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The first example of direct heterylation of calixpyrrole

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1,2,4-Triazine derivatives react with calixpyrrole to give stable nucleophilic addition products.

Key words: 1,2,4-triazines, 1,2,4-triazin-5(2*H*)-one, calixpyrrole, nucleophilic addition, σ^H-adduct.

Calix[4]pyrroles[1] have attracted particular attention because of their ability to bind not only transition metals[2] and neutral molecules[3] but also anions.[4] Although anions play a key role in chemistry[5] and biology,[6] receptors of negatively charged species remain poorly studied and the design of such compounds is topical in modern organic chemistry.

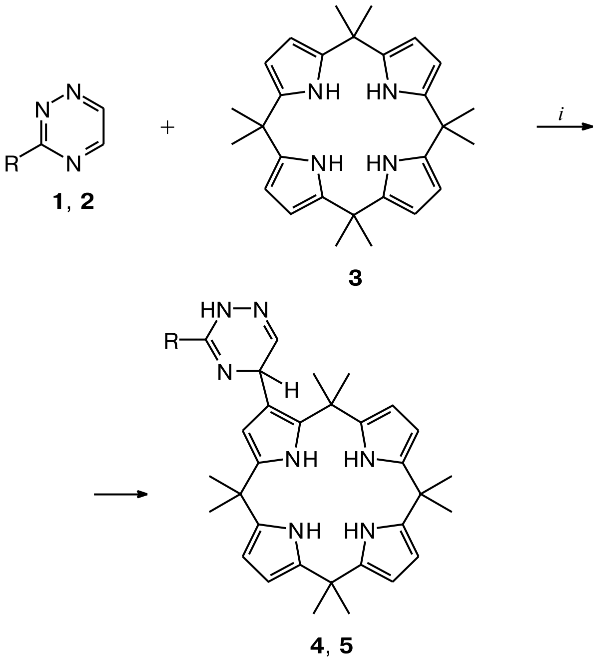
Calixpyrroles synthesized by [4+4]-cyclocondensation of pyrrole with ketones (by analogy with the first step of the Rothemund synthesis of porphyrins[7]) are accessible starting materials. However, only few examples of their functionalization have been documented to date.[8] Of special interest in this field is modification of the C-rim with retention of the pyrrole N atoms. As for heterylation of calixpyrrole, introduction of heterocyclic fragments not only creates additional sites of complexation but also affects the molecular conformation.

Earlier,[9—11] we have developed a simple technique for one-step coupling of "monomeric" furans, pyrroles, thiophenes, and their derivatives with various azines, their *N*-oxides, and cationic forms involving nucleophilic addition to the unsubstituted C-atom of the azine system. In the present work, this methodology was developed for the modification of calix[4]pyrrole. 1,2,4-Triazine derivatives belonging to the most electrophilic heterocycles were used as azines.

1,2,4-Triazines as such do not react with calixhetarenes. Protonic or Lewis acids activate the triazine ring, and the reactions of protonated 3-methylthio- (**1**) and 3-amino-1,2,4-triazines (**2**) with calixpyrrole (**3**) in CF_3COOH gave adducts **4** and **5** (Scheme 1). The ^1H NMR spectra of the reaction mixtures show signals at δ 5.3—5.5 characteristic of $C(5)_{sp^3}H$ protons.

Compound **4** was obtained in 62% yield from calix[4]pyrrole (**3**) and 3-methylthio-1,2,4-triazine (**1**) in the presence of $BF_3 \cdot Et_2O$.

Scheme 1



i. H^+ or $BF_3 \cdot Et_2O$.

R = SMe (**1**, **4**), NH_2 (**2**, **5**).

The reaction of calixpyrrole (**3**) with 3-phenyl-1,2,4-triazin-5(2*H*)-one (**6**) in the presence of acetic anhydride as an activator affords monoadduct **7** (Scheme 2).

Apparently, the reaction involves addition of the pyrrole ring to *N*(2)-acetyl-1,2,4-triazin-5-one protonated with acetic acid, similarly to the reported reaction of 3-R-1,2,4-triazin-5(2*H*)-ones with benzocrown ethers.[12]

In the ^1H NMR spectra, signals for the H(5) and H(6) atoms in compound **4** appear as a set of doublets, while

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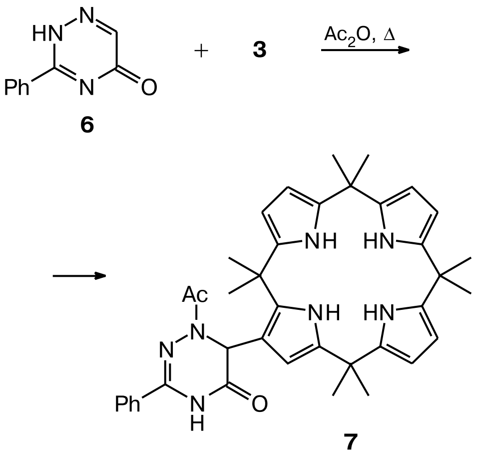
Scheme 2



signals for the CMe groups in compounds **4** and **7** appear as a set of singlets, which is due to the conformational lability of the system.

The described transformations represent first examples of modification of calixpyrrole with heterocyclic fragments. The formation of a C—C bond complements the methodology of cross-coupling in which metal complex catalysis is commonly used.

Experimental

The course of the reaction was monitored and the purity of the products obtained was checked by TLC on Sorbfil PTLC—UV plates in dichloromethane—methanol (10 : 1). ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 with Me_4Si as the internal standard. Elemental analysis was carried out on a Carlo Erba EA 1108 automatic analyzer. Melting points were determined on a Boetius stage and are uncorrected.

3-Amino-1,2,4-triazine was purchased from Lancaster Synthesis Ltd. **3-Methylthio-1,2,4-triazine,**[13] **3-phenyl-1,2,4-triazin-5(2*H*)-one,**[14] and **octamethylcalix[4]pyrrole (3)**[7] were prepared according to known procedures.

4-(3-Methylthio-1,2,4-triazin-5-yl)-*meso*-octamethylcalix[4]pyrrole (4). Boron trifluoride etherate (0.4 mL) was added to a stirred solution of 3-methylthio-1,2,4-triazine (**1**) (50 mg, 0.40 mmol) and calixpyrrole (**3**) (171 mg, 0.4 mmol) in 1 mL of MeOH. The reaction mixture was refluxed for 40 min and concentrated *in vacuo*. The residue was dissolved in water and neutralized with dilute Na_2CO_3. The precipitate that formed was filtered off and dried in air to give compound **4** (62%), m.p. >200 °C. Found (%): C, 69.23; H, 7.58; N, 17.32. $C_{32}H_{41}N_7S$. Calculated (%): C, 69.15; H, 7.44; N, 17.64. ^{1}H NMR, δ: 1.24—1.53 (set of singlets, 24 H, CH_3); 2.37 (s, 3 H, SMe); 4.42—4.46 (set of doublets, 1 H, C(5´)H); 6.54—6.56 (set of doublets, 1 H, C(6´)H); 7.68—8.01 (m, 6 H, calixpyrrole); 8.12 (s, 1 H, CH_{pyr}).

4-(1-Acetyl-5-oxo-3-phenyl-1,2,4-triazin-6-yl)-*meso*-octamethylcalix[4]pyrrole (7). A suspension of 3-phenyl-1,2,4-triazin-5(2*H*)-one (**6**) (50 mg, 0.29 mmol) and calixpyrrole (**3**) (124 mg, 0.29 mmol) in 3 mL of Ac_2O was refluxed for 2 h and concentrated *in vacuo*. The residue was triturated with diethyl ether to give compound **7** (42%), m.p. 159—160 °C. Found (%): C, 72.87; H, 6.91; N, 14.87. $C_{39}H_{45}N_7O_2$. Calculated (%): C, 72.76; H, 7.03; N, 15.23. ^{1}H NMR, δ: 1.15—1.56 (set of singlets, 24 H, CH_3); 5.58 (br.s, 1 H, C(6´)H); 7.63—7.64 (m, 8 H, Ph, calixpyrrole); 7.99—8.07 (m, 4 H, Ph, calixpyrrole); 8.31 (s, 1 H, CH_{pyr}).

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