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One-pot Selective Formylation and Claisen Rearrangement on Calix[4]arenes

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A versatile synthon with formyl and allyl groups at the upper rim of calix[4]arene has been synthesized in two steps. Selective formylation of 25,27-diallyloxy-26,28-dihydroxycalix[4]arene, along with the Claisen rearrangement of the allyl groups, was achieved by reaction with hexamethylenetetraamine (hexamine) in glacial acetic acid. A control reaction of the dipropyl analogue shows that the selective formylation takes place independently of the Claisen rearrangement. The crystal structure of the dimethylacetal derivative of 5,17-diformyl-11,23-diallylcalix[4]arene is reported.

Keywords: Calixarenes; Formylation; Claisen rearrangement

INTRODUCTION

The calixarenes continue to attract attention as convenient frameworks for the assembly of receptors and sensors for a wide range of substrates. The efficient and selective introduction of reactive functional groups on to the macrocycle is therefore of interest, as indicated by the number of recent papers focused on the formylation of the upper rim of the calixarene [1–8]. Many of these employ the Gross formylation where the electrophilic reaction of dichloromethyl methyl ether is promoted by a Lewis acid [2,4,6]. Formylation using hexamethylenetetraamine (hexamine) in glacial acetic acid [8] or trifluoroacetic acid [3] (Duff reaction) has also been reported, but has not been used for selective formylation. Chawla *et al.* [3] have triformylated the upper ring of a disubstituted calix[4]arene using these conditions. The same conditions have been used to convert the upper-rim bromomethylcalix[4]-arene to the tetraformyl derivative in good yield (Sommelet reaction) [5]. We were interested in developing a convenient procedure for selective formylation that avoided the use of the carcinogenic and volatile dichloromethyl methyl ether. We report here the use of the Duff reaction for the selective formylation of diallyl and dipropyl-calix[4]arenes.

The rationale for our approach was based on the lower reactivity of aromatic rings substituted with alkoxy groups than those substituted with hydroxy groups. Therefore, it was expected that the formylation of the diallylcalix[4]arene (**1**) [9] would provide the diformylcalix[4]arene (**2**) or, if the alkoxy-substituted rings were not sufficiently deactivated, the tetraformyl derivative. Treatment of (**1**) with twenty equivalents of hexamine in glacial acetic acid at reflux gave, after hydrolysis, a product with an IR spectrum that clearly indicated that formylation had occurred ($\upsilon = 1686\,\mathrm{cm}^{-1}$). The ^{1}H NMR spectrum indicated that all the aromatic rings were substituted at the *para*-position (relative to the OH/OR group) (singlets were observed at δ 6.95 and 7.62 for the aromatic protons). However, the integration of the formyl protons corresponded to two hydrogens and the four methylene protons of the allyloxy groups were no longer present; instead a four-hydrogen doublet was observed at δ 3.20. These data were consistent with the presence of the rearranged diformylcalix[4]arene (**3**) (Scheme 1).

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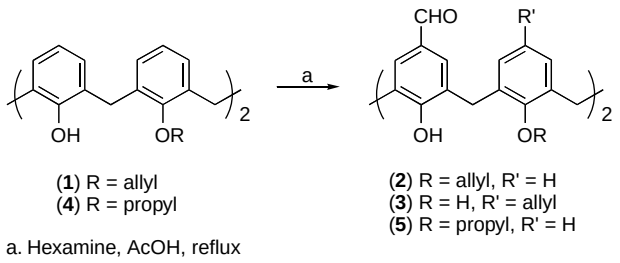
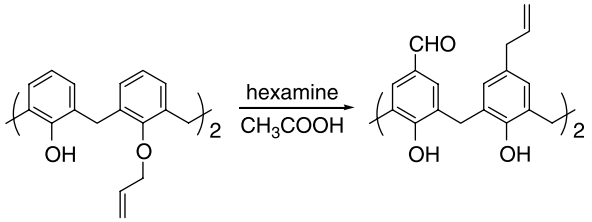


SCHEME 1 The selective formylation of distributed calix[4] arenes.

Confirmation of the structure was obtained from a single crystal X-ray structure of the dimethyl acetal derivative (**6**) of the calix[4]arene (**3**) [†]. The dimethyl acetal was obtained as a result of crystallization from ethyl acetate with diffusion of methanol; the ethyl acetate presumably contained sufficient acid to catalyse the acetal formation.



The calixarene assumes the typical cone conformation in the crystal (Fig. 1), with the phenol O atoms at the lower rim forming a hydrogen-bonded array. Interestingly, the calixarene cavity is not occupied by a solvent molecule as is typically the case, but instead a hermaphroditic dimer is formed, with the allyl group of an inversion-related macrocycle situated within the cavity defined by the aryl rings (Fig. 2).

The Claisen rearrangement of the allyloxy group into the *para*-allyl derivative was somewhat surprising as this is usually carried out thermally using *N*,*N*-diethylaniline at reflux (b.p. 217°C) [11]; here, the reaction was carried out in acetic acid at reflux (~115°C). In order to establish whether the observed Claisen rearrangement was independent of the formylation process, the diallyloxy derivative (**1**) was heated in boiling acetic acid overnight. The rearranged product, 5,17-diallyl-25,26,27,28-tetrahydroxycalix[4]arene (**7**) [9] was obtained as the only isolated product. In order to determine whether the formylation was indeed selective, the dipropyloxy derivative (**4**) [12] was treated under Duff formylation conditions. The ^{1}H NMR spectrum of the product obtained was consistent with a calixarene derivative which was disubstituted on both the upper and lower rim with formyl and propyl groups respectively, but did not indicate whether formylation had occurred on the phenolic ring. However, the HMBC spectrum (Fig. 3) of this formylation product confirmed the structure as that of the compound (**5**) [13]. Thus, cross peaks were observed between the OH & C^a, C^a & H^c, and H^c & C^e. A similar coupling sequence was observed for the alkylated ring, namely $C^{d'}$ & $H^{c'}$, $H^{c'}$ & $C^{a'}$ and $C^{a'}$ & $H^{e'}$.

In conclusion, this work describes a safe, convenient method for the selective formylation of calixarenes, which with the involvement of allyl substituents, can be combined with a Claisen rearrangement to give a polyfunctional upper-rim substituted calix[4]arene in two steps.

EXPERIMENTAL

Nuclear magnetic resonance spectra were acquired using Varian Gemini 200 (^{1}H at 200 MHz and ^{13}C at 50.3 MHz), Bruker 500 (^{13}C at 125 MHz) or Bruker 600 (^{1}H at 600 MHz) spectrometers. Infrared spectra were recorded on a Bruker Vector 22 FTIR spectrophotometer using potassium bromide discs. Melting points were measured on an Electrothermal 9100 apparatus. Elemental microanalyses were carried out by the Central Science Laboratory in the University of Tasmania. All solvents and reagents were analytical grade (AR) and were used as received from the suppliers.

25,27-Diallyloxy-26,28-dihydroxycalix[4]arene (**1**) [9] and 25,27-dipropoxy-26,28-dihydroxycalix[4]arene (**3**) [12] were prepared according to previously published methods. The ^{1}H NMR spectra and m.p. of these compounds were in agreement with those reported. 5,17-Diallyl-25,26,27,28-tetrahydroxycalix[4]arene (**7**) [9], obtained from the acid catalysed rearrangement of 11,23-diallyl-25,26,27,28-tetrahydroxycalix[4]arene (**1**) had an ^{1}H NMR spectrum and m.p. in agreement with those reported [9].

5,17-Diformyl-11,23-diallyl-25,26,27,28-tetrahydroxycalix[4]arene (3)

Hexamine (1.47 g, 10.50 mmol) and 25,27-diallyloxy-26,28-dihydroxycalix[4]arene (**1**) (0.25 g, 0.50 mmol) were dissolved in glacial acetic acid (8 mL) and heated at reflux for 24 h. Water (5 mL) was then added and the reflux continued for another 4 h. The mixture was then poured onto ice (20 g) and stirred for 1 h. The solution was extracted with ethyl acetate

[†] $C_{40}H_{44}O_8$, $M_r = 652.8$. Triclinic, space group $P\bar{1}$ (C_i^1, No.2), $a = 10.384(1)$, $b = 12.844(1)$, $c = 13.871(1)$ Å, $\alpha = 98.615(2)$, $\beta = 108.600(2)$, $\gamma = 99.084(2)°$, $V = 1691$ Å^3. D_c ($Z = 2$) = 1.282 g cm^{-3}. $\mu_{Mo} = 0.9$ cm^{-1}; specimen: 0.35 × 0.14 × 0.11 mm; $T_{min/max}$ (multiscan correction) = 0.91. $2\theta_{max} = 55°$; N_{total} (full sphere of CCD instrument data, T ca. 153 K) = 19258, $N_{unique} = 7819$ ($R_{int} = 0.027$), N_{obs} ($F > 4\sigma(F)$) = 5408 reflections; $R = 0.056$, R_w(weights: $(\sigma^2(F) + 0.0005F^2)^{-1}$): = 0.064. ($x$,$y$,$z$,$U_{iso}$)$_H$ constrained at estimates, OH modelled as disordered (see Fig. 1) from difference map evidence. $|\Delta\rho_{max}|$ 0.46(3) e Å^{-3}. CCDC: 253375

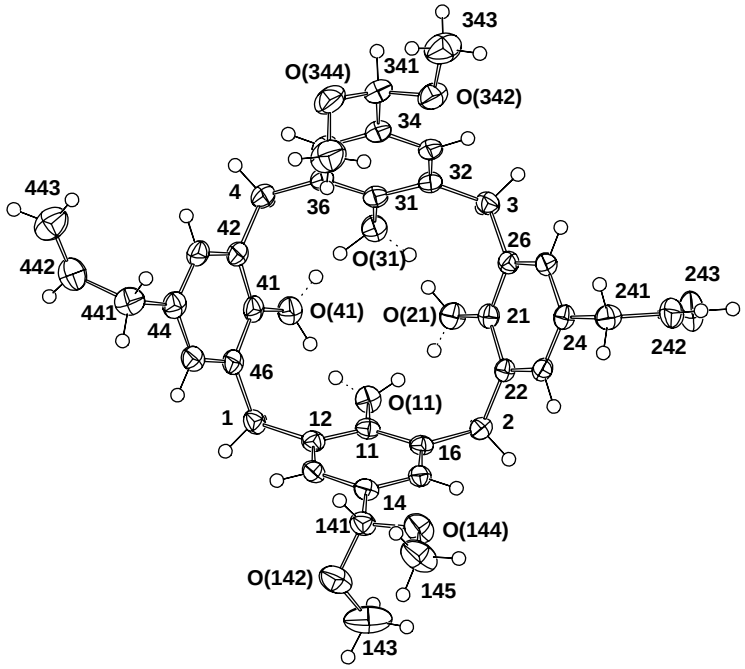


FIGURE 1 Projection of a molecule of **6**, down its *quasi*-symmetry axis, showing 50% probability amplitude ellipsoids for C,O, H having arbitrary radii of 0.1 Å. O(11)…O(21,41) are 2.676(2), 2.669(2), O(31)…O(21,41) 2.651(3), 2.662(2) Å. The (C_6) aromatic ring plane dihedral angles to the O_4 plane ($\chi^2 = 327$) are (planes 1–4): 60.27(7), 52.24(7), 57.92(8), 49.96(8)°.

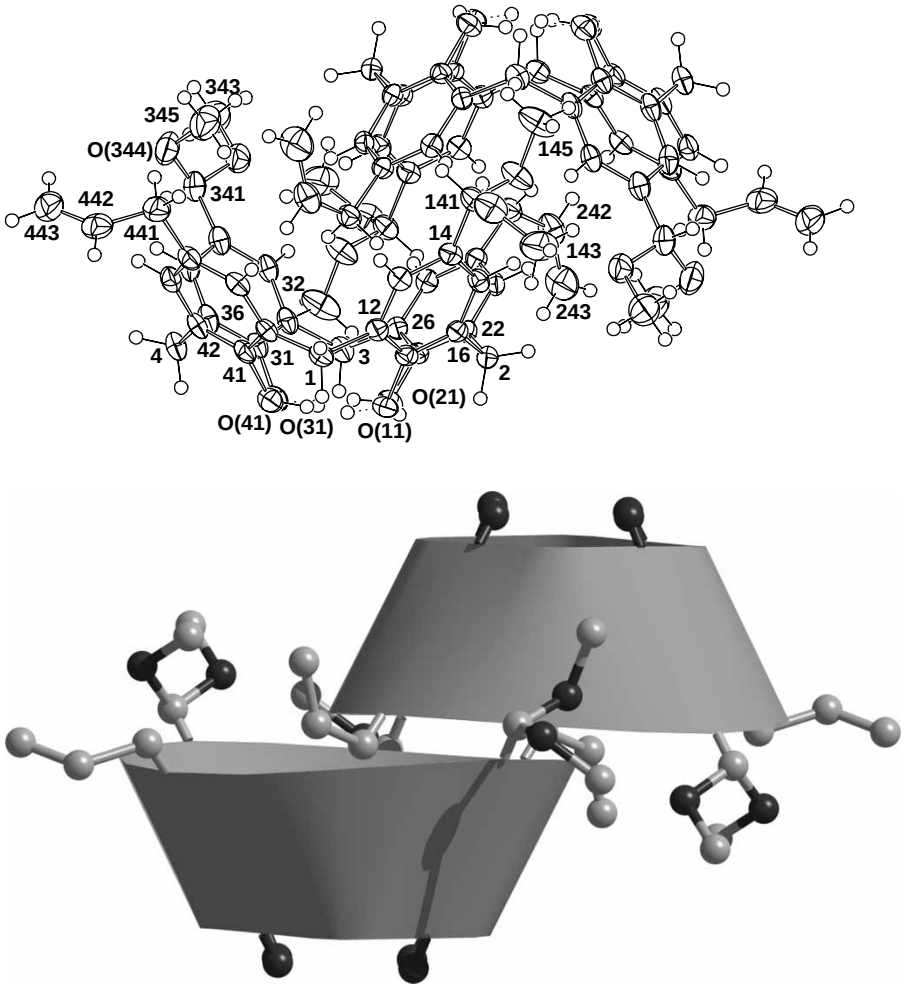


FIGURE 2 Ortep and stylised representation [10] of the pairwise intermeshing of inversion-related macrocycles, with an allyl group situated in the cavity of the neighbouring molecule. The closest allyl C atom approach to an aromatic ring centroid is 3.53 Å for C242···Ring 4.

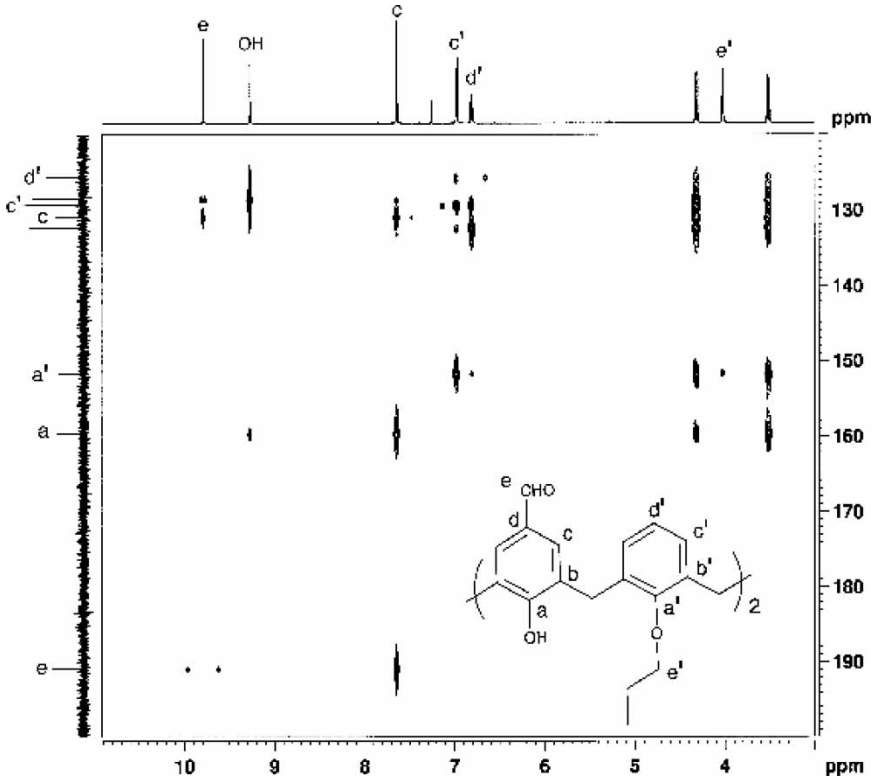


FIGURE 3 An expanded HMBC spectrum of the compound (**5**).

(4 ×, 30 mL). The organic fractions were combined and washed with saturated sodium bicarbonate solution (30 mL) then water (30 mL) and finally brine (30 mL). The solvents were removed and the crude product recrystallised from methanol/water (3:1, 15 mL) to give the product as a yellow powder (0.12 g, 0.21 mmol, 40%, m.p. 228°C (decomp)) which was characterised as the bis(dimethyl acetal) (**6**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.21 (d, $J = 6.6$ Hz, 4H, C**H**$_2$CH═), 3.66 (broad, s, 4H, Ar–C**H**$_2$–Ar), 4.25 (broad, s, 4H, Ar–C**H**$_2$–Ar), 5.0–5.1 (m, 4H, ═C**H**$_2$), 5.7–5.9 (m, 2H, ═C**H**), 6.94 (s, 4H, Ar), 7.61 (s, 4H, Ar), 9.77 (s, 2H, C**H**O). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.3 (Ar**C**H$_2$Ar), 39.9 (Ar**C**H$_2$CHCH$_2$), 116.7, 128.0, 129.6, 130.2, 131.8, 135.3, 137.8, 147.1, 155.5, (Ar, C═C), 191.2 (**C**HO) IR ν (KBr) 3179 cm^{-1} (OH), 2924 cm^{-1} (CH$_2$), 1686 cm^{-1} (C═O), 1593 cm^{-1} (Ar).

5,17-Bis(dimethoxymethyl)-11,23-diallyl-25,26,27,28-tetrahydroxycalix[4]arene (6)

A saturated solution of 5,17-diformyl-11,23-diallyl-25,26,27,28-tetrahydroxycalix[4]arene (**3**) in ethyl acetate was prepared and methanol was allowed to slowly diffuse into the solution to give the dimethyl acetal as orange crystals. $C_{40}H_{44}O_8$: requires C 73.6; H 6.8; Found: C 73.5; H 6.6%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.18 (d, $J = 7.0$ Hz 4H, Ar–C**H**$_2$CH) 3.26 (s, 12H, –OC**H**$_3$), 3.50 (broad, s, 4H, Ar–C**H**$_2$–Ar), 4.20 (broad, s, 4H, Ar–C**H**$_2$–Ar), 5.04 (m, 4H, ═C**H**$_2$), 5.20 (s, 2H, –C**H**(OCH$_3$)$_2$), 5.84 (m, 2H, ═C**H**), 6.86 (s, 4H, Ar–**H**), 7.12 (s, 4H, Ar–**H**), 10.20 (s, 4H, –O**H**). ^{13}C NMR‡ (50 MHz, $CDCl_3$) δ 32.5 (Ar–C**H**$_2$–Ar), 40.0 (Ar–**C**H$_2$CH), 53.4 (Ar–CH(O**C**H$_3$)$_2$), 103.6 (Ar–**C**H(OCH$_3$)$_2$), 116.2, 128.0, 128.7, 128.8, 129.8, 132.3, 134.3, 138.2, 147.6, 149.7 (Ar, C═C). IR ν (KBr) 3162 cm^{-1} (OH), 2938 cm^{-1} (CH$_3$), 1466 cm^{-1} (Ar).

5,17-Bis(formyl)-25,27-dipropoxy-26,28-dihydroxycalix[4]arene (5)

Hexamine (4.63 g, 33.0 mmol) was added to a solution of 25,27-dipropoxy-26,28-dihydroxycalix[4]arene (**4**) (0.32 g, 0.63 mmol) and trifluoroacetic acid (5 mL) in acetic acid (5 mL, glacial), and heated at reflux for 96 h. Water (5 mL) was added and the reflux continued for another 4 h. Water (50 mL) was added and the mixture stirred for 2 h. The precipitate was filtered and recrystallised from dichloromethane/methanol to

‡The acetal was unstable in $CDCl_3$ and decomposed to the formyl derivative (**3**) fairly rapidly. The ^{13}C NMR spectrum contained signals due to the formyl derivative even though the ^{1}H NMR spectrum obtained immediately beforehand showed the product to be the acetal and no signals attributable to the formyl derivative were observed. However, the proton spectrum of the same sample, obtained immediately after the ^{13}C NMR spectrum was recorded had a significant signal for the formyl proton. The $CDCl_3$ was passed through basic alumina prior to use.

give the product as a white powder (0.20 g, 0.35 mmol, 56%, mp. 313–315°C, Lit. [13] >320°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (t, $J = 7.4$ Hz, 6H, $-CH_3$), 2.06–2.12 (m, 4H, $-CH_2CH_3$), 3.51 (d, 4H, $J = 13.2$ Hz, Ar$-CH_2-$Ar), 4.02 (t, $J = 6.2$ Hz 4H, $-OCH_2$), 4.31 (d, 4H, Ar$-CH_2-$Ar) 6.80 (t, $J = 7.6$ Hz, 2H, Ar), 6.97 (d, 4H, Ar), 7.64 (s, 2H, Ar) 9.25 (s, 2H, OH), 9.79 (s, 2H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (CH_3), 23.4 (CH_3CH_2), 31.3 (ArCH_2Ar), 78.6 (OCH_2), 125.6, 128.5, 128.6, 129.4, 130.9, 132.4, 151.7, 159.6 (Ar), 190.9 (CHO).,IR ν (KBr) 3312 cm^{-1} (OH), 1684 cm^{-1} (C=O), 1465 cm^{-1} (Ar).

SUPPLEMENTARY MATERIAL

NMR spectra and characterization for compounds **3**, **5** & **6**, available from: http://espace.lis.curtin.edu.au/archive/00000497/.

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