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'Click chemistry' in the synthesis of new amphiphilic *1,3-alternate* thiacalixarenes

Vladimir A. Burilov,*[a] Ramil I. Nugmanov,[a] Regina R. Ibragimova,[a] Svetlana E. Solovieva[a,b] and Igor S. Antipin[a,b]

[a] *A. M. Butlerov Chemical Institute, Kazan (Volga Region) Federal University, 420008 Kazan, Russian Federation*
[b] *A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 843 273 2253; e-mail: ultrav@bk.ru*

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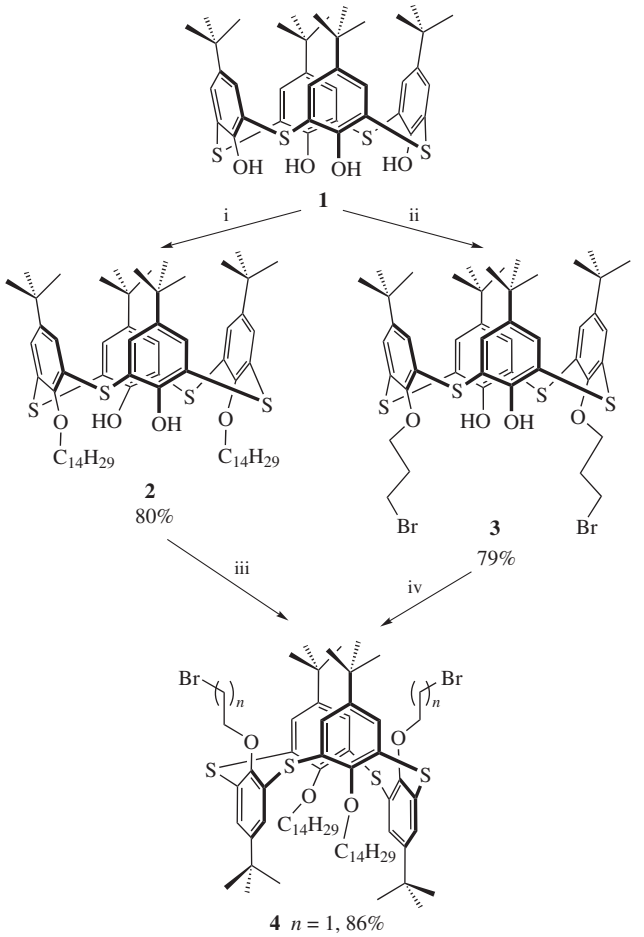
Azidoalkyl-substituted *1,3-alternate p-tert*-butylthiacalix[4]arenes were subjected to click reactions with alkynes affording thus novel amphiphilic derivatives of this series.

Molecular recognition of membrane embedded receptors plays a key role in the biological processes associated with the cell signaling or transmitting of signals across cell membranes[1] as well as for the design of bio-inspired materials.[2] The applications of vesicular membranes with incorporated artificial receptors as carrier systems, reaction containers, switchable devices and sensor materials are in recent literature.[3] From this point of view, preparation of broad series of synthetic amphiphiles with receptor properties for recognition of different substrates is challenging.[4] Thiacalix[4]arenes have a great potential as amphiphilic receptors due to their unique properties: number of substituents, variety of stereoisomeric configurations, easy functionalization and preorganization effect.[3(a),5] Thus, the functionalization of a lower rim with amphiphilic and binding fragments can lead to novel type of biomimetic receptor molecules.

To achieve a wide variety of binding sites as well as amphiphilic properties thiacalix[4]arenes adopting *1,3-alternate* conformation are most promising since selective functionalization of upper and lower rims allows one to create two molecular domains with different characteristics. In this work we accomplished synthesis of the amphiphilic 'clickable' platform based on the azidoalkyl derivatives of *p-tert*-butylthiacalix[4]arene bearing in mind that the presence of azido group provides an easy way to a variety of amphiphilic receptor molecules by click reactions.

The first step was a preparation of precursors **4**, **5** containing ω-bromoalkyl and long chain alkyl groups starting from *p-tert*-butylthiacalix[4]arene **1**[6] (Scheme 1).† Selective functionalization of phenolic groups of thiacalixarene was carried out under Mitsunobu reaction conditions.[7] Two sequences of alkylation/bromoalkylation reactions were investigated (see Scheme 1), both of them having given practically the same yield of the expected precursors. Two singlets of thiacalixarene aromatic protons in ^{1}H NMR and cross-peaks between aromatic and methylene protons of alkyl and bromoalkyl fragments in NOESY spectra clearly show that compounds **4** and **5** adopt *1,3-alternate* configuration.



Scheme 1 *Reagents and conditions*: i, *n*-$C_{14}H_{29}OH$ (2.5 equiv.), PPh_3, DEAD, PhMe, 40 °C, 24 h; ii, $Br(CH_2)_3OH$ (2.5 equiv.), PPh_3, DEAD, PhMe, 40 °C, 24 h; iii, $Br(CH_2)_2OH$ (4 equiv.), PPh_3, DEAD, PhMe, 70 °C, 24 h; iv, *n*-$C_{14}H_{29}OH$ (4 equiv.), PPh_3, DEAD, PhMe, 70 °C, 24 h.

† *Compounds* **2** *and* **3**. An appropriate alcohol (6.9 mmol), *p-tert*-butylthiacalix[4]arene **1**[6] (2 g, 2.8 mmol), triphenylphosphine (2.22 g, 8.3 mmol) and diethyl azodicarboxylate (1.32 ml, 8.3 mmol) were dissolved in 20 ml of dry toluene under inert atmosphere. The reaction mixture was stirred at 40 °C for 24 h, and then the solvent was evaporated *in vacuo*. The crude material was washed twice with ethanol to give products **2** or **3**.

For **2**: yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.78 (s, 18 H, CMe_3), 0.88 (t, 6 H, Me, *J* 6.8 Hz), 1.31–1.19 (m, 36 H, CH_2), 1.33 (s, 18 H, CMe_3), 1.45–1.37 (m, 4 H, CH_2), 1.61–1.50 (m, 4 H, CH_2), 2.08–1.92 (m, 4 H, CH_2), 4.48 (t, 4 H, $ArOCH_2$, *J* 6.9 Hz), 6.94 (s, 4 H, H_{Ar}), 7.65 (s, 4 H, H_{Ar}), 7.95 (s, 2 H, OH).

For **3**: yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.83 (s, 18 H, CMe_3), 1.33 (s, 18 H, CMe_3), 2.58 (p, 4 H, CH_2, *J* 6.3 Hz), 3.83 (t, 4 H, CH_2Br, *J* 6.74 Hz), 4.59 (t, 4 H, OCH_2, *J* 5.86 Hz), 7.01 (s, 4 H, H_{Ar}), 7.66 (s, 4 H, H_{Ar}), 7.80 (s, 2 H, OH).

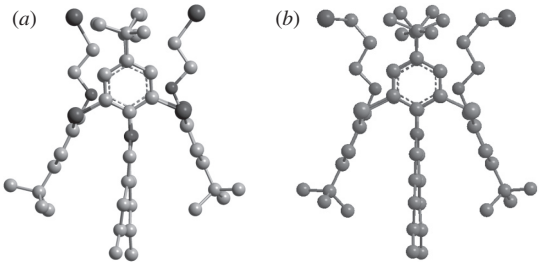


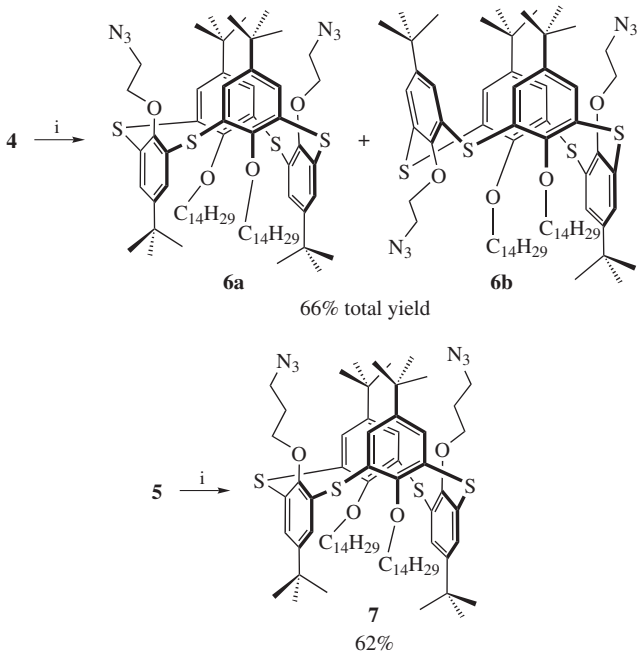
Figure 1 The conformation of (*a*) **4** and (*b*) **5** in global energy minimum (alkyl chain length is limited to five carbon atoms).

At the next stage, bromo derivatives **4** and **5** demonstrated a very low reactivity towards sodium azide even at 140 °C for 15 h (*cf.* ref. 8). To rationalize this, a quantum chemical structure optimization of macrocyles **4** and **5** was performed using PRIRODA 11 program (method DFT, functional PBE, bazis 3z).[9] The most stable conformation of **4** and **5** (Figure 1) reveals that the location of C–Br bonds is not suitable for the implementation of typical S_N2 mechanism because a nucleophile cannot attack the back of electrophilic center (–CH_2–Br) for the steric reasons (especially in calixarene **4**). Another possible S_N1 mechanism should occur with substantially higher activation barrier in the case of primary alkyl halides.

To accelerate these reactions, a microwave (MW) irradiation was applied. After optimization of MW assisted conditions we found that irradiation at 140 °C in DMF for 3 h gave the desired diazido derivatives **6** and **7** in good yields (62–66%) (Scheme 2).‡

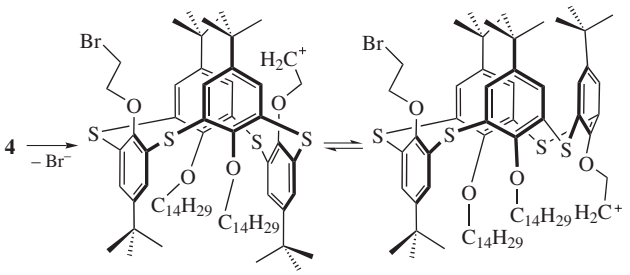
However, stereochemical result in these reactions was different. In case of bis(2-bromoethyl) derivative **4** the conformation of calixarene platform has changed in the process of nucleophilic substitution affording the required *1,3-alternate* **6a** along with 20% of the *partial cone* **6b** (NMR data). Unfortunately, our attempts to separate them by column chromatography were unsuccessful because their R_f values were close due to presence of two long chain alkyl substituents.

Earlier[10] it was established that *p-tert*-butylthiacalix[4]arenes containing three or more carbon atoms in lower rim substituents do not undergo isomerization at room temperature. Our attempts to achieve a thermal isomerization of **4** (140 °C, 3 h, DMF) failed



Scheme 2 *Reagents and conditions*: i, NaN_3 (10 equiv.), DMF, MW, 140 °C, 3 h.

and only the starting *1,3-alternate* conformer was isolated. This indicates that the 2-bromoethyl groups are bulky enough to hinder the rotation of the bromoalkylated phenolic rings through the main annulus of the thiacalix[4]arene under reaction conditions. So, the formation of *paco* isomer **6b** cannot be explained by isomerization of the reactant. Probably, the MW assisted reaction proceeds through the C–Br bond ionization according to S_N1 mechanism with the formation of positively charged fragment (Scheme 3). This fragment consisting of two carbon atoms does not prevent the rotation of corresponding phenolic unit through



Scheme 3

the main macrocycle plane formed by four sulfur atoms. Therefore, *1,3-alternate* → *partial cone* transformation becomes possible.

This suggestion is in the agreement with stereochemical result obtained for macrocycle **5** containing three methylene spacer groups between bromine atom and thiacalixarene platform. In this case the retention of *1,3-alternate* conformation of macrocycle **6** indicates that more bulky cationic fragment ($CH_2CH_2CH_2^+$) prevents the interconversion between conformers.

Structure of compound **7** was characterized by NMR, IR, EI and MALDI-TOF data. The band of azido groups at 2096 cm^{-1} in IR spectrum and molecular ion peak *m/z* 1278.8 (EI) denote the formation of bis-azido derivative. The *1,3-alternate* conformation of **7** was confirmed by 1D and 2D NMR experiments just as it was done for precursors **4** and **5**.

Further on, azido compound **7** was subjected to 1,3-dipolar cycloaddition.[11] For this purpose, activated alkyne (acetylenedicarboxylic acid) and non-active terminal alkynes (propargyl

Compounds **4** *and* **5**. Reactant **2** or **3** (2.02 mmol), diethyl azodicarboxylate (1.6 ml, 0.01 mol), triphenylphosphine (2.12 g, 8.09 mmol), and appropriate bromoalcohol (8.09 mmol) were dissolved in 30 ml of dry toluene under inert atmosphere. The mixture was stirred at 70 °C for 24 h, and then the solvent was evaporated *in vacuo*. The crude material was washed twice with ethanol to give product **4** or **5**.

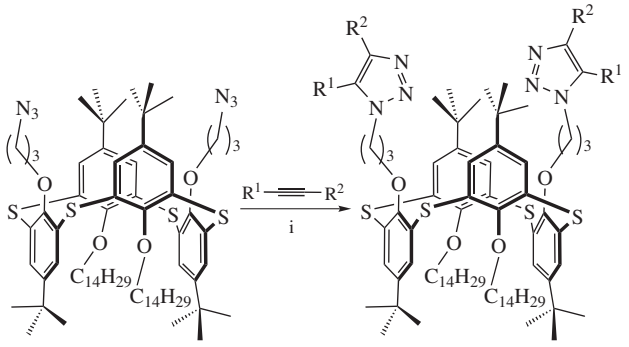
For **4**: yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.86 (t, 6H, Me, *J* 6.8 Hz), 1.25 (m, 48H, CH_2), 1.25 (s, 18H, CMe_3), 1.29 (s, 18H, CMe_3), 2.53–2.47 (m, 4H, CH_2Br), 3.81 (t, 4H, OCH_2, *J* 8.0 Hz), 4.08–4.00 (m, 4H, OCH_2), 7.24 (s, 4H, H_{Ar}), 7.34 (s, 4H, H_{Ar}).

For **5**: yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.89 (t, 6H, Me, *J* 6.79 Hz), 1.34–1.17 [m, 66H, $(CH_2)_{12}$, CMe_3], 1.31 (s, 18H, CMe_3), 1.68–1.58 (m, 4H, CH_2), 3.06 (t, 4H, CH_2Br, *J* 7.05 Hz), 3.77 (m, 8H, CH_2), 4.01 (t, 4H, OCH_2, *J* 6.59 Hz), 7.31 (s, 4H, H_{Ar}), 7.33 (s, 4H, H_{Ar}).

‡ *Azides* **6** *and* **7**. Compound **4** or **5** (0.39 mmol), sodium azide (0.26 g, 3.88 mmol) and DMF (30 ml) were placed in the glass vial (EasyPrep vial). The mixture was heated up to 140 °C in microwave oven CEM Mars 5 (400 W) for 3 h. Then it was treated with 10 ml of $CHCl_3$, washed three times with distilled water, dried over $MgSO_4$. The target compounds were collected by filtration as colorless solids after concentration *in vacuo* and addition of ethanol. Yield of **6a** + **6b** was 66%.

For ^{1}H NMR and NOESY spectra of the mixture of products **6a** and **6b**, see Online Supplementaty Materials.

For **7**: yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.88 (t, 6H, Me, *J* 6.76 Hz), 1.23 (m, 66H, CH_2, CMe_3), 1.29 (s, 18H, CMe_3), 2.94 (t, 4H, CH_2N_3, *J* 7.11 Hz), 3.81–3.72 (m, 8H, CH_2), 3.96 (t, 4H, OCH_2, *J* 6.86 Hz), 7.30 (s, 4H, H_{Ar}), 7.32 (s, 4H, H_{Ar}).



7

8 R^1 = H, R^2 = CH_2Ph, 51%
9 R^1 = H, R^2 = CH_2OH, 62%
10 R^1 = R^2 = COOH, 61%

Scheme 4 *Reagents and conditions*: i, CuI, NEt_3, PhMe, MW, 60 °C, 4 h.

alcohol and phenylacetylene) were investigated (Scheme 4) under Cu^I catalytic and non-catalytic conditions.§

Acetylenedicarboxylic acid gave the bis-triazole derivative **10** without catalyst after heating at 50 °C for 24 h with tenfold excess of the acid. No reaction was observed for propargyl alcohol and phenylacetylene. In case of non-active terminal alkynes a copper-catalyzed reaction was used.[12] Recently we elaborated the experimental conditions to perform this reaction under MW irradiation for the calixarene derivatives.[13] Under these conditions, a full conversion of phenylacetylene and propargyl alcohol was reached in 4 h.

Absence of the band at 2096 cm^{-1} in IR spectra, an appearance of triazole protons singlet at 7.5 ppm and other signals corresponding to the hydroxymethyl or phenyl fragments in ^1H NMR spectra as well as MALDI–TOF spectrometry data confirm the formation of bis-triazole derivatives **8**–**10** in rather good yields (50–60%).

§ Compound **7** (0.1 g, 0.008 mmol), alkyne (0.02 mmol), CuI (0.0014 g, 7.8×10^{-4} mmol), NEt_3 (2 ml) and 5 ml of toluene were placed in the glass vial (EasyPrep vial). The reaction mixture was heated up to 60 °C in microwave oven CEM Mars 5 (400 W) for 4 h. TLC (eluent hexane–ethyl acetate, 10:1) was carried out for the reaction monitoring. The mixture was treated with $CHCl_3$, washed with aqueous ammonia, then with distilled water, dried over $MgSO_4$. After concentration *in vacuo* and addition of ethanol the desired compound was collected by filtration as a colorless solid.

For **8**: yield 51%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.90 (t, 6H, Me, *J* 6.7 Hz), 1.05 (s, 9H, CMe_3, *J* 6.8 Hz), 1.21–1.36 [m, 66H, $(CH_2)_{12}$, CMe_3], 1.78–1.88 (m, 4H, CH_2), 3.69–3.83 (m, 4H, OCH_2), 4.08–4.20 (m, 8H, OCH_2, $TrzCH_2$), 7.28 (s, 4H, H_{Ar}, *J* 4.8 Hz), 7.30–7.49 (m, 8H, H_{Ar}, H_{Ph}), 7.50–7.59 (m, 2H, H_{Ph}), 7.82 (d, 4H, H_{Ph}, *J* 7.2 Hz), 7.93 (s, 2H, H_{Trz}). MS (MALDI-TOF), *m/z*: 1483.8 $[M-H]^+$, 1505.7 $[M-H+Na]^+$, 1545.7 $[M+Na+K]^+$.

For **9**: yield 62%. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.89 (t, 6H, Me, *J* 6.8 Hz), 1.09 (s, 18H, CMe_3), 1.20–1.30 [m, 66H, CMe_3, $(CH_2)_{12}$], 1.72–1.86 [m, 4H, CH_2 (Pr)], 3.74–3.81 (m, 4H, OCH_2), 4.04 (dd, 8H, OCH_2, $TrzCH_2$, *J* 15.3, 8.4 Hz), 4.79 (s, 4H, $TrzCH_2O$), 7.26 (s, 4H, H_{Ar}), 7.37 (s, 4H, H_{Ar}), 7.56 (s, 2H, H_{Trz}). MS (MALDI-TOF) *m/z*: 1392.69 $[M]^+$, 1413.66 $[M+Na-2H]^+$, 1429.66 $[M+K-2H]^+$.

Compound **10**. Reactant **6** (1 g, 0.08 mmol) and acetylenedicarboxylic acid (0.88 g, 0.78 mmol) were dissolved in 20 ml of dry acetone under inert atmosphere. The mixture was stirred at 60 °C for 24 h, and then the solvent was evaporated *in vacuo*. The crude product was washed with water and centrifuged several times. Compound **10** was obtained after drying *in vacuo* (0.6 g, 61%).

For **10**: ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 0.90 (t, 6H, Me, *J* 6.8 Hz), 1.06–1.11 (s, 18H, CMe_3), 1.24–1.32 [m, 66H, CMe_3, $(CH_2)_{12}$], 1.86–2.00 (m, 4H, CH_2), 3.78 (t, 4H, OCH_2, *J* 3.8 Hz), 4.10–4.24 (m, 4H, OCH_2), 4.57–4.77 (m, 4H, $TrzCH_2$), 7.30 (s, 4H, H_{Ar}), 7.40 (s, 4H, H_{Ar}). MS (MALDI-TOF), *m/z*: 1508.54 $[M]^+$, 1531.50 $[M+Na]^+$.

In conclusion, the perspective approach to the design of wide range of amphiphilic receptors on the calixarene platform, based on click-reactions of *1,3-alternate* derivatives of *p-tert*-butylthiacalix[4]arene containing long chain alkyl and azidoalkyl substituents with acetylenes, has been developed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.005.

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