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A general method for obtaining calix[4]arene derivatives in the *1,2-alternate* conformation

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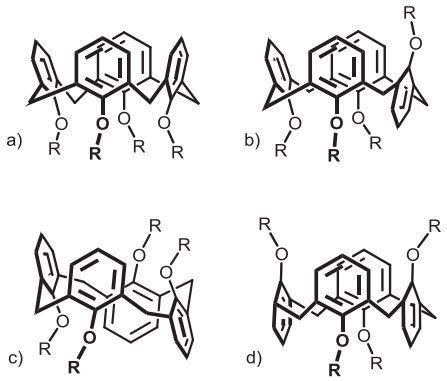
ABSTRACT

The *1,2-alternate* conformation, so far the least accessible atropisomer of calix[4]arene, is now easily available on a gram scale. The entire synthetic sequence consists of only two steps—(a) proximal dialkylation (R^1-I, NaH/DMF), and (b) another subsequent dialkylation (R^2-I, Me_3SiOK/THF). The selection of appropriate base/solvent combinations in both stages was the key prerequisite for the successful preparation of the *1,2-alternate* conformers, which are available without the use of any protecting groups.

1. Introduction

Calix[*n*]arenes[1] represent highly versatile macrocyclic compounds as can be demonstrated by their widespread applications as building blocks and/or molecular scaffolds in supramolecular chemistry. The simple preparation of these compounds, almost limitless freedom in their derivatization and excellent complexation abilities make calixarenes a highly desirable choice in the design of new receptors. Probably, the most attractive feature of these macrocycles is the tuneable 3D shape of their molecules, which is extremely useful in the design and synthesis of novel receptors. Thus, the introduction of bulky substituents (R=propyl or any higher alkyl group) at the phenolic subunits of calix[4]arene leads to the immobilisation of the macrocyclic skeleton into four basic conformations (atropisomers) called *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* (Scheme 1).

The chemistry of the *cone*, *partial cone* and *1,3-alternate* conformations has recently been well established, and all three atropisomers are accessible on a multigram scale via direct stereoselective alkylation of parent calix[4]arenes. Consequently, the three conformations are frequently used in the design of novel receptors, self-assemblies or more sophisticated calixarene-based supramolecular systems.[2] Unfortunately, until recently, a broader application of the *1,2-alternates* has been hindered by our limited knowledge of their chemistry, in particular, by the lack of a general synthetic methodology. Thus, the *1,2-alternate* conformation can be prepared using rather unusual alkylation agents, like 2-pyridylmethyl chloride (α-picolyl chloride),[3] or by the formation of short proximal bridges using oligoethylene glycol ditosylates.[4] Another, even rarer approach, is based on the steric



Scheme 1. The four basic conformers (atropisomers) of calix[4]arene.

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destabilization of the *cone* conformation of unsubstituted calix[4]arene by introducing substituents on the methylene bridges.[5]

In our previous work[6] we showed that calix[4]arenes immobilised in the *1,2-alternate* conformation can be prepared on a multigram scale using a simple dialkylation/dialkylation procedure.[6] Thus, alkylation of starting *p-tert*-butylcalixarene with propyl bromide/NaOH in a DMSO–H_2O mixture gave a proximally dipropylated derivative, which could be subsequently alkylated to give the corresponding *1,2-alternate*. Surprisingly, this procedure did not work with de-*tert*-butylated calixarene **1** leaving the corresponding *1,2-alternates* unavailable. In this paper we report on a simple and general synthetic procedure that selectively provides the *1,2-alternate* derivatives with unsubstituted upper rims, hence, paving the way for their applications in supramolecular chemistry.

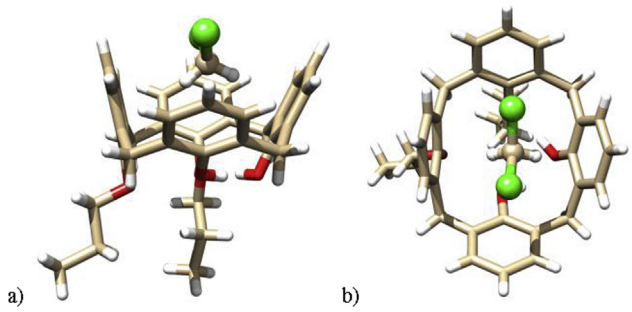


Fig. 1. X-ray structure of compound **2** showing the interactions of the CH_2Cl_2 molecule with the cavity, a) side view, b) same from above.

2. Results and discussion

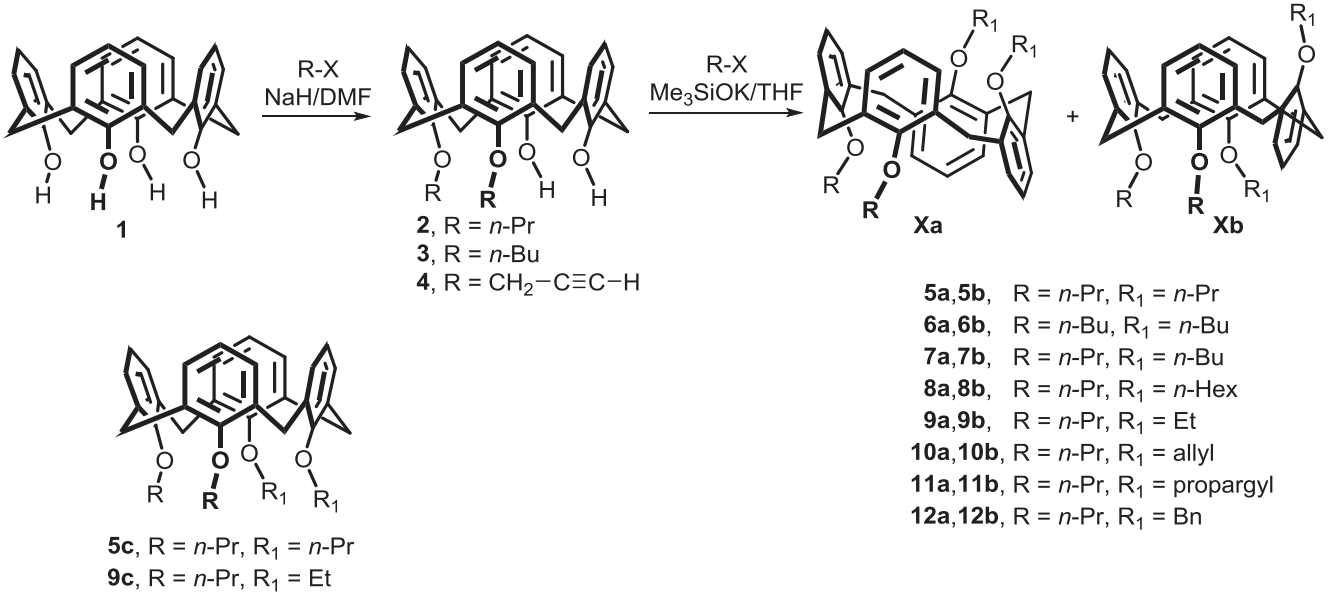
The synthesis starts with a proximal dialkylation of starting calix[4]arene **1** (Scheme 2). We employed a subtle modification of the reaction conditions[7] recently described for the preparation of compound **2**. Thus, calixarene **1** was dissolved in dry DMF and reacted with NaH (3.6 equiv), stirred for 15 min at room temperature and then treated with 1-iodopropane (2.15 equiv) as the alkylating agent. The reaction is surprisingly regioselective and proximally disubstituted isomer **2** was obtained in 54% yield using just simple precipitation of the crude reaction product from a MeOH–CH_2Cl_2 mixture (up to 5.0 g scale). This was highly desired as easy isolation without column chromatography step is an important prerequisite for large scale synthesis.

To show the general applicability of these reaction conditions, we carried out a similar alkylation using 1-iodobutane. The corresponding proximal dibutoxy derivative **3** was isolated in 30% yield. We mention that the same compound was already prepared by Lin et al.[8] using a very complicated procedure. Thus, the starting calixarene **1** was (i) monoalkylated, (ii) monobenzoylated into the distal position (52% yield), (iii) monoalkylated once again, and (iv) deprotected by hydrolysis of the benzoyl group (11% overall yield for last two steps). Interestingly, similar direct alkylation employing a protected propargyl bromide (3-bromo-1-(trimethylsilyl)-1-propyne) led to the isolation of compound **4** (44% yield) with free propargyl groups.

The structure of the dialkylated compounds was confirmed by ^{1}H NMR spectra and reflected the expected symmetry of these compounds. Thus, the presence of three well resolved doublets at 4.61 ppm, 4.50 ppm and 4.36 ppm in a 1:2:1 ratio with typical geminal coupling constants (J=12.5–13.3 Hz) for the axial protons of the methylene bridges clearly supported that compound **4** (400 MHz, $CDCl_3$, 293 K) was proximally alkylated and adopted the *cone* conformation.

Moreover, the structure of dipropoxy derivative **2** was unequivocally assigned using single crystal X-ray analysis. The compound crystalized in the monoclinic system, space group $P2_1/n$ as a 1:1 complex with CH_2Cl_2. The cavity of the calixarene is filled with a solvent molecule (Fig. 1) with close contacts between the hydrogen atoms of the CH bonds (CH_2Cl_2) and the neighbouring aromatic subunits. The distances between the hydrogen atoms and the phenolic planes 2.397 Å and 2.567 Å indicated the complex is held together by the C–H–π interactions.

To find the most suitable conditions for the formation of the *1,2-alternate* conformation, dipropoxy derivative **2** was screened for an optimal base/solvent/temperature combination. Obviously, subsequent propylation of **2** could lead to three different conformers: *1,2-alternate* **5a**, *partial cone* **5b** and *cone* **5c**. Fortunately, all these isomers possess well resolved signals in the aromatic region of their



Scheme 2. Synthesis of calix[4]arenes in the 1,2-alternate conformation.