArC(CH_3)_3$ ), 1.23 (9H, s,  $ArC(CH_3)_3$ ), 1.26 (9H, s,  $ArC(CH_3)_3$ ), 1.32 (9H, s,  $ArC(CH_3)_3$ ), 1.38 (9H, s,  $ArC(CH_3)_3$ ), 2.41 (3H, s,  $ArCH_3$ ), 2.51 (1H,  $OCH_2CH_2$ ), 2.64 (1H, d,  $OCH_2CH_2$ ), 2.86–4.20 (43H, m,  $OCH_2CH_2$ - and  $ArCH_2Ar$ ), 4.25 (1H, d,  $ArCH_2Ar$ ), 4.42 (1H, d,  $ArCH_2Ar$ ), 4.68 (1H, d,  $ArCH_2Ar$ ), 6.81 (1H, s,  $ArH$ ), 6.91 (1H, s,  $ArH$ ), 7.01 (1H, s,  $ArH$ ), 7.05 (1H, s,  $ArOH$ ), 7.07 (1H, s,  $ArH$ ), 7.09 (2H, s,  $ArH$ ), 7.13 (1H, s,  $ArH$ ), 7.20 (1H, s,  $ArH$ ), 7.24 (2H, d,  $ArH$ ), 7.30 (2H, d,  $ArH$ ), 7.41 (2H, s,  $ArH$ ), 7.77 (2H, d,  $ArH$ ), ESI-MS:  $m/z$  1503.3 ( $MH^+$ , 100%). Anal. Calcd. for  $C_{91}H_{122}O_{16}S$  (1502.85): C, 72.67, H, 8.18, Found: C, 72.51; H, 8.50.

## Results and discussion

In the literature, *p*-*tert*-butylcalix[6]-1,4-crown-4 (**1**) was prepared by the reaction of *p*-*tert*-butylcalix[6]arene with triethylene glycol ditosylate in acetonitrile, in the presence of  $K_2CO_3$  at 20% yield. The yield could be increased to 40% by using toluene instead of acetonitrile, as a solvent. The reaction of **1** with triethylene glycol ditosylate in DMF using NaH as a base gave **2a** at 66% yield. No **2a** could be detected in the preparation of calix[6]monocrown. This implied that the reaction conditions ( $K_2CO_3$ /acetonitrile or toluene) were too weak to produce **2a** directly. Maybe, the compound could be obtained under more severe conditions. As the selectivity usually decreases with increasing reagent activity and solvent polarity, raising reaction temperature seems to be a realistic choice. A solvent with higher boiling point and lower polarity is valuable for testing. After many attempts, we found that the reaction proceeded smoothly and speedily in xylene. The conversion of *p*-*tert*-butylcalix[6]arene was complete within 4 h, and more importantly, **2a** was found in the reaction products.

Following this line, a one-step method for the direct synthesis of **2a** was established. A method for the direct synthesis of its monosubstituted product was also found.

All the experiments were monitored by HPLC. The results are shown in Table 1.

The results showed that the yield was correlated with the amount of solvent, base and triethylene glycol ditosylate used. The amount of  $K_2CO_3$  seemed to play a central role. The maximum yield of **2a** was obtained when the molar ratio of  $K_2CO_3$  to *p*-*tert*-butylcalix[6]arene was 3:1 and triethylene glycol ditosylate to *p*-*tert*-butylcalix[6]arene was 2:1. Excess triethylene glycol ditosylate made the selectivity become poor and the yield decreased. Furthermore, the amount of solvent also affected the yield. As the amount of xylene decreased to 250 ml or increased to 1000 ml from 500 ml, the reaction became more complicated and the yield of **2a** decreased to 33.0 and 18.2%, respectively. The most favorable amount of solvent was 500 ml.

By HPLC we found that *p*-*tert*-butylcalix[6]arene was completely consumed within 4 h, while *p*-*tert*-butylcalix[6]-1,4-crown-4 and **2b** both appeared. The yield of **2a** reached maximum (63%) after 12 h. Further prolonging reaction time resulted in decreasing the yield, because the product was subjected to further functionalization, affording monosubstituted derivative **2b**. Increasing the reaction time and decreasing the amount of solvent, the yield of **2b** could increase to 48%.

The structure of **2b** was deduced from ESI-MS and  $^1H$ -NMR. In the  $^1H$ -NMR of **2b**, the signals of *p*-*tert*-butyl groups split into six groups in a ratio of 1:1:1:1:1:1 as expected. It implied that **2b** had no symmetry element and should be an inherent chiral compound. The structure of **2b** was further proved by the fact that **2b** was obtained from **2a** directly (Scheme 1).

## Conclusion

Using xylene as solvent, *p*-*tert*-butylcalix[6]-1,4-2,5-biscrown-4 and its tosyloxyethoxyethylate derivative **2b** were obtained in one step. The yield of **2a** was increased greatly and the reaction time was shortened considerably. Also, **2b** was obtained in the approved yield in the optimal conditions.

## Acknowledgement

Financial support from the National Natural Science Foundation of China (20272044) is gratefully acknowledged.

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