Pergamon

Tetrahedron Letters 43 (2002) 7073–7075

TETRAHEDRON LETTERS

One step facile synthesis of bromo calix[*n*]arenes

Satish Kumar, H. M. Chawla and R. Varadarajan*

Department of Chemistry, Indian Institute of Technology, New Delhi, India

Received 14 May 2002; revised 16 July 2002; accepted 26 July 2002

Abstract—Bromination of *p*-*tert*-butyl calix[*n*]arenes under different reaction conditions can provide either methylene bridge or ring substituted calix[*n*]arenes that are usually only amenable through long circuitous routes.

Calixarenes are macrocyclic metacyclophanes which are important molecules for designing a variety of molecular receptors through appropriate derivatization[1] at the upper rim or the lower rim of the calixarene architecture. Usually upper rim functionalization of calix[*n*]arenes is carried out by debutylation[2] of the *p*-*tert*-butyl group followed by subsequent reactions. For example, *para*-bromination of calix[*n*]arenes has been achieved by No et al.[3] through debutylation of *p*-*tert*-butylcalixarenes followed by reaction with bromine in chloroform. Similarly Gutsche et al.[4] have achieved *p*-bromination of calix[4]arene methyl ether with NBS in ethyl methyl ketone, using bromine in chloroform and Fe metal as a catalyst and also by demethylation of tetrabromotetramethoxycalix[4]arene using BBr_3. Bromination of tetramethoxycalix[4]arene has also been reported by Klenke et al.[5] to yield 2,8,14,20-tetrabromocalix[4]arene in 48% yield. From theoretical calculations, the latter reaction has been speculated to give predominantly the eeee (all equatorial) isomer. No experimental conditions seem to have been reported for obtaining bromocalix[*n*]arenes without involving a debutylation step or via *ipso*-substitution of *p*-*tert*-butylcalix[*n*]arenes. Although in the

Table 1. Bromination of *p*-*tert*-butyl calix[*n*]arene

Calix[*n*]arene	Solvent	Reagent	Product	Temperature	Time (h)	% Yield	Mp (°C)	Mp (°C) lit.
1[4]a	CH_2Cl_2	AcOH/Br_2+Fe	**2**[4]a	Rt	48	67	>280	>480,[4a] 314–318[4b] and 315–317[3]
1[6]a	CH_2Cl_2	AcOH/Br_2+Fe	**2**[6]a	Rt	48	59	>280	
1[8]a	CH_2Cl_2	AcOH/Br_2+Fe	**2**[8]a	Rt	48	56	>280	
1[4]b	CH_2Cl_2	AcOH/Br_2+Fe	**2**[4]b	Rt	48	71	250–251	249–251[4a]
1[6]b	CH_2Cl_2	AcOH/Br_2+Fe	**2**[6]b	Rt	30	62	>280	
1[8]b	CH_2Cl_2	AcOH/Br_2+Fe	**2**[8]b	Rt	48	41	>280	
1[4]b	MEK	NBS	**2**[4]b	Rt	48	65	270–272	269–270[4a] and 270–271[3]
1[6]b	MEK	NBS	**2**[6]b	Rt	48	67	>280	
1[8]b	MEK	NBS	**2**[8]b	Rt	48	63	>280	
1[4]a	$CHCl_3$	AcOH/HBr^x	**2**[4]a	Reflux	12	76	>280	>480,[4a] 314–318[4b] and 315–317[3]
1[6]a	$CHCl_3$	AcOH/HBr^x	**2**[6]a	Reflux	12	73	>280	
1[8]a	$CHCl_3$	AcOH/HBr^x	**2**[8]a	Reflux	12	73	>280	
1[4]b	CCl_4	NBS	**2**[4]c	Reflux	32	57	>280	
1[6]b	CCl_4	NBS	**2**[6]c	Reflux	32	55	>280	
1[8]b	CCl_4	NBS	**2**[8]c	Reflux	32	39	>280	

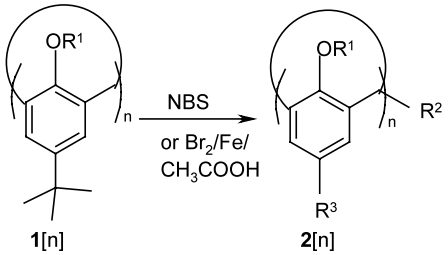
NBS = *N*-bromosuccinimide. MEK = ethyl methyl ketone. x = 47% aq. HBr solution was used.

* Corresponding author. Tel.: +91-11-659-1530; fax: +91-11-6862037; e-mail: varada@chemistry.iitd.ernet.in

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01548-4

present work, bromination experiments have been conducted with HBr in acetic acid, bromine in chloroform/acetic acid, CCl_4, and water, as well as via reactions of NBS in acetone and ethyl methyl ketone under a variety of reaction parameters, only optimized conditions are given in Table 1 which give *p*-bromocalixarenes and methylene bridge brominated calix[*n*]arenes directly (Scheme 1).[6]

The *p*-*tert*-butylcalixarenes and their methyl ethers used as substrates in this study were obtained by procedures reported in the literature[7] and were identified by comparison with authentic samples. The bromination reagents used were Br_2/CH_3COOH or HBr/CH_3COOH in conjunction with iron as a promoter as well as *N*-bromosuccinimide in CCl_4, ethyl methyl ketone or acetone. It has been found that *p*-*tert*-butylcalix[*n*]arenes and their methyl ethers undergo replacement of the *p*-*tert*-butyl group with bromine in the dark. The reaction of NBS with *p*-*tert*-butylcalix[*n*]arene led to the formation of a mixture of products which were difficult to separate. However, when the reaction was repeated with *p*-*tert*-butylcalix[*n*]arene methyl ether and NBS in ethyl methyl ketone, it gave *para*-bromo products in good yield. The percentage conversion was negligible when the reaction was attempted in acetone even after 72 h, indicating that the solvent plays an important role in the outcome of the reactions. In ethyl methyl ketone, the reaction of NBS was complete within 48 h at room temperature. No reaction was observed in the presence of light in these solvents. However, on refluxing the solution, the brominated products were revealed on TLC. ^{1}H NMR spectroscopy of the reaction mixture suggested that the solvent is brominated under light whilst insignificant bromination of solvent takes place in the dark. The reaction of NBS in chloroform and carbon tetrachloride led to a very low yield of the *para*-bromo product in the dark. Under reflux, however, the reaction produced an intractable mixture (TLC). When *p*-*tert*-butylcalix[*n*]arene methyl ether and NBS were refluxed in the presence of light in carbon tetrachloride, selectively bridge brominated calix[*n*]arenes were obtained. Although theoretical calculations and simulation experiments by Klenke et al.[5] have suggested the bridge brominated calixarenes to be equatorial compounds, the exact stereochemistry of the bridge brominated calixarenes in the present experiments could not be ascertained. Further work on the reaction mechanism and conformational analysis of the products is in progress.



Where	R^1		R^1	R^2	R^3
1[n]a	H	**2**[n]a	H	H	Br
1[n]b	Me	**2**[n]b	Me	H	Br
		2[n]c	Me	Br	*t*-Bu

Scheme 1.

We conclude that the bromination of *p*-*tert*-butylcalix[*n*]arenes under different conditions (Table 1) can be used for the preparation of ring or methylene bridge substituted products as identified and confirmed by physical and chemical data.[8]

Acknowledgements

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

References

1. (a) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713; (b) Shinkai, S. *Tetrahedron* **1998**, *49*, 8933.
2. Gutsche, C. D.; Lin, L. G. *Tetrahedron* **1986**, *42*, 1633.
3. Hwang, K. L.; Ham, S. H.; No, K. H. *Bull. Korean Chem. Soc.* **1993**, *14*, 79.
4. (a) Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795; (b) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.
5. Klenke, B.; Nather, B.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967.
6. (a) It is significant to note that one has to use a higher nascent bromine concentration, e.g., from NBS or bromine (more than 4 equiv.) to get the products in good yield; (b) Kumar, S.; Kurur, N. D.; Chawla, H. M.; Varadarajan, R. *Synth. Commun.* **2000**, *31*, 775; (c) Kumar, S.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2001**, *43*, 2495; (d) Kumar, S.; Chawla, H. M.; Varadarajan, R., unpublished work.
7. (a) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782; (b) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742; (c) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.
8. **General procedure**:
   (a) In a typical procedure *p*-*tert*-butylcalix[*n*]arene (0.5 g) was taken in dichloromethane (15 ml) and acetic acid (12 ml) in a 100 ml round bottom flask and iron filings/powder (0.1 g) were added to it. The whole reaction assembly was wrapped in aluminium foil to inhibit reactions initiated by light. Br_2 (5 ml) [3 ml for *p*-*tert*-butylmethyl ether] in dry dichloromethane (15 ml) and acetic acid (5 ml) were added dropwise over a period of 30 min at 0–5°C. The reaction mixture was stirred at 25°C for 24–48 h and then poured into 10% sodium bisulphite solution. The *p*-bromo calix[*n*]arene was separated by filtration, dried and washed with chloroform to give pure *p*-bromocalix[*n*]arene in 56–69% yield. In the case of *p*-bromocalixarene methyl ether, the product was extracted into dichloromethane. The organic layer was dried over Na_2SO_4, concentrated and the product precipitated by adding hexane. It was recrystallized from chloroform and methanol.

(b) *p-tert*-Butylcalix[*n*]arene methyl ether (1.0 g) was treated with NBS (5.5 g) in ethyl methyl ketone (40 ml) in the dark for 48 h at rt and worked up as above to give 65–69% of *p*-bromocalix[*n*]arene methyl ether.

(c) *p-tert*-Butylcalix[*n*]arene (1.0 g) was refluxed with HBr (50 ml), acetic acid (30 ml), chloroform (20 ml) and 0.25 g iron filings in the dark for 12 h and worked up as above to give *p*-bromocalix[*n*]arene.

(d) *p-tert*-Butylcalix[*n*]arene methyl ether (0.7 g) was taken in a 100 ml round bottom flask and NBS (2.5 g) and CCl_4 (45 ml) were added to it. The reaction mixture was refluxed for 32 h in the presence of light and poured into 10% sodium bisulphite solution. The organic layer was separated by extraction. Dichloromethane was used for further extraction of the product from the aqueous mixture. The combined organic extracts were concentrated and precipitated by adding hexane. The separated solid was recrystallized with $CHCl_3$/methanol to give 39–57% yield of bridge brominated calixarenes.

5,11,17,23-Tetrabromo-25,26,27,28-tetra hydroxycalix-[4]arene: **2**[4]a

IR (KBr, ν/cm^{-1}): 3398 (OH), 2929, 1524, 1464, 1343, 1262, 1216, 1005, 866. ^{1}H NMR (DMSO-d_6, 300 K, δ): 7.32 (8H, s, ArH), 4.0–3.82 (8H, bs, $ArCH_2Ar$). Anal. calcd for $C_{28}H_{20}O_4Br_4{\cdot}CHCl_3{\cdot}H_2O$: C, 39.70; H, 2.64; found: C, 39.86; H, 2.93%.

5,11,17,23,29,35-Hexabromo-37,38,39,40,41,42-hexahydroxy-calix[6]arene: **2**[6]a

IR (KBr/ν cm^{-1}): 3334 (OH), 1603, 1461, 1364, 1203, 1099, 862. ^{1}H NMR (DMSO-d_6, 300 K, δ): 7.36 (s, 12H, ArH), 4.68–3.86 (s, 12H, $ArCH_2Ar$). FAB-Mass (m/z): 1104 (M^+). Anal. calcd for $C_{42}H_{30}O_6Br_6.4H_2O$: C, 42.86; H, 3.26; found: C, 42.64; H, 3.52%.

5,11,17,23,29,35,41,47-Octabromo-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene: **2**[8]a

IR (KBr/ν cm^{-1}): 3243 (OH), 1602, 1448, 1373, 1210, 1049, 868. ^{1}H NMR (DMSO-d_6, 300 K, δ): 6.96 (s, 16H, ArH) 3.85 (s, 16H, $ArCH_2Ar$) 5.72 (s, 8H, OH). Anal. calcd for $C_{56}H_{40}O_8Br_8{\cdot}CHCl_3$: C, 42.80; H, 2.58; found: C, 42.87; H, 2.71%.

5,11,17,23 - Tetrabromo - 25,26,27,28 - tetramethoxy calix-[4]arene: **2**[4]b

IR (KBr/ν cm^{-1}): 2935, 1572, 1464, 1425, 1205, 1170, 1011, 860. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.36, 7.20, 7.06, 6.85, 6.51 (s, 8H, ArH) 4.27–3.55 (m, 8H, $ArCH_2Ar$) 3.66 and 3.02 (s, 12H, OCH_3). ^{13}C NMR ($CDCl_3$, 300 K, δ): 30.0, 34.8, 61.7, 61.0, 59.9 (OCH_3), 130.9, 131.7, 133.0, 134.5, 136.3, 137.4, 156.9. FAB-Mass (m/z): 796 (M^+). Anal. calcd for $C_{32}H_{28}O_4Br_4$: C, 48.27; H, 3.54; found: C, 48.18; H, 3.64%.

5,11,17,23,29,35 - Hexabromo - 37,38,39,40,41,42 - hexamethoxycalix[6]arene: **2**[6]b

IR (KBr/ν cm^{-1}): 2952, 1575, 1465, 1424, 1209, 1120, 1007, 862. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.07 (s, 12H, ArH) 3.87 (s, 12H, $ArCH_2Ar$) 3.52 (s, 18H, OCH_3). ^{13}C NMR ($CDCl_3$, 300 K, δ): 29.4, 60.5, 116.6, 131.4, 135.3, 155.2. FAB-Mass (m/z): 1194 (M^+). Anal. calcd for $C_{48}H_{42}O_6Br_6$: C, 48.27; H, 3.54; found: C, 47.99; H, 3.67%.

5,11,17,23,29,35,41,47-Octabromo-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene: **2**[8]b

IR (KBr/ν cm^{-1}): 2925, 1575, 1463, 1420, 1210, 1161, 1003, 862. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.03 (s, 16H, ArH), 3.96 (s, 16H, $ArCH_2Ar$), 3.49 (s, 24H, OCH_3). ^{13}C NMR ($CDCl_3$, 300 K, δ): 29.7, 60.7, 124.1, 130.3, 135.5, 155.5. FAB-Mass (m/z): 1592 (M^+). Anal. calcd for $C_{64}H_{56}O_8Br_8$: C, 48.27; H, 3.54; found: C, 47.93; H, 3.57%.

2,8,14,20-Tetrabromo-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene: **2**[4]c

IR (KBr/ν cm^{-3}): 2962, 1594, 1478, 1363, 1230. ^{1}H NMR ($CDCl_3$, 300 K, δ): 8.06–7.41 (m, 8H, ArH), 6.5–4.96 (m, 4H, $ArCH_2Ar$), 3.97–3.02 (m, 12H, OCH_3), 1.33 (s, 36H, *t*-Bu). ^{13}C NMR ($CDCl_3$/DMSO-d_6, 300 K, δ): 30.7, 33.9, 60.8, 125.2, 129.0, 133.4, 146.1, 149.8. FAB-Mass (m/z): 1020 (M^+). Anal. calcd for $C_{48}H_{60}O_4Br_4{\cdot}CHCl_3$: C, 52.24; H, 5.41; found: C, 52.12; H, 5.44%.

2,8,14,20,26,32 - Hexabromo - 5,11,17,23,29,35 - hexa - *tert*-butyl - 37,38,39,40,41,42 - hexamethoxy calix[6]arene: **2**[6]c

IR (KBr/ν cm^{-1}): 2961, 1479, 1431, 1363, 1199, 1112, 1000. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.64 (s, 12H, ArH), 6.99 (s, 6H, $ArCH_2Ar$), 3.55 (s, 18H, OCH_3), 1.21 (s, 54H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.2, 34.6, 40.6, 61.3, 128.0, 133.9, 147.2, 150.3. Anal. calcd for $C_{72}H_{90}O_6Br_6{\cdot}CHCl_3$: C, 53.56; H, 5.56; found: C, 53.07; H, 5.38%.

2,8,14,20,26,32,38,44 - Octabromo - 5,11,17,23,29,35,41,47-octa - *tert* - butyl - 49,50,51,52,53,54,55,56 - octamethoxy-calix[8]arene: **2**[8]c

IR (KBr/ν cm^{-1}): 2961, 1607, 1479, 1364, 1241, 1085. ^{1}H NMR ($CDCl_3$, 300 K, δ): 7.60 (s, 16H, ArH), 6.03 (s, 8H, $ArCH_2Ar$), 3.75 (s, 24H, OCH_3), 1.25 (s, 72H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 300 K, δ): 31.0, 34.4, 51.8, 63.1, 130.5, 133.2, 145.9, 155. Anal. calcd for $C_{96}H_{120}O_8Br_8{\cdot}2CHCl_3$: C, 52.24; H, 5.41; found: C, 51.90; H, 5.21%.