International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.11, pp 17-23, 2018

Direct Synthesis of Singly-Bridged Biscalixarenes and Crowned-Calixarenes

***Abha Naveen Kumar**

*Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400085, India

Abstract : Two tail-to-tail linked singly-bridged biscalix[6]/[4]arenes were directly synthesized by reaction of calix[6]/[4]arenes with diethyleneglycol ditosylate in presence of $KHCO_3$ as the base. It was found that this coupling depended on the kind of calixarene. With calix[4]arene, both corresponding biscalixarene and crowned-calixarene were obtained in this reaction. But in case of *p-tert*-butylcalix[4]arene, this reaction afforded corresponding crowned-calixarene only. In addition to that, coupling reaction also depends on the linker as evident by the synthesis of corresponding crowned-calixarenes/mono-O-alkylated derivatives, in case of *p-tert*-butylcalix[6]arene.

Keywords: Biscalix[6]arene, biscalix[4]arene, crowned-calix[4]arene, crowned-calix[6]arene.

Introduction

In the quest to design hosts with defined structures and functions, calixarenes are widely utilized for building elaborate systems containing more than one cyclic structure[1]. Biscalixarenes and crowned-calixarenes are examples of two such molecular systems, where inter/intra-molecular bridging provide not only new cavities for binding but also restricted flexibility of calixarenes[1]. For the synthesis of these macrobicyclic compounds, calixarenes are coupled with bifunctional reagents which results in inter- and/or intra-molecular bridging depending on the reaction conditions[1,2]. For example, 5,11,17,23-tetrakis[(propargyloxy)methyl]-25,26,27,28-tetra(benzyloxy)calix[4]arene in 1,3-alternate conformation afforded both kinds of products when oxidatively coupled, though intermolecularly coupled product is obtained in just 7% yield[3].

In the past, I along with my co-workers have been involved in developing protocols for regioselective functionalization of calixarenes[4], and in utilizing hosts based on calixarenes for targets like cesium[5,6] and fullerenes[7-9]. Recently, we have succeeded in accomplishing synthesis of biscalixarene **2** in single step by using $KHCO_3$-diethyleneglycol ditosylate combination (Figure 1)[10]. During this study, we found out that outcome of this coupling is sensitive to both base and linker[10].

Abha Naveen Kumar /International Journal of ChemTech Research, 2018,11(11): 17-23.

DOI= http://dx.doi.org/10.20902/IJCTR.2018.111103

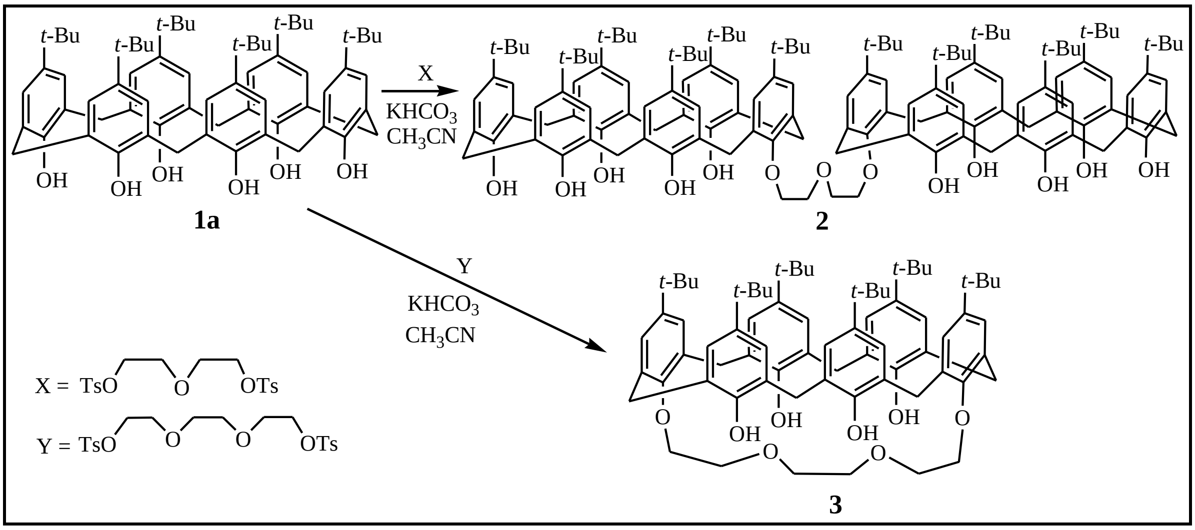


Figure 1: Synthesis of compounds 2 and 3 (taken from our previous work[10])

In the literature, direct reaction of calix[4]/[6]arenes with oligoethyleneglycol ditosylates afforded crowned-calixarenes[11-32] and/or multi-bridged biscalixarenes[31-33] as the reaction products; and in only few of the reports, formation of singly-bridged biscalixarenes like **2** was mentioned[10,34].

Keeping in view of these literature reports[11-34] and the novel finding of one-step synthesis of biscalixarene **2**[10], the present study to afford singly-bridged biscalixarenes using $KHCO_3$-diethyleneglycol ditosylate is undertaken. Also, the coupling of **1a** with oligoethylenegycol ditosylates and 1,ω-dibromoalkanes was further investigated in this report, to get better insight about this reaction.

Experimental

All the chemicals (Fluka and Aldrich) were of analytical grade and used as received, if not mentioned otherwise. Compound **1a, 1b, 1c** and **1d** were dried under vacuum at 100 °C for 6 h before use. Anhydrous $KHCO_3$ was obtained by heating material on flame and then stored in a dessicator. Acetonitrile was dried and distilled over P_2O_5. All the reactions were carried out in flame dried glass apparatus kept under an argon atmosphere. Melting points were taken on Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR (200 MHz) spectra in $CDCl_3$ were recorded with a Bruker AC 200 spectrometer at ambient temperature. Mass spectra were measured with a Q-TOF (YA-105) instrument.

General procedure for the synthesis of calixarene compounds 4-12: Compound **1a**/**1b**/**1c**/**1d** (5.1 mmol) and $KHCO_3$ (8.2 mmol) were dissolved in CH_3CN (100 mL) and stirred at reflux temperature for 3 h. The mixture was cooled to rt and oligoethyleneglycol ditosylate/1,ω-dibromoalkane (3.1 mmol) was added to it and further stirred at reflux temperature for 7 days. The solvent was removed under vacuo and water was added to the residue. The mixture was acidified with 1 N HCl and extracted with $CHCl_3$. The organic layer was washed with water, brine and dried (Na_2SO_4) and then concentrated to dryness. The residue was subjected to either column chromatography or preparative thin layer chromatography over silica gel (CH_2Cl_2/Hex) to yield the corresponding biscalixarene, crowned-calixarene or mono-O-alkylated derivative as the product.

Spectral data of compounds

Bis[2-(37,38,39,40,41-pentahydroxy-42-calix[6]arenyloxy)ethyl] ether (4): White solid. mp: 178-180 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.64 -3.84 (m, 26H), 4.45-4.47 (m, 6H), 6.68-6.81 (m, 10H), 6.84-7.00 (m, 16H), 7.07-7.14 (m, 10H), 8.69 (s, OH), 9.79 (br s, OH). ESI-MS: m/z 1341.8 ($[M-H]^+$, calcd. 1341.5). Anal. calcd. for $C_{88}H_{78}O_{13}$: C 78.67, H 5.85; found: C 78.60, H 5.87.

Bis[2-(25,26,27-trihydroxy-28-calix[4]arenyloxy)ethyl] ether (5): White solid. mp: 293-295 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.29-3.48 (m, 8H), 4.21-4.28 (m, 4H), 4.41-4.53 (m, 12H), 6.61-6.69 (m, 6H), 6.86-7.08 (m, 18H), 9.38 (s, 4H), 9.96 (s, 2H). ESI-MS: m/z 917.8 ([M-H]$^+$, calcd. 917.4). Anal. calcd. for $C_{60}H_{54}O_9$: C 78.41, H 5.92; found: C 78.30, H 5.94.

***25,26-Dihydroxycalix[4]arene-27,28-(crown-3) (6)*[35]:** White solid. mp: 120-122 °C (lit.[35] mp: 119-121 °C). ^{1}H NMR: δ 3.38-3.50 (m, 4H), 4.06-4.17 (m, 4H), 4.36-4.51 (m, 7H), 4.93 (d, *J* = 12.2 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 2H), 6.91-7.26 (m, 10H), 8.67 (s, 2H). ESI-MS: m/z 493.3 ([M-H]$^+$, calcd. 493.2). Anal. calcd. for $C_{32}H_{30}O_5$: C 77.71, H 6.11; found: C 77.76, H 6.10.

***5,11,17,23-Tetra-tert-butyl-25,27-dihydroxycalix[4]arene-26,28-(crown-3) (7)*:** White solid. mp: 246-248 °C. ^{1}H NMR: δ 0.93 (s, 18H), 1.30 (s, 18H), 3.33 (d, *J* = 13.0 Hz, 4H), 3.94 (s, 8H), 4.28 (d, *J* = 12.8 Hz, 4H), 6.76 (s, 4H), 7.07 (s, 4H); ESI-MS: m/z 717.7 ([M-H]$^+$, calcd. 717.5). Anal. calcd. for $C_{48}H_{62}O_5$: C 80.18, H 8.69; found: C 80.23, H 8.68.

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxycalix[6]arene-39,42-(crown-5) (8)*[18]:** White solid. mp: 180-182 °C (lit.[18] mp: 184-185 °C). ^{1}H NMR: δ 1.13 (s, 18H), 1.23 (s, 36H), 3.53-3.59 (m, 6H), 3.70-3.85 (m, 14H), 4.09 (m, 4H), 4.38 (d, *J* = 14.4 Hz, 4H), 6.99-7.06 (m, 12H), 7.79 (s, OH); ESI-MS: m/z 1130.4 ([M]$^+$, calcd. 1130.7). Anal. calcd. for $C_{74}H_{98}O_9$: C 78.55, H 8.73; found: C 78.67, H 8.70.

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxycalix[6]arene-39,42-(crown-6) (9)*:** White solid. mp: 227-229 °C. ^{1}H NMR: δ 1.12 (s, 18H), 1.28 (s, 36H), 3.51 (m, 8H), 4.05-4.20 (m, 20H), 4.38-4.44 (m, 4H), 6.97 (s, 4H), 7.10-7.11 (m, 8H), 7.76 (s, 4H); ESI-MS: m/z 1174.5 ([M]$^+$, calcd. 1174.8). Anal. calcd. for $C_{76}H_{102}O_{10}$: C 77.65, H 8.75; found: C 77.74, H 8.73.

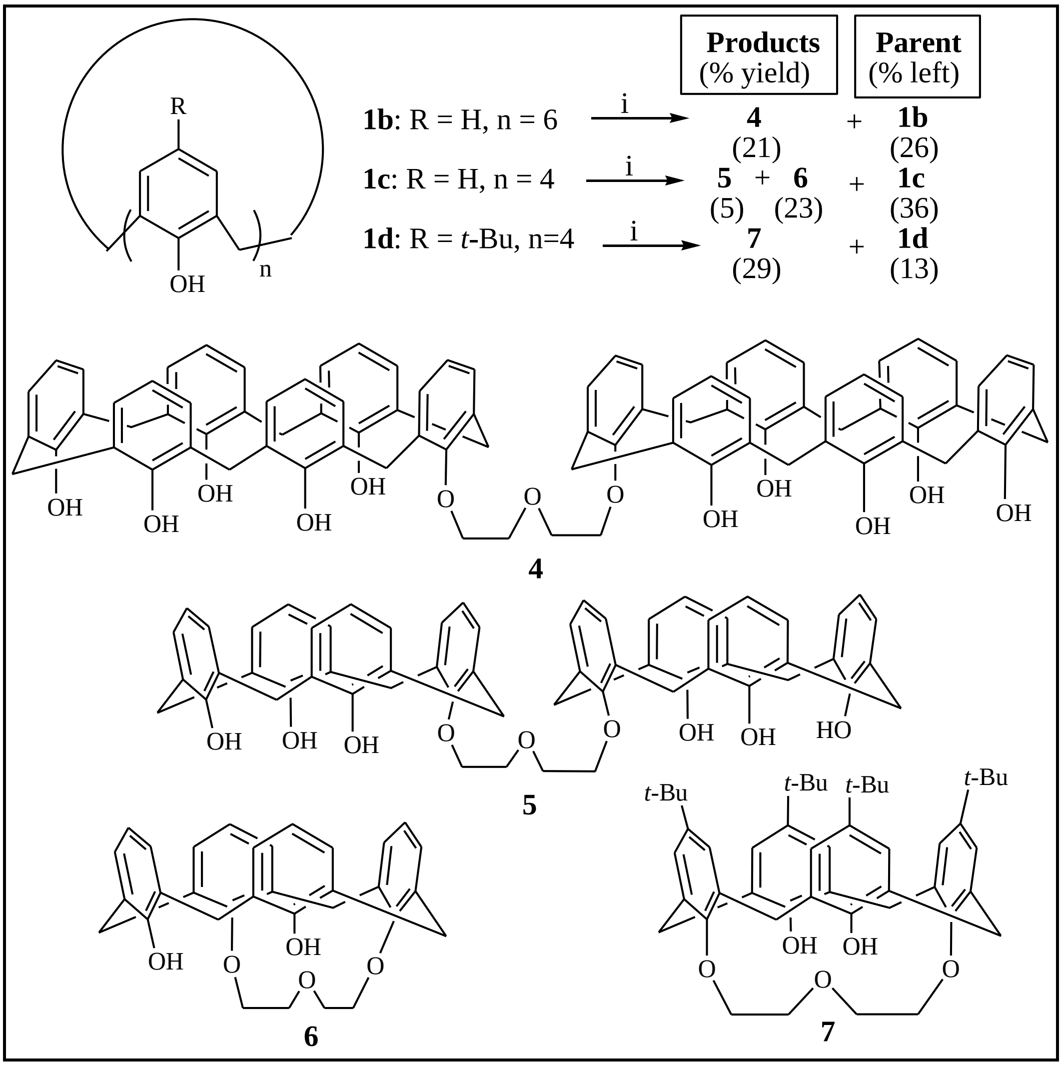
***5,11,17,23,29,35-Hexa-tert-butyl-37-monotosyloxyethoxy-38,39,40,41,42-pentahydroxycalix[6]arene (10)*:** White solid. mp: 176-178 °C. ^{1}H NMR: δ 1.12 (s, 9 H), 1.21-1.28 (m, 45 H), 2.04-2.46 (m, 3H), 3.40-3.60 (m, 6H), 3.91 (d, *J* = 13.6 Hz, 2H), 4.18-4.32 (m, 6H), 4.66 (s, 2H), 6.96 (s, 4H), 7.11 (s, 10H), 7.81 (d, *J* = 6.4 Hz, 2H), 8.47 (s, 2H), 9.43 (s, 1H), 9.62 (s, 2H); ESI-MS: m/z 1169.9 ([M-H]$^+$, calcd. 1169.7). Anal. calcd. for $C_{75}H_{94}O_9S$: C 76.89, H 8.09; found: C 76.97, H 8.10.

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxy-39,42-(pentanyldioxy)calix[6]arene (11)*:** White solid. mp: 190-192 °C. ^{1}H NMR: δ 1.20 (s, 18H), 1.30 (s, 36H), 2.07 (s, 4H), 2.33 (s, 2H), 3.59 (br s, 8H), 4.15 (m, 4H), 4.29 (s, 4H), 7.13-7.24 (m, 12H), 9.32 (s, 4H); ^{13}C NMR: δ 29.6, 31.3, 31.7, 32.2, 33.2, 33.9, 34.2, 75.2, 125.4, 126.0, 126.2, 127.3, 132.5, 142.4, 147.5, 150.0, 150.3; ESI-MS: m/z 1040.3 ([M]$^+$, calcd. 1040.7). Anal. calcd. for $C_{71}H_{92}O_6$: C 81.88, H 8.90; found: C 81.97, H 8.88.

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetrahydroxy-39,42-(hexanyldioxy)calix[6]arene (12)*[36]:** White solid. mp: 238-240 °C. ^{1}H NMR: δ 1.20 (s, 18H), 1.33 (s, 36H), 2.04-2.18 (m, 8H), 3.32-3.54 (m, 6H), 4.11 (m, 6H), 4.40 (d, *J* = 12 Hz, 4H), 7.09-7.19 (m, 12H), 9.08 (s, 4H); ESI-MS: m/z 1054.1 ([M-H]$^+$, calcd. 1053.7). Anal. calcd. for $C_{72}H_{94}O_6$: C 81.93, H 8.98; found: C 81.99, H 8.97.

Results and Discussion

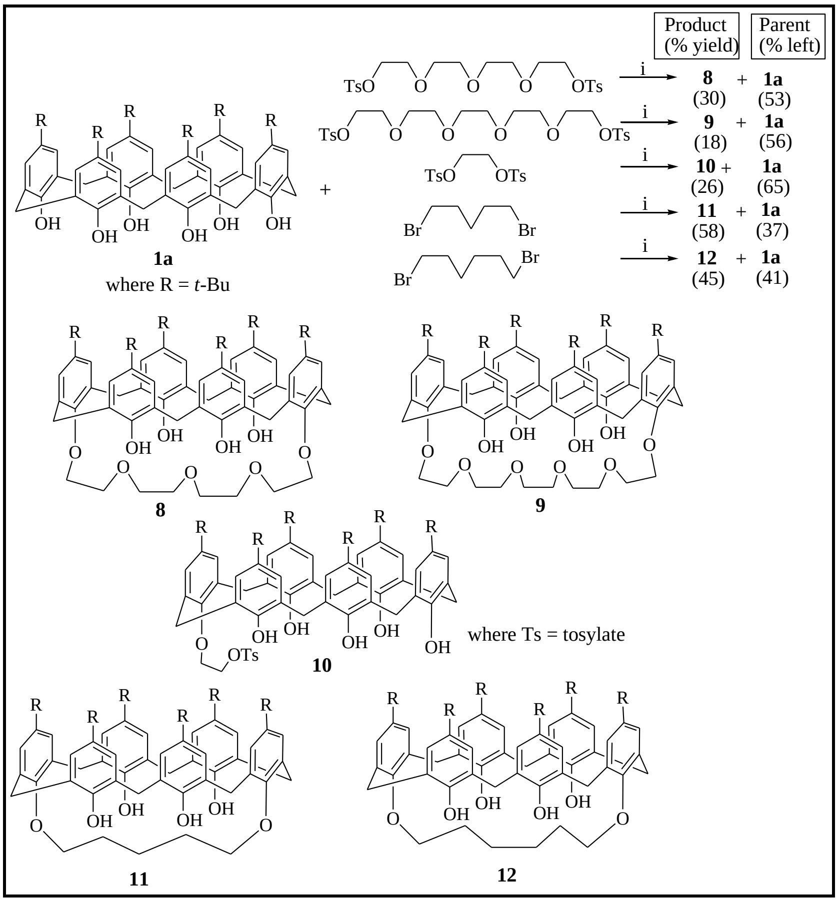
Piqued by the previous work[10], $KHCO_3$-diethyleneglycol ditosylate combination have been further explored in this report to afford singly-bridged biscalixarenes. Thus, the substrates calix[6]arene (**1b**), calix[4]arene (**1c**) and *p-tert*-butylcalix[4]arene (**1d**) were reacted with $KHCO_3$ and diethyleneglycol ditosylate as shown in Scheme 1.



Scheme 1: Reagents and conditions: (i) $KHCO_3$, diethyleneglycol ditosylate, CH_3CN, reflux.

Using calix[6]arene **1b** as the substrate, biscalix[6]arene **4** was obtained in 21% yield. When calix[4]arene **1c** was used as the substrate, biscalix[4]arene **5** was obtained in only 5% yield along with the (1,2)-calix[4]arenecrown-3 (**6**) product in 23% yield. When *p*-*tert*-butylcalix[4]arene **1d** was used as the substrate, (1,3)-*p*-*tert*-butylcalix[4]arenecrown-3 (**7**) was obtained in 29% yield. All the compounds synthesized were characterized by their respective analytical and spectral data.

During the previous work on synthesis of biscalix[6]arene **2** from **1a**, it was observed that changing the linker to triethyleneglycol ditosylate led to formation of calix[6]crown **3**[10]. This part of the study was conducted to further investigate the effect of linker over the outcome of this $KHCO_3$ mediated reaction of bifunctional linkers with **1a** (Scheme 2).



Scheme 2: Reagents and conditions: (i) $KHCO_3$, CH_3CN, reflux.

Thus, coupling of **1a** was carried out using tetra- and penta-ethyleneglycol ditosylates under the similar reaction conditions. In both the cases, respective calixcrowns **8** and **9** were obtained. But with a long spacer like pentaethyleneglycol ditosylate, percentage yield of the calixcrown **9** has decreased substantially to 18% (in the TLC analysis, few more bands were observed which were difficult to purify and analyze). Assignment of the 1,4-substitution pattern in the calixcrowns **8** and **9** was done unambiguously by their ^{1}H NMR spectrum; and was further substantiated in case of compound **8** where its melting point and spectral data matches well with the data for the reported compound[18], leaving no scope for ambiguity.

With ethyleneglycol ditosylate, corresponding mono-O-tosyloxy derivative **10** was obtained in 26% yield. Elemental analysis and spectral data of the compound **10** provide clear evidence for its formation. Its ^{1}H NMR spectrum contains two signals at δ 1.12 and 1.21-1.28 for *tert*-butyl protons in a 1:5 intensity ratio, attributable to the *tert*-butyl groups of O-substituted and hydroxyl-bearing aromatic rings, respectively. The spectrum contains three hydroxyl signals at δ 8.47, 9.43 and 9.62 in the intensity ratio of 2:1:2, respectively. The signal at δ 8.47 is due to OH groups, sandwiched between one OCH_2 group and one OH group. The signals at δ 9.43 and 9.52 are due to OH groups, sandwiched between two OH groups.

To check the effect of alkyl spacers on this reaction, 1,5-dibromopentane and 1,6-dibromohexane were used for the coupling under the similar reaction conditions (Scheme 2). In both the cases, corresponding crowned-calixarenes **11** and **12** were obtained in 58 and 45% yield, respectively. Elemental analysis and spectral data of the compounds **11** and **12** provide clear evidence for formation of the intramolecularly coupled product. Assignment of their structure was done unambiguously by NMR data and was further confirmed in case of compound **12** where its data matches well with the data for the reported compound[36].

Conclusion

In conclusion, two tail-to-tail linked singly-bridged biscalixarenes **4** and **5** are synthesized in one-step by direct condensation of diethyleneglycol ditosylate with corresponding calixarenes in presence of $KHCO_3$ as the base. Also investigation of reaction of **1a** with oligoethylenegycol ditosylates/1,ω-dibromoalkanes in presence of $KHCO_3$ as the base, revealed this coupling reaction to be sensitive to the bifunctional linker. Thus one-step syntheses of singly-bridged biscalixarenes, crowned-calixarenes and mono-O-alkylated derivative are achieved depending upon the reaction conditions (parent calixarene and linker). In addition to its synthetic utility, this study in conjunction with the previous literature reports contributes towards understanding of coupling of bifunctional linkers with calixarenes.

Acknowledgements

Thanks are due to SAIF, IIT-Mumbai for providing mass analysis; and Chemistry Division, BARC for elemental analysis.

References

1. Eds. Asfari Z., Bohmer V., Harrowfield J., Vicens J. and Saadioui M., Calixarenes 2001, Kluwer Academic Publishers, Dordrecht, Netherlands, 2001.
2. Li X., Gong S.-L., Zhang C.-L., Zheng Q. and Chen Y.-Y., (1+1) or (2+2) Coupling for bis(tosyloxyethoxy)benzenes with calix[4]arene and thiacalix[4]arene, Tetrahedron Lett., 2006, 47, 7695-7698.
3. Kanamathareddy S. and Gutsche C. D., Calixarenes: selective functionalization and bridge building, J. Org. Chem. 1995, 60, 6070-6075.
4. Semwal A., Bhattacharya A. and Nayak S.K., Ultrasound mediated selective monoalkylation of 4-tert-butylcalix[6]arene at the lower rim, Tetrahedron, 2002, 58, 5287-5290.
5. Ramanjaneyulu P.S., Kumar A.N. and Sharma M.K., Development of a new all solid contact Cs^+ ion selective electrode, J. Radioanal. Nucl. Chem., 2017, 313, 581-586.
6. Ramanjaneyulu P.S., Kumar A.N., Sayi Y.S., Ramakumar K.L., Nayak S.K. and Chattopadhyay S., A new ion selective electrode for cesium (I) based on calix[4]arene-crown-6 compounds, J. Hazard. Mater., 2012, 205–206, 81-88.
7. Ghosh K., Semwal A., Nayak S.K., Bhattacharya (Banerjee) S. and Banerjee M., Spectrophotometric study of the supramolecular complexes of [60]- and [70]fullerenes with biscalix[6]arene and crown[4]calix[6]arene, Spectrochim. Acta Part A, 2007, 66, 1122-1125.
8. Bhattacharya S., Nayak S.K., Semwal A. and Banerjee M., Energies of charge transfer and supramolecular interactions of some mono O-substituted calix[6]arenes with [60]fullerene by absorption spectrometric method, Spectrochim. Acta Part A, 2005, 61, 595-606.
9. Bhattacharya S., Nayak S.K., Semwal A., Chattopadhyay S. and Banerjee M., Study of host-guest interaction of [70]fullerene with substituted calix[6]arenes by absorption spectrometric method, J. Phys. Chem. A, 2004, 108, 9064-9068.
10. Kumar A.N., Ramkumar J., Chandramouleeswaran S. and Nayak S.K., One-step synthesis of a singly bridged biscalix[6]arene and evaluation of its alkali metal recognition properties, Org. Commun., 2017, 10:4, 304-313.
11. Arduini A., McGregor W.M., Paganuzzi D., Pochini A., Secchi A., Ugozzoli F. and Ungaro R., Rigid cone calix[4]arenes as π-donor systems: complexation of organic molecules and ammonium ions in organic media, J. Chem. Soc. Perkin Trans. 2, 1996, 839-846.
12. Arduini A., Fabbi M., Mantovani M., Mirone L., Pochini A., Secchi A. and Ungaro R., Calix[4]arenes blocked in a rigid cone conformation by selective functionalization at the lower rim, J. Org. Chem. 1995, 60, 1454-1457.
13. Arduini A., Domiano L., Pochini A., Secchi A., Ungaro R., Ugozzoli F., Struck O., Verboom W., Reinhoudt D.N., Synthesis of 1,2-bridged calix[4]arene-biscrowns in the 1,2-alternate conformation, Tetrahedron, 1997, 53, 3767-3776.

14. Asfari Z., Bressot C., Vicens J., Hill C., Dozol J.-F., Rouquette H., Eymard S., Lamare V. and Toumois B., Doubly crowned calix[4]arenes in the 1,3-alternate conformation as cesium-selective carriers in supported liquid membranes, Anal. Chem., 1995, 67, 3133-3139.
15. Yamamoto H., Sakaki T. and Shinkai S., Regioselective synthesis of 1,2- and 1,3-bridged calix[4]crowns: what are the factors controlling the regioselectivity, Chem Lett., 1994, 23, 469-472.
16. Yamamoto H. and Shinkai S., Molecular design of calix[4]arene-based sodium-selective electrodes which show remarkably high $10^{5.0}$–$10^{5.3}$ sodium/potassium selectivity, Chem Lett., 1994, 23, 1115-1118.
17. Li J., Chen Y. and Lu X., Selective bridging of *p-tert*-butylcalix[6]arene with polyethylene glycol ditosylates, Tetrahedron, 1999, 55, 10365-10374.
18. Casnati A., Jacopozzi P., Pochini A., Ugozzoli F., Cacciapaglia R., Mandolini L. and Ungaro R., Bridged calix[6]arenes in the cone conformation: new receptors for quaternary ammonium cations, Tetrahedron, 1995, 51, 591-598.
19. Chen Y., Li J., Xin J., Zhong Z., Gong S. and Lu X., Syntheses of lower-rim-1,3-crowned calix[6]arenes and their complexation abilities toward cations, Synth. Commun., 1999, 29, 705-711.
20. Chen Y. and Li H., Synthesis and characterization of *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-5, p-tert-butylcalix[6]-1,4-benzocrown-4-2,3-crown-5, Chem. Lett., 2000, 10, 1208-1209.
21. Chen Y., Yang F. and Gong S., Molecular design and synthesis of a calix[6]crown-based lithium-selective ionophore, Tetrahedron Lett., 2000, 41, 4815-4818.
22. Chen Y., Yang F. and Lu X., Synthesis of *p-tert*-butylcalix[6]-1,4-2,5-bis-crowns, Tetrahedron Lett., 2000, 41, 1571-1574.
23. Chen Y. and Chen Y., Synthesis of doubly bridged *p-tert*-butyl-calix[6]arene containing hard and soft ion binding sites, Tetrahedron Lett., 2000, 41, 9079-9082.
24. Yang F. and Chen Y., Ion complexation properties of calix[6]arene derivatives: I. 1,4-calix[6]crown-4 derivatives, Supramol. Chem., 2001, 12, 445-450.
25. Chen Y. and Li H., Syntheses of novel types of calix[6]bis-crowns and related compounds, New J. Chem., 2001, 25, 340-343.
26. Yang F. and Chen Y., An improved method for the synthesis of calix[6]-1,4-crown-4s, Hecheng Huaxue, 2002, 10, 151-153.
27. Ko S.W., Yang Y.S., Mun J.H., Park K.-M., Lee S.S. and Nam K.C., Highly cesium selective calix[6]arene receptors: synthesis, structure and cesium binding properties of calix[6]arene biscrown, Bull. Korean Chem. Soc., 2002, 23, 1379-1380.
28. Zhang S. and Echegoyen L., Selective binding of aromatic amines by self-assembled monolayers of a calix[6]crown-4 derivative, Org. Lett., 2004, 6, 791-794.
29. Galan H., de Mendoza J. and Prados P., Conformational control of calix[6]arenes through multiple bridges, Eur. J. Org. Chem., 2005, 19, 4093-4097.
30. Guan B., Gong S., Wu X., Li Z. and Chen Y., One-step synthesis of *p-tert*-butylcalix[6]-1,4-2,5-biscrown-4 and its tosyloxyethoxyethylate derivative, J. of Incl. Phenom. and Macrocycl. Chem., 2006, 54, 81–84.
31. Asfari Z., Weiss J., Pappalardo S. and Vicens J., Synthesis and properties of double-calix[4]arenes, doubly-crowned calix[4]arenes, and double-calixcrowns, Pure & Appl. Chem., 1993, 65, 585-590.
32. Li J.-S., Chen Y.-Y. and Lu X.-R., Syntheses of novel tripodal calix[n]cryptands (n = 4, 6) and their extraction abilities toward cations, Eur. J. Org. Chem., 2000, 485-490.
33. Kerdpaiboon N., Tomapatanaget B., Chailapakul O. and Tuntulani T., Calix[4]quinones derived from double dalix[4]arenes: synthesis, complexation, and electrochemical properties toward alkali metal ions, J. Org. Chem., 2005, 70, 4797-4804.
34. Zheng Q., Gong S. and Chen Y., One-step synthesis of singly bridged biscalix[4]arenes with oligooxyethyleneethyl spacers, Synth. Commun., 2007, 37, 2601-2608.
35. Mokhtari B. and Pourabdollah K., Effect of crown ring size and upper moiety on the extraction of s-block metals by ionizable calixcrown nano-baskets, Bull. Korean Chem. Soc., 2011, 32, 3979-3990.
36. Grun A., Balazs B. and Bitter I., Cyclization of *p-tert*-butylcalix[6]arene with diols under the Mitsunobu protocol: a conformational study of the peralkylated derivatives, Lett. Org. Chem., 2009, 6, 311-314.

*****