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Oxidation of Benzoylated Calix[4]arene

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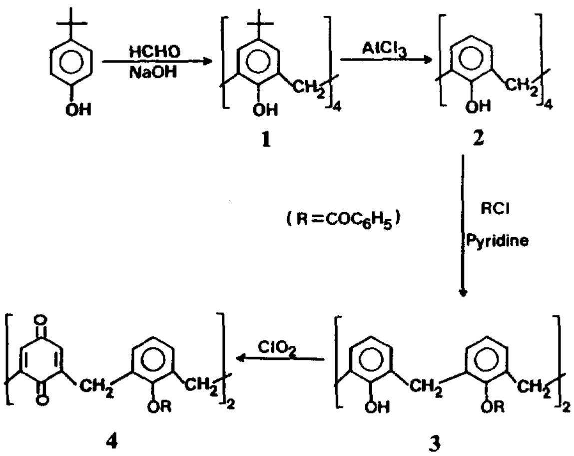
Calixarenes are cavity-containing macrocyclic compounds[1] that consist of several phenolic units in a cyclic array. Though several papers[2,3] have been reported for the preparation of functional calixarenes which can act as enzyme mimics[4], most calixarenes so obtained are symmetrically substituted. Besides the long stepwise synthesis developed by Hayes, Hunter[5] and Kämmerer[6], less symmetrical calixarenes have been synthesized by benzoylation[7] of calix[4]arene with benzoyl chloride in pyridine. Calix[4]arene yield only a tribenzoate under those conditions. Quinones are important ingredients for the biological studies[8] such as ubiquinones, alizarine and diosquinone which contain in their constitution either a 1,4- or 1,2-quinone moiety. Quinone calixarenes which contain a hydrophobic cavity as well as quinone groups could be developed into a selective guest oxidant. The purpose of present work is to exploit the benzoylation of calixarene to the preparation of less symmetrically functionalized calixarenes and to incorporate the quinone functionalities into the calixarene frame. In the present study we prepared the dibenzoylate calix[4]arene 3 under the carefully controlled conditions and oxidized it to the diquinone dibenzoyl calix[4]arene 4 with ClO_2. The tribenzoate calix[4]arene 5 which was prepared by Gutsche and Lee[7] also oxidized to the corresponding quinone calix[4]arene 6 with ClO_2.



Scheme 1

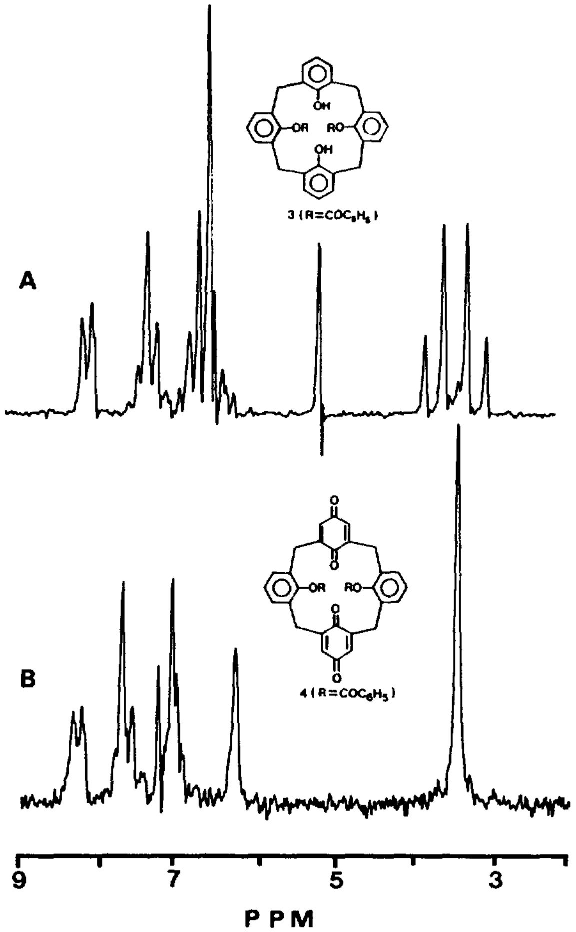


Figure 1. Proton NMR spectra of 3 and 4.

p-tert-Butyl calix[4]arene 1 can be easily prepared in good yield by the base-induced "one-step" condensation[9] of *p-tert*-butylphenol and formaldehyde. Aluminum chloride catalyzed removal[7] of the *p-tert*-butyl groups proceeds in excellent yield, making calix[4]arene 2 a readily available starting material for the introduction of functional groups onto the calixarene framework (Scheme 1). Aroylation of calix[4]arene with 2 equivalent of benzoyl chloride in pyridine at 0℃ yields a dibenzoylate calix[4]arene 3 (85% yield) with the trace amounts of mono- and tribenzoylated calix[4]arene, which can be easily purified by recrystallization with chloroform. ^{1}H-NMR spectrum of 3 (Figure 1) shows a singlet at 5.5 ppm for two hydroxyl protons and a pair of doublet at 3.3-4.1 ppm for the bridge methylene protons, indicating that benzoylation occurred to the 1,3-position of hydroxyl groups and dibenzoylated calix[4]arene 3 exists as a rigid cone conformation[10]. No other conformations such as partical cone or alternate or 1,2-benzoylations were observed. Oxidation

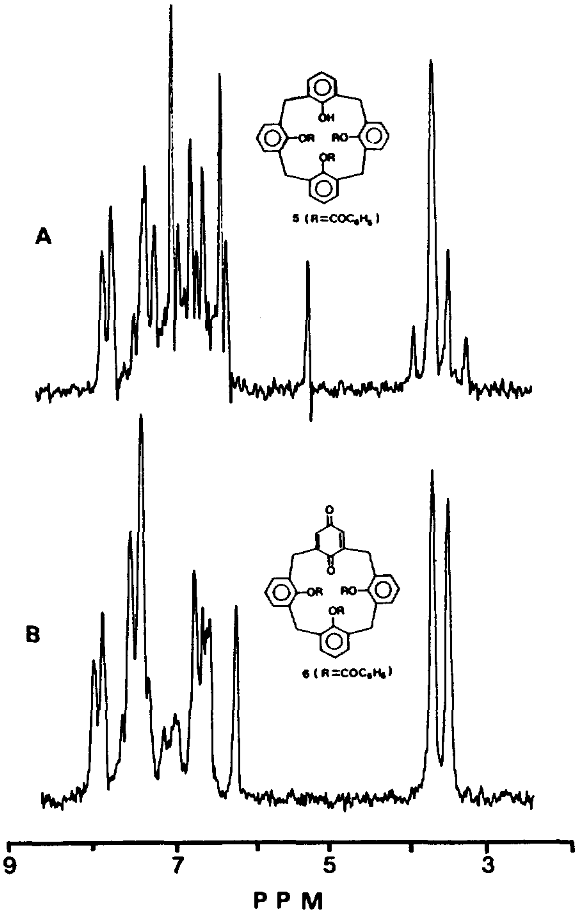


Figure 2. Proton NMR spectra of **5** and **6**.

of benzoylated calix[4]arene was tried with Fremy's salt[11,12] as well as Salcomines[13] and inorganic oxidation agents without success. Due to insolubility of calix[4]arene in aqueous solution Fremy's salt oxidation gave no observable amounts of quinonecalixarene. Other oxidants such as Salcomines are also ineffective; on the other hand, strong oxidant such as $KMnO_4$ produced the unmanagable materials. But chlorine dioxide which was generated by the reaction of sodium chlorite with aquous potassium persulfite solution[14] oxidized the benzoylated calix[4]arene smoothly to the corresponding quinone calix[4]arene. Reaction took about 4 hour to complete at room temperature. Crude product was recrystallized from $CHCl_3$-CH_3OH to give a yellow crystals; spectroscopic data[15] clearly demonstrated quinone formation with intact of benzoyl groups.

The ^1H-NMR spectrum of **4** (Figure 1) shows a singlet at 3.5 ppm for the bridge methylene protons, and a singlet at 6.2 ppm for the quinone protons and multiplets at 6.8 to 8.2 ppm for the aromatic protons. A sharp singlet at 3.5 ppm for the bridge methylene protons clearly indicated that the conformation of **4** is very flexible even at room temperature presumably due to the loss of hydrogen bonding between hydroxyl groups and carbonyl functionalities of ester groups. Exactly the same ^1H-NMR characteristic features were observed for the tribenzoylated calix[4]arene **5** which was prepared by Gutsche and Lee[6] and its chlorine dioxide quinone calix[4]arene **6** as shown in Figure 2. A ^1H-NMR spectrum **A** of the tribenzoylated calix[4]arene **5** shows a pair of doublets and a singlet at 3.3-4.0 ppm for the bridge methylene protons indicating that it is the typical trisubstituted cone conformation[10] of calix[4]arene and a singlet at 5.5 ppm for the one hydroxyl protons. A ^1H-NMR spectrum **B** for the corresponding quinone products **6** shows two singlets for the bridge methylene protons and a singlet at 6.2 ppm for the quinone protons. Due to trisubstitution of calix[4]arene two singlets for the bridge methylene protons indicate that the conformation[10] of tribenzoylated quinone calix[4]arene is flexible. The IR spectrum of **4** shows a 1645 cm^{-1} absorption band for the quinone carbonyl groups, completely disappearance of 3530 cm^{-1} band for OH removal and 1735 cm^{-1} band for benzoylester band.

Chlorine dioxide can be easily prepared and stored for a long time without much loss of activity. The fact that chlorine dioxide oxidize calixarene smoothly suggest that it can be a very useful oxidants for the phenolic compounds in various solvents either aqueous or organic. Usefulness of ClO_2 as a phenol oxidant would be worthwhile to explore and the phenol oxidation projects are in progress.

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15. ^1H-NMR of **3** ($CDCl_3$) δ 6.8-8.2 (m, 22, ArH), 5.5 (s, 2, OH), 3.3-4.0 (pair of d, J=12 Hz, 8, $ArCH_2Ar$). ^{13}C-NMR of **3** ($CDCl_3$ and DMSO-d_6) δ 164.2 (-COO-), 152.4, 145.5, 133.6, 132.2, 130.1, 128.9, 128.5, 128.1, 125.5, and 119.3 (Ar), 32.4 ($ArCH_2Ar$). mp. of **3**: 269-271℃. IR of **3** (KBr) 3520 (OH), 1741 cm^{-1} (-COO-). Anal. Calc. for $C_{42}H_{32}O_6$:

C, 79.73; H, 5.10. Found: C, 79.26; H, 4.99.

^{1}H-NMR of **4** ($CDCl_3$) δ 6.6-8.5 (m, 16, ArH), 6.2 (s, 4, -C=CH-CO-), 3.4 (s, 8, $ArCH_2Ar$). ^{13}C-NMR of **4** ($CDCl_3$) δ 188.2 and 186.1 (-CO-), 164.7 (-COO-), 147.5, 134.5, 132.5, 130.5, 129.1 and 125.8 (Ar), 33.2 ($ArCH_2Ar$). M.P. of **4**: 241-251°C (dec.). IR of **4** (KBr) 1732 (-COO-), 1658 cm^{-1} (-CO-). UV of **4** ($CHCl_3$) 320 (log ε=3.39), 440 nm (log ε=1.87). Anal. Calc. for $C_{42}H_{28}O_8 \cdot 3/4\ CHCl_3$: C, 68.44; H, 3.86. Found: C, 69.71; H, 3.65.

^{1}H-NMR of **6** ($CDCl_3$) δ 6.4-8.1 (m, 24, ArH), 6.2 (s, 2, -C=CH-CO-), 3.6 and 3.4 (two s, 8, $ArCH_2Ar$). ^{13}C-NMR of **6** ($CDCl_3$) δ 187.6 and 185.8 (-CO-), 164.3 and 164.1 (-COO-), 148.3, 147.7, 147.3, 134.1, 133.9, 133.4, 133.3, 132.9, 131.7, 131.0, 130.8, 130.2, 129.7, 128.7, 128.6, 128.1, 128.0, 125.6 and 124.9 (Ar), 37.1 and 333.6 ($ArCH_2Ar$). m.p. of **6**: 309-316°C (dec.). IR of **6** (KBr) 1736 (-COO-), 1665 cm^{-1} (-CO-). UV of **6** ($CHCl_3$) 320 (log ε=1.65). Anal. Calc. for $C_{49}H_{34}O_8 \cdot 1/4\ CHCl_3$: C, 75.77; H, 4.42. Found: H, 4.49.

A New Procedure To N-Arylcyanothioformamides From 5-Arylimino-4-Chloro-5H-1,2,3-Dithiazoles

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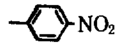
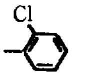
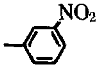
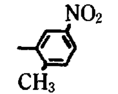
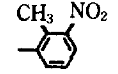
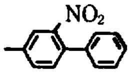
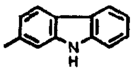
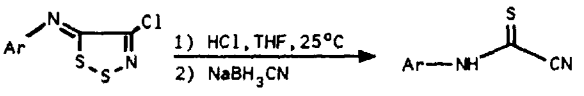
5-Arylimino-4-chloro-5H-1,2,3-dithiazoles **1** have been known as an interesting class of compounds with their biological activities as fungicids, ovicides, insecticides, herbicides[1] and pharmaceuticals[2], and also their potential utility as synthetic intermediates. One reaction reported involves the hydrolysis of **1** under basic condition: N-arylcyanothioformamides **2** were prepared by hydrolysis in a mixture of aq. NH_3 and EtOH (14-86%).[2] Hydrolysis of **1** with aq. NaOH was also reported to give **2** but the yields were not described.[3] Although synthesis of **2** is mainly achieved by the reaction of arylisothiocyanates with cyanides[4] along with nucleophilic displacement of C-benzenesulfonylthioformamide by cyanide.[5] No N-(aminoaryl)cyanothioformamide, to our knowledge, has been reported except for N-(N,N-dialkylaminoaryl)cyanothioformamides.[4a,6] This might be due to uneasy access of aminoarylisothiocyanate and C-benzenesulfonyl-N-(aminoaryl)thioformamide.

For synthesis of N-(aminoaryl)cyanothioformamide from 5-aminoarylimino-4-chloro-5H-1,2,3-dithiazoles, a better method for the synthesis of **2** from **1** was a precondition due to the difficulty in separation of the reaction mixtures obtained using the known method.[3] We have found that a heterogeneous reduction of hydrochloride salt of **1** with sodium cyanoborohydride gave good to excellent yield of **2**: HCl gas was bubbled into the solution of **1** (4 mmol) in dry THF (50 m*l*) at 0°C until hydrochloride salt of **1** precipitated. The mixture was stirred (10 min), followed by the addition of $NaBH_3CN$ (6 mmol) in dry THF (20 m*l*). After the solid had disappeared, the mixture was stirred (10 min) at room temperature, followed by the addition of water (20 m*l*), which was neutralized with saturated sodium bicarbonate. After removal of THF in vacuo, the residual aqueous solution was extracted with CH_2Cl_2 (3×20 m*l*). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was chromatographed on silica gel (10×3 cm, Merck 70-230 mesh). After sulfur and an unknown mixture were removed by sequential elution with petroleum ether/CH_2Cl_2 (2 : 1, 60 m*l*) and CH_2Cl_2 (30 m*l*), **2** was eluted with CH_2Cl_2/EtOAc (1 : 1, 60 m*l*). Yields and physical properties of **2** are summarized in Table 1 and all unknown compounds (**2e**-**2h**) have been characterized by their ^{1}H-NMR, IR and MS data.[7]

Table 1. Yields and Physical Properties of N-arylcyanothioformamides **2**

2	Ar	Yield^a(%)	mp^b(°C)	Color
a		71	130-131 ($CHCl_3$/n-hexane) (lit[7] 126.5-128.5)	orange
b		84	128-130 ($CHCl_3$/n-hexane) (lit[6] 128-130)	grey yellow
c		75	106-108 ($CHCl_3$/n-hexane) (lit[7] 108-110.5)	reddish yellow
d		88	103-104 (petroleum ether/CH_2Cl_2) (lit[7] 99-102)	grey yellow
e		93	118-119 (petroleum ether/CH_2Cl_2)	red
f		78	97-98 (petroleum ether/CH_2Cl_2)	yellow
g		90	146-147 (petroleum ether/Et_2O)	orange
h		100	158-159 (dec) (CH_2Cl_2/n-hexane)	yellow

^{a}Yield of isolated product. ^{b}mp was determined on a Fisher-Johns melting point apparatus as uncorrected.



1 2

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