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SYNTHESIS OF HEXAHYDROXYCALIX[6]ARENE DERIVATIVES

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ABSTRACT: The present work relates to a novel process for preparing 2,8,14,20,26,32-hexa(4-chloro)phenyl-5,11,17,23,29,35-hexa-tertbutyl 37,38,39,40,41,42-hexahydroxycalix[6]arene (**V**); 2,8,14,20,26,32-hexa(3-chloro)phenyl-5,11,17,23,29,35-hexa-tertbutyl-37,38,39,40,41,42-hexahydroxycalix[6]arene(VI); 2,8,14,20,26,32-hexa(3,4-dimethoxy)phenyl-5,11,17,23,29,35-hexa-tertbutyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (VII) in presence of a base.

KEYWORDS: Hexahydroxycalix[6]arene, Macrocycles, Cancer immunotherapy

INTRODUCTION

Calixarenes are currently enjoying considerable interest in the field of supermolecular chemistry because their derivatives can form inclusion complexes with cations or with neutral molecules. They have been widely used as building blocks for the synthesis of ionophores either of the polydentate type or macro bicyclic as the calixcrowns, which show efficiency and selectivity according to the calixarene ring size and conformation. For this purpose calixarenes are readily converted into a wide variety of derivatives at the lower rim by alkylation of phenolic groups such as polydentate ester, carboxylate, ether, amide and keto groups.[1]

Hexahydroxycalix[6]arene are synthetic macrocycles readily available by condensation of 4-tert-butylphenol with formaldehyde under alkaline conditions.[2] From these starting materials a large variety of more or less sophisticated compounds have been obtained.[3] Derivatization reactions usually involve the phenolic hydroxyl groups (acylation, alkylation

or even elimination or replacement), the p-position (all kinds of electrophilic substitution, eventually after elimination of the tert-butyl groups), or the phenolic units as a whole (oxidation to p-quinones and subsequent reactions).Numerous selective procedures, involving certain phenolic units are available not only in the calix[4]arene series.[4] but increasingly also for calix[6]arenes.[5] and more recently even for calyx derivatives.[6-8] Calix[6]arene 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.[9] Calixarenes have also been used in the recovery of Cesium and Uranium ion selective electrodes and field-effect transistors.[10] Other applications such as phase transfer agents, hydrolysis catalysts and separation of organic molecules have also been reported.[10-11]

EXPERIMENTAL SECTION

Synthesis of 2,8,14,20,26,32-hexa(4-chloro) phenyl-5,11,17,23,29,35-hexa-tertbutyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (V)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 4-chlorobenzaldehyde (II) (5 mmol) was dissolved in 15ml of 1,4-dimethylbenzene and then 0.5 ml of $5NK_2CO_3$ were added. Immediately solution became turbid and white precipitate formation started. The mixture was heated in heating mantle with stirring using reflux condenser at about 120 ^{0}C for 3 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 ^{0}C to afford white solid of 2,8,14,20,26,32- hexa(4-chloro)phenyl -5,11,17,23,29,35 –hexa-tert butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (V), (yield: 35.4%), (m.p.>400^{0}C).

Spectral data for the compound (V)

IR (KBr) : 835 (v-Cl) 860(v-tetrasubstituted); 1076(v-C-Ostr.); 1489 (v-CH deforming, -$C(CH_3)_3$; 1612(v-Ar-H str); 2962(v-CH str., CH3-); 3439(v-Ar-OH str.). **^{1}H-NMR (DMSO-d6)**: 1.026–1.055 (s,54H, $[CH_3]_3$); 3.327 and 2.487 (solvent peaks); 5.670 and 5.817 (s,6H, C-H); 6.294–7.445 (m,36H,Ar-H); 9.211 (s,6H,Ar-OH). **^{13}C-NMR (DMSO-d6)**: 31.95 (-**C**$(CH_3)_3$); 33.80 (-$C(CH_3)_3$); 72.54 and 73.08,(**C**-H); 123.89, 127.99, 128. 91, 130.35, 131.24, 137.79, 145.47 (Ar-C); 155.49 (Ar(C)-OH). **UV (THF)**: λmax 282.2, 254.0. (Abs. 0.162, 0.204). **Mass (M^+)**, m/z = 1635

Synthesis of 2,8,14,20,26,32-hexa(3-chloro) phenyl-5,11,17,23,29, 35 -hexa-tertbutyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (VI)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 3-chlorobenzaldehyde (III) (5 mmol) was dissolved in 15ml of 1,4-dimethylbenzene and then 0.5 ml of $5NK_2CO_3$ were added.The mixture was heated in heating mantle with stirring using reflux condenser at about 120 ^{0}C 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 ^{0}C to afford white solid of of 2,8,14,20,26,32- hexa (3-chloro)phenyl -5,11,17,23,29,35 –hexa-tert butyl - 37,38,39,40,41,42- hexahydroxycalix[6]arene (VI), (yield: 30.6%), (m.p. >400^{0}C).

Spectral data of the compound (VI)

IR (KBr): 790 (v-Cl); 1056 (v-C-O str.); 1496 (v- CH deforming, -C (CH3)3; 1637(v-Ar-H str); 2962(v- CH str., CH_3-); 3447 (v-Ar-OH str.). **UV (DMSO)**: λmax 230.2, Abs. 0.150. **Mass (M^+)**, m/z=1635.

Synthesis of 2,8,14,20,26,32-hexa(3,4-dimethoxy)phenyl-5,11,17,23,29, 35 -hexa-tertbutyl-37,38,39,40,41,42-hexahydroxycalix[6]arene (VII)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 3,4 - dimethoxy benzaldehyde (IV) (5 mmol) was dissolved in 15ml of 1,4-dimethylbenzene and then 0.5 ml of 5N K_2CO_3 were added. The mixture was heated in heating mantle with stirring using reflux condenser at about 120 ^{0}C 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 ^{0}C to afford buff coloured solid of 2,8,14,20,26,32 - hexa (3,4-dimethoxy) phenyl -5,11,17,23,29,35 –hexa-tertbutyl -37,38,39,40,41,42-hexahydroxycalix[6]arene (VII), (yield:35.4 %), (m.p.>400^{0}C).

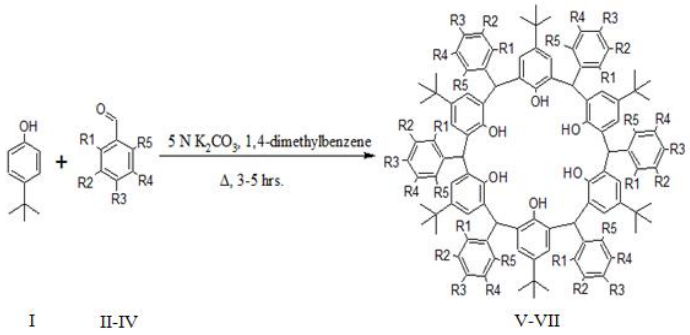
Spectral data of the compound (VII)

IR (KBr): 789 (v-Ar); 1047 (v-C-O str.); 1489 (v- CH deforming, -C (CH3)3;1635 (v-Ar-H str);2962(v- CH str., -CH3);3437(v-Ar-OH str.); **Mass(M^+)** ,m/z = 1788.

RESULTS AND DISCUSSION

The literature survey on hexahydroxycalix[6]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 hexahydroxycalix[6]arene derivatives with phenyl substituents on methylene bridges have afforded hexahydroxycalix[6]arene.



	R1	R2	R3	R4	R5
II, V	H	H	Cl	H	H
III, VI	H	Cl	H	H	H
IV,VII	H	OCH_3	OCH_3	H	H

CONCLUSION

In conclusion we have developed a short synthesis of a hexahydroxycalix[6]arene having phenyl/substituted phenyl functionalities on all the methylene bridges of the calixarenes.

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