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A NOVEL SYNTHESIS OF p-PHENYLCALIX[4]ARENES *VIA* TETRAIODO DERIVATIVES

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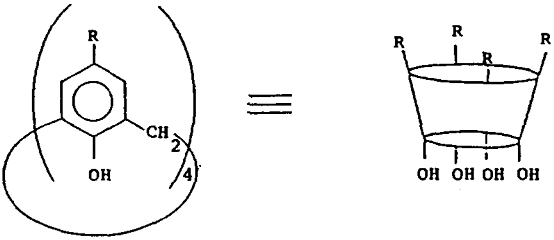
Abstract - The synthesis of p-iodocalix[4]arenes *via* thallated and mercurated macrocycles is described. These compounds are key intermediates for the obtainement of flexible and rigid p-phenylcalix[4]arenes with extended hydrophobic cavities.

The inclusion of neutral molecules inside the cavity of cyclodextrins[1] or cyclophane-type host molecules[2] is an area of current interest in Supramolecular or Host-Guest Chemistry.[3] Among the various synthetic hosts, calixarenes[4] have been the object of several investigations in the last decade. Solid state[5] and solution[6] studies have clearly indicated that these macrocycles are capable of molecular recognition toward neutral organic molecules.

In particular calix[4]arenes (I) form, with aromatic guest molecules, different types of inclusion complexes depending on the nature of the substituents R on the *para* position of the aromatic nucleus ("upper rim")[7]. An attractive target in this context is the synthesis of p-phenylcalix[4]arenes which have an extended hydrophobic cavity suitable for the inclusion of large organic molecules.



I

At the moment no general method is available which allows the synthesis of p-phenylcalixarenes. Gutsche has synthesized p-phenylcalix[4]arene (4) with an overall yield of 0.5% after several steps.[8]

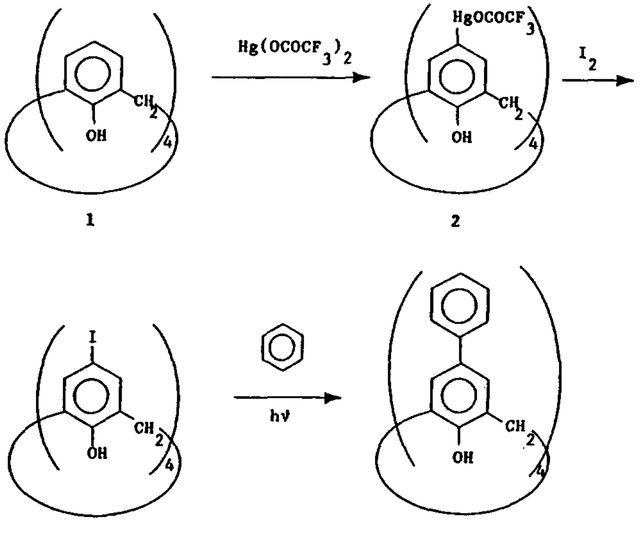
Our first objective was to explore new procedures to obtain p-phenylcalixarenes by functionalization of the "upper rim" of calix[4]arenes.

Since the arylation of p-lithiocalix[4]arene methyl ether has been reported to be unsuccessful,[9] we approached this problem trying to synthesize the tetraiodo derivatives of calix[4]arenes to be used as precursors for further transformations. Iodoaromatic compounds, infact, are very useful reagents for carbon-carbon bond formation.[10]

Because of the failure of several direct iodination attempts we obtained p-iodocalix[4]arene by exchange reaction of thallium and mercury metallated calix[4]arenes.

p-Phenylcalix[4]arene

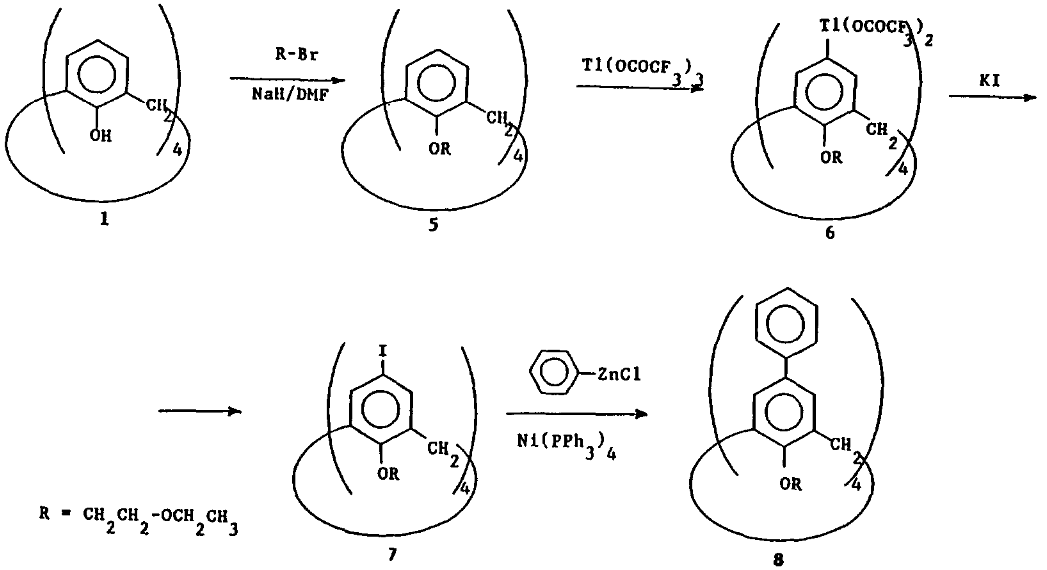
Reaction of calix[4]arene (1) with Hg(TFA)$_2$ in refluxing CHCl$_3$ gave almost quantitative yield of tetramercury derivative (2) (m.p. 190°C dec.), ^{1}H, ^{13}C and ^{199}Hg NMR are in agreement with a mobile structure[11] with the metal bonded to the para position of the phenol nucleus.[12] The metal-iodine exchange was carried out reacting (2) with I$_2$ in CHCl$_3$. The tetraiodo derivative (3) was obtained with 40% yield as a brown compound that was dissolved in benzene and photolized[13] to yield, after column chromatography 15% yield of p-phenylcalix[4]arene (4).[8]



p-Phenylcalix[4]arene derivative in a cone conformation

In order to obtain more rigid systems we studied the introduction of phenyl groups on calix[4]arenes, in fixed cone structure prepared by stereospecific functionalization of the hydroxyl groups on the "lower rim".[14] Groups to be introduced were chosen on the basis of their low reactivity and of the possibility to obtain more soluble compounds.

Chang has reported[15] the introduction of ethoxyethyl chains on p-tert-butylcalix[4]arene. Using this method the reaction of calix[4]arene (1) with CH$_3$CH$_2$OCH$_2$CH$_2$Br and NaH in DMF at 80°C for 5 h afforded the corresponding tetraethoxyethyl calix[4]arene (5) in 72% yield. ^{1}H NMR indicates that this compound exists in a fixed cone conformation (^{1}H NMR δ 4.50 and 3.14 dd Ar-CH_2-Ar, J = 13.3 Hz).[16]



The mercuration of compound (5) according to the previously described procedure failed and therefore we turned our attention to metallation with Tl^{III}.

Thallation reaction was carried out reacting in nitrogen atmosphere and in the dark (5) and $Tl(TFA)_3$ (0.88 M in C_6H_6) in $CHCl_3$ for 2 h at room temperature.

After evaporation of the solvent, CH_3CN was used to dissolve the residue and a saturated solution of KI in H_2O was added. After work-up 35% yield of pure compound (7) was obtained.[17]

Attempts to photolize the tetraiodo derivative (7) in benzene failed so the Ni-catalyzed cross coupling of this product with phenylzinc chloride was performed[18] obtaining product (8) with a 95% yield.[19]

CONCLUSIONS

Iodination of calix[4]arenes can be performed in fair yields using thallated and mercurated derivatives.

p-Phenylcalix[4]arene can be synthesized in reasonable yield from the parent tetraiodo macrocycle; this synthesis is an improvement of the already reported step-wise synthesis.

We are currently studying improvement of the yields of these reactions and the introduction of other binding groups on the "upper rim" of calix[4]arene skeleton using the tetraiodo macrocycles as starting material.

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16.- 25,26,27,28-Tetraethoxyethylcalix[4]arene (5): m.p. 115-117°C, ^{1}H NMR (CDCl$_3$): 6.62 (12H, bs, ArH), 4.13 (8H, t, OCH$_2$-CH$_2$OAr, J = 5.5 Hz), 3.86 (8H, t, OCH$_2$-OAr), 3.56 (8H, q, OCH$_2$CH$_3$, J = 6.9 Hz), 3.14 and 4.50 (8H, AB system, Ar-CH$_2$Ar, J = 13.3 Hz), 1.22 (12H, t, OCH$_2$-CH$_3$). Mass spectrum, m/e: 713 (M$^+$).

17.- 25,26,27,28-Tetraethoxyethyl-p-iodocalix[4]arene (7): m.p. 167-69°C; ^{1}H NMR (CDCl$_3$) 6.98 (8H, s, Ar-H), 4.37 and 3.02 (8H, AB system, Ar-CH$_2$-Ar), 4.07 (8H, t, OCH$_2$CH$_2$OAr, J = 5.0 Hz), 3.74 (8H, t, OCH$_2$-CH$_2$OAr), 3.47 (8H, q, OCH$_2$CH$_3$, J = 6.9 Hz), 1.16 (12H, t, OCH$_2$-CH$_3$). Mass spectrum, m/e: 1216 (M$^+$).

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19.- 25,26,27,28-Tetraethoxyethyl-p-phenylcalix[4]arene (8): m.p. 163-65°C; ^{1}H NMR (CDCl$_3$) 7.18 and 7.03 (s, 28H, ArH), 4.73 and 3.37 (d, 8H, AB system, Ar-CH$_2$-Ar, J = 13.1 Hz), 4.32 and 4.02 (t, 16H, OCH$_2$-CH$_2$-O, J = 5.8 Hz), 3.66 (q, 8H, OCH$_2$-CH$_3$, J = 7.0 Hz), 1.33 (t, 12H, OCH$_2$-CH$_3$). Mass spectrum, m/e: 1017 (M$^+$).

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