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Regioselective upper rim substitution of calix[4]arenes

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ABSTRACT

The electrophilic substitution of 25,27-dipropoxy-26,28-dinosyloxycalix[4]arene leads exclusively to the *para*-substitution of the alkylated phenol rings, while in the next step, the protecting nosyl group can be easily removed using a basic hydrolysis. The overall process yields dialkoxycalix[4]arenes with the substitution on the alkylated rings—the substitution pattern, which is complementary to the common dialkoxycalix[4]arenes with substituted nonalkylated phenolic units. The usefulness of this protection/deprotection procedure was documented by the synthesis of novel type of calixarene dipropoxy derivatives, and by the preparation of a novel anion receptor based on this substitution pattern.

1. Introduction

Calixarenes,[1] a class of synthetic macrocycles consisting of phenolic units linked together by methylene bridges, are very frequently used in the design of sophisticated receptors and host molecules. Among them, derivatives of calix[4]arene deserve special attention due to their unique three-dimensional structures and/or easy chemical modifications. As the chemistry of calix[4]arene is well established, many regioselective or stereoselective derivatisation methods are currently in use.[1] The existence of four basic conformations-atropoisomers (*cone*, *partial cone*, 1,2-*alternate* and 1,3-*alternate*) makes calix[4]arene derivatives ideal candidates for applications in supramolecular chemistry.[2] Typically, the calix[4]arene moiety, blocked in the specific conformation, serves as a molecular scaffold, which enables the introduction of selected functional groups or structural fragments into precisely defined mutual positions in space. Depending on the substitution, these highly preorganised molecules can then be used as receptors for ions or neutral molecules.[3]

Dialkoxy derivatives of calix[4]arene are easily accessible from the basic calixarene and they are commonly used as the starting point in the derivatisation of calixarenes.[4] The electrophilic substitution of these compounds attacks exclusively the *para*-positions of nonsubstituted phenolic units leading finally to the substitution pattern A (Fig. 1).[5] During our experiments with regioselective derivatisation of the calixarene skeleton we found that dipropoxy dibenzoyloxy derivatives are nitrated only on alkylated rings while the phenolic units bearing benzoyl ester groups remained untouched by the substitution. This rather unexpected result attracted our attention to the use of ester functions as protecting groups in the aromatic electrophilic substitution reaction. In this paper we report the advantageous application of nosyl groups in the lower-rim protection/deprotection strategy allowing the preparation of derivatives possessing so far almost unknown[6] substitution pattern B in high yields.

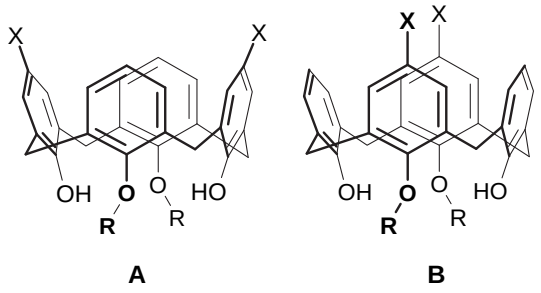

Fig. 1. Two different substitution patterns in dialkylated calix[4]arenes.

2. Results and discussion

The alkylation of basic calix[4]arene (PrI/K_2CO_3/acetone) gave a distally dialkylated compound **1**,[7] which was used as the starting point for subsequent regioselective transformations. Our initial attempts at the acylation of free OH groups were carried out with benzoyl chloride. Unfortunately, these reactions did not give good

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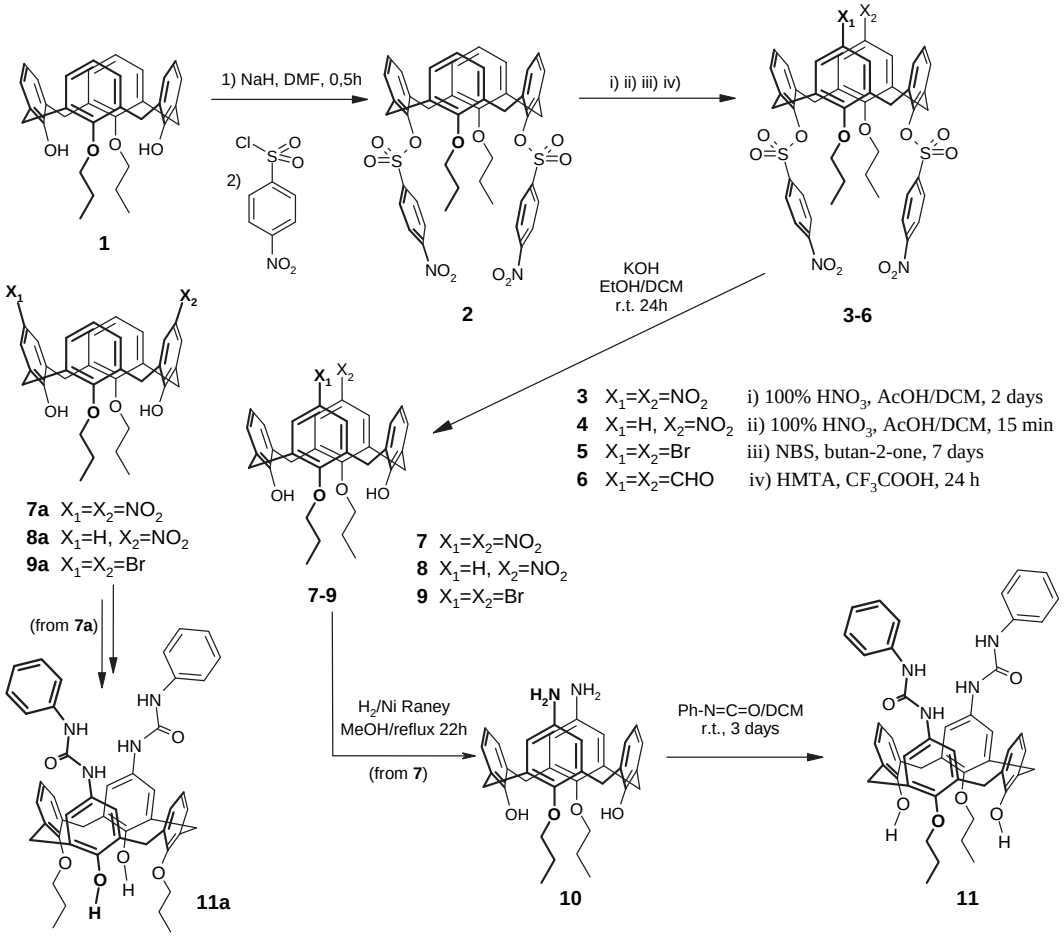
yields of diacylated compounds. Moreover, the product was usually obtained as an inseparable mixture of two conformations (*cone* and *partial cone*) that hindered analysis and subsequent applications of these compounds. During our preliminary study we found that *p*-nitrobenzene sulfonyl chloride (nosyl chloride) is a suitable agent for lower rim acylation as it smoothly led to ester **2** in a 90% yield.

The regioselectivity of the electrophilic substitution of **2** was studied using nitration[8] as a model reaction. It was carried out using 100% HNO_3 in a AcOH/DCM mixture at room temperature. Depending on the reaction conditions (reaction time, excess of a nitric acid) both mono- and dinitro derivatives **4** and **3** can be obtained in 62% and 85% yields, respectively. In all cases, contrary to our expectations, only one regioisomer was isolated from the reaction mixture (Scheme 1). The ^{1}H NMR spectrum of **3** clearly proves the formation of distally *p*-disubstituted product. Thus, derivative **3** possesses one singlet of nitrosubstituted phenyl rings (δ 8.22 ppm), a doublet and triplet due to the unsubstituted rings (δ 6.33 and 6.55 ppm) with typical interaction constant ($J \approx 7.8$ Hz) in the aromatic part of spectrum. At the same time, characteristic doublets of bridging $-CH_2-$ units (3.89 and 3.28 ppm, $J \approx 13$ Hz) exactly correspond to the *cone* conformation of the calixarene skeleton .

signals. Unfortunately, we have not succeeded with growing of suitable monocrystals for X-ray crystallography. To clarify the place of attack we have carried out the next step—deprotection of calixarene lower rim. Stirring of **3** with KOH in a EtOH/DCM mixture and subsequent acidification with aqueous HCl gave dinitro dipropoxy compound in a 92% yield. The comparison with the original sample of **7a** (formed by direct nitration[5a] of dipropoxy calixarene **1**) revealed that the structure of our compound corresponds to formula **7** with nitro groups on alkylated phenol moieties (substitution pattern B, Fig. 1). Interestingly, while the splitting pattern and multiplicity of signals in ^{1}H NMR spectra of **7** and **7a** are identical, the corresponding chemical shifts are very distinct. Thus, the signal of OH group in derivative **7** appears at 7.96 ppm, while the same group in compound **7a** is shifted to 9.44 ppm because of the electron-withdrawing effect of the $-NO_2$ substituent.

Hence, a simple synthetic strategy consisting of (i) protection of the lower rim with nosyl group, (ii) electrophilic substitution of the upper rim and (iii) final deprotection of nosylate, gives us an opportunity to synthesise dialkoxycalixarenes with complementary substitution pattern to those isomers formed by direct electrophilic substitution of dialkylated compounds (compare **7** vs **7a**). Interestingly, under no conditions (higher temperature, long reaction



Scheme 1. Preparation of 5,17-disubstituted-26,28-dipropoxycalix[4]arene-25,27-diols **7**–**9** and anion receptor **11**.

On the other hand, the ^{1}H NMR spectra did not allow the unequivocal assignment of the correct position of the nitro groups as theoretically two regioisomers are possible: (i) *para*-position of alkoxysubstituted rings, or (ii) *para*-position of aromatic moieties bearing sulfonates. It is evident that both regioisomers should possess the same multiplicity and the identical splitting pattern of

time, high excess of 100% nitric acid) we were able to isolate higher nitrated products (tri- or tetra-nitrated). This demonstrates a very strong deactivating effect of nosyl groups if compared with alkoxy derivatives, which is reflected in the strict regioselectivity of dinosylated intermediate (compound **2**) in electrophilic substitution.