ScienceAsia 28 (2002) : **25-28**

Selective Oxidation of 25,27-Bis-(3-formylphenoxylethoxy)-*p-tert*-butylcalix[4]arene

Mongkol Sukwattanasinitt*, Rojrit Rojanathanes, Siriporn Jiwpanich, Thawatchai Tuntulani and Vithaya Ruangpornvisuti
Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand.
* Corresponding author, E-mail: smongkol@chula.ac.th

Received 26 Jan 2001
Accepted 28 Sep 2001

ABSTRACT Reaction of 25,27-bis-(3-formylphenoxyethoxy)-*p-tert*-butylcalix[4]arene (1) with 20% mole of KCN in ethanol and *i*-propanol yielded monoethylester (2) (50%) and monoisopropylester (3) (15%). Compound 1 was not oxidized by air in the absence of KCN under reflux. The Cannizzaro reaction of 1 in ethanol using KOH gave bis-alcohol (4), acid-alcohol (5).

KEYWORDS: calix, oxidation, aldehyde, ester, cyanide.

INTRODUCTION

Owing to its pre-organized structure, calix[4] arene has become one of the most popular molecular platforms for synthesis of highly selective receptors for molecular and ionic guests.[1] The simplicity of structural modification on the lower rim of calix[4]arene has furnished a variety of calix[4]arene derivatives.[2-6] Recently the derivatives containing multiple benzaldehyde groups have been demonstrated to be useful for syntheses of several host molecules with selective binding properties.[7-10]

We are currently interested in preparation of functional supermolecules from the bisaldehyde derivatives. During this investigation, a serendipitously selective oxidation reaction of calix[4]arene containing two aromatic aldehydic functional groups was encountered. This reaction presents an unprecedented cyanide-catalyzed autoxidation of aldehyde and a new convenient route to unsymmetrical substituted calix[4]arenes. We report here a study of this selective oxidation and full characterization of its product.

The simple calixarene derivatization using the template method always yields 1,3-alternate or trisubstituted calixarenes. Syntheses of mono substituted or different substituted calixarenes is a drawback of this template method. Using this oxidation, the symmetry of the molecule can be destroyed easier. This is an alternative route to successive preparation of unsymmetrical calixarene derivatives, which can be further functionalized to chiral host molecules. From unsymmetrical disubstituted calixarenes, a simple methylation of a phenolic group on the lower rim will form unsymmetrical tri-substituted calixarenes, which are chiral molecules. These chiral molecules can be used as chiral hosts for some chiral recognition processes. Therefore, this oxidation will be a useful technique, as it aids in synthesizing this type of chiral calixarenes.

MATERIALS AND METHODS

All reagents were purchased from Fluka® (Buch, Switzerland) and Merck®(Darmstadt, Germany). Solvents such as acetonitrile, methylene chloride and alcohols were reagent grade stored over molecular sieves. In anhydrous reactions, solvents were dried by standard procedures and distilled before use.[16] For extraction and chromatography, solvents were commercial grade and were distilled prior to use.

The melting points were determined using an Electrothermal 900 melting point apparatus (Electrothermal Engineering, Essex, UK). Elemental analyses were performed on Perkin-Elmer PE 2400 Series II (Perkin-Elmer, Massachusetts, USA). Infrared photometry experiments were done on a Nicolet Impact 410 FT-IR (Thermo Nicolet, Wisconsin, USA), using thin film samples prepared from solutions in methylene chloride on KBr windows. Mass analyses were carried out on a FISONS VG TRIO 2000 mass spectrometer (Fisons, Sussex, UK). The NMR spectra were acquired on a Bruker ACF 200 NMR (Bruker, Fällanden, Switzerland), using $CDCl_3$ as a solvent.

Bisaldehyde (1). In a 1 L, 2-necked round bottom flask equipped with a magnetic stirring bar and a reflux condenser, *p-tert*-butylcalix[4]arene (7.8 mmol, 5.00 g) and K_2CO_3 (57.9 mmol, 8.00 g) were suspended in CH_3CN (300 mL). The mixture was

stirred for 30 minutes at ambient temperature and 3-(2-bromoethoxy)-benzaldehyde (17.5 mmol, 4.00 g) was then added dropwise. The mixture was refluxed for 60 hours and then allowed to cool to ambient temperature. The mixture was filtered and washed with acetone and CH_2Cl_2. The filtrate was combined and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and then extracted with aqueous HCl (2 M). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was crystallized in CH_2Cl_2/CH_3OH yielding the desired product as a white solid (4.7 mmol, 4.42 g, 60%): mp (decompose) = 184.8-185.3ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.27 (s, 18H), 3.32 (d, 4H, J = 13.0 Hz), 4.3-4.4 (m, 12H), 6.85 (s, 4H), 7.04 (s, 4H) 7.20–7.45 (m, 8H), 9.93 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.1, 31.7, 33.8, 34.0, 66.9, 73.7, 113.4, 122.4, 123.6, 125.2, 125.7, 127.8, 130.2, 132.8, 137.8, 141.5, 147.1, 149.7, 150.5, 159.2, 192.1; IR (neat) ν_{max} 3336 (phenolic O-H stretching), 3050, 2958, 2869 (aldehydic C-H stretching), 2731 (aldehydic C-H stretching), 1697 (aldehydic C=O stretching), 1597, 1485, 1450, 1265 cm^{-1}; Anal. Calcd for $C_{62}H_{72}O_8$: C, 78.78; H, 7.68; Found: C, 76.80; H, 7.95.

Ethylester-aldehyde (2). In a 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser, 1 (0.6 mmol, 0.50 g) and KCN (0.15 mmol, 0.01 g) were dissolved in 95% ethanol (20 mL). The mixture was refluxed for 24 hours and then allowed to cool to ambient temperature. The solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and then extracted with aqueous HCl (2 M). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was crystallized in CH_2Cl_2/CH_3OH yielding the product 2 as a white solid (0.3 mmol, 0.25 g., 50%): mp(decompose) = 133-134ºC.; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 18H), 1.30 (s, 18H), 1.40 (t, 3H, J = 8.0 Hz), 3.34 (d, 4H, J = 12.0 Hz), 4.34-4.43 (m, 14H), 6.88 (s, 4H), 7.07 (s, 4H), 7.18 (d, 1H, J = 8.0 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.35 (t, 1H, J = 8.0 Hz), 7.43-7.50 (m, 5H), 7.61 (d, 1H, J = 4.0 Hz), 7.67 (s, 1H), 9.92 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.2, 31.0, 31.6, 31.7, 33.8, 34.0, 53.2, 61.0, 66.8, 66.9, 73.7, 113.7, 114.8, 120.3, 122.2, 122.3, 123.3, 125.1, 125.7, 127.7, 129.4, 130.1, 131.7, 132.8, 137.7, 141.4, 147.1, 149.7, 150.4, 158.5, 159.1, 166.4, 192.1; IR (KBr pellet) ν_{max} 3363 (Ar-OH), 3047, 2958, 2870 (aldehydic C-H stretching), 2727 (aldehydic C-H stretching), 1716 (carboxylate C=O stretching), 1701 (aldehydic C=O stretching), 1589, 1485, 1446, 1277, 1200 cm^{-1}; Anal. Calcd for $C_{64}H_{76}O_9$: C, 77.70; H, 7.74; Found: C, 77.80; H, 7.77.

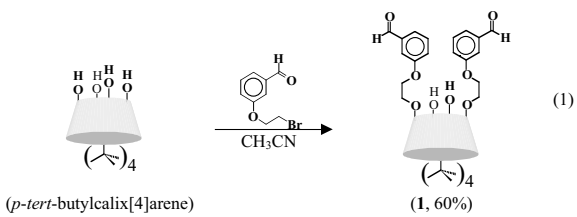
i-Propylester-aldehyde (3). In a 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser, 1 (0.6 mmol, 0.50 g) and KCN (0.15 mmol, 0.01 g) were dissolved in 95% *i*-propanol (20 mL). The mixture was refluxed for 24 hours and then allowed to cool to ambient temperature. The solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and then extracted with aqueous HCl (2 M). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was crystallized in CH_2Cl_2/CH_3OH yielding the product 3 as a white solid (0.1 mmol, 0.09 g, 15%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.25 (s, 18H), 1.33 (d, 6H, J = 6.0 Hz), 3.29 (d, 4H, J = 13.0 Hz), 4.09-4.41 (m, 14H), 6.84 (s, 4H), 7.02 (s, 4H), 7.20-7.43 (m, 8H), 7.55 (s, 1H), 7.62 (d, 1H, J = 7.5 Hz), 9.92 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.9, 31.1, 31.3, 31.7, 33.8, 34.0, 66.8, 68.5, 73.7, 113.7, 114.9, 120.2, 122.2, 122.3, 123.3, 125.2, 125.7, 127.8, 129.4, 130.1, 132.2, 137.7, 141.4, 147.1, 149.7, 150.6, 158.5, 159.2, 165.9, 192.1; Anal Calcd for $C_{65}H_{78}O_9 \bullet CH_2Cl_2$: C, 72.84; H, 7.41; Found: C, 73.25; H, 7.55.

Cannizzaro reaction of the bisaldehyde (1). In a 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser, 1 (0.6 mmol, 0.50 g) and KOH (3.6 mmol, 0.20 g) were dissolved in 95% ethanol (15 mL). The mixture was refluxed for 24 hours and then allowed to cool to ambient temperature. The solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and then extracted with aqueous HCl (2 M). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The products were isolated by column chromatography (silica gel 60, Merck®) using EtOAc/CH_2Cl_2 (20/80) as an eluent yielding two products as white solids. The first product is the bisalcohol (4) (0.09 mmol, 0.08 g, 16%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.25 (s, 18H), 3.29 (d, 4H, J = 13.0 Hz), 4.30-4.40 (m, 12H), 4.60 (s, 4H), 6.84-7.02 (m, 16H), 7.20-7.29 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 30.9, 31.1, 31.7, 33.8, 34.0, 64.9, 66.6, 74.0, 112.7, 114.6, 119.4, 125.2, 125.7, 129.5, 132.9, 141.5, 142.7, 147.1, 149.9, 150.5, 158.8. The other product is

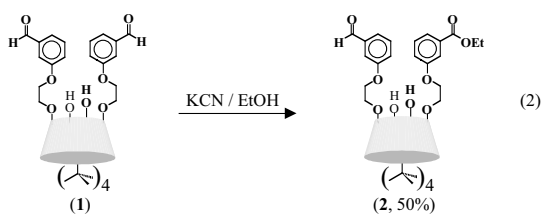
the alcohol-acid (5) (0.02 mmol, 0.02 g, 4%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 18H), 1.03 (s, 18H), 1.24 (s, 36), 3.30 (dd, 4H, J = 13, 6.5 Hz), 4.20 – 4.42 (m, 14H), 4.66 (s, 1H), 7.05–7.11 (m, 4H), 9.88 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.1, 31.7, 33.8, 34.0, 65.1, 66.6, 67.0, 74.1, 74.1, 112.8, 114.4, 114.8, 119.6, 121.9, 122.9, 125.1, 125.7, 127.9, 129.5, 130.9, 132.8, 141.5, 142.2, 147.0, 147.0, 150.0, 150.0, 150.5, 158.7, 158.6, 170.0.

Results and Discussion

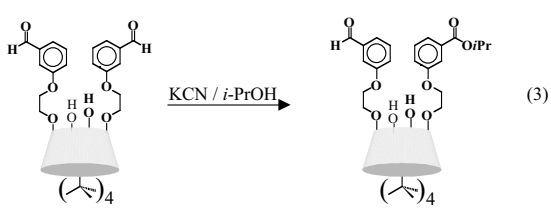
During our attempt to prepare benzoin derivative of calix[4]arene from the reaction of 25,27-bis-(3-formylphenoxyethoxy)-*p*-*tert*-butylcalix[4]arene 1, which was synthesized according to the literature procedure (eq 1),[11, 12] with 20% mole of KCN in ethanol, we observed a single product on TLC (eq 2). The product was isolated by recrystallization in methanol/CH_2Cl_2 to give a white crystalline material. The ^{1}H NMR and ^{13}C NMR spectra of the isolated material suggested that it was not the expected benzoin but the monoethyl ester 2 (50%). All the signals in ^{1}H NMR and ^{13}C NMR can be assigned corresponding to the proposed structure of the product with the aid of 2-D NMR spectroscopy, COSY, NOESY and HMBC.



(*p*-*tert*-butylcalix[4]arene) (**1**, 60%) (1)



(**1**) (**2**, 50%) (2)



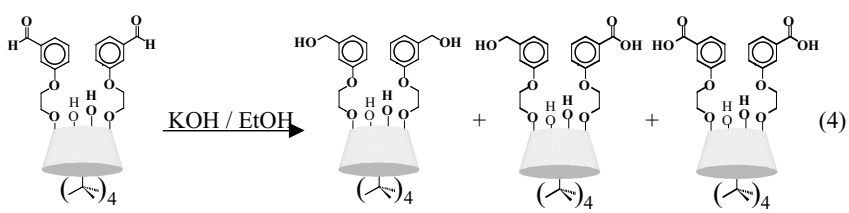
(**1**) (**3**, 15%) (3)

The mono-*i*-propyl ester 3 was synthesized through the reaction of KCN and aldehyde 1 in *i*-propanol (eq 3). As the product is unpredicted and the reaction showed rather unusual selectivity, we decided to investigate this reaction in further detail.

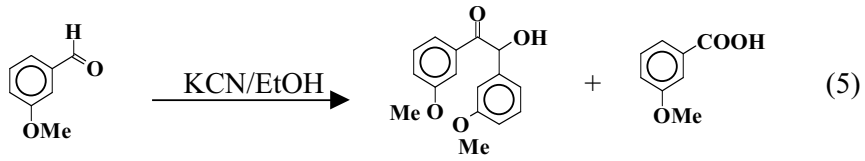
Two mechanistically different types of reactions, Cannizzaro reaction and autoxidation, may be responsible for the formation of the observed product. When the autoxidation reaction of 1 was performed in the present of air but without KCN, the TLC trace did not show any product but only the unreacted starting material, even after 5 days of reflux. The results indicated that the autoxidation of 1 did not proceed without KCN. The Cannizzaro reaction of bisaldehyde 1 was performed in ethanol using KOH yielding two products as white solids (eq 4). The first product is the bisalcohol 4 and the second isolated product is the alcohol-acid 5. The observation of the bisalcohol 4 suggested that there should be another product, the biscarboxylic acid 6. However, an attempt in to isolate 6 was not successful. As this reaction did not produce the aldehyde-ester 2, the Cannizzaro reaction could not account for the formation of the product 2 and 3 from 1.

As the experiments described previously did not provide any positive evidence supporting for either autoxidation or Cannizzaro reaction, a study of the model compound, *m*-anisaldehyde was initiated to acquire more information.

The reaction of *m*-anisaldehyde with 20% mole of KCN in ethanol, using the same reaction condition as the oxidation of the bisaldehyde 1 gave the corresponding benzoin 7 as a major product along with a minor oxidation product, *m*-methoxybenzoic acid 8 (eq 5). In the presence of KCN, the autoxidation is, therefore, a competitive reaction of benzoin



(**1**) (**4**, 16%) (**5**, 4%) (**6**) (4)



(**7**, 42%) (**8**, 20%)

formation. Interestingly, esterification of the autoxidation product 8 was not observed in this reaction.

According to the results described above, we proposed a mechanism of the formation of product 2 from 1 as a result of esterification of the autoxidation product of 1. The oxidation was catalyzed by cyanide anion and the esterification was presumably catalyzed by an acidic proton on the lower rim of *p-tert*-butylcalix[4]arene. The most intriguing point of this reaction is the selectivity of the autoxidation step, in which only one of the two aldehyde groups was oxidized. The reason for this selectivity remains elusive to us. We however suspect that it had something to do with the phenolic OH groups of the lower rim of *p-tert*-butylcalix[4] arene. These phenolic OH groups may act as intramolecular hydrogen bond donors to induce a geometry that protects one of the aldehyde groups from the attack of the cyanide anion. This unique geometry of bisaldehyde calixarene 1 may also prevent the formation of the corresponding benzoin from the reaction of 1.

It is important to point out that this autoxidation reaction differs significantly from similar oxidations reported in the literature. Corey and coworkers used 5 equivalents of NaCN and 10-15 equivalents of oxidizing agent, Ag_2O, to synthesize carboxylic acids from the corresponding conjugated aldehydes.[13, 14] Castells and his colleagues reported ester formation by using thiazolium salt or cyanide ion as a catalyst with nitrobenzene as an oxidizing agent.[15] In our reaction, however, no external oxidizing agent besides oxygen from air was required. We are now working toward a synthesis of chiral calixarenes using this selective autoxidation reaction.

Acknowledgements

This work was financially supported by the Thailand Research Fund (TRF) and the National Science and Technology Development Agency (NSTDA).

References

1. Arduini A, Pochini A, Secchi A and Ugozzoli F (1989) *Calixarenes 2001* (Editted by Asfari Z, BÖhmer V, Harrowfield J and Vicens J), pp 457-475. The Royal Society of Chemistry, Cambridge, UK.
2. Pitarch M, McKee V, Nieuwenhuyzen M and McKervey MA (1998) Synthesis of bridged, multifunctional calixarenes via ring closing metathesis. *J Org Chem* 63, 946-51.
3. Kim JS, Suh IH, Kim JK and Cho MH (1998) Selective sensing of cesium ions by novel calix[4]arene bis(dibenzocrown) ether in an aqueous environment. *J Chem Soc Perkin Trans* 1, 2307-11.
4. Leray I, O'Reilly F, Jiwan JLH, Soumillion JP and Valeur B (1999) A new calix[4]arene-based fluorescent sensor for sodium ion. *Chem Commun,* 795-6.
5. Jin T (1999) A new Na^+ sensor based on intramolecular fluorescence energy transfer derived from calix[4]arene. *Chem Commun,* 2491-2.
6. Beer P D, Timoshenko V, Maestri M, Passaniti P, Balzani V and Balzani B (1999) Anion recognition and fluorescent sensing by new ruthenium(II) and rhenium(I) bipyridyl calix[4] diquinone receptors. *Chem Commun,* 1755-6.
7. Seangprasertkij R, Asfari Z, Arnaud F and Vicens J (1994) Schiff-base *p-tert*-butylcalix[4]arenes – synthesis and metal-ion complexation. *J Org Chem* 59, 1741-4.
8. Pothsree T, Magee-Seangprasertkij R and Tuntulani T (1997) A di-aza-benzo crown-ether derived from *p-tert*-butyl calix[4] arenes – synthesis complexation of zinc cation. *J Incl Phenom* 29, 99-107.
9. Rojsajjakul T, Veravong S, Tumcharern G, Seangprasertkij-Magee R and Tuntulani T (1997) Synthesis and characterization of polyaza crown ether derivatives of calix[4]arene and their roles of anion receptors. *Tetrahedron* 53, 4669-80.
10. Tuntulani T, Ruangpornvisuti V, Tantikunwatthana N, Ngampaiboonsombut O, Seangprasertkij-Magee R, Asfari Z and Vicens J (1997) Synthesis of tripodal amine capped benzo crown *p-tert*-butylcalix[4]arene and its host-guest chemistry. *Tetrahedron Lett* 38, 3985-8.
11. Seangprasertkij R, Asfari Z, Arnaud F, Weiss J and Vicens J (1992) A schiff-base *p-tert*-butylcalix[4]arene – synthesis and metal-ion complexation. *J Incl Phenom* 14, 141-7.
12. Navakun K, Ruangpornvisuti V and Tuntulani T (2000) *p-tert*-butylcalix[4]arene derivatives containing azathiol receptors and their recognition towards Hg(II). *J Incl Phenom* 38, 113-22.
13. Corey EJ and Gilman NW (1968) New methods for the Oxidation of aldehydes to carboxylic acids and esters. *J Am Chem Soc* 90, 5616-8.
14. Lai G, Anderson WK (1997) A simplified procedure for the efficient conversion of aromatic aldehydes into esters. *Synth Commun* 27, 1281-3.
15. Castells J and Pujol F (1982) Oxidative benzoin reactions. *Tetrahedron* 38, 337-46.
16. Perrin DD, Armarego WLF (1988) *Purification of Laboratory Chemicals,* 3rd ed pp 16-17. Pergamon Press, Oxford, UK.