Pergamon

Tetrahedron Letters, Vol. 36, No. 13, pp. 2311-2314, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00242-1

Synthesis of a New *Ortho-tert*-butylphenol-based Calix[4]arene

Giovanni Sartori*, Franca Bigi, Cecilia Porta, Raimondo Maggi and Raffaella Mora

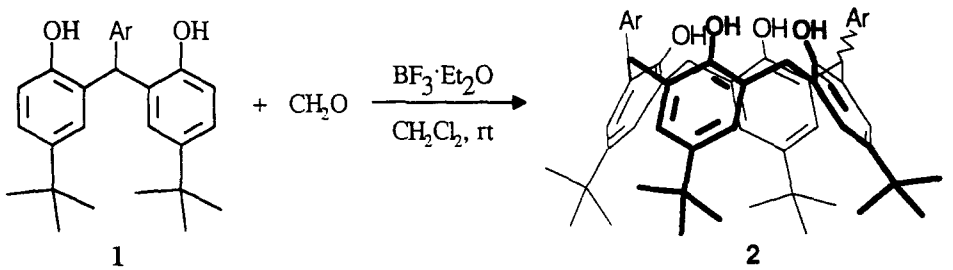
Dipartimento di Chimica Organica e Industriale dell'Università
Viale delle Scienze, I-43100 Parma, Italy

Abstract: The *ortho-tert*-butylphenol derived calix[4]arene **5** with the OH groups arranged in a *extra*-annular fashion is synthesized by condensation of 2,2'-dihydroxy-3,3'-di-*tert*-butyldiphenylmethane **4** with formaldehyde under $BF_3{\cdot}Et_2O$ catalysis. The crucial role of *tert*-butyl groups in promoting the macrocyclization process is emphasized.

In recent years cyclic condensation products from phenols and aldehydes (calixarenes and resorcinarenes) are under active investigation for preparing ligands capable of including guest molecules in these cavities[1].

Following our program aimed at the design and synthesis of new macrocyclic compounds with controlled structure, we have recently reported the preparation of *para-tert*-butylcalix[4]arenes **2** bearing two aryl groups on the methylene bridges in diametrical positions[2]. Macrocycles **2** were obtained in moderate yield (~ 20%) as a mixture of E and Z isomers by Lewis acid promoted condensation of triphenylmethanes **1**[3] with formaldehyde (Scheme 1).

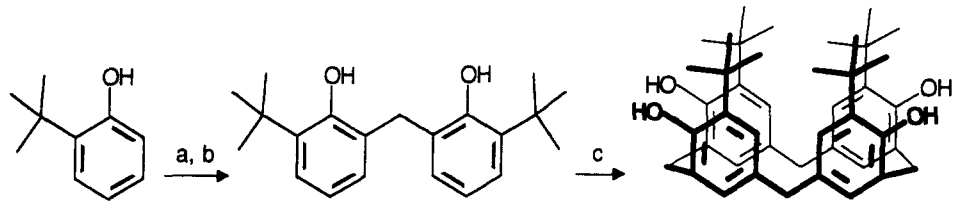
Scheme 1



1 **2**

Being convinced that a wide range of large size phenol-based molecules can be prepared using this approach, we ventured to apply the above methodology to the synthesis of macrocycle **5** by condensation of **4** with formaldehyde (Scheme 2).

Scheme 2



3 4 5

a) EtMgBr/Et_2O; b) CH_2O/Toluene, 80 °C, 10 h (yield=70%).

b) $CH_2O/BF_3{\cdot}Et_2O/CH_2Cl_2$, 25 °C, 3 h (yield=30%).

2,2'-Dihydroxy-3,3'-di-*tert*-butyldiphenylmethane **4** was first prepared by metal-template *ortho*-regioselective reaction of 2-*tert*-butylphenoxymagnesium bromide with formaldehyde (yield=70%)[4]. Further $BF_3{\cdot}Et_2O$ promoted condensation of **4** with a second molecule of formaldehyde afforded the macrocyclic compound **5** (30% yield) in which four 2-*tert*-butylphenol units are interconnected at the 4 and 6 positions throught methylene bridges. Similar calix[4]arene-type compounds with the hydroxylic groups on the outside periphery of the macrocycle were previously reported in the literature[5].

Compound **5** shows a considerable conformational mobility in solution as can be seen from NMR analysis. In fact, ^{1}H NMR spectrum of **5** (in $CDCl_3$ at 300 MHz) exibits two singlets (δ=3.79 and 3.81 ppm) in the methylene region at 300 K and no appreciable changing of the signal pattern is observed when the sample is cooled or heated (Figure 1).

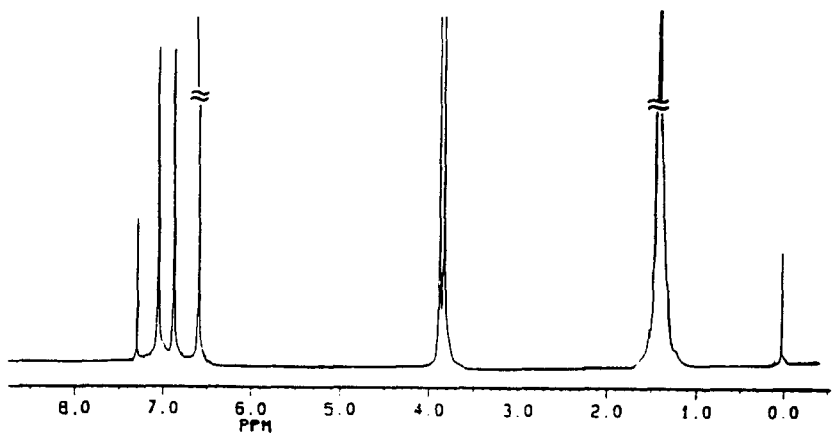
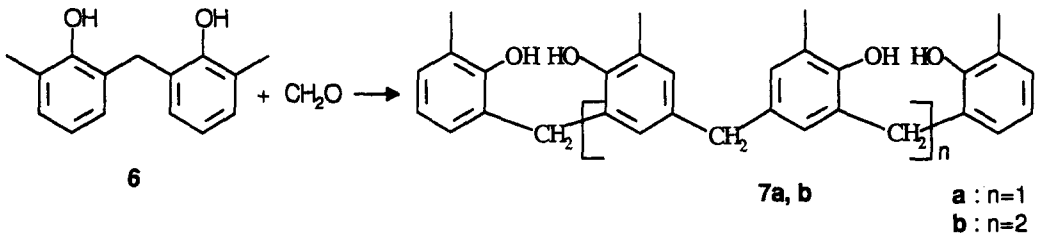


Figure 1. ^{1}H NMR spectrum of **5** (300 MHz, 300 K) in $CDCl_3$.

Attempting to extend the reaction to variously substituted diphenylmethanes and to determine a possible influence of the *tert*-butyl substituent in the present macrocyclization process, the substrate **6**[4] was condensed with formaldehyde under similar experimental conditions.

Scheme 3



No cyclization was observed and a mixture of *ortho-para* methylene bridged tetra- and hexacresols **7a** and **7b** was recovered in 10% and 35% yield respectively (Scheme 3).

These results suggest a tremendous effect of the *tert*-butyl group in promoting the macrocyclization process in agreement with the previously reported studies concerning the synthesis of calixarenes from *para* substituted phenols and formaldehyde under basic conditions[1,6].

In conclusion, we have developed an approach toward the synthesis of a new calix[4]arene with the OH groups arranged in a *extra*-annular fashion. Further studies which utilize these compounds for the preparation of cyclic ligands are currently in progress and our results will be reported in due course.

Experimental Procedures and data

General Procedure. To a mixture of the aromatic substrate **4** or **6** (0.01 mol) and paraformaldehyde (0.012 mol, 0.36 g) in dry CH_2Cl_2 (50 mL) at 25 °C under nitrogen, $BF_3{\cdot}Et_2O$ (0.001 mol, 0.14 g) was added. The resulting mixture was stirred for 3 hours at 25 °C, then quenched with 2N HCl (50 mL) and extracted with CH_2Cl_2 (2x50 mL). Solvent removal and flash-chromatography of the residue with hexane/ethyl acetate mixture (90/10) yielded the products.

All compounds provided analytical and spectroscopic data consistent with their structures:

4, 12, 16, 24-Tetrahydroxy-5, 11, 17, 23-tetrakis(1,1-dimethylethyl)calix[4]arene (5). Yield 1.94 g (30%), white solid; m.p. dec. 172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), 300 K: δ 1.42 (s, 36H, $(CH_3)_3C$), 3.79 (s, 4H, CH_2), 3.81 (s, 4H, CH_2), 6.28 (s, 4H, OH), 6.81 (d, J=2.0 Hz, 4H, Harom), 7.01 (d, J=2.0 Hz, 4H, Harom); MS (C.I.): m/z=649 (M^++1, 100%), 482 (38); IR (KBr): 3095,1190 cm^{-1}. Attempts to obtain satisfactory elemental analysis of calixarene **5** were unsuccessful, nevertheless we believe that the identity of the compound reported is correct[7].

4,4'-Dihydroxy-3,3'-bis(2''-hydroxy-3''-methylbenzyl)-5,5'-dimethyldiphenylmethane (7a). Yield 0.47 g (10%), white solid; m.p. 183 °C; ^{1}H NMR ($CDCl_3$-CD_3OD, 300 MHz), 300 K: δ 2.11 (s, 6H, CH_3), 2.17 (s, 6H, CH_3), 3.63 (s, 2H, CH_2), 3.80 (s, 4H, CH_2), 6.67 (br s, 2H, H-2 and H-2' or H-6 and H-6'), 6.70 (t, J=7.5 Hz, 2H, H-5''), 6.86 (br s, 2H, H-6 and H-6' or H-2 and H-2'), 6.90 (d, J=7.5 Hz, 2H, H-6'' or H-4''), 7.02 (d, J=7.5 Hz, 2H, H-4'' or H-6''); MS (E.I.): m/z=468 (M^+, 55%), 241 (100); IR (KBr): 3030, 1205 cm^{-1}; Found: H 6.84%, C 79.55%; calcd for $C_{31}H_{32}O_4$: H 6.88, C 79.46%.

2,2'-Dihydroxy-3,3'-dimethyl-5,5'-bis[3''-bis(2'''-hydroxy-3'''-methylbenzyl)-4''-hydroxy-5''-methylbenzyl]-diphenylmethane (7b). Yield 2.48 g (35%), white solid; m.p. 187 °C; ^{1}H NMR ($CDCl_3$-CD_3OD, 300 MHz), 300 K: δ 2.05 (s, 12H, CH_3), 2.10 (s, 6H, CH_3), 3.57 (s, 4H, CH_2), 3.70 (s, 2H, CH_2), 3.74 (s, 4H, CH_2), 6.55-6.65 (m, 6H, Harom), 6.75-6.85 (m, 6H, Harom), 6.94 (dd, J=7.5 and J=1.2 Hz, 2H, H-4''' or H-6'''); MS (E.I.): m/z=708 (M^+, 22%), 481 (54), 241 (100); IR (KBr): 3030, 1197 cm^{-1}; Found: H 6.88%, C 79.58%; calcd for $C_{47}H_{48}O_6$: H 6.82%, C 79.63%.

Acknowledgements

This work was supported by the Consiglio Nazionale delle Ricerche (C.N.R., Roma), Progetto Finalizzato Chimica Fine e Secondaria II and by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (M.U.R.S.T.). The authors are grateful to the Centro Interdipartimentale Misure (CIM) for the use of NMR and mass instruments.

References and notes

1) a) Gutsche, C. D. *Calixarenes*; Stoddard Ed., The Royal Society of Chemistry, London, **1989**; b) Vicens, J.; Böhmer, V. "Calixarenes. A versatile Class of Macrocyclic Compounds". Kluwer Academic Publishers, Dordrecht, **1991**; c) Cram, D. J.; Cram, J. M. "Container Molecules and their Guests"; The Royal Society of Chemistry: Cambridge, **1994.**

2) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Porta, C. *J. Chem. Soc. Perkin Trans. I*, **1994**, *13*, 1657.

3) a) Casiraghi, G.; Casnati, G.; Cornia, M.; Sartori, G.; Ungaro, R. *J. Chem. Soc.*, **1974**, 2077; b) Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Sartori, G.; Ungaro, R. *J. Chem. Soc. Perkin I*, **1978**, 322.

4) Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc. Perkin I*, **1978**, 318.

5) a) Chasar, D. W. *J. Org. Chem.*, **1985**, *50*, 545; b) Dahan, E.; Biali, S. E. *J. Org. Chem.*, **1989**, *54*, 6003; c) Tabatai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.*, **1990**, *31*, 3295.

6) Asfari, Z.; Vicens, J. *Makromol. Chem., Rapid Commun.*, **1989**, *10*, 181.

7) a) Böhmer, V.; Jung, K.; Wolff, A. *J. Org. Chem.*, **1992**, *57*, 790; b) Gutsche, C. D.; See, K. A. *J. Org. Chem.*, **1992**, *57*, 4527.

(*Received in UK* 6 *December* 1994; *revised* 30 *January* 1995; *accepted* 3 *February* 1995)