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DIRECT C-C COUPLING OF *MESO*-OCTAMETHYLCALIX[4]PYRROLE WITH 6-NITROAZOLOPYRIMIDINES

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Abstract – It has been found that the reaction of *meso*-octamethylcalix[4]pyrrole with four equivalents of 6-nitroazolopyrimidine is accompanied by the C-C coupling of unsubstituted carbon atom in azines with β -position of pyrrole rings and results in the formation of tetrapyrimidine-substituted calix[4]pyrroles without introduction of any catalysts. Mono- and di-substituted calixpyrroles have been isolated.

INTRODUCTION

Recently the number of publications dealing with the synthesis and modification of calix[4]pyrroles^{1,2} has been increasingly growing. Their huge success is due to several factors. Calixpyrroles are readily accessible by condensation of pyrrole and acetone in the presence of strong acids,³ and being anion receptors⁴ can be widely used in the production of fluorescent,⁵ colorimetric⁶ and electrochemical⁷ sensors for anions. In spite of these useful properties there are a few methods for the synthesis of C-rim functionalized calixpyrrole.⁸⁻¹⁰ Therefore introduction of substituents into pyrrole ring, affecting complexation properties is of great interest.

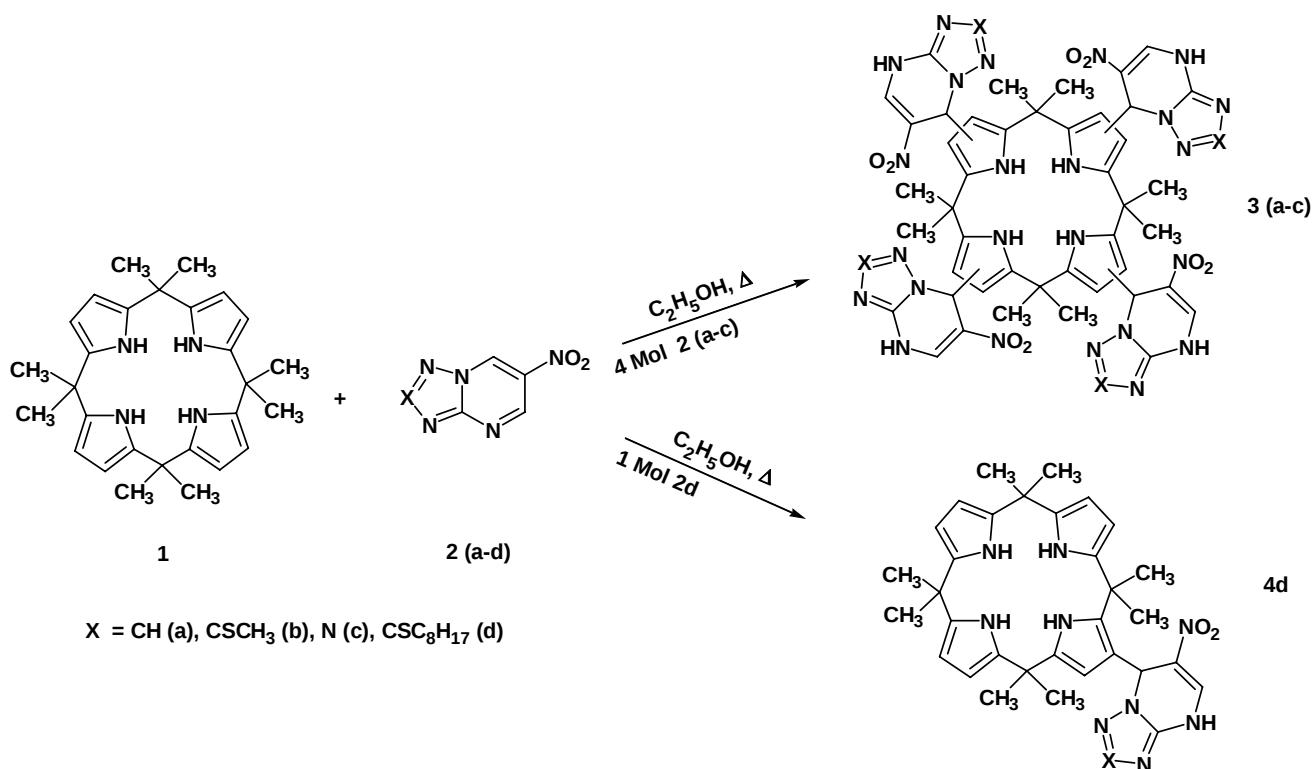
RESULTS AND DISCUSSION

The present investigation is devoted to the modification of calixpyrrole by 6-nitroazolopyrimidines, which early showed a high activity in the reactions with π -excess carbo- and heterocycles.¹¹ Thus, 6-nitro[1,5-a]azolopyrimidines can be modified by the reaction with aromatic (N,N-dialkylanilines, phenols, their ethers) and heteroaromatic (indoles, pyrroles) nucleophiles without any charge activation of azine ring. These processes are based on the methodology of nucleophilic attack on unsubstituted carbon atom in azines.¹²

Unsubstituted β -positions of the pyrrole rings involved in macrocycle formation have less nucleophilicity than α -positions. However the high electrophilicity of azolopyrimidines makes it possible to react with calixpyrrole. It should be underlined that heterylation of calixpyrrole appears without any acid activation of azine which is commonly used for coupling of azines with nucleophiles. This fact is very important because calixpyrroles are highly sensitive to acid cleavage.

Refluxing of the ethanolic solution of calix[4]pyrrole (**1**) and four equivalents of pyrimidines (**2 a-c**) results in the mixture of isomeric tetrasubstituted calixpyrroles (**3 a-c**) in 43-57 % yields (Scheme 1).

In the case of **2a** 7-ethoxy-6-nitrotriazolo[1,5-*b*]pyrimidine, obtained by the recrystallization of **2a** from ethanol, was introduced in the reaction. But earlier it has been established that in the solution such compounds can be smoothly aromatized by elimination of ethanol and further step involves nucleophilic attack on unsubstituted C(7)-carbon atom of aromatic pyrimidine.¹³



Scheme 1

Compound **4c** having two pyrimidine rings was isolated as a by-product in 28 % yield in the reaction with tetrazolopyrimidine (**2c**).

It should be noted that the reaction of **1** with 6-nitro-2-octylthio-s-triazolo[1,5-*a*]pyrimidine (**2d**) leads to difficult-to-separate mixture, and only mono-substituted calix[4]pyrrole (**4d**) has been isolated.

Earlier it has been established that calix[4]pyrroles can act as hydrogen-bonding acceptors of different alcohols.¹⁵ In according to this knowledge the complexation of **3a** with 2(C_2H_5OH) has been proved by

NMR spectra and elemental analytical data.

STRUCTURE ASSIGNMENT

The spectral data for the obtained compounds (Table 1) are in full agreement with the proposed structures. In the ^1H NMR spectra of **3** and **4** resulting from a nucleophilic addition of calix[4]pyrrole (**1**) at unsubstituted C(7)-carbon atom of the pyrimidine ring the resonance signal of H-(7) attached at sp^3 -hybridized carbon atom is observed at δ 5.40-5.80 ppm. In the ^1H NMR spectra all groups of signals appear as set of signals, which is due to the formation of products with irregular structure and conformational lability of the systems.

Table 1. ^1H NMR spectral data of the obtained compounds (δ , ppm; J , Hz)

No	Pyrimidine signals				Calix[4]pyrrole signals	
	C(7)-H	C(5)-H	N(4)-H	X	C(β')-H	CH ₃ -groups
3 a	5.36–5.71 (4H, set of singlets)	8.31–8.43 (4H, set of singlets)	11.79 (4H, br s)	7.63–7.99 (set of singlets, 4H, C(2)-H)	6.89–7.03 (4H, set of singlets)	1.24–2.43 (24H, set of singlets)
3b	5.43-5.78 (4H, set of singlets)	8.37-8.48 (4H, set of singlets)	11.69 (4H, br s)	2.12-2.18 (set of singlets, 12H, C(2)–CH ₃)	6.88-7.00 (4H, set of singlets)	1.36-1.42 (24H, set of singlets)
3c	5.27-5.60 (4H, set of singlets)	8.34-8.56 (4H, set of singlets)	11.65 (4H, br s)	-	7.24-7.37 (4H, set of singlets)	1.23-1.80 (24H, set of singlets)
4c	5.45-5.80 (2H, set of singlets)	8.11-8.34 (2H, set of singlets)	12.02 (2H, br s)	-	6.45 (2H, s); 7.23 (4H, set of signals)	1.23-1.60 (24 H)
4d	5.40 (1H, s)	8.39 (1H, s)	11.75 (1H, br s)	2.95 (t, J = 6.4 Hz, 2H, SCH ₂); 1.50 -1.83 (m, CH ₂), 0.84 (t, J = 6.9 Hz, 3H, CH ₃)	6.97 (1H, s); 5.73-5.88 (6H, set of signals)	1.24, 1.34, 1.39 (24H, singlets)

In this paper we have reported a new approach for heterylation of calix[4]pyrrole which enables one to incorporate a heterocyclic fragment into unsubstituted calixarenes through a one-step procedure without any activation of both calixpyrrole and pyrimidine fragments. This method is based on direct C-C coupling of the β -carbon atom of pyrrole ring with high-active electron-deficient 6-nitro-azolopyrimidines, and it appears to be another example of successful application in macrocyclic chemistry a methodology which exploits a nucleophilic attack on unsubstituted carbon atom in azines.¹²

EXPERIMENTAL

Flash chromatography was performed on Lancaster 0.040-0.063 mm (230-400 mesh) silica gel using CHCl_3 - CH_3OH (20:1 and 10:1) as an eluent. All melting points are uncorrected and were measured on a Boetius melting point apparatus. Elemental analyses were performed on Carlo Erba 1108 CHNO Analyzer. The ^1H -NMR spectra were recorded on a Bruker DRX 400 (400MHz) spectrometer with TMS as an internal standard. The LCMS spectra were obtained on Shimadzu LCMS-2010 in *i*-PrOH solutions at flow rate of 1.0 mL/min. Compounds (**2a-c**) were synthesized according to known procedure.¹⁵

6-Nitro-2-octylthio-s-triazolo[1,5-a]pyrimidine (2d). A solution of nitromalonic aldehyde (1.71 g, 15.00 mmol) in 15 mL of water was added to the solution of 3-octylthio-5-aminotriazole (2.28 g, 10.00 mmol) in 11 mL of 2N HCl. The reaction mixture was then stirred for 20 min at rt and the resulting precipitate was filtered off and recrystallized from ethanol. Yield 2.56 g (83 %), mp 86-88 °C; ^1H NMR (δ) 10.30 (d, $J = 2.4$ Hz, 1H, Ar), 9.44 (d, $J = 2.4$ Hz, 1H, Ar), 2.90 (t, $J = 6.4$ Hz, 2H, CH_2), 1.58-1.50 (m, 2H, CH_2), 1.28-1.21 (m, 10H), 0.87 (t, $J = 6.9$ Hz, 3H, CH_3). Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{N}_5\text{O}_2\text{S}$: C, 50.47; H, 6.19; N, 22.64. Found: C, 50.50; H, 6.19; N, 22.62.

Tetra- β -(6-nitro-1,2,4-triazolo-4,7-dihydropyrimidin-7-yl)-meso-octamethylcalix[4]pyrrole (3a). A suspension of meso-octamethylcalix[4]pyrrole (100 mg, 0.23 mmol) and 7-ethoxy-6-nitrotriazolo[1,5-a]pyrimidine (194 mg, 0.92 mmol) in 7 mL of ethanol was refluxed for 1 h. The reaction mixture was then filtered off and the resulting precipitate was dried at the room temperature. The residue was dissolved in CH_2Cl_2 and separated by flash chromatography using CHCl_3 - CH_3OH (20:1) as an eluent. Yield 142 mg (57 %), mp 320 °C (decomp). ^1H NMR (δ) 11.79 (br s, 4H, N(4)-H), 8.31-8.43 (set of singlets, 4H, C(5)-H), 7.63-7.99 (set of singlets, 4H, C(2)-H), 6.89-7.03 (set of singlets, 4H, C(β')-H), 5.36-5.71 (set of singlets, 4H, C(7)-H), 3.29 (q, $J = 7.2$ Hz, 4H, $\text{CH}_3\text{CH}_2\text{OH}$), 1.24-2.43 (set of singlets, 24H, CH_3), 1.28 (t, $J = 7.2$ Hz, 6H, $\text{CH}_3\text{CH}_2\text{OH}$). Anal. Calcd for $\text{C}_{48}\text{H}_{48}\text{N}_{24}\text{O}_8 \cdot 2 \text{C}_2\text{H}_5\text{OH}$: C, 52.88; H, 5.12; N, 28.47. Found: C, 52.86; H, 5.08; N, 28.44. LCMS-spectra (m/z) 1087/1088, 592/594, 757/759 and 922/924 in negative/positive modes.

Tetra- β -(6-nitro-2-methyl-s-triazolo[1,5-*b*]-4,7-dihydropyrimidin-7-yl)-meso-octamethylcalix[4]-pyrrole (3b). A suspension of meso-octamethylcalix[4]pyrrole (100 mg, 0.23 mmol) and 6-nitro-2-methyl-s-triazolo[1,5-*a*]pyrimidine (165 mg, 0.92 mmol) in 5 mL of ethanol was refluxed for 2 h until reagents were completely dissolved. The reaction mixture was then poured into 100 mL of water and the product was extracted by n-butanol. Solvent was removed *in vacuo*. The residue was treated with Et₂O and the precipitate was filtered off. ¹H NMR spectra is given in the Table 1. Elemental analysis data and melting points are given in the Table 2.

General procedure for the synthesis of nitro-azolo-4,7-dihydropyrimidin-7-yl-substituted meso-octamethylcalix[4]pyrrole (3c, 4c, 4d). A suspension of meso-octamethylcalix[4]pyrrole (100 mg, 0.23 mmol) and 6-nitroazolo[1,5-*a*]pyrimidine (153 mg, 0.92 mmol) in 7 mL of ethanol was refluxed for 7-32 h until reagents were completely dissolved. The solvent was removed *in vacuo*, the oil residue was dissolved in CH₂Cl₂ and separated by flash chromatography using CHCl₃-CH₃OH (20:1) as an eluent. Yields, melting points and elemental analysis data are given in Table 2.

Table 2. Yields, melting points and elemental analysis data of obtained compounds (3-4)

No	Reaction time (hours)	Yield (%)	mp (°C)	Formula	Calculated /Found, %		
					C	H	N
1	2	3	4	5	6	7	8
3b	2	47	314-315	C ₅₂ H ₅₆ N ₂₄ O ₈ S ₄	49.05/48.86	4.43/4.62	26.40/26.12
3c	25	43	> 240	C ₄₄ H ₄₄ N ₂₈ O ₈	48.35/48.03	4.06/4.42	35.88/35.52
4c	25	27	230 _{decomp}	C ₃₆ H ₄₀ N ₁₆ O ₄	56.83/56.56	5.30/5.61	29.46/29.15
4d	32	13	133-135	C ₄₁ H ₅₅ N ₉ O ₂ S	66.73/66.29	7.51/7.64	17.08/16.92

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