WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 847-851. Research Article ISSN 2277– 7105

SYNTHESIS OF OCTAHYDROXYCALIX [8] ARENE DERIVATIVES

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Article Received on
09 Oct 2015,

Revised on 30 Oct 2015,
Accepted on 19 Nov 2015

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ABSTRACT

The present synthesis relates to a novel process for preparing 2,8,14,20,26,32,38,44- octaphenyl-5,11,17,23,29,35,41,47- octa-tert butyl 49,50,51,52,53,54,55,56-octahydroxycalix [8] arene (VI); 2,8,14,20,26,32,38,44- octa (4-fluoro) phenyl -5,11,,17,23,29,35,41,47-octa-tertbutyl 49,50,51,52,53,54,55,56-octahydroxycalix [8] arene (VII):- 2,8,14,20,26,32,38,44- octa (4-methoxy) phenyl-5,11,,17,23,29,35,41,47- octa-tertbutyl 49,50,51,52,53,54,55,56-octahydroxycalix [8] arene (VIII); 2,8,14,20,26,32,38,44- octa(3-mthoxy)phenyl 5,11,,17,23,29,35,41,47- octa-tertbutyl 49,50,51,52,53, 54,55,56- octahydroxycalix [8] arene (IX) in presence of a base.

KEYWORDS: Octahydroxycalix [8] arene, Macrocycles, Cancer immunotherapy.

INTRODUCTION

Calix[n]arenes are macarocycles where n represents the number of phenolic units bridged by methylene groups, are ideal building blocks in supramolecular chemistry for the development of scaffolds with a preorganized structure, a well-defined cavity size and modifiable positions for the introduction of a variety of functional groups. The development of novel calixarene derivatives with the capability to act as receptors, sensors, catalysts, or ion transporters designed for specific purposes has been exploited to a great extent with the smaller member of the family calixarenes. The development of systems based on the larger members of the calixarene and thiacalixarene families, namely calix [8] arene and thiacalix [8] arene, has been slow relative to its smaller analogues. This is likely due to the number of phenolic OH and aromatic positions available for functionalization, for which the regioselective introduction of substituents remains a challenging synthetic task. As a consequence, reports

on crystallographically characterized calix [8] arene derivatives are relatively sparse. While the solution structures can be determined by a variety of methods, notably NMR spectroscopy, crystallographic characterization still represents the most reliable proof of the spatial arrangement of the macrocycles, particularly when the mobility of the large calix [8] arene is concerned.[1] Calixarenes are applied in enzyme mimetics, ion sensitive electrodes or sensors, selective membranes, non-linear optics and in HPLC stationary phases. In addition, in nanotechnology calixarenes are used as negative resist for high-resolution electron beam lithography.[2]

Calixarene was used as scaffold to assemble a construct bearing four Tn-antigen unit, at upper rim and immune adjuvant P3CS, at the lower rim. The construct showed a cluster effect in the production of Tn specific IgG antibodies in mice when compared to an analogous monovalent construct. This reveals perspectives for potential application in cancer immunotherapy.[3] Calixarenes have also been used in the recovery of Cesium and Uranium ion selective electrodes and field-effect transistors. Other applications such as phase transfer agents, hydrolysis catalysts and separation of organic molecules have also been reported.[4-5]

EXPERIMENTAL SECTION

Synthesis of 2,8,14,20,26,32,38,44- octa phenyl -5,11,,17,23,29,35,41,47- octa-tert butyl 49,50,51,52,53, 54,55,56, octahydroxycalix[8]arene (VI)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and benzaldehyde (II) (5 mmol) was dissolved in 15ml 1, 4-dimethylbenzene and 0.5ml of 5N K_2CO_3 were added. The mixture was heated in a heating mantle with stirring using reflux condenser at about 120^0C for 3½ hrs. The reaction mixture was allowed to cool to room temperature and white solid formed was filtered. It was washed with methanol and then with water. It was dried in oven at 110^0C to afford fine white powdered solid of 2,8,14,20,26,32,38,44- octaphenyl – 5,11,17,23,29,35,41,47-octa-tertbutyl-49, 50, 51, 52, 53, 54, 55, 56, octahydroxycalix [8] arene (VI), (yield:42.4%), (m .p.327^0C).

Spectral data of the compound (VI)

IR (KBr)

837(v-substitutedbenzene); 1067 (v-C-O str.)1399 (v-C-H deforming -$C(CH_3)_3$;1630(v-Ar-Hstr);2962(v-C-Hstr.,CH_3-); 3434 (v-Ar-OH str.)**^{1}H-NMR (DMSO-d_6)** : 1.016 (s, 72H, -$C[CH_3]_3$), 5.674 (s, 8H, C-H), 6.290 – 7.827 (m, 56H, Ar-H 8.553 (s, 8H, Ar-(C)-OH).**^{13}C-NMR(DMSO-d_6)**: 31.90(-$C(CH_3)_3$), 33.77(-$C(CH_3)_3$), 39.16,39.44,39.71,39.99,40.27,40.55,

73.11(-C-H), 127.26, 128.01, 128.58, 129.35, 137.71, 142.27, 146.30 (Ar-C), 155.64 (Ar(C)-OH).**UV (DMSO)**: λ_{max} 228.8 (0.407), 280.2(0.325), **Mass(M^+)**, m/z = 1904.

Synthesis of 2,8,14,20,26,32,38,44- octa (4-fluoro) phenyl -,11,,17,23,29,35,41,47-octa-tertbutyl49,50,51,52, 53, 54,55,56, octahydroxycalix [8] arene (VII)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 4-flurobenzaldehyde (III) (5 mmol) was dissolved in 15ml 1,4-dimethylbenzene and 0.5ml of 5N K_2CO_3 were added. The mixture was heated in heating mantle with stirring using condenser at about 120^0C for 4½ hrs. The reaction mixture was allowed to cool to room temperature and white solid formed was filtered. It was washed with methanol and then with water. It was dried in oven at 110^0C to afford white solid of 2,8,14,20,26,32,38,44-octa (4-fluoro) phenyl – 5,11,17,23,29,35,41,47-octa-tertbutyl- 49,50,51,52,53,54,55,56,octahydroxy calix [8] arene (VII), (yield:30.5%), (m .p.>400^0C).

Spectral data of the compound (VII)

IR (KBr)

866(v-F); 1064 (v-C-O str.); 1495 (v-C-H deforming -$C(CH_3)_3$; 1607 (v-Ar-H str); 2962 (v-C-H str., -CH_3); 3439(v-Ar-OH str.). **Mass(M^+)**, m/z = 1984.

Synthesis of 2,8,14,20,26,32,38,44- octa (4-methoxy) phenyl -5,11,,17,23,29,35,41,47-octa-tertbutyl 49,50,51,52, 53,54,55,56- octahydroxycalix [8]arene (VIII)

Mixture of 4-tertbutylphenol (I) (5 mmol) and 4-methoxybenzaldehyde (IV) (5 mmol) was dissolved in 15ml 1, 4-dimethylbenzene and 0.5ml of 5N K_2CO_3 were added. The mixture was heated in heating mantle with stirring using reflux condenser at about 120^0C for 4 hrs. The reaction mixture was allowed to cool to room temperature and white solid formed was filtered. It was washed with methanol and then with water. It was dried in oven at 110^0C to afford white solid of 2,8,14,20,26,32,38,44-octa (4-methoxy) phenyl–5,11,17,23,29,35,41,47- octa-tertbutyl- 49,50,51,52, 53,54,55,56-octahydroxy calix [8] arene (VIII), (yield:28.6%), (m .p.>400^0C).

Spectral data of the compound (VIII)

IR (KBr)

801(Ar); 1062 (v-C-Ostr.); 1494 (v-C-H deforming-$C(CH_3)_3$; 1634 (v-Ar-H str); 2961(v-C-H str., -CH_3); 3434 (v-Ar-OH str.); **^{1}H-NMR (DMSO)**: 1.016

and 1.041, (s, 72H, -C[CH_3]$_3$); 3.723 (s, 24H, -OCH_3); 5.607 and 5.765 (s, 8H, C-H); 6.301 – 7.253 (m, 48H, Ar-H); 9.099 (s,8H,Ar-OH)., **Mass(M^+)**, m/z = 2144.

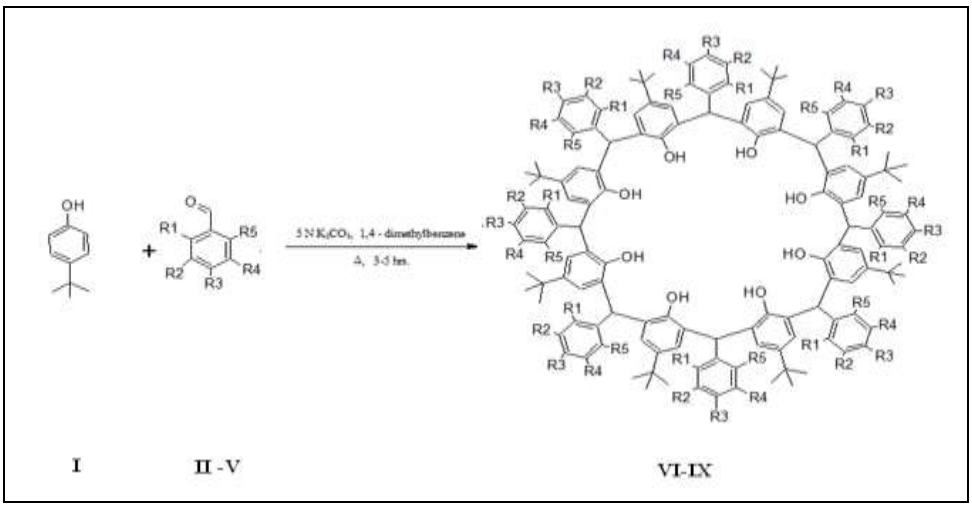
Synthesis of 2,8,14,20,26,32,38,44- octa (3-mthoxy) phenyl -5,11,,17,23,29,35,41,47- octa-tertbutyl 49,50,51,52,53 54,55,56- octahydroxycalix [8] arene (IX)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 3-methoxybenzaldehyde (V) (5 mmol) was dissolved in 15ml 1,4-dimethylbenzene and 0.5ml of 5N K_2CO_3 were added. The mixture was heated in heating mantle with stirring using condenser at about 120^{0}C for 5 hrs. The reaction on workup as described in the experimental section afforded white solid of 2,8,14,20,26,32,38,44-octa (3-methoxy) phenyl – 5,11,17,23,29,35,41,47-octa-tertbutyl-49,50,51,52, 53,54,55,56-octahydroxy calix [8] arene (IX), (yield:32.5%), (m .p.>400^{0}C).

Spectral data of the compound (IX)

IR (KBr)

789 (v- Ar); 1057(v-C-O str.); 1638 (v-Ar-H str); 2958(v-C-H str., -CH_3); 3448(v-Ar-OH str.). **Mass (M^+)**, m/z = 2144.



	R1	R2	R3	R4	R5
II,VI	H	H	H	H	H
III,VII	H	H	F	H	H
IV,VIII	H	H	OCH_3	H	H
V,IX	H	OCH_3	H	H	H

RESULTS AND DISCUSSION

The literature survey on octahydroxycalix [8] arene synthesis revealed that aromatic aldehydes have not been employed. This is probably due to the use of strong bases like KOH,

NaOH etc. which may bring about Cannizzaro's reaction rather than the formation of calixarenes. A Process of preparing octahydroxycalix [8] arene derivatives with phenyl substituents on methylene bridges have afforded octahydroxycalix [8] arene.

CONCLUSION

In conclusion we have developed a short synthesis of a octahydroxycalix [8] arene having phenyl/substituted phenyl functionalities on all the methylene bridges of the calixarenes.

ACKNOWLEDGEMENT

We wish to thank UGC, New Delhi for the award of FIP to SVR and the Department of Chemistry, University of Mumbai.

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