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Selective Adamantylation of *p*-H-Calix[4]arene in Trifluoroacetic Acid

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Abstract: It is shown for the first time that unsubstituted p-H-calix[4]arene can be selectively adamantylated at the upper rim by reaction with functionally substituted 1-hydroxyadamantanes in trifluoroacetic acid medium.

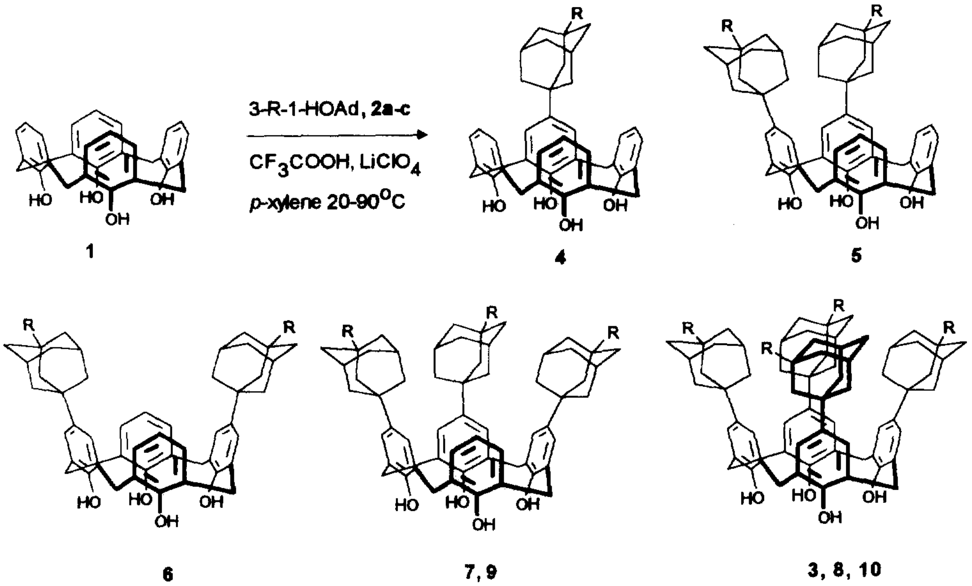
Calixarenes have attracted widespread attention because of their potential for forming host-guest complexes and serving as a useful building block in supramolecular chemistry. Usually parent calixarenes begin to act as synthetic receptor only after appropriate regio- and stereoselective functionalization of phenolic oxygen at the lower rim and/or aromatic para positions on phenyl ring at the upper rim.[1,2]. However, although a great number of derivatization procedures have been used, methods which permit to carry out modification at the upper rim is highly limited. Probably this is connected with the difficulty of selective functionalization of the upper rim. Most of such routes are based on previously selectively modified calixarenes as starting materials.[3-7] There were also reported several examples of direct regioselective nitration, formylation and chlorosulphonylation of calix[4]arene derivatives having four equally protected positions at the lower rim[4,8,9]. There is no doubt that a development of effective approaches for the selective functionalization of the upper rim of calixarenes unsubstituted at the lower rim offers the greatest promise, because in that case very useful building blocks for supramolecular design can be created. To the best of our knowledge the successful examples of this kind are limited by reactions of aminomethylation[10] and diazo-coupling[11] of *p*-H-calix[4]arene.

Recently in our lab it was shown[12] that direct adamantylation of *p*-H-calix[4]arene with 3-R-1-hydroxyadamantanes (R =H, alkyl) in trifluoroacetic acid (TFA) is a convenient synthetic method of production of completely adamantylated tetramers. As the electrophilic aromatic substitution with hydroxyadamantanes in TFA is very sensitive to the stereoelectronic effects of substituents both of adamantanols and of arenes[13], our principal objective was to develop preparative routes to the partially adamantylated at the upper rim calix[n]arenes. It was clear that the alkylation of *p*-H-calix[4]arene **1** with 1-hydroxyadamantane or 3-alkyl-1-hydroxyadamantanes would not allow to get partially adamantylated products because of the fact that the more alkyl substituents are introduced at the upper rim the faster further alkylation proceeds.

In this paper we studied the adamantylation in TFA of *p*-H-calix[4]arene **1** with a number of 3-aryl-1-hydroxyadamantanes **2a-c** containing electron donor (Me for **2a**) or electron withdrawing ($MeSO_2$ for **2b** and

NO_2 for **2c**) substituents in aromatic ring. Reaction conditions and the obtained results are presented at scheme and Table 1. The main question was whether the stereoelectronic effects of substituents at adamantane nucleus were able to retard the reaction at the stages of partial alkylation.

Although the reaction of *p*-H-calix[4]arene with 3-*p*-tolyl-1-hydroxyadamantane **2a** proceeded slower in comparison with 1-hydroxyadamantane and $LiClO_4$ was necessary like a catalyst for its acceleration only tetraadamantylated derivative **3** proved to be obtained. A different situation arose with 3-(4-methylsulfonylphenyl)-1-hydroxyadamantane **2b**. The reaction was revealed to take place only in the presence of lithium perchlorate and its result depended on reaction temperature significantly. Thus, all possible partially (mono-, two di-, tri-) or completely (tetra-) adamantylated calixarenes **4-8** were isolated as a result of the reaction of unprotected tetramer **1** with alcohol **2b**. Bis-adamantylation proceeded predominately at 20-50°C, triadamantylated derivative **7** was formed as a major product at 60-70°C, for the exhaustive adamantylation it was necessary that the reaction was carried out at 80-90°C. In regard to monoadamantylation there is no possibility to obtain compound **4** in considerable quantity because diadamantylation takes place even under 20 °C.



R = 4-MeC_6H_4 for **2a**, **3**; R = 4-$MeSO_2C_6H_4$ for **2b**, **4-8**; R = 4-$NO_2C_6H_4$ for **2c**, **9**, **10**; Ad = adamantane

Mono-, tri- and tetraadamantylated derivatives **4**, **7**, **8** as individual compounds and two unseparated diadamantylated regioisomers **5**, **6** are easily isolated by column chromatography of crude reaction mixtures. Analytically pure samples of compounds **5**, **6** could be obtained after preparative TLC. Interestingly, bis-adamantylation gave 1,2-regioisomer **5** as the major product (on the basis of ^{13}C NMR spectrum **5** : **6** ≈ 2 : 1). In this case the observed regioselectivity is contrary to that revealed for 1,3- bis-heterofunctionalisation (formylation, nitration and chlorosulfonylation)[4,8,9] and analogous to regioselectivity in a diazo-coupling reaction[11].

In regard to the reaction of *p*-H-calix[4]arene **1** with 3-(4-nitrophenyl)-1-adamantanol **2c** it was found that the mixture of tri- and tetraadamantylated derivatives **9, 10** was produced at 85±5 °C. The selective formation (60%) of compound **9** was achieved if the reaction was carried out at 65±5 °C for 10 hours.

Table 1. - Adamantylation of calix[4]arene **1** with 1-hydroxyadamantanes **2a-c** in TFA[14].

Entry	Alcohol	Alcohol (equiv)	TFA (equiv)	Time (h)	Temp. (°C)	Products, (yield, %)[a]
1	**2a**	6	60	15	55±5	**3** (83)
2	**2b**	3	60	144	20±5	**4** (15), **5+6** (80)
3	**2b**	5	50	6	45±5	**4** (30), **5+6** (60)
4	**2b**	4	50	10	65±5	**5+6** (42), **7** (52)
5	**2b**	5	50	15	65±5	**5+6** (32), **7** (65), **8** (3)
6	**2b**	5	50	10	75±5	**7** (50), **8** (30)
7	**2b**	8	50	10	85±5	**8** (86)
8	**2c**	5	50	10	65±5	**9** (60)
9	**2c**	6	80	6	85±5	**9** (21), **10** (50)

[a] Yield of isolated product.

It is important that di- and triadamantylated calix[4]arenes **5-7, 9** can be obtained in large scale so that these compounds might become useful starting materials for preparing calix[4]arenes with mixing functionality at the upper rim.

Preliminary NMR studies of new calix[4]arenes revealed typical ^{1}H and ^{13}C spectra for cone conformation. The well-resolved doublet signals of the axial and equatorial methylene bridge protons at δ 4.2-4.3 and 3.4-3.5 ppm as well as the methylene carbon absorption at δ 31.5-31.6 ppm were detected for all tetra-adamantylated derivatives **3, 8, 10**.

More complicated spectral behavior was observed for partially adamantylated calix[4]arenes **4-7, 9**. Although ^{1}H NMR spectral data confirmed cone conformation for **4-7, 9** (broad doublets at δ 4.2-4.3 and 3.4-3.5 ppm), ^{13}C NMR spectra was proved to be more beneficial as both for the establishment of structure and for conformational studies. Thus, in ^{13}C NMR spectra of compounds **4, 7, 9** having three identical substituents at the upper rim (AAAB ring system) we found two signals of methylene groups at δ31.5-33.0 ppm. Spectra of diadamantylated derivatives **5** and **6** show three well-resolved signals at δ 32.25, 32.01 and 31.67 (1:2:1) for **5** and one signal at δ 32.05 for **6**. Therefore, compounds **5** should be the 1,2-regioisomer (AABB ring system), compound **6** - 1,3-regioisomer (ABAB ring system). The number, intensities and multiplicities of the rest signals were in according to the symmetry of the molecules. As an illustration, the assignment of ^{13}C chemical shifts of 5, 11, 17-tri[3-(4-methylsulfonylphenyl)-1-adamantyl]-25, 26, 27, 28-tetrahydroxycalix[4]arene **7** is presented[15]. It is important that well-resolved ^{13}C NMR spectrum of **7** actually shows that signals of C^1, C^2 and C^3 carbons for distal adamantane fragments (at 5 and 17 positions) differs from the correspondent carbon signals in another adamantane fragment at 11 position. ^{13}C Chemical shifts of CH aromatic carbon atoms belonging to calixarene cavity are also useful for the diagnostics of selectively adamantylated isomers **4-7, 9**:

signals at δ128.9-128.5 and 122.2-122.0 are assigned to CH carbons of unsubstituted phenolic rings, signals at δ125.0-125.7 - to CH carbons of adamantylated phenyl units.

In conclusion, the present study established selective synthetic method of partially adamantylated calix[4]arenes. So, we found that direct adamantylation of *p*-H-calix[4]arene in TFA led to the selective formation of di- and triadamantylated products if adamantane nucleus had a powerful withdrawing substituents. This fact combined with the observation that we had got cone conformation of calixarenes in all instances permits to explain the retardness of alkylation by action of electronic preferably than steric factors on the course of the reaction. Investigation of the possibility of calixarene selective alkylation by another functionally substituted adamantanes is in progress now.

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14. A suspension of calix[4]arene **1** and alchohol **2a-c** (3-8 equiv) in a mixture of equal volumes of TFA (50 -80 equiv) and *p*-xylene in presence of catalytic amount of lithium perchlorate was kept under conditions indicated in Table 1. After reaction being completed, TFA and co-solvent were removed at reduced pressure. The crude product was treated by refluxing ethanol, the precipitate formed was filtered and purified by column chromatography (Merck Silica gel, benzene-chloroform). For all new compounds satisfactory microanalyses were obtained: C ± 0.35, H ± 0.41, N ± 0.35, S ± 0.36.
15. For characterictic example the ^{13}C NMR data (75.4 MHz, $CDCl_3$, 293 K, ppm) of compound 7 are as following : δ C^{ArAd}: 156.72, 156.69 (1:2, ArC), 137.52, 137.49 (2:1, ArC), 127.04, 127.01 (2:1, ArCH), 125.84, 125,77 (2:1, ArCH), 44.31 ($MeSO_2$); δ C^{ArAd}: 36.36, 36.30 (2:1, C^1), 48.75, 48,54 (2:1, C^2), 37.74, 37.69 (2:1, C^3), 41.84 (b.s, $C^{4,8}$)*, 29.10 ($C^{5,7}$), 35.36 (C^6), 41.74 ($C^{9,10}$)*; δ $C^{\text{calixarenes cavity}}$: 148.67, 146.81, 146.37, 143.47, 143.43 (ArC), 128.77 (ArCH), 128.23, 127.95, 127.72, 127.41 (ArC), 125.31, 125.20 , 125.01, 122.00 (ArCH); 32.25, 32.01 (1:1, $Ar\underline{C}H_2Ar$). * - assignements may be interchanged.

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