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Stereoselective Synthesis of Lower and Upper Rim Functionalized Tetra-α Isomers of Calix[4]pyrroles

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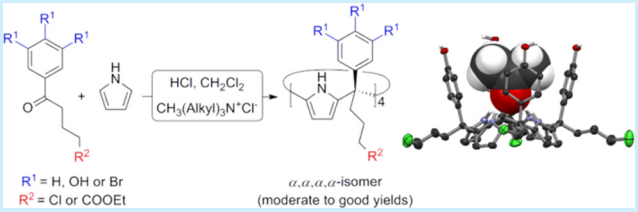
Supporting Information

ABSTRACT: Hydroxyaryl alkyl ketones with functionalized alkyl chains often fail to produce the corresponding tetra-α calix[4]pyrroles in Brönsted acid mediated condensations with pyrrole. A remarkable effect exerted by the addition of methyltrialkylammonium chloride during the acid-mediated syntheses of a series of *meso*-(tetrahydroxyaryl)-*meso*-tetraalkylcalix[4]pyrroles featuring alkyl terminal chloro or ester groups is reported. The ammonium salt enhances the cyclocondensation reaction and induces the almost exclusive formation of the tetra-α isomers.



meso-Tetraaryl-*meso*-tetramethylcalix[4]pyrroles, so-called aryl-extended calix[4]pyrroles, are *meso*-non-hydrogen-substituted porphyrinogens bearing one aryl group on each of the four *meso*-carbons.[1−4] These compounds can exist as four different configurational isomers termed α,α,α,α, α,α,α,β, α,α,β,β, and α,β,α,β in analogy with the porphyrin literature (Figure 1).

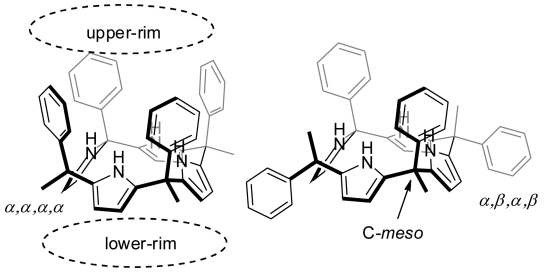


Figure 1. Molecular structures of the α,α,α,α and α,β,α,β configurational isomers of *meso*-tetraaryl-*meso*-tetramethylcalix[4]pyrroles in cone conformations.

The term α or β indicates whether the aryl substituent is directed "up" or "down" with respect to the mean plane defined by the four *meso*-carbons. In turn, each configurational isomer can adopt multiple conformations depending on the relative orientation of the pyrrole units, i.e., cone, 1,3-alternate, 1,2-alternate, or partial-cone. In the cone conformation, the tetra-α isomer of aryl-extended calix[4]pyrroles features an aromatic cavity functionalized at the closed end with four pyrrole NHs that is reminiscent of enzymatic binding pockets.

The unique properties of the tetra-α isomer of aryl-extended calix[4]pyrroles have been exploited in several applications such as the self-assembly of molecular dimeric capsules,[5] the transport of ions and ion-pairs across lipophilic membranes,[6] and the development of new functional materials.[7]

Aryl-extended calix[4]pyrroles are typically synthesized by the acid-mediated condensation reaction of an aryl methyl ketone with pyrrole. Generally, this reaction produces a mixture of the four different configurational calix[4]pyrrole isomers and a plethora of open oligomers.[1−3]

With the aim of tuning the binding properties of the polar- and closed-ended cavity of the aryl-extended calix[4]pyrroles, different functional groups have been introduced on the aryl substituents (upper rim) of the tetra-α isomers.[3,8] The upper rim functionalization allows the construction of more elaborate cavitand[9] and capsule[10] architectures. The second *meso*-position, geminal to the aryl ring (lower rim, Figure 1), is an ideal location for attaching groups with versatile functions without much effect on the binding and recognition properties of the parent methyl tetra-α aromatic cavity. In close analogy with resorcin[4]arenes[11] and calix[4]arenes,[12] lower-rim functionalization can increase the potential applications of aryl-extended calix[4]pyrroles, including solubility in different media, anchoring to solid surfaces and further functionalization.

Most reported syntheses of aryl-extended calix[4]pyrroles either as pure isomers[1−3,13,14] or isomeric mixtures[15−19] target compounds with a simple methyl group attached to the *meso*-carbons. To date and to the best of our knowledge, only two examples featuring four substituents other than methyl groups have been reported.[20,21] These examples described aryl-extended calix[4]pyrroles with a single type of functional group, either on the upper rim or the lower rim substituents. It is worth mentioning that tetramethylcalix[4]pyrroles featuring

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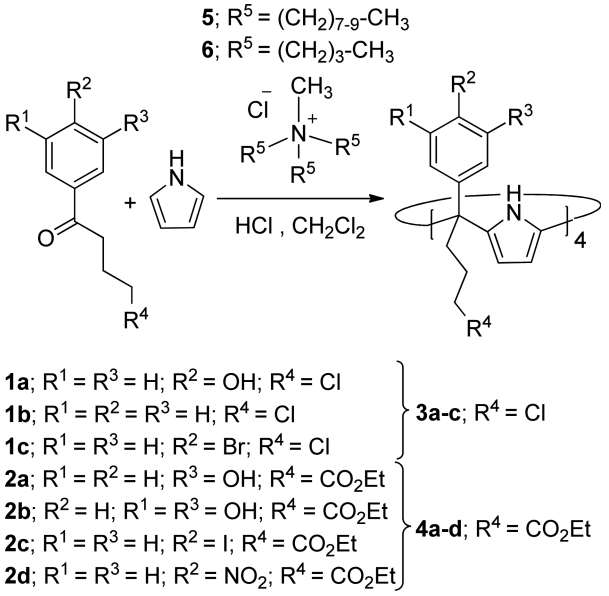
two *cis-p*-fluorophenyl groups that are geminal to hydroxyl- or carboxyethyl-terminated alkyl substituents in nonadjacent *meso*-carbons are known.[22]

The condensation reaction of aryl alkyl ketones with pyrrole to produce the corresponding calix[4]pyrroles is significantly less efficient than the reaction with their aryl methyl counterparts, which may explain the limited examples. The reduced reaction efficiency can be attributed to steric clashes between the substituent in the α-position to the ketone function and the β-pyrrole protons in the transition states of the condensation reactions, especially in the final macrocyclization. For example, the presence of a terminal alkyne in the alkyl chain in the synthesis of the tetra-α isomer gave only a 1% yield.[21] Here, we describe an unprecedented template synthetic strategy that overcomes these problems.

Our approach is based on the simple addition of methyltrialkylammonium chloride salt to the acid-mediated condensation reaction of the aryl alkyl ketone and pyrrole. This methodology is by no means general, but it does provide modest to good yields of calix[4]pyrroles mainly possessing hydroxyl groups at their upper rims and terminal chloro or ester functions on their *meso*-alkyl substituents.

In our hands, the standard acid-mediated conditions (3 equiv of HCl (4 M dioxane) in dichloromethane solution) were not successful in the macrocyclization reactions of 4-chloro-1-(4′-hydroxyphenyl)-1-butanone **1a**, ethyl 5-(3′-hydroxyphenyl)-5-oxopentanoate **2a**, or ethyl 5-(3′,5′-dihydroxyphenyl)-5-oxopentanoate **2b** with pyrrole (Scheme 1). We detected only the formation of polymeric products in the crude reaction mixtures.

Scheme 1. Synthesis of Aryl-Extended Calix[4]pyrroles 3a–c and 4a–d, Functionalized at the Upper and Lower Rims[a]



[a]Structures of the methyltrialkylammonium salts **5** and **6** used as additives are shown.

The template effect exerted by cations and anions in cyclization reactions is well established.[23,24] Moreover, calix[4]-pyrroles are heteroditopic receptors for alkylammonium salts in nonpolar solvents[25,26] and show high affinities for methylammonium chlorides. Accordingly, we decided to explore the use of methyltrialkylammonium chloride salts as templates in the HCl-mediated cyclocondensation of pyrrole with hydroxyphenyl alkyl ketones **1a** and **2a**,**b**.

We selected two inexpensive and commercially available methyltrialkylammonium chloride salts for our experiments: (a) Aliquat 336, **5**, which is a mixture of C_8–C_{10} methyltrialkyl ammonium chloride salts enriched in the C_8 chains that can be removed by silica filtration, and (b) methyltributylammonium chloride (MTBACl) **6**, which can be removed by simply washing the organic solution of the crude reaction mixture with water. Both organic salts provided similar results in the cases tested, although the MTBACl was preferred for purification ease.

We found through TLC and ^{1}H NMR analyses of the crude reaction mixtures that the addition of **5** or **6** to the HCl-mediated reactions improved the formation of the macrocycles **3a** and **4a**,**b** to a significant extent. Remarkably, the additives also favored the formation of the tetra-α isomers as the macrocyclic products (in some cases, only traces of other isomers, mainly $\alpha,\alpha,\beta,\beta$, were detected by ^{1}H NMR analyses of the reaction crude mixtures). As mentioned above, macrocyclization reactions promoted by the exclusive use of HCl usually provide a difficult-to-separate mixture of calix[4]pyrrole configurational isomers. The significant increase in stereoselectivity induced by the added salts also had a beneficial impact on the purification of the crude reaction mixtures. Calix[4]pyrroles **3a** and **4a**,**b** were isolated as pure tetra-α isomers in yields ranging from 18 to 62% (Table 1, entries 2, 8, and 10) by column chromatography

Table 1. Condensation of Aryl Alkyl Ketones 1 and 2 with Pyrrole Mediated by HCl (4 M Dioxane Solution)[a]

entry	ketone	additive (3 equiv)	product	yield[b] (%)
1	**1a**	none	**3a**	0
2	**1a**	**5** or **6**	**3a**	28–31
3	**1b**	none	**3b**	0
4	**1b**	**5** or **6**	**3b**	18–19
5	**1c**	none	**3c**	0
6	**1c**	**6**	**3c**	5[c]
7	**2a**	none	**4a**	0
8	**2a**	**5** or **6**	**4a**	20–23
9	**2b**	none	**4b**	0
10	**2b**	**6**	**4b**	62
11	**2c**	none	**4c**	0[c]
12	**2c**	**5** or **6**	**4c**	0
13	**2d**	none	**4d**	0[c]
14	**2d**	**6**	**4d**	0

[a]Reaction conditions: **1** or **2**, pyrrole (1 equiv), CH_2Cl_2, argon, 18 h. [b]Isolated yield of the tetra-α isomer after column chromatography. [c]$\alpha,\alpha,\alpha,\beta$ and $\alpha,\alpha,\beta,\beta$ isomers were mainly formed (see the Supporting Information).

purification. The isolated products were characterized by a complete set of high resolution spectra, and their configuration assignments were verified by single-crystal X-ray diffraction (Figure 2).[27]

During investigation of the substrate scope of the new method, we found that it lacks generality. For ketones in terminal alkyl ester series, the presence of certain electron-withdrawing groups on the *para*-position of the phenyl ring (**2c** and **2d**) had a dramatic influence on the attempted template macrocyclization: we could not detect the presence of calix[4]pyrroles in the corresponding reaction mixtures (entries 12 and 14). However, mixtures of calix[4]pyrrole isomers, not

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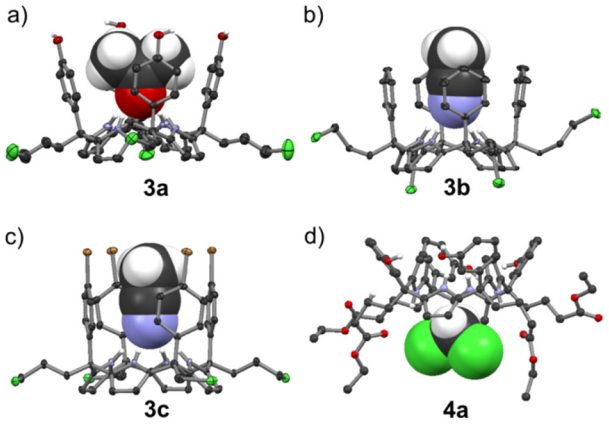

Figure 2. X-ray structures of *meso*-aryl-*meso*-alkylcalix[4]pyrroles: (a) **3a**, (b) **3b**, (c) **3c**, and (d) **4a**. Structures **3a**–**c** are shown in ORTEP view with thermal ellipsoids set at 50% probability. The structure of **4a** is a preliminary solution of the diffracted data and is shown in ball and stick representation. Nonpolar hydrogen atoms have been omitted for clarity. Polar hydrogens (NHs and OHs) are shown as fixed-size spheres of 0.15 Å radius. Solvent molecules (acetone, acetonitrile, and dichloromethane) are shown as CPK models.

including the tetra-α isomer, were produced under identical reaction conditions in the absence of the ammonium chloride additive for **2c** and **2d** (entries 11 and 13).

In contrast, for the cyclocondensation reaction with ketones having a terminal chloro substituent, the absence of the *p*-hydroxy group (**1b**) produced good results and the isolated yield of **3b** was 19% (entry 4). The cyclocondensation also proceeded in the presence of the additive when the hydroxyl group was replaced by a bromine atom (**1c**). However, in this case, we obtained a mixture of configurational calix[4]pyrrole isomers, in which the tetra-α isomer was a minor component.

In the course of these studies, we also learned that the aryl alkyl ketone must have at least three methylene units between the carbonyl group and the terminal functional group. All of our cyclization attempts employing aryl alkyl ketones with functionalized alkyl chains shorter than three methylene units were unsuccessful. Again, we attribute this lack of reactivity to strong steric clashes occurring between the β-substituent and the β-pyrrole protons in the transition state of their condensation reactions. Owing to one methylene reduction in alkyl chain length, the steric effect of the α-methylene substituent becomes predominant.

At this time, the specific role of the methyltrialkylammonium chloride salts is not completely understood. We propose a template effect that would probably involve both components of the ion pair. The methyltrialkylammonium cation is a good fit for the shallow aromatic cavity provided by the calix[4]-pyrrole core in the cone conformation. The chloride anion is known to form stronger hydrogen bonds with phenol OHs than with pyrrole NHs.[1,28] The combination of these properties probably favors the cyclocondensation of linear oligomers and the reaction's steroselectivity. The suppression of the condensation reaction by addition of the ammonium salt in the series of ketones having alkyl-terminal esters and electron-withdrawing groups in the phenyl groups is puzzling, and currently, we do not have any sensible explanation.[29]

In conclusion, we describe the efficient preparation of *meso*-tetraaryl-*meso*-tetraalkylcalix[4]pyrroles functionalized at their upper and lower rims. The method uses the addition of methyltrialkylammonium chloride salts to the HCl-mediated condensation reaction of the aryl alkyl ketone and pyrrole in CH_2Cl_2. Although the reported procedure is not wide in scope, it solves two synthetic problems in the preparation of certain calix[4]pyrroles: (a) it promotes the macrocyclization reaction, which is suppressed in the absence of the ammonium salt, and (b) produces a calix[4]pyrrole mixture highly enriched in the tetra-α isomer. This latter feature simplifies the isolation of the compounds in moderate to good synthetic yields. The functional groups incorporated at the lower and upper rims of the calix[4]pyrroles can be further chemically transformed and pave the way for new applications and properties of this family of compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03505.

Detailed synthetic procedures and characterization data for the new compounds **2a**–**d**, **3a**–**c**, and **4a**,**b** and their ^{1}H and ^{13}C NMR spectra (PDF)
X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **3b** (CIF)
X-ray crystallographic data for **3c** (CIF)

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Notes

The authors declare no competing financial interest.

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