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Synthesis of New *meso*–Substituted Heterocyclic Calix[4]arenes *via* S_N^H Approach

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Dedicated to Academician of the Russian Academy of Sciences A. I. Konovalov on the occasion of his 80th birthday

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An effective synthetic approach to heterocyclic derivatives of meso-substituted calixarenes has been suggested by using the S_N^H methodology based on the direct, non-catalyzed by transition metals, C-C coupling of 1,2,4-triazines with the lithium salts of tetramethoxycalix[4]arenes.

Keywords: Calix[4]arenes, azines, C-C coupling, nucleophilic substitution of hydrogen (S_N^H).

Синтез новых *мезо*–замещенных гетероциклических каликс[4]аренов на основе S_N^H подхода

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Предложен эффективный синтетический подход к синтезу новых мезо-замещенных гетероциклических производных каликс[4]аренов, основанный на некатализируемом переходными металлами С-С сочетании 1,2,4-триазинов с литиевыми солями тетраметоксикаликс[4]аренов.

Ключевые слова: Каликс[4]арены, азины, С-С сочетание, нуклеофильное замещение водорода (S_N^H).

Introduction

Calixarenes are known to be one of the key structural units in supramolecular chemistry.[1] An enhanced interest in this promising class of macrocyclic compounds is due to wide opportunities of their practical use.[2] Indeed, calixarenes proved to be effective receptors for selective extraction of metal ions,[3] catalysts,[4] chemosensors,[5,6] transmembrane ion transporters,[7,8] materials for nonlinear optics,[9] biologically active substances,[10] *etc*.[11]

The structural organization of calixarenes has an effect on their complexing properties.[12] A common approach in the design of functionally substituted calixarenes is modification of these macrocyclic molecules either at the lower rim *via* the reactions of OH groups, or at the upper rim through functionalization of C(sp^2)–H bonds of the aromatic rings. As far as chemical transformations, that result in modification of the CH_2 groups *via* functionalization of C(sp^3)–H bonds, are concerned, the data on these reactions have scarcely been presented in the literature.[13-15] Only a few examples

have recently been described, and all of them are associated with the ability of the bridging CH_2 groups to undergo lithiation.[16-19] The reactions of the lithiated calixarenes with electrophiles afford the corresponding *meso*-substituted derivatives.[20] It should be noted that the data regarding the direct modification of the lithium salts of calixarenes with heterocyclic fragments have never been reported. Since a lot of data on heterocyclic compounds concern their applications in catalysis, coordinational, analytical, and medicinal chemistry, azinyl derivatives of calixarenes appear to be of great interest.[21-27]

In this communication we would like to report for the first time, that the direct heteroarylation of calixarenes at the bridging CH_2-fragment is possible by using the methodology of nucleophilic substitution of hydrogen (S_N^H) in azines.[28-34] The S_N^H process is known to be a specific kind of cross-coupling reactions, that does require neither transition metal catalysis, nor the presence of halogen or other good-leaving groups in the structure of reactants. Due to these features S_N^H reactions demonstrate a high atom efficiency, [35,36] and appear to be environmentally benign processes.

Experimental

The ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a Bruker Avance II spectrometer in a mixture of CD_3CN and $CDCl_3$ (2:8). The assignment of ^{1}H and ^{13}C signals was performed by a combination of 2D homonuclear ^{1}H–^{1}H (COSY) and heteronuclear ^{1}H–^{13}C (HSQC and HMBC) experiments. The mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra EI mass spectrometer with sample ionization by electron impact (EI). The IR Spectra were recorded on an IR Fourier spectrophotometer Bruker Alpha equipped with a device for measuring incomplete internal reflection. The elemental analysis was carried out on a Perkin Elmer 2400-II CHNS/O analyzer. The course of the reactions was monitored by TLC on 0.25 mm silica gel plates (60F 254). Column chromatography was performed on silica gel (60, 0.035-0.070 mm (220-440 mesh)). The solvents were purified and dried by standard procedures. TMEDA, DDQ, *n*-BuLi (1.6 M solution in hexane) were purchased from Sigma-Aldrich. 25,26,27,28-Tetramethoxycalix[4]arene **1a**, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene **1b**,[37] 3,6-diphenyl-1,2,4-triazine **3**[38] were prepared according to the published procedures.

*General method for the synthesis of calixarenes **5a**,**b***. To a vigorously stirred solution of TMEDA (0.43 ml, 2.9 mmol) in dry THF (4 ml) cooled to -78 °C 1.6 M solution of *n*-BuLi in hexane (1.44 ml, 2.3 mmol) was added under argon. After 40 min a solution of the corresponding 25,26,27,28-tetramethoxycalix[4]arene **1** (1 mmol) in anhydrous THF was added. The resulting cherry red mixture containing 2-lithio-25,26,27,28-tetramethoxycalix[4]arene **2**[17] was allowed to warm up to ambient temperature and then was stirred for additional 2 h. Then the mixture was cooled down to –78 °C and a solution of 3,6-diphenyl-1,2,4-triazine **3** (464 mg, 2.0 mmol) in dry THF (6 mL) was added. The resulting yellow solution was allowed to warm up to ambient temperature, and then water (0.04 m1, 2.0 mmol) was added and the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography with the EtOAc–$CHCl_3$ (4:6) mixture as an eluent, and the resulting eluate was concentrated to dryness under reduced pressure.

*2-(3,6-Diphenyl-4,5-dihydro-1,2,4-triazin-5-yl)-25,26,27,28-tetramethoxycalix[4]arene, **5a*** (570 mg, 0.8 mmol, 80 % on calixarene **1a**). M.p. 188-190 °C. Found: C 78.91, H 6.04, N 5.83 %. $C_{47}H_{43}N_3O_4$ requires C 79.08, H 6.07, N 5.89. *m/z* (EI) (%) 713 [M^+] (100). IR (DRA) ν_{max} cm^{-1}: 693, 760, 811, 838, 916, 974, 1020, 1157, 1204, 1221, 1247, 1276, 1294, 1338, 1427, 1464, 1506, 2820, 2866, 2916, 2933, 2977, 3027, 3061, 3133, 3376.^{1}H NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_H ppm: 9.67 (1H, s, N(*4'*)H), 7.62-7.66 (1H, m, Ar), 7.50-7.54 (1H, m, Ar), 7.46-7.48 (1H, m, Ar), 7.36-7.40 (1H, m, Ar), 7.27-7.33 (1H, m, Ar), 7.10-7.14 (4H, m, Ar), 7.00-7.09 (5H, m, Ar), 6.75-6.86 (3H, m, Ar), 6.40-6.46 (1H, m, Ar), 6.01-6.06 (1H, m, Ar), 6.03 (1H, dd *J*=11.46 Hz, *J*=11.36 Hz, C(*5'*)H), 5.24 (1H, dd *J*=11.46 Hz, *J*=11.36 Hz, C(*2*)H), 4.05-4.23 (12H, m, 3H ArC*H*$_2$Ar + 6H OMe), 3.78-3.82 (3H, m, OMe), 3.27-3.39 (3H, m, ArC*H*$_2$Ar). ^{13}C NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_c ppm: 153.8, 152.9, 152.2, 147.2, 136.2, 135.7, 135.2,135.0, 134.9, 134.8, 131.8, 131.2, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.2, 127.9, 126.9, 126.3, 126.0, 125.2, 65.2, 65.0, 64.9, 64.8, 64.3, 52.0 (C(*5'*)), 34.0 (C(*2*)H), 29.6, 29.4.

*2-(3,6-Diphenyl-4,5-dihydro-1,2,4-triazin-5-yl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetra-methoxycalix[4]arene, **5b*** (768 mg, 0.82 mmol, 82 % on calixarene **1b**). M.p. 172-174 °C. Found: C 80.31, H 8.24, N 4.23 %. $C_{63}H_{75}N_3O_4$ requires C 80.64, H 8.06, N 4.48. *m/z* (ESI) (%) 937 (100) [M^+]. IR (DRA) ν_{max} cm^{-1}: 691, 771, 800, 874, 1020, 1121, 1178, 1203, 1261, 1319, 1362, 1393, 1419, 1436, 1456, 1482, 1506, 1578, 1602, 1626, 2819, 2869, 2932, 2960, 3394. ^{1}H NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_H ppm: 9.68 (1H, s, N(*4'*)H), 7.59-7.62 (1H, m, Ar), 7.46-7.52 (4H, m, Ar), 7.37-7.39 (1H, m, Ar), 7.29-7.31 (2H, m, Ar), 7.12-7.17 (5H, m, Ar), 7.07-7.09 (1H, m, Ar), 7.02-7.04 (1H, m, Ar), 6.92-6.94 (1H, m, Ar), 6.07 (1H, d *J*=11.50 Hz, C(*5'*)H), 5.23 (1H, d *J*=11.50 Hz, C(*2*)H), 4.08-4.16 (3H, m, ArC*H*$_2$Ar), 4.03-4.06 (9H, m, OMe), 3.73 (3H, s, OMe), 3.25-3.33 (m, 3H, ArC*H*$_2$Ar), 1.25 (9H, s, *t*-Bu), 1.12 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 0.91 (9H, s, *t*-Bu). ^{13}C NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_c ppm: 153.6, 151.7, 151.0, 150.8, 150.7, 148.8, 148.7, 148.5, 147.9, 147.4, 136.5, 134.6, 134.5, 134.4, 134.2, 131.8, 131.1, 128.7, 128.6, 126.8, 126.1, 126.0, 125.9, 125.8, 123.7, 123.2, 65.03, 64.9, 64.7, 64.4, 55,9 (C(*5'*)), 35.7 (C(*2*)H), 34.5, 34.2, 34.1, 33.8, 31.8, 31.2, 31.1, 31.0, 30.8, 30.2, 29.9, 29.8.

*General method for the synthesis of calixarenes **6a**,**b***. To a vigorously stirred solution of calixarenes **5a**,**b** (1 mmol) in dry THF (4 ml) DDQ (0.272 mg, 1.2 mmol) was added at ambient temperature. The mixture was stirred for 15 min, then filtered through neutral alumina, washed several times with EtOAc, and concentrated in vacuo. The residue was subjected to silica gel column chromatography with the EtOAc–hexane mixture (2:8) as an eluent, and the resulting eluate was concentrated to dryness under reduced pressure.

*2-(3,6-Diphenyl-1,2,4-triazin-5-yl)-25,26,27,28-tetra-methoxycalix[4]arene, **6a*** (576 mg, 0.95 mmol, 95 % on calixarene **5a**). M.p. 216-218 °C. Found: C 79.51, H 6.02, N 5.73 %. $C_{47}H_{43}N_3O_4$ requires C 79.30, H 5.85, N 5.90. *m/z* (ESI) (%) 711 (100) [M^+]. IR (DRA) ν_{max} cm^{-1}: 646, 690, 707, 737, 794, 831, 917, 961, 1018, 1089, 1205, 1246, 1291, 1322, 1339, 1391, 1437, 2817, 2866, 2931, 2977, 3013, 3060. ^{1}H NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_H ppm: 8.56 (2H, m, Ar), 7.40-7.58 (8H, m, Ar), 7.03-7.22 (2H, m, Ar), 6.83-6.94 (3H, m, Ar), 6.61-6.73 (6H, m, Ar), 6.34-6.54 (1H, m, Ar), 5.92,6.34 (1H, s, C(*2*)H), 4.25-4.32, 4.12-4.17 (2H, m, ArC*H*$_2$Ar), 3.72-3.77 (4H, m, 1 H ArC*H*$_2$Ar + 3H OMe), 3.65 (3H, s, OMe), 3.57 (1H, m, ArC*H*$_2$Ar), 3.42-3.48 (4 H, m, 1 H ArC*H*$_2$Ar + 3H OMe), 3.16 (3H, m, 3H OMe), 2.85 (1H, m, ArC*H*$_2$Ar). ^{13}C NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_c ppm: 161.3, 159.4, 159.4, 158.5, 158.3, 157.9, 157.2, 157.1, 145.1, 143.8, 143.5, 137.9, 137.2, 135.3, 135.1, 134.9, 134.8, 131.6, 129.7, 129.4, 129.2, 129.0, 128.8, 128.6, 128.3, 128.2, 128.1, 125.9, 122.5, 121.7, 61.6, 60.7, 59.4, 59.0, 41.0 (C(*2*)H), 31.5, 30.6, 30.4.

*2-(3,6-Diphenyl-1,2,4-triazin-5-yl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene, **6b*** (860 mg, 0.92 mmol, 92 % on calixarene **5b**). M.p. 279-281 °C. Found: C 80.44, H 8.02, N 4.21 %. $C_{63}H_{73}N_3O_4$ requires C 80.82, H 7.86, N 4.49. *m/z* (ESI) (%) 935 (100) [M^+]. IR (DRA) ν_{max} cm^{-1}: 637, 692, 762, 797,

871, 943, 975, 1014, 1110, 1122, 1200, 1242, 1296, 1315, 1391, 1427, 1459, 1498, 2819, 2866, 2901, 2932, 2955. ^{1}H NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_H ppm: 8.65-8.74 (2H, m, Ar), 8.09-8.22 (2H, m, Ar), 7.51-7.79 (8H, m, Ar), 7.18-7.24 (6H, m, Ar), 5.84, 6.43 (1H, s, C(*2*)H), 4.17-4.30 (9H, m, 3H ArCH_2Ar + 3H OMe), 3.83 (6H, s, OMe), 3.44-3.53 (m, 3H, ArCH_2Ar), 1.20-1.28 (36H, m, *t*-Bu). ^{13}C NMR ($CDCl_3$-CD_3CN 8:2, 298 K) δ_c ppm: 161.0, 160.9, 158.8, 158.6, 158.3, 155.1, 150.8, 150.7, 148.9, 148.6, 144.7, 135.4, 135.1, 135.0, 134.6, 134.3, 133.9, 132.0, 131.6, 130.7, 129.9, 129.5, 128.9, 128.7, 128.6, 128.4, 128.3, 127.2, 126.2, 125.9, 125.8, 124.6, 65.2, 65.1, 41.2 (C(*2*)H), 36.3, 34.6, 34.6, 34.3, 33.8, 31.9, 31.5, 31.4, 31.2, 31.1, 30.4, 30.0, 29.0.

Results and Discussion

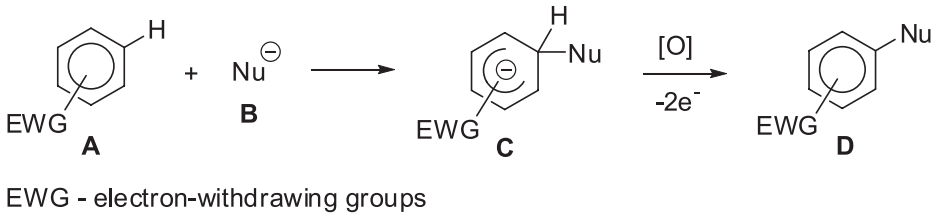
Novel calix[4]arenes bearing azinyl fragments at the *meso*-position have been synthesized through the direct, non-catalyzed by transition metals, cross-coupling reaction of π-deficient azaaromatic compounds with the lithium salts of tetramethoxycalixarenes. The approach is based on using the methodology of nucleophilic substitution of hydrogen (S_N^H) in heteroaromatic systems.[28-33]

According to the current concept of the S_N^H reactions, one of the most plausible mechanisms of nucleophilic substitution of hydrogen in (hetero)arenes is the two-steps "addition-oxidation" S_N^H(AO) protocol (Scheme 1). The first step involves addition of lithiocalixarene, acting as a nucleophilic reagent **B**, to the C=N bond of (hetero)arenes **A**. The resulting intermediates **C**, so-called σ^H-adducts, have a broad scale of stability – from an extremely low state to a relatively stable form. The second step of the S_N^H process is oxidative aromatization of σ^H-adducts, which takes place by means of air oxygen or another external oxidant to give S_N^H products **D**.

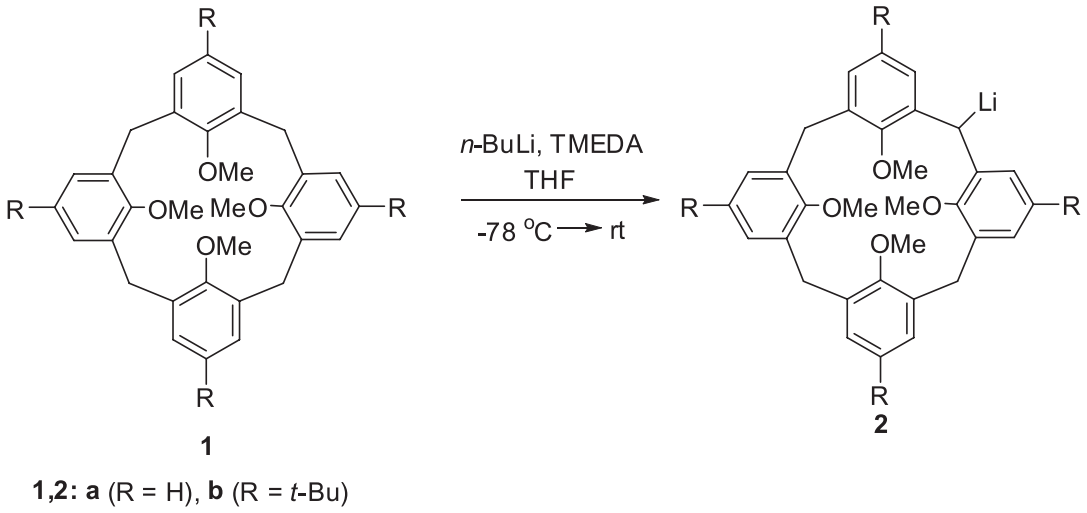
2-Lithium-25,26,27,28-tetramethoxycalix[4]arenes **1a**,**b** have been obtained according to the known procedure, based on deprotonation of a calixarene methylene group by action of *n*-BuLi under argon atmosphere (Scheme 2).[17] In order to stabilize lithioderivatives **2a**,**b**, TMEDA was used as a chelating additive. The reaction is initiated at -78 °C, as indicated by the observed pink colour of the reaction mixture. As the reaction temperature is enhanced to ambient, the reaction mixture colour being gradually changed into bright red. It should be noted that both unsubstituted at the upper rim calix[4]arene **1a** and 5,11,17,23-tetra-*tert*-butyl-substituted analogue **1b** undergo the *meso*-lithiation.

3,6-Disubstituted 1,2,4-triazines were selected as model compounds in the S_N^H reactions of lithiocalixarenes **2a**,**b** with azines. The choice is due to an enhanced electrophilic character and a high reactivity of these azaaromatic heterocycles. It is well known that 1,2,4-triazines have a profound tendency to undergo nucleophilic addition at C(5) to give rather stable intermediates, 4,5-dihydrotriazines, [39] which could be considered as an experimental proof of the S_N^H(AO) mechanism, as evidenced, for instance, by isolation of σ^H-adducts from the reaction of organolithium reagents with 1,2,4-triazines.

Indeed, dihydrotriazine derivatives **5a**,**b** were obtained in 80-82 % yields from the reaction of lithioca-



Scheme 1.

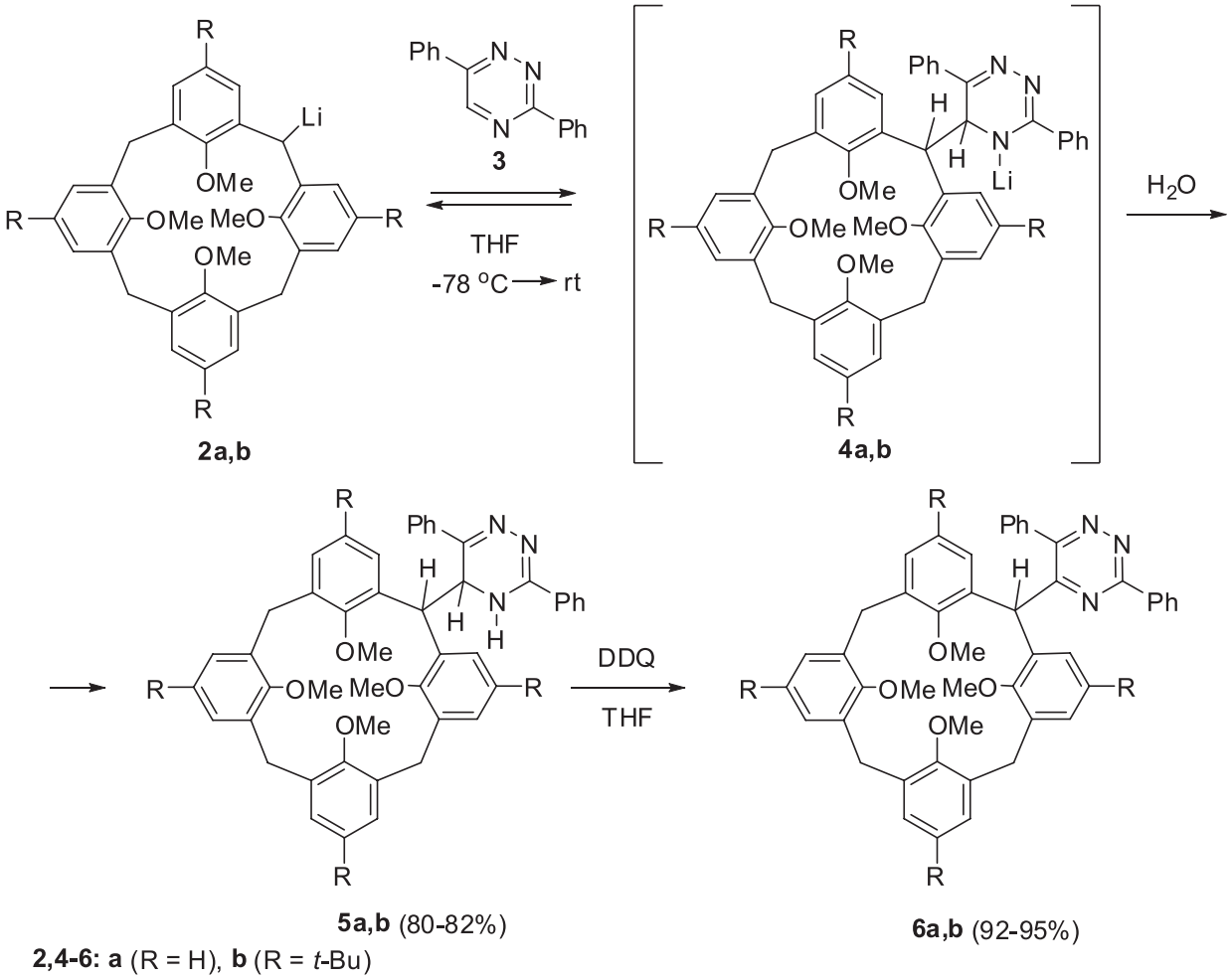


Scheme 2.

lixarenes **2a**,**b** with 3,6-diphenyl-1,2,4-triazine **3**, followed by treatment of intermediates **4a**,**b** with water (Scheme 3). Dihydro compounds **5a**,**b** proved to be rather stable σ^H-adducts, which do not undergo oxidation during a prolonged storage in air. Good yields of dihydrotriazines **5a** (80 %) and **5b** (82 %) indicate that *tert*-butyl substituents at the upper rim of the calix[4]arene do not have a significant effect on the reactivity of *meso*-lithioderivatives **2a** and **2b**. The second step of the S_N^H(AO) process, oxidative aromatization of adducts **5a**,**b**, was carried out in THF at ambient temperature with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant, thus giving the corresponding S_N^H products **6a**,**b** in 92-95 % yields. It is worth noting that effectiveness of DDQ has also been shown in other S_N^H(AO) processes.[39-42]

Heterocyclic derivatives of calixarenes **5a**,**b** and **6a**,**b** were isolated by using SiO_2 column chromatography. All new compounds were characterized by the data of elemental analysis, mass spectrometry, IR, ^{1}H, and ^{13}C NMR spectroscopy, including homonuclear ^{1}H–^{1}H (COSY) and heteronuclear ^{1}H–^{13}C (HSQC and HMBC) correlation experiments. In the IR spectra of calixarenes **5a**,**b** characteristic absorption bands, corresponding to the NH group stretching vibrations are observed at ν 3376-3394 cm^{-1} (contrary to the IR spectra of aromatic analogues **6a**,**b**). Also the molecular ion peaks $[M]^+$ were registered in their mass spectra. The methoxy calix[4]arenes are likely to possess a high conformational flexibility in many organic solvents, imposing some restrictions on their studying by means of NMR spectroscopy. In order to solve this problem, a convenient preparative technique,[17] based on fixation of conformers through coordination of the methoxy calixarenes with Na^+ ions was applied. The approach allows a number of the resonance signals in NMR spectra to be interpreted. The procedure involves addition of an excess amount of NaI, previously dissolved in CD_3CN, to a calixarene solution in $CDCl_3$. Typical NMR spectra of σ^H-adduct **5a** and the corresponding S_N^H product **6a** are presented in Figures 1 and 2, respectively.

A single set of signals in the ^{1}H (Figure 1a) and ^{13}C NMR spectra of σ^H-adducts **5a,b** indicates that compounds **5a,b** exist in the only conformational state. The resonance signals of CH_2 and OMe groups are located at δ 3.27-4.23 ppm for **5a** and at δ 3.25-4.16 ppm for **5b**, respectively. The signals of aromatic protons are observed as multiplets at δ 6.39-7.66 ppm for 5a and at δ 6.92-7.62 ppm for **5b**. The N(*4*')H protons are registered at δ 9.67 ppm for **5a** and at δ 9.68 ppm for **5b**. In the ^{1}H NMR spectra of compounds **5a,b** the C(*2*)H protons of the bridging sp^3-hybridized fragment resonate at δ 5.24 ppm in case of compound **5a** and at δ 5.23 ppm for **5b**, while the C(*5*')H resonance signal of the dihydrotriazine moiety is observed at δ 6.03 ppm for **5a**



Scheme 3.

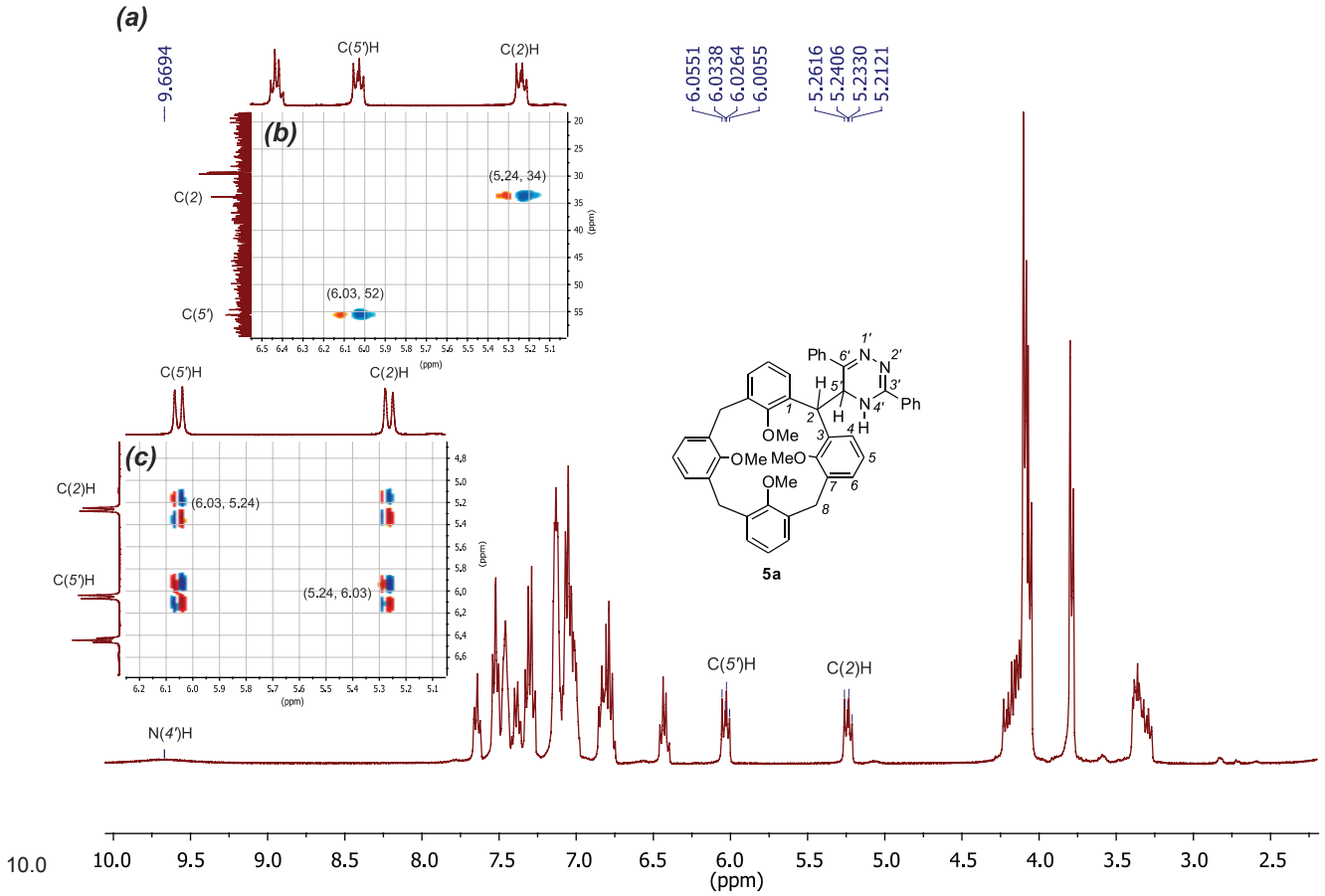


Figure 1. NMR spectra of **5a** with NaI: ^{1}H (*a*), 2D ^{1}H–^{13}C HSQC (*b*), and 2D ^{1}H–^{1}H COSY (*c*) in the mixture of CD_3CN and $CDCl_3$ at 295 K.

and δ 6.07 ppm for **5b**. In the ^{13}C NMR spectra of **5a,b** the carbon-13 resonance signals of C(*2*) and C(*5*') are registered at δ 34.0 and 52.0 ppm for **5a**, 35.7 and 55.9 ppm for **5b**, respectively. The presence of cross-peaks (5.24, 34.0) and (6.03, 52.0) in the 2D ^{1}H–^{13}C HSQC spectra of **5a**, as well as (5.23, 35.7) and (6.07, 55.9) for **5b**, indicates at the direct links between protons and the corresponding carbon nuclei (Figure 1b). Symmetrical cross-peaks (6.03, 5.24) in the 2D ^{1}H–^{1}H COSY correlation spectra of **5a**, as well as (5.24, 34) for **5b**, confirm the *vicinal* location of C(*2*)H and C(*5*') H protons (Figure 1c). The resonance signals of *tert*-butyl substituents for **5b** are recorded at δ 0.91-1.25 ppm.

Contrary to the σ^H-adducts **5a**,**b**, several sets of signal are registered in the ^{1}H and ^{13}C NMR spectra of aromatic products **6a**,**b**, thus indicating that these calixarenes exist in several conformational states. In the ^{1}H NMR spectra the resonance signals of CH_2 and OMe protons are located in the field of δ 2.85-4.32 ppm for **6a** and δ 3.44-4.30 ppm for **6b**, respectively (Figure 2a). The resonance signals of aromatic protons are observed as multiplets at δ 6.36-8.56 ppm for **6a** and at δ 7.18-8.74 ppm for **6b**. There are no signals of the dihydrotriazine ring (neither sp^3-hybridized CH nor NH). The C(*2*)H *meso*-proton signals resonate at δ 5.92 ppm and at δ 6.34 ppm for **6a**, as well as at δ 5.84 ppm and δ 6.43 ppm for **6b**. In the ^{13}C NMR spectra of **6a,b** the signals of C(*2*) carbons are registered at δ 41.0 ppm for **6a** and at δ 41.2 ppm for **6b**, respectively. In the 2D ^{1}H–^{13}C HSQC spectra of **6a**,**b** the presence of two cross-peaks (6.34, 41.0) and (5.92, 41.0) for **6a**, as well as (5.84, 41.2) and (6.43, 41.2) for **6b** (Figure 2b), corresponding to direct interactions of C(*2*)H protons with C(*2*), indicates that the calixarenes **6a**,**b** exist in multiple conformational states. The resonance signals of *tert*-butyl substituents for **6b** are recorded at δ 1.20-1.28 ppm.

Also it should be noted that the ^{1}H and ^{13}C NMR spectral data for calixarenes **5a**,**b** and **6a**,**b** are correlated nicely with those obtained for 25,26,27,28-tetramethoxycalix[4]arenes bearing alkyl, benzyl, and carboxyl groups at the *meso*-position.[16]

Conclusions

A principal opportunity for the direct modification of calixarenes at the *meso*-position with triazinyl fragments has been presented. The suggested S_N^H approach allows to obtane calixarenes, bearing either dihydrotriazine or triazine fragments at the *meso*-position.

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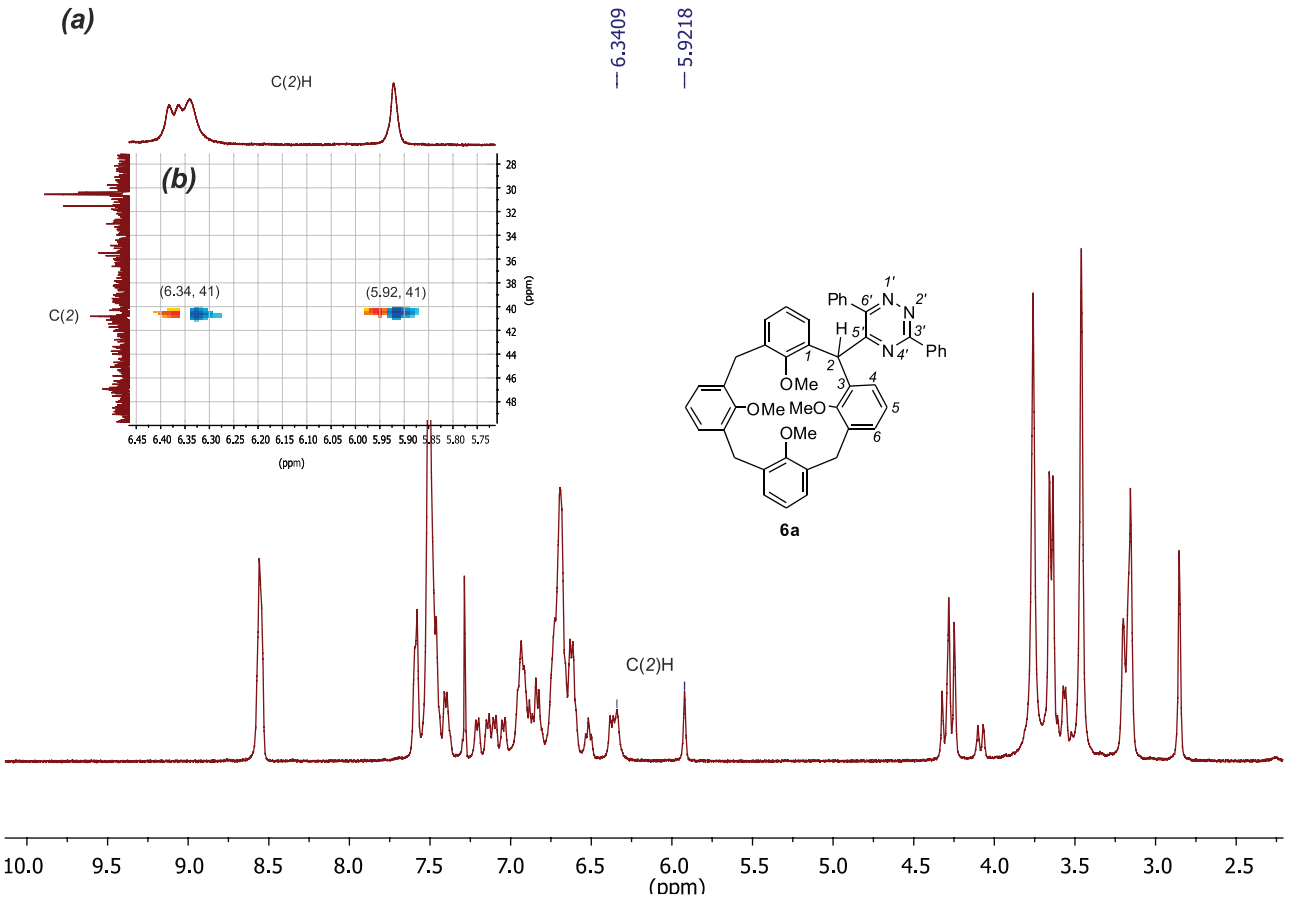

Figure 2. NMR spectra of **6a** with NaI: ^{1}H (*a*), and 2D ^{1}H–^{13}C HSQC (*b*) in the mixture of CD_3CN and $CDCl_3$ at 295 K.

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