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An Efficient Method for Synthesis of the Bis(spirodienone) Derivative of *p-tert*-Butylcalix[4]arene and Effect of *para* Substituents on the Analogous Reaction†

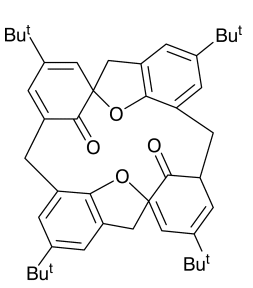
Wen-Guang Wang, Wen-Chun Zhang and Zhi-Tang Huang*

Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

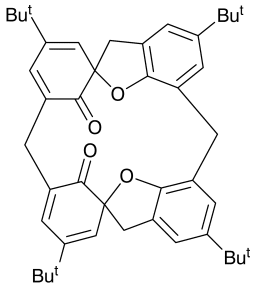
An improved method for synthesis of bis(spirodienone) derivative of *p-tert*-butylcalix[4]arene has been developed by mildly oxidizing the latter with I_2 and PEG 200 as a phase-transfer catalyst; the resulting compound containing two cyclohexadienone rings at distal positions (1, 3) is formed in quantitative yield.

A few years ago Biali and co-workers[1–6] published a series of distinguished works introducing an interesting strategy for converting the calixarenes by mild oxidation into their derivatives known as spirodienones containing carbonyl and five-membered cyclic ether having functionalities like those of a variety of natural ionophores. These compounds reveal a fascinating picture of calixarenes not only because of their special structures but also of their high potential for developing a completely new class of receptor molecules with remarkable host properties.

As the first approach along this line, Litwak and Biali[1] reported the treatment of *p-tert*-butylcalix[4]arene **1a** with 2 equivalents of tetrabutylammonium tribromide in a two-phase basic system [aqueous NaOH (28% w/w)–$CHCl_3$]. This resulted in the formation of a mixture of bis(spirodienone) derivatives from which the two main ones, **2a** (**A**) and **2a** (**B**), were separated by column chromatography in yields of 30 and 17%, respectively. Although this procedure was employed in other related works by Biali and co-workers,[2–6] further application of these compounds remained suspended because of their low yields. A more efficient synthetic method will be discussed in this paper.



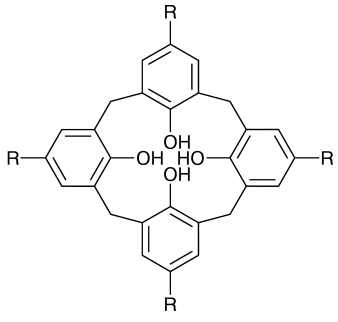
2a (A)



2a (B)

We have found that a selective synthesis of compound **2a** (**A**) can be achieved in quantitative yield by mild oxidation of **1a** with I_2 and PEG 200 instead of tetrabutylammonium tribromide as the oxidant and the phase transfer catalyst in a two-phase basic system [aqueous KOH (25%)–$CHCl_3$ instead of aqueous NaOH (28%)–CH_2Cl_2]. The large excess of strong base is decisive to make this reaction proceed. No reaction was observed when a weak base (K_2CO_3) or a small amount of KOH was employed. Compared with the literature method, this procedure has three advantages: (i) only one bis(spirodienone) isomer **2a** (**A**) is formed without any of the isomeric product **2a** (**B**) under these conditions; (ii) the purification method (by recrystallization) is much easier than that of the literature method (by chromatography) and (iii) the reaction takes place smoothly at room temperature instead of the reported harsh conditions.

These findings and the advantages described above have prompted us to check the generality of this method for synthesizing more spirodienone derivatives in high yields starting from different *p*-alkylcalix[4]arenes, and that will enable us to investigate the effect of the *para* substituents of calix[4]arenes on this reaction. Accordingly, this new method was tried on five different *p*-alkyl calix[4]arenes bearing *tert*-alkyl (**1b**, **1c**), *sec*-alkyl (**1f**) and primary alkyl groups (**1d**, **1e**) at the upper rim, respectively, which were not used in virtually all the previous work.



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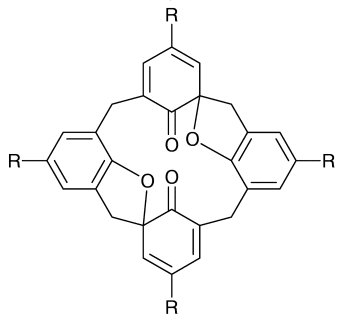
$KOH/H_2O–CHCl_3$ | I_2, PEG 200



2 (A)

a R = Me_3
b R = $MeCH_2Me_2C$
c R = $Me[CH_2]_9CMe_2$
d R = $C_6H_5[CH_2]_2$
e R = *n*-C_7H_{15}
f R = Me_2CH

The *para* substituents of calix[4]arenes play an important role in determining the outcome of this reaction. It is clear from Table 1 that the expected bis(spirodienone) derivatives **2b**–**2e** (**A**) could also be obtained as the sole isomeric product, apart from a large amount of starting materials, by mildly oxidizing the corresponding *p*-alkylcalix[4]arenes **1b**–**1e**. The two *tert*-alkyl substituted calix[4]arenes **1b** and **1c** also reacted smoothly, giving relatively higher yields of 70 and 50%, respectively. However the yields of **2d** and **2e**

*To receive any correspondence.

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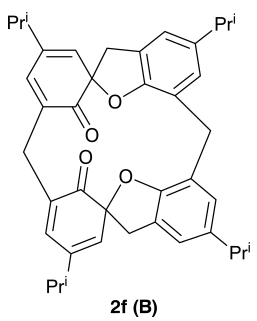
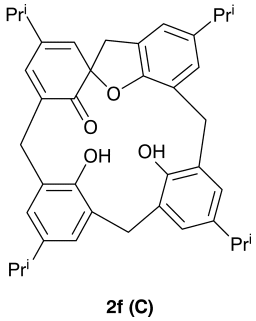
Table 1 Yields, reaction times and chemical properties of the products

Compound	Reaction time (h)	Isolated yield (%)	mp/°C	IR [ν(C=O)]
2a (A)	2	95	271–272	1670 s, 1650 w
2b (A)	6.5	70	245–247	1682 s, 1638 w
2c (A)	5	50	94–95	1684 s, 1640 w
2d (A)	6	10	178–180	1682 s, 1655 w
2e (A)	7	35	151–153	1688 s, 1634 w
2f (A)	24	15	240–243	1682 s, 1637 w
2f (B)	24	5	230–232	1681 s, 1638 w
2f (C)	24	10	>300	1682 s, 1635 w

were low. As for the isopropylcalix[4]arene (**1f**), apart from the 1,3-distal bis(spirodienone) product **2f** (**A**), the other two compounds, bis(spirodienone) **2f** (**B**) with two cyclohexadienone rings at proximal positions (1, 2) and mono(spirodienone) **2f** (**C**), were also isolated in poor yields. The structures of **2f** (**A**) and **2f** (**B**) could be distinguished by the ^{1}H NMR spectra of the methylene region which exhibited four doublets in a 1:1:1:1 ratio for (**A**) and in six doublets in a 1:1:2:1:2:1 ratio for (**b**), respectively.[3] The structure of **2f** (**C**) was easily distinguished by the different pattern of the ^{1}H NMR spectrum, especially the phenolic proton signals, and the mass spectrum.[6]



2f (B)



2f (C)

In summary, a new, simple and efficient method for the synthesis of the bis(spirodienone) derivative of *p-tert*-butylcalix[4]arene **2a** (**A**) in quantitative yield was developed. In addition, a series of analogs **2b**–**2f** deriving from different *p*-alkylcalix[4]arenes were synthesized by using this method. The product outcome was strongly dependent on the *para*-alkyl group of calix[4]arene.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with Varian Unity 200 and Varian Germinal 300 spectrometers, IR spectra with a Perkin-Elmer 782 spectrometer and mass spectra on a Finnigan MAT 90 instrument. We could not get satisfactory microanalytical data for the products, as also experienced by Biali and co-workers.[3]

General Procedure.—To a suspension of compound **1** (1.42 mmol) in $CHCl_3$ (18 ml) and a 25% aqueous KOH solution (19 ml) were added I_2 (1.42 g) and PEG 200 (5 g). The reaction mixture was stirred at room temperature for 2–24 h. Chloroform (50 ml) and water (50 ml) were added, and the organic layer was successively washed with brine and water and then dried ($MgSO_4$). After the organic solvent was evaporated, the residue was recrystallized from $CHCl_3$–CH_3OH to afford **2a** (**A**) or chromatographed to afford **2b**–**2f** (silica, eluent $CHCl_3$-light petroleum).

Compound **2a** (**A**).—Yellow crystals, mp 271–272 °C. ^{1}H NMR ($CDCl_3$): δ 7.10 (s, 2 H, ArH), 7.02 (s, 2 H, ArH), 6.62 (d, 2 H, CH), 5.84 9d, 2 H, CH), 4.13 (d, $J = 14.0$, 2 H, CH_2), 3.76 (d, $J = 15.0$, 2 H, CH_2), 3.03 (d, $J = 15.0$, 2 H, CH_2), 2.85 (d, $J = 14.0$ Hz, 2 H, CH_2), 1.25 [s, 18 H, $C(CH_3)_3$], 1.02 [s, 18 H, $C(CH_3)_3$]. ^{13}C NMR ($CDCl_3$): δ 195.7, 153.5, 144.4, 143.2, 138.5, 134.7, 127.2, 126.1, 125.4, 122.6, 119.9, 81.7, 38.1, 34.3, 31.6, 28.4, 27.9. MS: 645 ($[M + 1]^+$, 100%).

Compound **2b** (**A**).—Yellow crystals, mp 245–247 °C. ^{1}H NMR ($CDCl_3$): δ 7.03 (s, 2 H, ArH), 6.95 (s, 2 H, ArH), 6.52 (d, 2 H, CH), 5.81 (d, 2 H, CH), 4.10 (d, $J = 14.2$, 2 H, CH_2), 3.78 (d, $J = 15.4$ Hz, 2 H, CH_2), 3.03 (d, $J = 15.4$, 2 H, CH_2), 2.82 (d, $J = 14.2$ Hz, 2 H, CH_2), 1.64 (q, 4 H, CH_3CH_2), 1.30 [s, 12 H, $(CH_3)_2C$], 1.28 (q, 4 H, CH_3CH_2), 1.00 [s, 6 H, $(CH_3)_2C$], 0.98 [s, 6 H, $(CH_3)_2C$], 0.70 (t, 6 H, CH_3CH_2), 0.61 (t, 6 H, CH_3CH_2). ^{13}C NMR ($CDCl_3$): δ 195.5, 153.4, 142.7, 141.2, 138.2, 134.9, 129.1, 126.2, 126.0, 122.7, 120.6, 81.8, 37.8, 37.3, 33.2, 29.0, 28.9, 27.8, 26.4, 25.5, 9.2, 8.6. MS: 700 (M^+, 65%).

Compound **2c** (**A**).—Yellow crystals, mp 94–95 °C. ^{1}H NMR ($CDCl_3$): δ 7.02 (s, 2 H, ArH), 6.95 (s, 2 H, ArH), 6.50 (d, 2 H, CH), 5.81 (d, 2 H, CH), 4.10 (d, $J = 14.0$, 2 H, CH_2), 3.78 (d, $J = 15.0$, 2 H, CH_2), 3.01 (d, $J = 15.0$, 2 H, CH_2), 2.82 (d, $J = 14.0$ Hz, 2 H, 2 H, CH_2), 1.58 (m, 8 H, CH_3CH_2), 1.40–1.15 (m, 84 H, alkyl *H*), 0.99 (t, 6 H, CH_3CH_2), 0.86 (t, 6 H, CH_3CH_2). ^{13}C NMR ($CDCl_3$): 195.5, 152.6, 147.7, 142.8, 138.0, 135.2, 128.8, 126.3, 125.9, 122.6, 120.4, 82.0, 45.1, 42.0, 40.9, 40.0, 37.5, 37.2, 37.1, 32.0, 30.6, 30.3, 29.8, 29.7, 29.6, 29.4, 28.0, 27.1, 27.0, 26.6, 26.3, 25.0, 24.9, 24.3, 22.7, 21.5, 14.2, 14.0. MS: 1149 ($[M + 1]^+$, 100%).

Compound **2d** (**A**).—Yellow crystals, mp 178–180 °C. ^{1}H NMR ($CDCl_3$): δ 7.40–7.00 (m, 20 H, PhH), 6.95 (s, 2 H, ArH), 6.80 (s, 2 H, ArH), 6.35 (s, 2 H, CH), 5.79 (s, 2 H, CH), 4.12 (d, $J = 14.0$, 2 H, CH_2), 3.70 (d, $J = 15.0$, 2 H, CH_2), 2.98 (d, $J = 15.0$, 2 H, CH_2), 2.88 (m, 12 H, CH_2CH_2), 2.70 (d, $J = 14.0$ Hz, 2 H, CH_2), 2.40 (m, 4 H, CH_2CH_2).

Compound **2e** (**A**).—Pale yellow crystals, mp 151–153 °C. ^{1}H NMR ($CDCl_3$): δ 6.97 (s, 2 H, ArH), 6.85 (s, 2 H, ArH), 6.28 (s, 2 H, CH), 5.35 (s, 2 H, CH), 4.18 (d, $J = 16.0$, 2 H, CH_2), 4.02 (d, $J = 13.0$, 2 H, CH_2), 3.10 (d, $J = 13.0$, 2 H, CH_2), 2.94 (d, $J = 16.0$ Hz, 2 H, CH_2), 2.58 (t, 8 H, $CH_2C_6H_{13}$), 1.60 (m, 8 H, CH_2CH_3), 1.40–1.00 [m, 32 H, $CH_2(CH_2)_4C_2H_5$], 0.92 (t, 6 H, CH_3), 0.90 (t, 6 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 195.9, 153.0, 148.9, 142.8, 140.3, 135.6, 129.1, 125.9, 123.3, 122.6, 120.0, 81.7, 35.7, 35.6, 35.4, 34.0, 32.1, 31.9, 31.5, 30.3, 30.2, 29.7, 29.2, 28.6, 26.4, 22.7, 14.1, 14.0.

Compound **2f** (**A**).—Yellow crystals, mp 240–243 °C. ^{1}H NMR ($CDCl_3$): δ 6.96 (s, 2 H, ArH), 6.87 (s, 2 H, ArH), 6.43 (s, 2 H, CH), 5.79 (s, 2 H, CH), 4.12 (d, $J = 13.9$, 2 H, CH_2), 3.75 (d, $J = 15.6$, 2 H, CH_2), 3.02 (d, $J = 15.6$, 2 H, CH_2), 2.84 (d, $J = 13.7$ Hz, 2 H, CH_2), 2.87 [hep, 2 H, $CH(CH_3)_2$], 2.29 [hep, 2 H, $CH(CH_3)_2$], 1.25 (d, 12 H, CH_3), 1.00 (dd, 12 H, CH_3). ^{13}C NMR ($CDCl_3$); δ 195.9, 153.8, 142.2, 141.0, 140.7, 134.8, 127.4, 126.5, 126.3, 122.9, 120.9, 81.6, 38.0, 33.5, 32.7, 29.6, 27.6, 24.4, 21.7, 20.1. MS: 588 (M^+, 100%).

Compound **2f** (**B**).—Yellow crystals, mp 230–232 °C. ^{1}H NMR ($CDCl_3$): δ 7.24 (s, 2 H, ArH), 6.91 (s, 2 H, ArH), 6.63 (d, 2 H, CH), 5.86 (d, 2 H, CH), 4.29 (d, $J = 12.5$, 1 H, CH_2), 4.03 (d, $J = 13.2$, 1 H, CH_2), 3.72 (d, $J = 16.5$, 2 H, CH_2), 3.22 (d, $J = 13.2$, 1 H, CH_2), 2.96 (d, $J = 16.5$, 2 H, CH_2), 2.82 [hep, 2 H, $CH(CH_3)_2$], 2.59 (d, $J = 12.5$ Hz, 1 H, CH_2), 2.43 [m, 2 H, $CH(CH_3)_2$], 1.22 (m, 12 H, CH_3), 0.99 (m, 12 H, CH_3). MS: 588 (M^+, 100%).

Compound **2f** (**C**).—White crystals, mp >300 °C. ^{1}H NMR ($CDCl_3$): δ 7.38 (s, 1 H, OH), 7.35 (s, 1 H, OH), 6.96 (s, 2 H, ArH), 6.85 (s, 2 H, ArH), 6.45 (s, 1 H, ArH), 6.41 (s, 1 H, ArH), 5.80 (s, 1 H, CH), 5.75 (s, 1 H, CH), 4.20–4.02 (3d, 3 H, CH_2), 3.75 (2d, 2 H, CH_2), 3.02 (2d, 2 H, CH_2), 2.85 (d, 1 H, CH_2), 2.80 [hep, 2 H, $CH(CH_3)_2$], 2.30 [hep, 2 H, $CH(CH_3)_2$], 1.24 (d, 12 H, CH_3), 1.02 (d, 12 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 195.9, 153.9, 142.8, 142.2, 141.1, 140.9, 140.8, 140.7, 136.8, 134.8, 133.9, 131.9, 129.5, 127.8, 127.7, 127.5, 126.6, 126.5, 126.3, 126.2, 126.0, 122.9, 120.9, 81.6, 38.0, 37.6, 37.0, 36.4, 33.6, 32.7, 27.7, 27.1, 24.7, 24.4, 21.7 and 20.1. MS: 590 (M^+, 80%).

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