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SYNTHESIS OF 4-t-BUTYLCALIX [4] ARENES HAVING SUBSTITUTED PHENYL ON METHYLENE BRIDGES

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ABSTRACT

The present communication relates to a novel method for preparing 2,8,14,20- tetra (3,4,5,- trimethoxy) phenyl – 5,11,17,23 tetra-tert-butyl 25,26,27,28- tetrahydroxycalix [4] arene (V);2,8,14,20-tetra(2,4,6-trimethoxy)phenyl–5,11,17,23tetra-tert-butyl 25,26,27,28-tetrahydroxycalix [4] arene (VI):- 2,8,14,20- tetra (4- dimethylamino) phenyl – 5,11,17,23 tetra-tert-butyl 25,26,27,28- tetrahydroxycalix [4] arene (VII) in presence of a base.

KEYWORDS: Calix[4]arenes, Macrocycles, Cancer immunotherapy.

INTRODUCTION

Calixarenes are synthetic macrocycles readily available by condensation of 4-tert-butylphenol with formaldehyde under alkaline conditions. From these starting materials a large variety of more or less sophisticated compounds have been obtained. 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).

Another possible modification of the calixarene skeleton involves the methylene bridges, which however are not easily amenable to chemical reactions. Oxidation to carbonyl groups and their subsequent reduction to alcohol functions have been reported for tert-butylcalix.[4] arene. Such substituents not only offer an additional possibility to introduce further functionalities into the basic calixarene scaffold but also cause interesting stereochemical

problems and possibilities. However, 4-tert-butyl lcalix[4]arenes have not been synthesised by replacing formaldehyde with aromatic aldehydes. We now report for the first time the synthesis of 4-tert-butylcalix[4]arenes from 4-tert-butyl lphenol and aromatic aldehydes.

Calixarenes are applied in enzyme mimetics, ion sensitive electrodes orsensors, selective membranes, non-linear optics and in HPLC stationary phase.In addition, in nanotechnology, calixarenes are used as negative resist for high-resolution electron beam lithography. A tetrathia[4] arene is found to mimic aquaporin proteins.[1] This calixarene adopts a 1,3-alternate conformation (methoxy groups populate the lower ring) and water is not contained in the basket but grabbed by two opposing tert-butyl groups on the outer rim in a pincer. The non-porous and hydrophobic crystals are soaked in water for 8 hours in which time the calixarene : water ratio acquires the value of one.Calixarenes are able to accelerate reactions taking place inside the concavity by a combination of local concentration effect and polar stabilization of the transition state. An extended resorcin[4]arene cavitand is found to accelerate the reaction rate of a Menshutkin reaction between quinuclidine and butylbromide by a factor of 1600.[2] Calix[4]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.**[3] Calixarenes.[4, 5] 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.

EXPERIMENTAL SECTION

Reaction of 4-tertbutyl phenol (I) with 3,4,5 - trimethoxy benzaldehyde (II) in presence of K_2CO_3 : Formation of 2,8,14,20- tetra (3,4,5,- trimethoxy) phenyl – 5,11,17,23 tetra-tertbutyl 25,26,27,28- tetrahydroxycalix [4] arene (V)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 3,4,5,- trimethoxy benzaldehyde (II) (5 mmol) was dissolved in 15 ml 1,4-dimethylbenzene and then 0.5ml to 5N K_2CO_3 were added. The solution was heated in heating mantle at about 120 ^{0}C with stirring using refluxe condenser for 4 hrs. White solid starts separating after ½ an hour. It was washed with methanol and then withwater. It was dried in oven at 110^{0}C to afford white solid of 2,8,14,20-tetra (3,4,5-

trimethoxy) phenyl – 5,11, 17,23-tetra-tertbutyl-25,26,27,28-tetrahydroxycalix [4] arene (V), (Yield: 28.6%), (m.p.>400^{0}C).

Spectral data of the compound (V)

IR spectrum (KBr) : 784 (v- Ar);1040 (v-C-O str.);1420 (v-C-H deforming, -C(CH_3)$_3$;1642(v-Ar-H str);2303 (v-C-H str., CH3-);3436 (v-Ar-OH str.); Mass(M+) m/z=1312.

Reaction of 4-tertbutyl phenol (I) with 2,4,6, - trimethoxy benzaldehyde (III) in presence of K_2CO_3 : Formation of 2,8,14,20- tetra (2,4,6,- trimethoxy) phenyl – 5,11,17,23 tetra-tertbutyl 25,26,27,28- tetrahydroxycalix [4] arene (VI)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 2,4,6,- trimethoxy benzaldehyde (III) (5 mmol) was dissolved in 15 ml 1,4-dimethylbenzene and then 0.5ml of 5N K_2CO_3 were added. The solution was heated in heating mantle at about 1200C with stirring using refluxe condenser 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^{0}C to afford white solid of s 2,8,14,20-tetra (2,4,6-trimethoxy) phenyl – 5,11, 17,23-tetratertbutyl-25,26,27,28-tetrahydroxycalix [4] arene (V), (yield: 24.2%),(m.p.>4000C).

Spectral data of the compound (VI)

IR (KBr) : 793 (v- Ar);1057 (v-C-O str.);1420 (v-C-H deforming, -C(CH_3)$_3$; 1640(v-Ar-H str);2303 (v-C-H str., CH3-);3436 (v-Ar-OH str.);**1H-NMR (**$CDCl_3$**) :** 2.019 (s, 36H, -C(CH_3)3);3.836 (s, 36H, -C(OC_{H3})3);6.035 (s, 4H, C-H);7.267 (s, 16H, Ar-H);10.305 (s, 4H, Ar-(C)-OH). Mass (M+) m/z=1312.

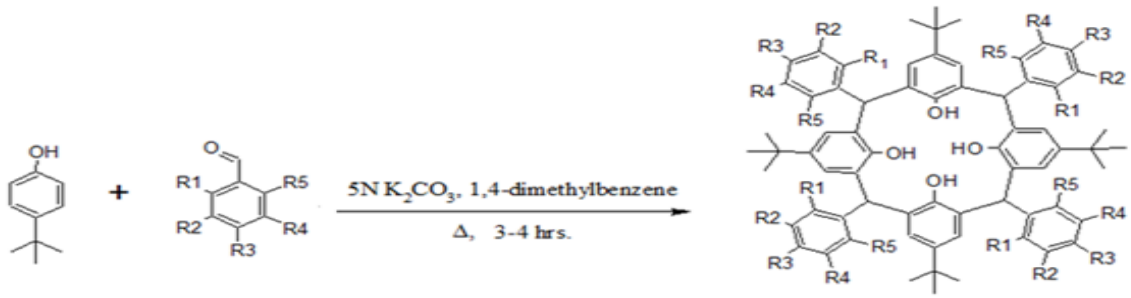
Reaction of 4-tertbutyl phenol (I) with 4- dimethylamino benzaldehyde (III) in presence of K_2CO_3 : Formation of 2,8,14,20- tetra (4- dimethylamino) phenyl – 5,11,17,23 tetra-tertbutyl 25,26,27,28- tetrahydroxycalix [4] arene (VII)

Mixture of 4-tertbutyl phenol (I) (5 mmol) and 4- dimethylamino benzaldehyde (III) (5 mmol) was dissolved in 15 ml 1,4-dimethylbenzene and then 0.5ml to 5N K_2CO_3 were added. The solution was heated in heating mantle at about 1200C with stirring using refluxe condenser for 4 hrs. 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-tetra (4- dimethylamino) phenyl – 5,11, 17,23-tetratertbutyl- 25,26,27,28-tetrahydroxycalix [4] arene (VI), (Yield: 28.6%), (m.p.>4000C).

Spectral data of the compound (VII)

IR spectrum (KBr) : 780 (v- Ar);1072 (v-C-O str.);1420 (v-C-H deforming, -$C(CH_3)_3$;1638(v-Ar-H str);2303 (v-C-H str., CH_3-);3436 (v-Ar-OH str.); **Mass(M+)** m/z=1124

Scheme



I II-IV V-VII

	R1	R2	R3	R4	R5
II, V	H	OCH_3	OCH_3	OCH_3	H
III, VI	OCH_3	H	OCH_3	H	OCH_3
IV,VII	H	H	$N(CH_3)_2$	H	H

RESULTS AND DISCUSSION

The literature survey on 4-alkyl calix[4] 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 4-tertbutyl calix[4] arene derivatives with phenyl substituents on methylene bridges (Scheme) afforded V-VII.

CONCLUSION

In conclusion we have developed a short synthesis of a 4-tert-butyllcalix[4]arenes having substituted phenyl functionalities on all the methylene bridges of the calixarene.

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