

One step synthesis of calix[n]quinones through the HClO₄/PbO₂ mediated oxidation of calix[n]arenes

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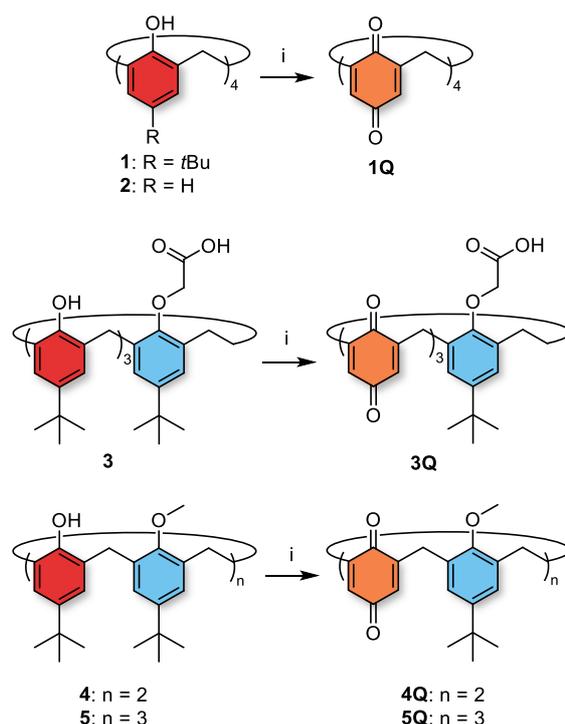
Abstract: A procedure using HClO₄ and PbO₂ allows the straightforward oxidation of *para*-substituted and unsubstituted calix[n]arenes into the corresponding calix[n]quinones in ca. 82% yield per quinone unit. These mild conditions constitute a good alternative to the classical procedure that involves highly toxic thallium(III) salts in trifluoroacetic acid.

Introduction

Calix[n]quinones have attracted considerable attention over the last decades for their host-guest, electrochemical and photophysical properties.^[1] In this regard, it was recently shown that calix[4]quinones can be used as the cathode of rechargeable lithium-ion batteries.^[2] Moreover, calix[n]quinones and the corresponding hydroquinone derivatives constitute interesting synthetic intermediates for the further functionalization of calixarenes.^[3] Nonetheless, the straightforward and efficient synthesis of calix[n]quinones from the parent *p*-*t*Bu-calix[n]arenes remains challenging. Indeed, on the one hand, multi-step syntheses involving prior *de-tert*-butylation of the *p*-*t*Bu-phenol units proceed generally in low global yields. On the other hand, the most efficient and popular procedure for the direct oxidation of the *p*-*t*Bu-phenol units into quinones employs extremely toxic thallium(III) salts in trifluoroacetic acid.^[4] Moreover, these harsh conditions lead to variable yields. A similar approach involving sodium perborate instead of heavy metal-based oxidant has been reported with moderate yields but this methodology is applicable to *de-tert*-butylated calixarenes only.^[5] Anodic oxidation of calixarenes into the quinone derivatives has been also reported but this method can be only applied on relatively small scales and requires specific apparatus.^[6] In 1998, Omura reported that the oxidation of *o,o',p'*-trisubstituted phenols into the corresponding *p*-benzoquinones can be achieved by using PbO₂ and 70% aqueous HClO₄ in acetone.^[7] This PbO₂/HClO₄ mediated oxidation still involves a toxic heavy metal-based oxidant yet friendly in comparison with thallium(III) salts extreme toxicity. Herein, we show that these mild conditions can be applied to the direct oxidation of various (*p*-*t*Bu)-calix[n]arenes into the corresponding calix[n]quinones.

Results and Discussion

The PbO₂/HClO₄ mediated oxidation was evaluated on various *O*-substituted and unsubstituted calix[n]arenes **1-5** (Scheme 1). First, preliminary experiments conducted with *p*-*t*Bu-calix[4]arene **1** showed that a minimum of 2 equiv. of PbO₂ per phenol unit are required to fully consume the starting material and the partially oxidized intermediates (TLC analysis). Besides, the oxidation did not proceed in absence of HClO₄, while a large excess of HClO₄ (> ca. 100 equiv. per phenol unit) led to degradation products. As shown below, when the oxidation of **5** was attempted with less than 15 equiv. of HClO₄ per phenol unit, a lower yield was obtained (*vide infra*). All these results led us to use the conditions originally described by Omura (i.e. 2.5 equiv. of PbO₂ and 15 equiv. of HClO₄ per phenol unit in both cases) for the oxidation of calixarenes **1-5**. However, in our case, the reactions were carried out in a CH₂Cl₂/acetone mixture instead of acetone in order to improve the solubility of the starting calixarenes. It should be noted that the reaction did not proceed in CH₂Cl₂ without acetone. The concentration of phenol units was set to 0.06 M in order to reach a combination of sufficient solubility of the starting calixarenes and rather short reaction times (i.e. < 2h). In all cases, TLC and/or ESI-MS monitoring of the reactions showed that these conditions allow the oxidation to proceed smoothly at room temperature.



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Scheme 1. PbO₂/HClO₄ mediated oxidation of calix[n]arenes into calix[n]quinones. i) PbO₂ (2.5 equiv./ArOH), HClO₄ 70% (15 equiv./ArOH), CH₂Cl₂/acetone, rt, 2h.

The yields were determined by quantitative ¹H NMR analysis of the crude reaction products or after isolation of the oxidized products (Table 1). Their similarity shows that almost no product was lost during the purification process. When performed on calix[4]arene **2** and its *p*-*t*Bu-derivative **1**, the PbO₂/HClO₄ mediated oxidation afforded the fully oxidized compound **1Q** with isolated yields of 34% and 42%, respectively. At first glance, these yields can appear as moderate but the formation of **1Q** from **1** and **2** required four successive oxidations and the average yields per oxidized unit are actually quite good (77% and 82% respectively). Reaction of **3** allowed the isolation of the desired trisquinone **3Q** with a yield of 55% and an average oxidation yield per quinone unit of 87%. When performed on calix[4]arene **4** and calix[6]arene **5**, for which each phenol moiety is separated by an unreactive *O*-substituted phenol unit, the average oxidation yield per quinone remained in the same range (ca. 85%). In this case, **4Q** and **5Q** were purified by flash chromatography on silica gel. This stands in contrast with quinones **1Q** and **3Q** for which classical flash chromatography purification was precluded because of their high polarity.

Table 1. Reaction yields for the direct oxidation of calix[n]arenes **1-5** into the corresponding calix[n]quinones [reaction conditions: PbO₂ (2.5 equiv./ArOH), HClO₄ 70% (15 equiv./ArOH), CH₂Cl₂/acetone, rt, 2h].

Substrate	Product	NMR yield ^[a]	Isolated yield	Average yield per oxidation
1	1Q	46%	42%	82% ^[c]
2	1Q	36%	34%	77% ^[c]
3	3Q	65%	55%	87% ^[c]
4	4Q	n/d ^[b]	72%	85% ^[d]
5	5Q	63%	59%	86% ^[c]

[a] Determined by quantitative ¹H NMR analysis of the crude product. [b] Not determined because of broad and overlapping peaks. [c] Calculated on the basis of the NMR yield. [d] Calculated on the basis of the isolated yield.

This first series of results shows that the PbO₂/HClO₄ mediated oxidation can efficiently lead to calixquinones in one step from (*p*-*t*Bu-)calix[n]arenes. In the case of compounds **1Q**, **4Q** and **5Q**, the yields are similar or higher than those previously reported with thallium(III) salts (14%,^[4a] 79%^[8] and 19%^[9] respectively). It is noteworthy that compound **3Q** was not reported previously. In all cases, the oxidation yield per quinone unit is centered around 82%, suggesting that the number of initial phenol units as well as their position in the calix[n]arene macrocycle has no influence on the overall yield. As no starting material nor intermediate were observed in the crude product, the yield loss might therefore be a consequence of a polymerization process that could arise from macrocycle opening or covalent coupling of oxidized phenol units.^[7] This hypothesis is strengthened by the

fact that, in all cases, extremely broad signals were observed in the ¹H NMR spectrum of the crude product (see the SI). In order to minimize the putative polymerization process, the influence of the concentration of calixarene **5** on the reaction yield was evaluated (Table 2). In all cases (entries 1-5), the reactions were monitored by TLC analysis and stopped after consumption of the starting material as well as of the intermediates. In comparison to the conditions used in the first set of experiments (i.e. **[5]** = 0.020 M), diluted reaction conditions only resulted in slightly lower yields (entries 2 and 3 vs 1). It is noteworthy that raising the concentration of HClO₄ at its initial value (entry 1) led to more degradation products (entry 4) as observed by ¹H NMR analysis of the crude material. This result indicates that the oxidation efficiency depends more on the number of HClO₄ equivalents than on the total acid concentration of the solution. Note that the use of less than 15 equiv. of HClO₄ per phenol unit also led to a lower yield (entry 5), suggesting that the conditions originally described by Omura for *o,o',p*-trisubstituted phenols are also optimal for the oxidation of calixarenes.

Table 2. Influence of the concentration of calixarene **5** and of HClO₄ on the oxidation yield. Reaction conditions: 2.5 equiv. of PbO₂ in CH₂Cl₂/acetone (1:1, v/v).

Entry	[5] (M)	[HClO ₄] (M)	equiv. of HClO ₄ /ArOH	NMR yield of 5Q ^[a]
1	0.020 ^[b]	0.90	15	63%
2	0.010	0.45	15	56%
3	0.0020	0.090	15	56%
4	0.0020	0.90	150	22%
5	0.020	0.20	3.3	38%

[a] Determined by quantitative ¹H NMR analysis of the crude product. [b] "Usual" reaction conditions added as reference.

Finally, the PbO₂/HClO₄ mediated oxidation was also carried out on *p*-*t*Bu-calix[6 and 8]arenes. Although the reaction seems to proceed in both cases, the broad ¹H NMR signals (attributed to polymeric products) were so intense that we were unable to purify the corresponding quinones or to determine a yield by quantitative NMR (see the SI).

Conclusions

We have reported a PbO₂/HClO₄ mediated oxidation that allows the synthesis of calix[n]quinones in a single step starting from the corresponding (*p*-*t*Bu-)calix[n]arenes. In comparison to the previously reported method that involves highly toxic thallium(III) salts in trifluoroacetic acid, this procedure uses more friendly conditions and proceeds in better yields. Extension of this oxidation method to more sophisticated calixarenes is currently under investigation.

Experimental Section

Solvents were distilled prior to use. Silica gel (230–400 mesh) was used for flash chromatography. NMR spectra were recorded either at 7.0 or 9.4 Tesla. Traces of residual solvents were used as internal standards for ^1H (7.26 ppm for CHCl_3 , 2.05 ppm for acetone- d_6 and 2.50 ppm for DMSO- d_6) and ^{13}C (77.16 ppm for CDCl_3 , 29.84 ppm for acetone- d_6 and 39.52 ppm for DMSO- d_6) chemical shift referencing. Abbreviations: s: singlet, d: doublet, Q: benzoquinone unit. NMR yields were calculated by quantitative NMR analyses of the crude products with added terephthalaldehyde as a reference. The high resolution mass spectra were recorded with Q-TOF ESI+ spectrometers. Electrospray ionization (ESI) mass spectra were recorded with an ESI-MS apparatus equipped with an ion-trap using the following settings: ESI+, spray voltage = 5 kV, capillary temperature = 160°C, capillary voltage = 46 V, tube lens offset voltage = 30 V; ESI-, spray voltage = 4.5 kV, capillary temperature = 160°C, capillary voltage = -15 V, tube lens offset voltage = -30 V. Melting points (mp) are uncorrected. ATR-FTIR spectra were recorded at room temperature. The starting calixarenes were either commercial (**1**, **2**, **5**) or synthesized according to procedures described in the literature (**3**,^[10] **4**^[11]). Aqueous phases and celite contaminated with lead after work-up should be treated according to heavy metals related regulations. Calix[n]quinones should be stored at low temperature since darkening and slow degradation was sometime observed for samples left several days at room temperature.

General procedure used for the oxidation of calixarenes into calixquinones 1Q–5Q. A solution or suspension of the starting calixarene in $\text{CH}_2\text{Cl}_2/\text{acetone}$ (1:1, v/v, $[\text{ArOH}] = 0.12 \text{ M}$) was added dropwise to a stirred mixture of PbO_2 (2.5 equiv./ArOH) and HClO_4 70% (15 equiv./ArOH) in $\text{CH}_2\text{Cl}_2/\text{acetone}$ (1:1, v/v, same volume as the calixarene solution) at room temperature. After 2 h of stirring, the mixture was filtered on celite and the celite was rinsed with $\text{CH}_2\text{Cl}_2/\text{acetone}$ until all the colored solution went through it. The solution was then extracted successively with water until the aqueous layer reached pH 6–7. The organic layer was concentrated under vacuum. The resulting crude product (orange/brown solid) was purified yielding a yellow solid.

Calix[4]tetraquinone 1Q. From *p*-*t*Bu-calix[4]arene **1**: the general procedure was used on 100 mg of **1** (0.154 mmol) yielding 79 mg of crude product. A fraction was used for quantitative NMR. The remaining 77 mg of crude product were purified by trituration (sonication) in 300 μL of acetone, centrifugation and removal of the supernatant. This purification process was repeated three times, affording **1Q** (30 mg, 0.062 mmol). Isolated yield: 42%. Spectral data are in accordance with the literature.^[12] From calix[4]arene **2**: the general procedure was carried out on 50 mg of **2** (0.12 mmol) yielding 46 mg of the crude product. A fraction was used for quantitative NMR. The remaining 44 mg of crude product were purified by trituration (sonication) of the solid in 200 μL of acetone, centrifugation and removal of the supernatant. This purification process was repeated six times, affording **1Q** (19 mg, 0.040 mmol). Isolated yield: 34%. Spectral data are in accordance with the literature.^[12]

***p*-*t*Bu-calix[4]arene-monoacid-trisquinone 3Q.** The general procedure was carried out on 71 mg of **3** (0.100 mmol) yielding 60 mg of the crude product. A fraction was used for quantitative NMR. The remaining 45 mg of crude product were purified by trituration (sonication) of the solid in 200 μL of acetone, centrifugation and removal of the supernatant. This purification process was repeated four times, affording **3Q** (24 mg, 0.041 mmol). Isolated yield: 55%. Mp: >180°C (deg.). IR (ATR) ν (cm^{-1}) = 1657, 1300, 1199, 1064, 919, 891. ^1H NMR (400 MHz, DMSO- d_6 , 298K) δ (ppm) = 12.84 (s, 1H, COOH), 6.93 (s, 2H, ArH), 6.87 (d, $^4J = 2.3 \text{ Hz}$, 2H, QH), 6.70 (d, $^4J = 2.3 \text{ Hz}$, 2H, QH), 6.50 (s, 2H, QH), 4.40 (s, 2H, OCH₂), 3.88 (d, $^2J = 13.5 \text{ Hz}$, 2H, Ar-CH₂-Q), 3.41–3.49 (m, 4H, CH₂), 3.24 (d, $^2J = 13.4 \text{ Hz}$, 2H, Q-CH₂-Q), 1.07 (s, 9H, *t*Bu). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz,

DMSO- d_6 , 298K) δ (ppm) = 188.0, 186.8, 185.5, 184.6, 170.4, 154.0, 147.0, 146.0, 145.8, 145.7, 133.8, 133.6, 132.6, 129.5, 126.3, 70.2, 33.7, 31.6, 31.0, 29.0. HRMS (ESI+): calcd for $\text{C}_{34}\text{H}_{32}\text{NO}_9$ $[\text{M}+\text{NH}_4]^+$ 598.2072, found 598.2073.

***p*-*t*Bu-calix[4]arene-1,3-dimethyl-2,4-bisquinone 4Q.** The general procedure was used on 102 mg of **4** (0.151 mmol) yielding 98 mg of the crude product. A fraction was used for quantitative NMR. The remaining 94 mg of crude product were purified by flash chromatography [$\text{CH}_2\text{Cl}_2/\text{acetone}$ (98:2, v/v)] affording **4Q** (62 mg, 0.105 mmol). Isolated yield: 72%. Spectral data are in accordance with the literature.^[8] R_f [$\text{CH}_2\text{Cl}_2/\text{acetone}$ (98:2, v/v)] = 0.42.

***p*-*t*Bu-calix[6]arene-1,3,5-trimethyl-2,4,6-trisquinone 5Q.** The general procedure was used on 300 mg of **5** (0.295 mmol). The crude product was purified by flash chromatography (CH_2Cl_2) affording **5Q** (156 mg, 0.175 mmol). Isolated yield: 59%. Spectral data are in accordance with the literature.^[9b] R_f [$\text{CH}_2\text{Cl}_2/\text{acetone}$ (98:2, v/v)] = 0.29.

Acknowledgements

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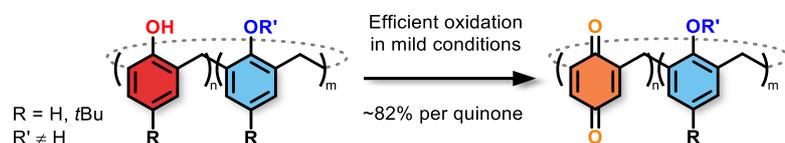
Keywords: calixarenes • quinones • oxidation • synthetic methods • macrocycles

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Entry for the Table of Contents

SHORT COMMUNICATION



Direct oxidation of *para*-substituted and unsubstituted calix[*n*]arenes into the corresponding calix[*n*]quinones was achieved with HClO₄ and PbO₂ in *ca.* 82% yield per quinone unit. This method constitutes an efficient alternative to the classical procedure that involves highly toxic thallium(III) salts.

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