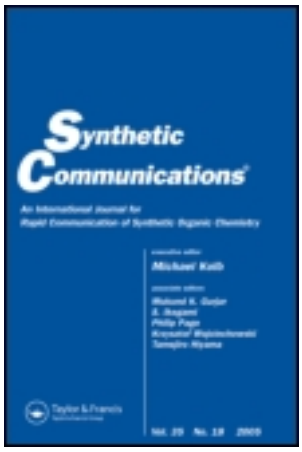


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

CONVENIENT ONE POT PROCEDURE FOR SYNTHESIS OF FORMYLATED CALIX[n]ARENES

H. M. Chawla [a] & Anuradha Santra [a]

[a] Chemistry Department, Indian Institute of Technology, New Delhi, 110 016, India

Version of record first published: 09 Nov 2006

To cite this article: H. M. Chawla & Anuradha Santra (2001): CONVENIENT ONE POT PROCEDURE FOR SYNTHESIS OF FORMYLATED CALIX[n]ARENES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:17, 2605-2611

To link to this article: http://dx.doi.org/10.1081/SCC-100105385

SYNTHETIC COMMUNICATIONS, 31(17), 2605–2611 (2001)

CONVENIENT ONE POT PROCEDURE FOR SYNTHESIS OF FORMYLATED CALIX[n]ARENES

H. M. Chawla* and Anuradha Santra

Chemistry Department, Indian Institute of Technology,
New Delhi 110 016, India

ABSTRACT

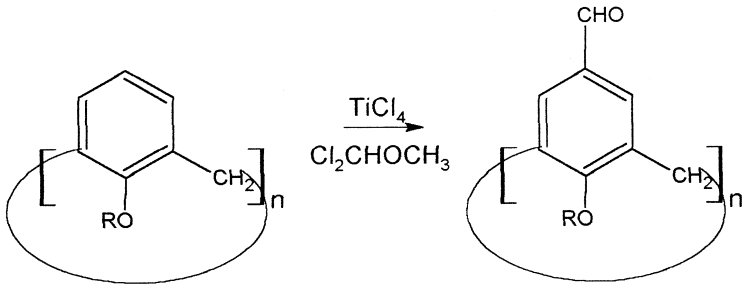
A convenient one pot procedure for obtaining formyl calix [n]arenes via condensation with 1,1-dichloromethylmethyl-ether is described.

Calix[n]arenes are phenolic metacyclophanes[1,2] obtained through base or (less often) acid catalysed condensation of p-substituted phenols with formaldehyde.[3,4] The presence of both hydrophilic and hydrophobic sites at the lower and upper rim of the calixarene molecular basket provides a cavity whose dimensions can be easily varied[1,2] to allow development of diverse applications and potential molecular devices.[2,5–9] Various aspects of calixarene chemistry have been reviewed.[10–13]

Although functionalization of lower rim calixarene hydroxyls is relatively well understood, upper rim derivatization requires careful selection of reagents and experimental conditions.[14–16] Introduction of a formyl group at the upper rim provides an important intermediate that can be employed for a variety of chemical transformations. Generation of formyl derivatives

*Corresponding author.

through Reimer-Tiemann reaction provides very low yields and complicated mixtures.[17] The alternative procedure requiring chloromethylation, hydrolysis and oxidation of the benzylic alcohol involves a large number of steps and offers only low yields of final products.[18,19] Claisen migration of allylated calixarenes followed by ozonolysis or oxidative double bond cleavage also suffers from similar disadvantages.[16] Formylation of alkoxy calixarenes by hexamethylene tetramine in trifluoroacetic acid[20] requires a long reaction time and the reaction is considered good only for calix[4]arenes (very poor yields are obtained for calix[8]arenes). Friedel Crafts reactions on long chain alkyloxy calixarenes by dichloromethyl methylether and subsequent



hydrolysis have been reported to provide a mixture of mono-, di-, tri- and tetraaldehydes of calix[4]arenes which are often difficult to separate.[18] This procedure also suffers from the disadvantage that the conformation of the calixarene framework is dependent upon the alkyl halide used[21] and the reported method is valid only for calix[4]arenes, often running into difficulties when attempted on higher calix[n]arenes ($n > 4$). Details published recently by Pochini and coworkers indicate that the dichloromethyl methyl ether (active formylating reagent) is used in a twenty to fifty fold excess.[21] The quantity of dichloromethyl methyl ether reportedly used even for monoformylation was twenty times the required stoichiometric quantity. Similarly, the catalyst ($TiCl_4$) is used in over twenty to sixty molar equivalents. Such high concentrations of reagents add to overall costs and affect large scale work on applications of calixarenes in diverse fields. It has been found that the reaction is very sensitive to temperature and invariably an intractable mixture of products is obtained even for simple calix[4]arenes. The prerequisite for the reaction, i.e., prior alkylation with long chain alkyl halides, also consumes huge quantities of the reagents and hence is inconvenient. The yields of products obtained are low and extensive chromatographic and other separation methods are required. The low temperatures required for the reaction are also impractical for large-scale preparations.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

In this communication we present our results on development of reaction conditions for obtaining formylated calixarenes in good yields. One not only can obtain formylated calix[4]arenes but also higher formyl calix [n]arenes (n = 6, 8). The products are easily isolable and the process involves inexpensive methyl iodide for protecting the calixarene to preserve initial calixarene conformation. The quantities of reagents employed are low. It is significant to note that no dealkylation takes place under the reaction conditions, and products obtained are clean.

In a typical experiment, a solution of dichloromethyl methyl ether in dichloromethane was added to a solution of octamethylated calix[8]arene in dichloromethane. A solution of freshly distilled titanium tetrachloride or $SnCl_4$ in CH_2Cl_2 was added quickly (2 min). The reaction mixture was stirred and maintained at 38–42°C for one hour after which it was quenched by adding ice cold water. The dichloromethane soluble portion when passed through a column of silica gel using ethyl acetate-hexane as the eluent gave the formylated calixarene derivative which could be identified by IR, NMR and molecular weight determination. It has also been determined that use of titanium tetrachloride as catalyst gives better yields than does the use of stannic chloride.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300DPX instrument. IR spectra were recorded on a Nicolet 5DX spectrometer. Molecular weight determinations were carried out by using a Knauer vapour pressure osmometer and mass spectra were recorded on a Jeol SX mass spectrometer. Dichloromethane and chloroform were dried over phosphorus pentoxide before use. $SnCl_4$ was prepared by passing chlorine over granulated tin followed by vacuum distillation of the crude stannic chloride.

Synthesis of *p*-tert-Butyl Calix[4]arene

Condensation of *p*-tert-butyl phenol (25 g, 0.166 mol) and formaldehyde (37%, 0.2075 mol) in the presence of sodium hydroxide (0.3 g, 7.5×10^{-3} mol) by the procedure reported by Gutsche et al.[1] gave the title compound as a colourless crystalline compound (15.3 g, 57%). m.p. > 250°C, ^{1}H NMR ($CDCl_3$, δ): 10.4 (s, 4H, D_2O exch, OH), 7.05 (s, 8H, ArH), 4.2 (d, J = 12 Hz, 4H, $ArCH_2Ar$), 3.5 (d, J = 12 Hz, 4H, $ArCH_2Ar$), 1.25 (s, 36H, $C(CH_3)_3$).

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Synthesis of 25,26,27,28-Tetrahydroxy Calix[4]arene

A slurry of *p*-t-butyl calix[4]arene (13.3 g, 20 mmol), phenol (9.02 g, 96 mmol) and $AlCl_3$ (14 g, 105 mmol) was stirred in toluene (125 ml) at room temperature for 1 h under a nitrogen atmosphere. The mixture was poured into 250 ml of 0.2N HCl and the organic phase was separated and toluene evaporated. Addition of MeOH yielded a precipitate which was filtered and recrystallized from $CHCl_3$-MeOH to give colourless crystals (6.5 g, 75%). m.p. > 260°C (lit.[2] 315–318°C); ^{1}H NMR ($CDCl_3$, δ): 10.2 (s, 4H, D_2O exch, OH), 7.04 (d, 8H, ArH), 6.72 (t, 4H, ArH), 4.2 (bs, 4H, $ArCH_2Ar$), 3.5 (bs, 4H, $ArCH_2Ar$).

Synthesis of *p*-tert-Butyl Calix[8]arene

The procedure adopted for synthesis of the title compound has been reported earlier.[1] The formation of *p*-tert-butylcalix[8]arene was confirmed by comparison with a standard sample of *p*-tert-butylcalix[8]arene (16.7 g, 62%). m.p. > 250°C; ^{1}H NMR ($CDCl_3$, δ): 9.6 (s, 8H, D_2O exch, OH), 7.17 (s, 16H, ArH), 4.36 (d, J = 12.8 Hz, 8H, $ArCH_2Ar$), 3.50 (d, J = 12.8 Hz, 8H, $ArCH_2Ar$), 1.25 (s, 36H, $C(CH_3)_3$).

Synthesis of 49,50,51,52,53,54,55,56-Octahydroxycalix[8]arene

A slurry of *p*-tert-butyl calix[8]arene (7.0 g, 5.4 mmol), phenol (5.1 g, 54 mmol) and $AlCl_3$ (9.0 g, 67.5 mmol) was stirred in toluene (150 ml) at room temperature for 1h under a nitrogen atmosphere after which the reaction mixture was poured into 0.2N HCl (150 ml) to yield an emulsion from which toluene was distilled to yield a grey solid which was washed with acetone, HCl, MeOH, $CHCl_3$, acetone and ethyl ether to give a colourless solid (3.96 g, 86%). m.p. > 260°C; ^{1}H NMR (pyridine-d_5) δ 6.0–7.0 (m, 3H, ArH), 3.5 (bs, 2, $ArCH_2Ar$).

Synthesis of 25,26,27,28-Tetramethoxycalix[4]arene

Tetrahydroxycalix[4]arene (1.27 g, 3 mmol) dissolved in THF (50 ml) containing DMF (5 ml) was refluxed with NaH (1 g, 25 mmol) and CH_3I (9.12 g, 64 mmol) for 12 h. The product obtained after evaporation

of solvent was washed with water and recrystallized from MeOH-$CHCl_3$ to yield colourless crystals (0.95 g, 66%). m.p., 232–234°C (Lit[16] m.pt. 234–235°C); ^{1}H NMR: ($CDCl_3$, δ) 6.84–6.54 (m, 12H, ArH), 4.3–3.1 (m, 20H, $ArCH_2Ar$ and -OCH_3); molecular mass (vapour pressure osmometry) 492 (calcd 480).

Synthesis of 49,50,51,52,53,54,55,56-Octamethoxy Calix[8]arene

A mixture containing octahydroxycalix[8]arene (2.0 g, 2.4 mmol), NaH (2.2 g, 92 mmol) and CH_3I (18 g, 127 mmol) in THF (100 ml) and DMF (10 ml) was refluxed for 12 h. The solvent was removed on a rotary evaporator and water (100 ml) was added to the residue. The collected solid was recrystallized from MeOH-$CHCl_3$ to give colourless crystals (1.7 g, 75%). m.p., 255–258°C (lit[3] m.p. 256–258°C); ^{1}H NMR ($CDCl_3$) δ 6.8 (s, 24H, ArH), 4.0 (s, 16H, $ArCH_2Ar$), 3.5 (s, 24H, -OCH_3); molecular mass (vapour phase osmometry) 1002 (calcd 960).

Synthesis of 5,11,17,23-Tetraformyl-25,26,27,28-tetrakis(methoxy)calix[4]arene

A solution of 1,1-dichloromethyl methyl ether (2.03 g, 17.7 mmol) in CH_2Cl_2 (10.0 ml) was added to a solution of tetramethylated calix[4]arene (0.24 g, 0.5 mmol) in $CHCl_3$ (10.0 ml) with stirring at room temperature followed by addition of a solution of titanium tetrachloride (4.5 g, 23.7 mmol) in $CHCl_3$(10.0 ml) in one portion as quickly as possible. The reaction mixture was stirred for a further period of 1h and then treated with water (~ 50 ml). The organic layer was separated, washed twice with water and dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by passing through a column (silica gel; 60–120 mesh) and eluted with hexane-ethyl acetate (75:25) to yield tetraformyl calix[4]arene as pale yellow crystals (0.18 g, yield 60.8%). m.p.. 218–220°C; Anal. calcd for $C_{36}H_{32}O_8$: C, 72.97; H, 5.40. Found: C, 72.86; H, 5.59. IR (ν_{max}, KBr): 1693 (s), 1597 (s), 1471 (m), 1428.3 (m), 1385 (m), 1283 (s), 1128 (s), ^{1}H NMR ($CDCl_3$, δ), 2.96–4.44 (m, 20H, $ArCH_2Ar$, OCH_3), 6.82, 7.84, 7.19, 7.64 (4s, 8H, ArH), 9.9, 9.57, 9.44 (2s, 1d, 4H, CHO), MS m/z 593 ($M+H^+$); UV ($CHCl_3$) λ_{max}: 269 nm. Though this compound seems to have been prepared by Komori et al. through a different route, no spectral data has been published.[20]

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Synthesis of 5,11,17,23,29,35,41,47-Octaformyl 49,50,51,52,53,54,55,56-Octakis(methoxy) Calix[8]arene

To a solution of **6** (0.82 g, 0.86 mmol) in dichloromethane (20 ml), a solution of dichloromethyl methyl ether (2.54 g, 22.1 mmol) in dichloromethane (15 ml) was added with stirring. Immediately after, a solution of freshly distilled titanium tetrachloride (4.3 g, 22.8 mmol) in dichloromethane (15 ml) was added to the reaction mixture very quickly with vigorous stirring. The reaction temperature was maintained between 38–42°C by using an oil bath. Stirring was continued for 1h and ice cold water (50 ml) was slowly added to the solution. The reaction mixture was further stirred for 15 min and extracted with dichloromethane. The organic layer was washed twice with water (50 ml×2) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue purified by passing through a column of silica gel (50 g, 60–120 mesh) to give pale yellow solid (0.69 g, 68%). m.p. > 250°C. Anal. calcd for $C_{72}H_{64}O_{16}$: C, 72.97; H, 5.40. Found: C, 72.83; H, 5.33. Molecular mass (vapour pressure osmometry) 1160 (Calcd 1184); IR (ν_{max}, KBr): 1693(s), 1598(s), 1472(m), 1428(sh), 1385(m), 1283(s); ^{1}H NMR ($CDCl_3$, δ): 9.67 (s, 8H, CHO), 6.95 (s, 16H, ArH), 4.12 (s, 16H, $ArCH_2Ar$), 3.6 (s, 24H, -OCH_3); UV($CHCl_3$, λ_{max}) 265 nm.

ACKNOWLEDGMENT

The authors are thankful to Department of Science & Technology and CSIR for financial assistance and a research fellowship to A.S.

REFERENCES

1. Gutsche, C.D.; *Calixarenes, monographs in supramolecular chemistry*, Vol. 1, Stoddart, J.F. Ed.; The Royal Society of Chemistry, Cambridge, 1989.
2. Bohmer, V. *Calixarenes, a versatile class of macrocyclic compounds*, Kluwer Academic, Dordrecht, 1989.
3. Gutsche, C.D.; Iqbal, M. Org. Synth. **1990**, *68*, 234.
4. Gutsche, C.D.; Iqbal, M.; Stewart, D. J. Org. Chem. **1986**, *51*, 742.
5. Steward, D.R.; Gutsche, C.D. J. Am. Chem. Soc. **1999**, *121*, 4136–4146.
6. Kubo, Y.; Maeda, S.; Nakamura, M.; Tokita, S. J. Chem. Soc. Chem. Commun. **1994**, 1725.

7. Daitch, C.E.; Hampton, P.D.; Duesler, E.D.; Alam, T.M. J. Am. Chem. Soc. **1996**, *118*, 7769–7773.
8. Kobo, Y.; Maruyama, S.; Ohhara, N.; Nakamivea, M.; Tokita, S. J. Chem. Soc. Chem. Commun. **1995**, 1727.
9. Reichwein, A.; Verboom, W.; Reinhoudt, D.N. J. Chem. Soc. Perkin Trans. **1994**, 1167.
10. Bohmer, V. Angew. Chem. Int. Engl. **1995**, *34*, 713–745.
11. Ikeda, A.; Shinkai, S. Chem. Rev. **1997**, *97*, 1713–1734.
12. De Namor, F.D.; Cleverley, R.M.; Zapata-Osmachea, M.L. Chem. Rev. **1998**, *98*, 2498–2525.
13. Diamond, D.; Mckervey, A. Chem. Rev. **1996**, 15–24.
14. Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. Tetrahedron **1989**, *45*, 2177.
15. Zhang, W.C.; Zheng, Y. S.; Huang, Z.T. Syn. Commun. **1997**, *27*(21), 3763–3767.
16. Gutsche, C.D.; Pagoria, P.F. J. Org. Chem. **1985**, *50*, 5795–5802, Gutsche, C.D.; Lin, L.G. Tetrahedron **1986**, *42*, 1633.
17. Aggarwal, Y.K.; Jain, V.K. Personal communication.
18. Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. J. Chem. Soc. Chem. Commun. **1991**, 936.
19. Van Loon, J.D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D.N. J. Org. Chem. **1990**, *55*, 5639.
20. Komori, T.; Shinkai, S. Chemistry Letters **1992**, 901.
21. Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A.R.; Ugozzoli, F. J. Org. Chem. **1995**, *60*, 1448–1453.

Received in the UK June 1, 2000

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016