Pergamon

Tetrahedron Letters 43 (2002) 2495–2498

TETRAHEDRON LETTERS

A one-step, one-pot synthesis of *p*-acyl calix[*n*]arenes

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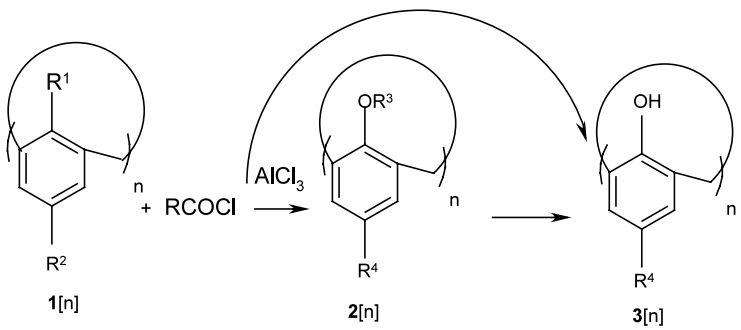
Received 22 August 2001; revised 6 February 2002; accepted 18 February 2002

Abstract—A one-step, one-pot procedure for conversion of *p*-*tert*-butylcalix[*n*]arenes to their *p*-acyl derivatives has been achieved.

Calixarenes are cavity-containing macrocyclic compounds with two distinct hydrophobic (upper rim) and hydrophilic (lower rim) regions in their molecular architecture. They have considerable potential to be developed into varied molecular hosts for recognition of ions and neutral organic compounds. A large number of publications have appeared on various aspects of calixarenes and a number of reviews on the subject have been published.[1] Invariably, the starting materials for a variety of these transformations are *p*-*tert*-butylcalix[*n*]arenes. Lower rim functionalization of phenolic hydroxyls in calixarenes are comparatively straightforward reactions[2], but upper rim functionalization (i.e. acylation) generally involves de-*tert*-butylation with $AlCl_3$/phenol to provide moderate yields of the intermediates for further manipulation.[3] *p*-Aroylation/acylation of calixarenes is normally achieved in three steps which include de-*tert*-butylation, treatment with an acyl halide to yield *p*-acyl calix[*n*]arene esters, with subsequent hydrolysis of the resultant esters to yield the target acylated calixarenes. Alternatively, the target molecules can be obtained by etherification[4] or esterification of the lower rim hydroxyls followed by Lewis acid catalyzed Friedel–Crafts acylation with acyl halides. Subsequent dealkylation or deesterification of the acylated calix[*n*]arene ethers/esters provides the target molecules. Both these synthetic approaches either provide the desired compounds in low yields or involve



Where R^1	R^2	R^3	R^4	R^4
1[n]a	OH, H	**2**[n]a CO-C_6H_5	CO-C_6H_5	**3**[n]a CO-C_6H_5
1[n]b	OH, *t*-Bu	**2**[n]b CO-2-OH-C_6H_4	CO-2-OH-C_6H_4	**3**[n]b CO-2-OH-C_6H_4
1[n]c	OMe, *t*-Bu	**2**[n]c $COC(CH_3)_3$,	CO-$C(CH_3)_3$	**3**[n]c CO-$C(CH_3)_3$
		2[n]d CO-CH_3	*t*-Bu	**3**[n]f CO-4-NO_2-C_6H_4
		2[n]e CO-CH_3CH_2	*t*-Bu	

n = 4, 6, 8

Scheme 1.

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0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00325-8

a number of reactions which lead to complicated reaction mixtures requiring the usual chromatographic separations at each stage. Rarely, the synthesis of *p*-acyl calix[*n*]arenes has been achieved in a single step from readily available starting molecules. In the recent past, *p*-acyl calix[*n*]arenes have been prepared by No and Kim[5] and Chawla et al.[6] via the Fries rearrangement of calix[4]arene esters and by Huang and co-workers[7] and Nanda,[8] via a Friedel–Crafts acylation of calix[4]arene in nitrobenzene. While the Fries migration provides poor yields (25–38%), the Friedel–Crafts acylation in nitrobenzene involves cumbersome removal of the solvent by steam distillation. The Friedel–Crafts acylation reaction also leads to the formation of side products and in addition may result in a change in the original conformation. In this communication, we report an efficient one-pot, one-step procedure for the synthesis of *p*-acyl calix[*n*]arenes from *p-tert*-butylcalix[*n*]arenes which has been repeated several times and optimized to obtain the best yields of *p*-acyl calix[*n*]arenes (Scheme 1). The products have been identified by ^{1}H NMR, ^{13}C NMR, IR and FAB mass spectrometry as well as by comparison with data available in the literature (Table 1).[3–9]

Two procedures were adopted in our work to prepare the *p*-acyl calix[*n*]arenes. In procedure A, nitrobenzene was used as the solvent, while in procedure B, dichloromethane was used as the solvent. It has been observed that the acylation occurs in higher yields (85–90%)[9] and the compounds obtained were purer in dichloromethane than when nitrobenzene was used as the solvent which does not seem to offer the expected advantage of getting *p*-acyl calix[*n*]arenes despite a cumbersome step of steam distillation for product isolation. The only side reaction observed in the procedure being reported is dealkylation of some calixarene ethers which can be advantageous in some cases because *p*-acyl calix[*n*]arenes are obtained directly from the starting materials. It is significant to note that the present method can be utilized to obtain either **2** or **3**. To obtain **3** directly from **1**, one needs to add the reaction mixture in nitrobenzene to a dilute HCl solution and carry out the steam distillation. Alternatively, to stop the reaction at stage **2** the reaction mixture must be added to cold water (also for reactions carried out in nitrobenzene followed by steam distillation) followed by extraction of the product into dichloromethane.

Table 1. Acylation of *p-tert*-butylcalix[*n*]arenes with acyl chlorides

Starting calix[*n*]arene	RCOCl (R)	Solvent	Product	Time (h)	% Yield	mp (°C)	mp (°C) (Lit.)
1[4]a	C_6H_5	CH_2Cl_2	**2**[4]a	24	83	114–115	–
1[4]b	C_6H_5	CH_2Cl_2	**2**[4]a	24	80	114–115	–
1[4]b	C_6H_5	$C_6H_5NO_2$	**2**[4]a[b]	24	75	113–115	–
1[4]b	C_6H_5	$C_6H_5NO_2$	**3**[4]a[c]	24	67	>280	176–178[7] and 331–332[4]
1[4]c	C_6H_5	CH_2Cl_2	**2**[4]a	48	62	118–119	–
1[6]a	C_6H_5	CH_2Cl_2	**2**[6]a	24	80	190–192	–
1[6]b	C_6H_5	CH_2Cl_2	**2**[6]a	24	86	190–191	–
1[6]b	C_6H_5	$C_6H_5NO_2$	**2**[6]a[b]	24	74	190–192	–
1[6]b	C_6H_5	$C_6H_5NO_2$	**3**[6]a[c]	24	61	261–262	258–260[7]
1[6]c	C_6H_5	CH_2Cl_2	**2**[6]a	48	65	192–194	–
1[8]a	C_6H_5	CH_2Cl_2	**2**[8]a	24	83	126–128	–
1[8]b	C_6H_5	CH_2Cl_2	**2**[8]a	24	84	125–126	
1[8]b	C_6H_5	$C_6H_5NO_2$	**2**[8]a[b]	24	71	124–126	–
1[8]b	C_6H_5	$C_6H_5NO_2$	**3**[8]a[c]	24	59	213–214	213–215[7]
1[8]c	C_6H_5	CH_2Cl_2	**2**[8]a	48	65	130–132	–
1[4]b	2-CH_3O-C_6H_4	CH_2Cl_2	**2**[4]b[a]	40	75	170–171	
1[4]b	$(CH_3)_3C$	CH_2Cl_2	**2**[4]c	38	63	78–80	–
1[4]b	CH_3	CH_2Cl_2	**2**[4]d	48	69	>280	383–386[3]
1[6]b	CH_3	$C_6H_5NO_2$	**2**[6]d	24	59	>280	–
2[8]b	CH_3	CH_2Cl_2	**2**[8]d	48	73	>280	–
1[6]b	CH_3	CH_2Cl_2	**2**[6]d	48	67	>280	–
1[4]b	C_2H_5	CH_2Cl_2	**2**[4]e	48	72	>280	–
1[4]b	4-NO_2-C_6H_4	CH_2Cl_2	**3**[4]f	32	39	>280	–
2[4]a	–	MeOH/aq. NaOH	**3**[4]a	6	91	178–180	176–178[7] and >331 –332[4]
2[6]a		MeOH/aq. NaOH	**3**[6]a	6	88	261–263	258–260[7]
2[8]a		MeOH/aq. NaOH	**3**[8]a	6	90	214–215	213–215[7]
2[4]b		MeOH/aq. NaOH	**3**[4]b	6	89	>280	–
2[4]c		MeOH/aq. NaOH	**3**[4]c	4	67	>280	–

[a] The reaction also gives small amounts of methylated derivatives.
[b] Reaction mixture was added to cold water.
[c] Reaction mixture was added to dil. HCl soln.

The reaction is believed to proceed via *ipso*-substitution of the *p*-*tert*-butyl group by the acyl carbocation. The *tert*-butyl group can be easily displaced in accordance with the migratory aptitude of the leaving group in *ipso* electrophilic substitution as $t\text{-Bu}^+ \gg \text{I}^+ > \text{C}_6\text{H}_5\text{CO}^+ = \text{Br}^+ > \text{Cl}^+$ as observed by Perrin et al.[10] as well as by us in our experiments on *ipso*-nitration.[11] This view is confirmed by the fact that the reaction fails in the case of *ipso* acetylation because of the comparative lower stability of CH_3CO^+ as compared to $C_6H_5CO^+$ and 2-OCH_3-C_6H_4-CO^+. For the same reason, no reaction was observed in the case of propanoyl chloride and acetyl chloride and a low yield was obtained in the case of $(CH_3)_3CCOCl$. Further work to ascertain the mechanism and utility of the reaction in the design of novel molecular receptors is in progress.

Acknowledgements

The authors are thankful to UGC for a fellowship (S.K.) and DST for providing financial support (H.M.C.).

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9. *General procedure*: In a typical procedure *p*-*tert*-butylcalix[*n*]arene (0.5 g) is treated with aluminum chloride in dry dichloromethane (25 ml) followed by dropwise addition of acyl chloride (5 ml) in dry dichloromethane (20 ml) over a period of 30 min at 0–5°C. The reaction mixture is stirred at 25°C for 24 h and then poured into ice-water mixture. The dichloromethane layer is successively washed with 0.1N hydrochloric acid and 10% sodium bicarbonate solution to remove the unreacted acyl chloride. The dichloromethane layer on concentration provides *p*-acyl calix[*n*]arene esters which can be hydrolyzed to provide the *p*-acyl calix[*n*]arenes.
   Identification of the products:[12] NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument, IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks, while CHN analyses were obtained using a Perkin–Elmer 240C elemental analyzer. Mass spectra were recorded on a Jeol SX-102 spectrometer.
   ***p*-Tetrabenzoyltetrabenzoyloxycalix[4]arene: 2**[4]a
   IR (KBr, ν/cm^{-1}): 3060, 2924, 1727 (ester CO), 1652 (ketone CO), 1598, 1450, 1319, 1263, 1170, 1092, 1059, 1023. ^{1}H NMR ($CDCl_3$, 300 K, δ): 8.10–7.3 (25H, m, ArH), 7.21–6.52 (23H, m, ArH), 3.85–3.46 (8H, m, $ArCH_2Ar$). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.1, 126.1, 128.4, 129.9, 131.3, 132.1, 133.6, 134.6, 137.1, 145.3, 146.9, 148.7, 150.9, 164.2, 194.8 (CO). FAB MS: (m/z): 1256 (M^+). Anal. calcd for $C_{84}H_{56}O_{12}$ (1255.3): C, 80.24; H, 4.48. Found: C, 79.71; H, 4.76.
   ***p*-Hexabenzoylhexabenzoyloxycalix[6]arene: 2**[6]a
   IR (KBr, ν/cm^{-1}): 3061, 2923, 1735.5 (ester CO), 1653 (ketone CO), 1599, 1450, 1263.9, 1173, 1059. ^{1}H NMR ($CDCl_3$, 300 K, δ): 8.06–6.97 (72H, m, ArH), 3.7 (12H, s, $ArCH_2Ar$). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.0, 126.1, 128.4, 129.7, 131.7, 132.3, 132.8, 133.6, 133.8, 135.2, 137.0, 147.2, 150.9, 163.9, 194.8 (CO). FAB MS: (m/z) = 1885 $(M-1)^+$. Anal. calcd for $C_{126}H_{84}O_{18}$ (1886): C, 80.24; H, 4.48. Found: C, 79.65; H, 4.66.
   ***p*-Octabenzoyloctabenzoyloxycalix[8]arene: 2**[8]a
   IR (KBr, ν/cm^{-1}): 3062, 2961, 1736 (ester CO), 1659.7 (ketone CO), 1600, 1450.6, 1263, 1173, 1059, 1023. ^{1}H NMR ($CDCl_3$, 300 K, δ): 8.05–7.23 (67H, m, ArH), 7.05–6.80 (29H, m, ArH), 3.62 (s, 16H, $ArCH_2Ar$). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.1, 126.1, 128.1, 128.4, 129.9, 131.7, 132.2, 133.6, 133.8, 135.1, 137.0, 147.1, 150.9, 163.8, 194.7 (CO). Anal. calcd for $C_{168}H_{112}O_{24}$ (2512): C, 80.24; H, 4.48. Found: C, 79.75: H, 4.43.
   ***p*-Tetra(2-hydroxybenzoyl)tetra(2-hydroxybenzoyloxycalix[4]arene: 2**[4]b
   IR (KBr, ν/cm^{-1}): 3423 (OH), 1684 (ester CO), 1614 (ketone CO), 1583, 1484, 1301, 1155. ^{1}H NMR ($CDCl_3$, 300 K, δ): 8.36–6.89 (m, 40H, ArH), 3.92–3.70 (m, 8H, $ArCH_2Ar$), 4.81 (s, 8H, OH). ^{13}C NMR (DMSO-d_6, 343 K, δ): 30.3, 111.9, 116.5, 117.0, 120.2, 123.4, 126.0, 128.1, 129.8, 129.8, 131.2, 132.5, 133.2, 135.0, 156.3, 160.3, 165.2, 170.4, 193.1 (CO). Anal. calcd for $C_{84}H_{56}O_{20}\cdot H_2O$ (1403.4): C, 71.89; H, 4.16. Found: C, 71.33; H, 4.18.
   ***p*-Tetra(2,2-dimethylpropanoyl)tetra(2,2-dimethylpropanoyl)oxycalix[4]arene: 2**[4]c
   IR (KBr, ν/cm^{-1}): 1743 (ester CO), 1666 (ketone CO), 1593, 1477, 1108. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.81–6.90 (m, 8H, ArH), 4.22–3.34 (m, 8H, $ArCH_2Ar$), 1.41–0.90 (m, 72H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6, 300 K δ): 25.2, 27.2, 28.2, 30.8, 43.1, 128.6, 130.1, 145.6, 148.6, 156.9, 157.4, 159.1, 176.9, 179.6, 201.8, 203.9 (CO). Anal. calcd for $C_{68}H_{88}O_{12}\cdot CHCl_3$ (1216.8): C, 68.11; H, 7.37. Found: C, 67.39; H, 7.16.
   ***p*-Tetrabenzoyltetrahydroxycalix[4]arene: 3**[4]a
   IR (KBr, ν/cm^{-1}): 3459 (OH), 1646 (ketone CO), 1596.8, 1446.5, 1322, 1013. ^{1}H NMR (DMSO-d_6, 300 K, δ): 7.53–6.52 (m, 28H, ArH), 4.33 (bs, 8H, $ArCH_2Ar$). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.1, 126.1, 128.3, 129.9, 132.3, 133.5, 137.0, 147.3, 164.2, 194.1 (CO). FAB MS: (m/z): 840. Anal. calcd for $C_{56}H_{40}O_8\cdot 2H_2O$ (876.9): C, 76.70; H, 5.06. Found: C, 76.55; H, 4.92.
   ***p*-Hexabenzoylhexahydroxycalix[6]arene: 3**[6]a
   IR (KBr, ν/cm^{-1}): 3218 (OH), 1695 (ketone CO), 1602, 1486, 1204, 1025. ^{1}H NMR (DMSO-d_6, 300 K, δ): 7.96–6.63 (m, 42H, ArH), 3.85 (s, 12H, $ArCH_2Ar$). ^{13}C NMR (DMSO-d_6, 300 K, δ): 31.4, 119.4, 128.1, 129.1, 130.9, 131.3, 135.3, 138.7, 152.3, 194.1 (CO). FAB MS: (m/z): 1261. Anal. calcd for $C_{84}H_{60}O_{12}\cdot 3H_2O$ (1315.4): C, 76.70; H, 5.06. Found: C, 76.02; H, 5.03.

***p*-Octabenzoyloctahydroxycalix[8]arene: 3**[8]a
IR (KBr, ν/cm^{-1}): 3245 (OH), 1653 (ketone CO), 1596, 1484, 1484, 1322, 11212, 1122. ^1H NMR (DMSO-d_6, 300 K, δ): 7.56–6.63 (m, 56H, ArH), 3.79 (s, 16H, $ArCH_2Ar$). ^{13}C NMR (DMSO-d_6, 300 K, δ): 31.9, 120.9, 128.2, 128.5, 129.2, 131.0, 136.5, 149.3, 150.4, 194.2 (CO). FAB MS (m/z): 1680 (M^+-1). Anal. calcd for $C_{112}H_{80}O_{16}$ (1681): C, 79.98; H, 4.79. Found: C, 79.75; H, 4.43.

***p*-Tetra(2-hydroxybenzoyl)calix[4]arene: 3**[4]b
IR (KBr, ν/cm^{-1}): 3467 (OH), 1624 (ketone CO), 1583, 1456, 1303, 1200, 1011. ^1H NMR (DMSO-d_6, 300 K, δ): 7.78–6.76 (m, 24H, ArH), 4.42, 4.38 (d, 4H, $J=12$ Hz, $ArCH_2Ar$), 4.09, 4.05 (d, 4H, $J=12$ Hz, $ArCH_2Ar$), 12.95 (bs, 4H, OH), 12.50 (s, 4H, OH). Anal. calcd for $C_{56}H_{40}O_{12}\cdot 4H_2O$ (977): C, 68.85; H, 4.95. Found: C, 69.18; H, 4.85.

***p*-Tetra(2,2-dimethylpropanoyl)calix[4]arene: 3**[4]c
IR (KBr, ν/cm^{-1}): 3186 (OH), 2959, 1667 (ketone CO), 1594, 1458.9, 1365, 1288, 1134. ^1H NMR ($CDCl_3$, 300 K, δ): 7.64 (s, 8H, ArH), 4.06 (bs, 8H, $ArCH_2Ar$), 1.20 (s, 36H, *t*-Bu), 10.1 (s, 4H, OH). Anal. calcd for $C_{48}H_{56}O_8$ (778.9): C, 74.0; H, 7.50. Found: C, 73.94; H, 7.35.

***p*-Tetra(4-nitrobenzoyl)calix[4]arene: 3**[4]f
IR (KBr, ν/cm^{-1}): 3177 (OH), 2956, 1693 (ketone CO), 1601, 1461, 1290, 1190. ^1H NMR (DMSO-d_6, 300 K, δ): 8.37–8.28 (m, 6H, ArH), 8.17–8.10 (m, 18H, ArH), 4.5–3.6 (bs, 8H, $ArCH_2Ar$). Anal. calcd for $C_{56}H_{36}O_{20}N_4\cdot 4H_2O$ (1156.9): C, 58.13; H, 3.83; N, 4.84. Found: C, 58.20; H, 3.71; N, 4.91.

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