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Communication

Calix[*n*]quinones Synthesis

One Step Synthesis of Calix[*n*]quinones through the $HClO_4$/PbO_2-Mediated Oxidation of Calix[*n*]arenes

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Abstract: A procedure using $HClO_4$ and PbO_2 allows the straightforward oxidation of *para*-substituted and unsubstituted calix[*n*]arenes into the corresponding calix[*n*]quinones in approximately 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, multistep 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 a 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 also been reported but this method can only be 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 PbO_2 and 70 % aqueous $HClO_4$ in acetone.[7] This PbO_2/$HClO_4$-mediated oxidation still involves a toxic heavy-metal-based oxidant yet safer 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.

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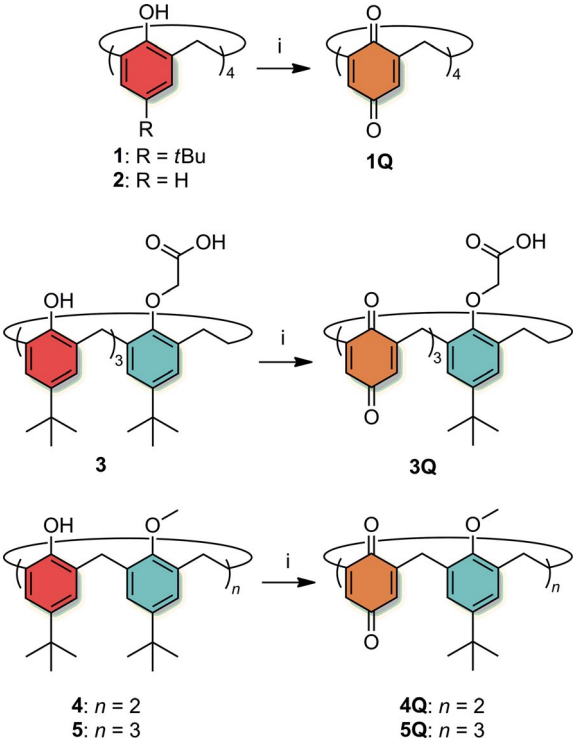
Results and Discussion

The PbO_2/$HClO_4$-mediated oxidation was evaluated on various *O*-substituted and unsubstituted calix[*n*]arenes **1**–**5** (Scheme 1).



Scheme 1. PbO_2/$HClO_4$-mediated oxidation of calix[*n*]arenes into calix[*n*]quinones. i) PbO_2 (2.5 equiv./ArOH), $HClO_4$ 70 % (15 equiv./ArOH), CH_2Cl_2/acetone, room temp., 2 h.

First, preliminary experiments conducted with *p*-*t*Bu-calix[4]arene **1** showed that a minimum of 2 equiv. of PbO_2 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 the absence of $HClO_4$, whereas a large excess of $HClO_4$ (> 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 $HClO_4$ 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 PbO_2 and 15 equiv. of $HClO_4$ per phenol unit in both cases) for the oxidation of calixarenes **1**–**5**. However, in our case, the reactions were carried out in a CH_2Cl_2/acetone mixture instead of acetone to improve the solubility of the starting calixarenes. It should be noted that the reaction did not proceed in CH_2Cl_2 without acetone. The concentration of phenol units was set to 0.06 M to reach a combination of sufficient solubility of the starting calixarenes and rather short reaction times (i.e. < 2 h). 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.

The yields were determined by quantitative ^{1}H 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 PbO_2/$HClO_4$-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 (82 and 77 %, 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: PbO_2 (2.5 equiv./ArOH), $HClO_4$ 70 % (15 equiv./ArOH), CH_2Cl_2/acetone, room temp., 2 h].

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 ^{1}H 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 PbO_2/$HClO_4$-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 thalium(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 ^{1}H NMR spectrum of the crude product (see the Supporting Information). 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 $HClO_4$ at its initial value (entry 1) led to more degradation products (entry 4) as observed by ^{1}H NMR analysis of the crude material. This result indicates that the oxidation efficiency depends more on the number of $HClO_4$ equiv. than on the total acid concentration of the solution. Note that the use of less than 15 equiv. of $HClO_4$ 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 $HClO_4$ on the oxidation yield. Reaction conditions: 2.5 equiv. of PbO_2 in CH_2Cl_2/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 ^{1}H NMR analysis of the crude product. [b] "Usual" reaction conditions added as a reference.

Finally, the PbO_2/$HClO_4$-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 ^{1}H 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 Supporting Information).

Conclusions

We have reported a PbO_2/$HClO_4$-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 milder

and safer 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 ^{1}H (δ =7.26 ppm for $CHCl_3$, 2.05 ppm for [D_5]acetone and 2.50 ppm for [D_5]DMSO) and ^{13}C (δ =77.16 ppm for $CDCl_3$, 29.84 ppm for [D_6]acetone and 39.52 ppm for [D_6]DMSO) 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 for the Oxidation of Calixarenes Into Calixquinones 1Q-5Q: A solution or suspension of the starting calixarene in CH_2Cl_2/acetone (1:1, v/v, [ArOH] = 0.12 M) was added dropwise to a stirred mixture of PbO_2 (2.5 equiv./ArOH) and $HClO_4$ 70 % (15 equiv./ArOH) in CH_2Cl_2/acetone (1:1, v/v, same volume as the calixarene solution) at room temperature. After 2 h of stirring, the mixture was filtered through celite and the celite was rinsed with CH_2Cl_2/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 to yield a yellow solid.

Calix[4]tetraquinone 1Q: *From p-tBu-calix[4]arene **1**:* the general procedure was used on 100 mg of **1** (0.154 mmol) to yield 79 mg of crude product. A fraction was used for quantitative NMR spectroscopy. 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) to yield 46 mg of the crude product. A fraction was used for quantitative NMR spectroscopy. 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) to yield 60 mg of the crude product. A fraction was used for quantitative NMR spectroscopy. 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): $\tilde{\nu}$ = 1657, 1300, 1199, 1064, 919, 891 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]DMSO, 298 K): δ = 12.84 (s, 1 H, COOH), 6.93 (s, 2 H, ArH), 6.87 (d, ^4J = 2.3 Hz, 2 H, QH), 6.70 (d, ^4J = 2.3 Hz, 2 H, QH), 6.50 (s, 2 H, QH), 4.40 (s, 2 H, OCH_2), 3.88 (d, ^2J = 13.5 Hz, 2 H, Ar-CH_2-Q), 3.41–3.49 (m, 4 H, CH_2), 3.24 (d, ^2J = 13.4 Hz, 2 H, Q-CH_2-Q), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D_6]DMSO, 298 K): δ = 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 ppm. HRMS (ESI+): calcd. for $C_{34}H_{32}NO_9$ [M + 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) to yield 98 mg of the crude product. A fraction was used for quantitative NMR spectroscopy. The remaining 94 mg of crude product were purified by flash chromatography [CH_2Cl_2/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 [CH_2Cl_2/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 [CH_2Cl_2/acetone (98:2, v/v)] = 0.29.

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[1] a) Y. O. Kim, Y. M. Jung, S. B. Kim, B. H. Hong, K. S. Kim, S. M. Park, *J. Phys. Chem. B* **2004**, *108*, 4927–4936; b) Y.-R. Kim, R. S. Kim, S. K. Kang, M. G. Choi, H. Y. Kim, D. Cho, J. Y. Lee, S.-K. Chang, T. D. Chung, *J. Am. Chem. Soc.* **2013**, *135*, 18957–18967; c) V. Felix, M. G. B. Drew, P. R. A. Webber, P. D. Beer, *Phys. Chem. Chem. Phys.* **2006**, *8*, 521–532; d) M. Hissler, A. Harriman, P. Jost, G. Wipff, R. Ziessel, *Angew. Chem. Int. Ed.* **1998**, *37*, 3249–3252; *Angew. Chem.* **1998**, *110*, 3439; e) P. D. Beer, P. A. Gale, Z. Chen, M. G. B. Drew, J. A. Heath, M. I. Ogden, H. R. Powell, *Inorg. Chem.* **1997**, *36*, 5880–5893; f) P. R. A. Webber, G. Z. Chen, M. G. B. Drew, P. D. Beer, *Angew. Chem. Int. Ed.* **2001**, *40*, 2265–2268; *Angew. Chem.* **2001**, *113*, 2325; g) P. R. A. Webber, P. D. Beer, G. Z. Chen, V. Felix, M. G. D. Drew, *J. Am. Chem. Soc.* **2003**, *125*, 5774–5785.

[2] a) W. Huang, Z. Zhu, L. Wang, S. Wang, H. Li, Z. Tao, J. Shi, L. Guan, J. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 9162–9166; *Angew. Chem.* **2013**, *125*, 9332; b) K. Pirnat, R. Dominko, R. Cerc-Korosec, G. Mali, B. Genorio, M. Gaberscek, *J. Power Sources* **2012**, *199*, 308–314; c) B. Genorio, K. Pirnat, R. Cerc-Korosec, R. Dominko, M. Gaberscek, *Angew. Chem. Int. Ed.* **2010**, *49*, 7222–7224; *Angew. Chem.* **2010**, *122*, 7380.

[3] a) P. A. Reddy, C. D. Gutsche, *J. Org. Chem.* **1993**, *58*, 3245–3251; b) A. M. King, C. P. Moore, K. R. A. Samankumara Sandanayake, I. O. Sutherland, *J. Chem. Soc., Chem. Commun.* **1992**, 582–584; c) H. Yamamoto, K. Ueda, K. R. A. Samankumara Sandanayake, S. Shinkai, *Chem. Lett.* **1995**, 497–498; d) N. Y. Kim, S.-K. Chang, *J. Org. Chem.* **1998**, *63*, 2362–2364.

[4] a) P. A. Reddy, R. P. Kashyap, W. H. Watson, C. D. Gutsche, *Isr. J. Chem.* **1992**, *32*, 89–96; b) E. J. Cho, S. S. Hwang, J. M. Oh, L. H. Kyoung, S. Jeon, K. C. Nam, *Bull. Korean Chem. Soc.* **2001**, *22*, 782–784; c) M. D. Lankshear, A. R. Cowley, P. D. Beer, *Chem. Commun.* **2006**, 612–614; d) M. D. Lankshear, I. M. Dudley, K.-M. Chan, A. R. Cowley, S. M. Santos, V. Felix, P. D. Beer, *Chem. Eur. J.* **2008**, *14*, 2248–2263; e) S. C. Picot, B. R. Mullaney, P. D. Beer, *Chem. Eur. J.* **2012**, *18*, 6230–6237.
[5] C.-F. Chen, Q.-Y. Zheng, Z.-T. Huang, *Synthesis* **1999**, 69–71.
[6] a) R. Vataj, A. Louati, C. Jeunesse, D. Matt, *Electrochem. Commun.* **2000**, *2*, 769–775; b) S. Meddeb-Limem, S. Besbes-Hentati, H. Said, M. Bouvet, *Electrochim. Acta* **2011**, *58*, 372–382.
[7] K. Omura, *Synthesis* **1998**, 1145–1148.
[8] O. Ben Youchret-Zallez, S. B. Hentati, M. Bouvet, H. Said, *J. Inclusion Phenom. Macrocyclic Chem.* **2012**, *73*, 129–134.
[9] In two steps: a) De-*tert*-butylation: J. P. M. van Duynhoven, R. G. Janssen, W. Verboom, S. M. Franken, A. Casnati, A. Pochini, R. Ungaro, J. de Mendoza, P. M. Nieto, *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822; b) Oxidation: A. Casnati, L. Domiano, A. Pochini, R. Ungaro, M. Carramolino, J. O. Magrans, P. M. Nieto, J. López-Prados, P. Prados, J. de Mendoza, R. G. Janssen, W. Verboom, D. N. Reinhoudt, *Tetrahedron* **1995**, *51*, 12699–12720.
[10] C.-C. Zeng, J. Y. Becker, *Tetrahedron* **2004**, *60*, 1643–1650.
[11] H. M. Chawla, N. Pant, Bindu Srivastana, *Tetrahedron Lett.* **2005**, *46*, 7259–7262.
[12] Y. Morita, T. Agawa, *J. Org. Chem.* **1992**, *57*, 3658–3662.

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