ORGANIC LETTERS

2011
Vol. 13, No. 15
4032–4035

S-Alkylation of Thiacalixarenes: A Long-Neglected Possibility in the Calixarene Family

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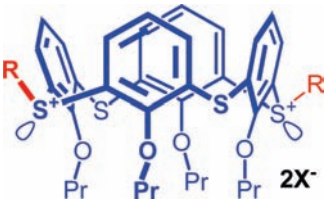
Received June 9, 2011

ABSTRACT



Despite the high nucleophilicity of sulfur atoms, thiacalixarenes have been alkylated only on oxygen atoms thus far. Using strong alkylating agents (triflates, trialkyloxonium salts), the substitution of the sulfur bridges has been successfully accomplished. The corresponding sulfonium salts of thiacalix[4]arene are formed regio- and stereoselectively as a completely new type of substitution pattern in thiacalixarene chemistry. These compounds possess interesting conformational behavior and could be used as unusual alkylating agents with uncommon selectivity.

Thiacalix[4]arenes[1] have attracted the attention of the supramolecular community since their first report in 1997. The incorporation of sulfur atoms instead of common $-CH_2-$ bridges imparts the molecules with many novel and unique properties if compared with classical calixarenes. Thus, the sulfur bridges can be regio- or stereoselectively oxidized into the corresponding sulfone or sulfoxide moieties[2]—a feature that is virtually impossible in the chemistry of common calix[*n*]arenes.[3] Thiacalix[4]arenes also possess remarkably higher complexation ability for the transition-metal cations (due to the sulfur–metal interactions) and/or very unusual conformational preferences or dynamic behavior in solution. Last but not least, it was repeatedly demonstrated that thiacalixarenes show amazingly different chemical behavior in comparison with classical analogues. In this context, a recently described *meta* substitution[4] of the thiacalix[4]arene skeleton, leading directly to inherently chiral derivatives, makes these compounds perfect candidates for the role of molecular scaffolds or building blocks in supramolecular chemistry.

During the past decade, many suitable derivatization methods have been described in thiacalixarene literature. Surprisingly, although the thiacalix[4]arene skeleton has been treated many times with various alkylating agents, no single example of *S*-alkylation has been reported so far.[5] This fact is even more striking when we are reminded of the general textbook knowledge; sulfur-based nucleophiles are known for their very good reactivity in the S_N2 alkylation

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(1) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971.

(2) For recent reviews on thiacalixarenes, see: (a) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291. (b) Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675.

(3) For books on calixarenes, see: (a) Gutsche, C. D. *Calixarenes An introduction*, 2nd ed.; Royal Society of Chemistry: Cambridge, 2008. (b) Vicens, J., Harrowfield, J., Backlouti, L., Eds. *Calixarenes in the Nanoworld*; Springer: Dordrecht, 2007. (c) Mandolini, L.; Ungaro, R. *Calixarenes in Action*; Imperial College Press: London, 2000.

(4) (a) Kundrat, O.; Kroupa, J.; Böhm, S.; Budka, J.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2010**, *75*, 8372. (b) Kundrat, O.; Cisarova, I.; Böhm, S.; Pojarova, M.; Lhotak, P. *J. Org. Chem.* **2009**, *74*, 4592. (c) Kundrat, O.; Dvorakova, H.; Cisarova, I.; Pojarova, M.; Lhotak, P. *Org. Lett.* **2009**, *11*, 4188. (d) Kundrat, O.; Dvorakova, H.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2010**, *75*, 407.

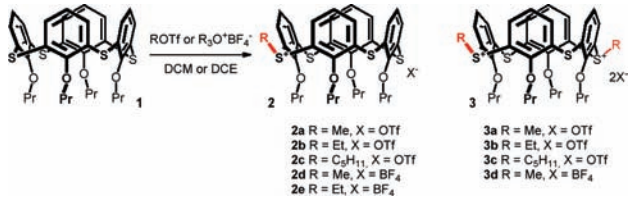
(5) The S-alkylated compound was isolated from the Mitsunobu reaction of **1** with ethylene glycol where the bridge from the phenolic oxygen to the neighboring sulfur atom was formed: Csokai, V.; Gruen, A.; Balazs, B.; Toth, G.; Horvath, G.; Bitter, I. *Org. Lett.* **2004**, *6*, 477.

10.1021/ol201546y
Published on Web 07/08/2011

reactions. Because of the presence of (up to) four positive charges preorganized within a macrocyclic ring, *S*-alkylated thiacalix[4]arenes could play the role of anion receptors as an analogy with well-known polyammonium cage-like structures.[6] Hence, we decided to study this phenomenon to gain deeper understanding of possibilities and limitations of sulfur alkylation in a thiacalixarene series.

Derivative **1**[7] immobilized in the *cone* conformation was selected as a representative of tetra-*O*-alkylated thiacalix[4]arenes. This compound is known to yield stereoselectively the *rccc*-isomer of tetrasulfinylcalixarene during its oxidation;[8,9] therefore, one may expect similar preferences on the sulfur atoms in the alkylation reactions (Scheme 1). Compound **1** was treated with commercially available alkylating reagents (12 equiv of methyl derivatives were used): iodide, tosylate, brosylate, nosylate, mesylate, triflate, and trimethyloxonium tetrafluoroborate (Meerwein's salt).[10] The reactions were carried out at room temperature or at reflux for 3 days.

Scheme 1. *S*-Alkylation Reactions of *Cone* Derivative **1**



Depending on the reagent used, we observed mainly no reaction (in the case of iodide, tosylate, brosylate, nosylate, and mesylate), and unreacted starting compound **1** was recycled from the reaction mixture (Table 1, entries 1−5). On the other hand, in the case of triflate, the formation of new compounds was observed. Thus, stirring **1** with 12 equiv of MeOTf in DCM (entry 6) for 3 days gave monoalkylated compound **2a** (58% yield). While the use of acetonitrile did not lead to better yield (entry 8), DCE as a solvent (entry 7) gave a much higher yield of **2a** after 1 h of reflux (93%). Interestingly, the larger excess of the alkylating agent (36 equiv) led smoothly to dialkylated compound **3a** in a very good yield (89% in DCM, 88% in DCE, entries 9 and 10). Using the Meerwein's salt Me_3OBF_4, similar results were achieved. Again, depending on the excess of the alkylating agents, derivatives **2d** and **3d** were obtained in acceptable yields (56% and 48%, respectively, entries 14 and 15).

To review the general applicability of these reaction conditions, reagents bearing longer alkyl groups have been also tested. Thus, ethyl triflate in DCM at rt did not show any alkylation reaction, while the same reaction under reflux gave mono derivative **2b** in an acceptable yield (47%). The change of solvent to DCE and longer reaction time enabled us to isolate bis-derivative **3b** in an essentially quantitative yield. Interestingly, the alkylation with Et_3OBF_4 gave only monoalkyl compound **2e** (87% yield) after 10 days reflux in DCE. This indicates that the application of Meerwein's salts with longer alkyl chains is limited only to the monoalkylation of **1**. As the corresponding agents with longer alkyl groups are commercially unavailable, pentyl triflate was prepared from pentan-1-ol and was used without any purification for the subsequent alkylation of **1**. Depending on the reaction conditions, mono-*S*-pentyl and bis-*S*-pentyl derivatives **2c** and **3c** were smoothly obtained in 55 and 71% yields, respectively, thus indicating a general applicability of alkyl triflates for the thiacalixarene *S*-alkylation. It is worth mentioning that the new derivatives, unlike starting thiacalixarene **1**, are very well soluble in polar solvents like methanol, acetone, or ethanol. Taking into account the ionic character of *S*-alkylated compounds, unexpectedly low melting temperatures were measured (mp 65 °C for **2d** or 95 °C for **2b**), which is surprising among thiacalixarene derivatives possessing usually very high melting points.

Table 1. Reaction Conditions Survey for *S*-Alkylation of **1**

entry	reagent[a]	equiv (time)	solvent[c]/ temp	yield of **2** (%)	yield of **3** (%)
1	MeI	12 (3 d)	DCM/rt	0[b]	0
2	MeOTs	12 (3 d)	DCM/rt	0[b]	0
3	MeOBs	12 (3 d)	DCM/rt	0[b]	0
4	MeONs	12 (3 d)	DCM/rt	0[b]	0
5	MeOMs	12 (3 d)	DCM/rt	0[b]	0
6	MeOTf	12 (3 d)	DCM/rt	**2a** (58)	0
7	MeOTf	12 (1 h)	DCE/reflux	**2a** (93)	0
8	MeOTf	12 (3 d)	MeCN/reflux	**2a** (30)	0
9	MeOTf	36 (2 d)	DCM/reflux	0	**3a** (89)
10	MeOTf	36 (18 h)	DCE/reflux	0	**3a** (88)
11	EtOTf	12 (2 d)	DCM/rt	0[b]	0
12	EtOTf	24 (3 d)	DCM/reflux	**2b** (47)	0
13	EtOTf	36 (5 d)	DCE/reflux	0	**3b** (98)
14	Me_3OBF_4	12 (5 d)	DCE/reflux	**2d** (56)	**3d** (31)
15	Me_3OBF_4	36 (10 d)	DCE/reflux	**2d** (17)	**3d** (48)
16	Et_3OBF_4	36 (10 d)	DCE/reflux	**2e** (87)	0

[a] OTs = *p*-toluenesulfonate, OBs = 4-bromobenzenesulfonate, ONs = 4-nitrobenzenesulfonate, OTf = triflate. [b] No reaction observed (starting material recovered). [c] DCE = 1,2-dichloroethane.

The structures of alkylated products were assigned by MS. Thus, MS ESI$^+$ analysis of monoalkylated compounds showed signals at m/z = 679.20 for *S*-methyl **2a** or **2d** and m/z = 693.24 for *S*-ethyl salts **2b** and **2e**, which correspond to the molecular weights of cations formed.

(6) Sessler, J. L.; Gale, P. A.; Cho, W. S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, 2008; pp 27−130.
(7) Himl, M.; Pojarova, M.; Stibor, I.; Sykora, J.; Lhotak, P. *Tetrahedron Lett.* **2005**, *46*, 461.
(8) Lhotak, P.; Moravek, J.; Smejkal, T.; Stibor, I.; Sykora, J. *Tetrahedron Lett.* **2003**, *44*, 7333.
(9) For other modifications of sulfur bridges, see: Morohashi, N.; Kojima, M.; Suzuki, A.; Ohba, Y. *Heterocycl. Commun.* **2005**, *11*, 249–254.
(10) For the alkylation of diphenyl sulfide, see: Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218.

Similarly, the signals at m/z = 347.3 and 843.1 for bis-*S*-methyl **3a** and m/z = 360.4 and 870.9 for bis-*S*-ethyl salts **3b** were observed. While lower mass signals correspond to naked dications (z = 2), higher mass peaks belong to the species with the charge +1 where dications and one triflate anion are not fully separated during MS analysis, and as a result, the ion-pair of dication−anion $[calix^{2+}TfO^{-}]^{+}$ was formed. In this context, although a high excess of the alkylating agent (36 equiv) and prolonged reaction times (up to 10 days) were used, the formation of tris- or even tetrakis-*S*-alkylated salts has never been observed.

The splitting pattern and multiplicity of ^{1}H NMR spectra of bis-alkylated products indicate that the second alkyl group attacked the sulfur atom in a distal (opposite) position. In other words, using the calixarene numbering, the sulfur atoms at positions 2 and 14 are alkylated. The high symmetry of diethyl derivative **3b** is obvious in the aromatic part of the spectrum (see the Supporting Information, Figures 21 and 22); one triplet at 7.21 and two doublets at 7.48 and 7.40 ppm clearly support the distal substitution pattern. Dialkylation seems to be highly regioselective as no other regioisomer has been observed in the reaction mixtures. The driving force for this regioselectivity is probably the minimization of repulsion between both sulfonium cations. The expected stereoselectivity of the alkylation reactions (Scheme 1) was proven by NOE experiments at 193 K. The close contacts of *S*-alkyl methylene protons with aromatic hydrogens demonstrated that the *S*-alkyl chains are pointing in the direction opposite to that of the propoxy groups on the lower rim of the thiacalix[4]arene skeleton. It means that the alkylating reagents attacked the *cone* conformer **1** from the upper-rim direction to minimize possible steric repulsions with the lower-rim substituents.

The final evidence of structure was obtained by a single-crystal X-ray diffraction study. The crystals of **3b** are in a triclinic cell, and structure solution was performed in the space group *P*-1. The asymmetric unit contains two independent molecules in the *pinched cone* conformation, with both *S*-ethyl groups pointing above the main plain defined by four sulfur atoms (see the Supporting Information, Figures 37−40).

Tetraalkylated thiacalixarenes in the *cone* conformation are known to exhibit the *pinched cone*−*pinched cone* interconversion (Figure 1). As the coalescence temperature of this equilibrium is much higher than that of classical calixarenes,[11] the ^{1}H NMR spectra of these compounds possess usually very broad signals at ambient temperatures. Therefore, the ^{1}H spectra of starting **1** and the salts **2a** and **3a** were compared to gain a deeper insight into the influence of the *S*-alkylation to the *pinched cone*−*pinched cone* equilibrium phenomenon. Narrowing of the signals in **2a** and **3a** (298 K, acetone-d_6) in comparison to **1** indicates the acceleration of the *pinched cone*−*pinched cone* interconversion, which is more pronounced in the case of bis-*S*-alkylated compounds. The dynamic NMR study of **2a** (Figure 1) showed that the ^{1}H NMR spectrum at 298 K corresponds to the time averaged signals due to the fast exchange between the both *pinched cone* conformations. Lowering the temperature led to the substantial broadening of signals, finally reaching the coalescence temperature of the interconversion around 250 K. Spectra measured at the lowest accessible temperature (193 K) showed perfectly resolved signals. The doubled number of signals clearly indicates that the *pinched cone*−*pinched cone* interconversion proceeds under slow-exchange conditions.

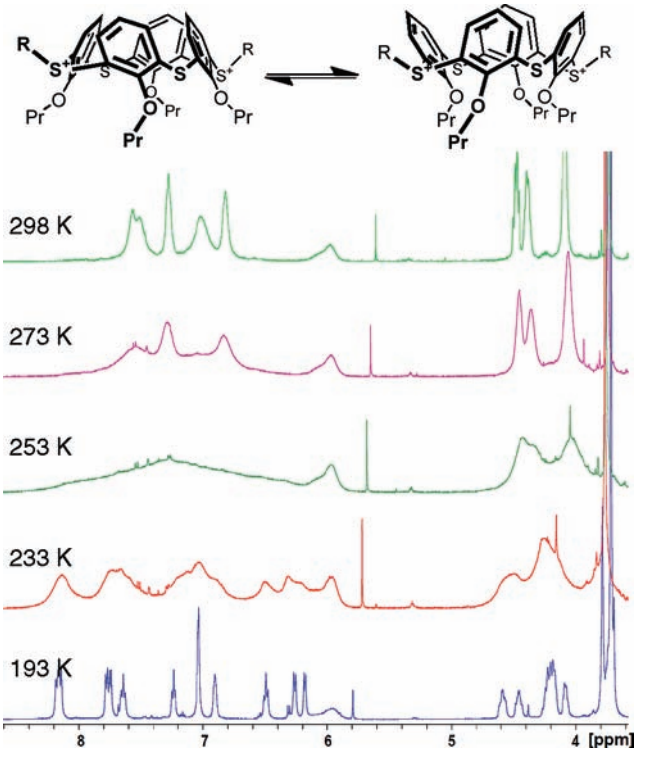


Figure 1. ^{1}H NMR spectra of mono-*S*-methyl **2a** (acetone-d_6, 500 MHz) at various temperatures.

Due to the presence of one or two positively charged atoms, we attempted the application of *S*-alkylated thiacalixarenes **2** and **3** as anion receptors. Surprisingly, when the ^{1}H NMR titration of **2a** with TBA^+I^- was performed at room temperature in acetone-d_6, the signals corresponding to **2a** gradually disappeared, while the signals of tetrapropoxythiacalixarene **1** appeared (Figure 2). This implies that iodide was alkylated by *S*-alkylated thiacalixarene itself. As iodide is a very good nucleophile, we used the nitrate as an example of weaker nucleophiles. Again, the presence of **1** indicated the alkylation of NO_3^- with **2a**.

(11) The coalescence temperature of **1** in $CDCl_3$ is 270 K, while the classical calix[4]arene analogue possesses the coalescence at 188 K (CD_2Cl_2): Cajan, M.; Lhotak, P.; Lang, J.; Dvorakova, H.; Stibor, I.; Koca, J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1922.

(12) For the alkylation of selected nucleophiles by dialkylphenylsulfonium salts, see: Umemura, K.; Matsuyama, H.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2593.

Unfortunately, a direct observation of the expected alkylation product (methyl nitrate) was made impossible because of the massive overlapping with the signals of TBA cation and the alkoxy group of **1** and **2a** in the aliphatic part of the ^{1}H NMR spectrum.

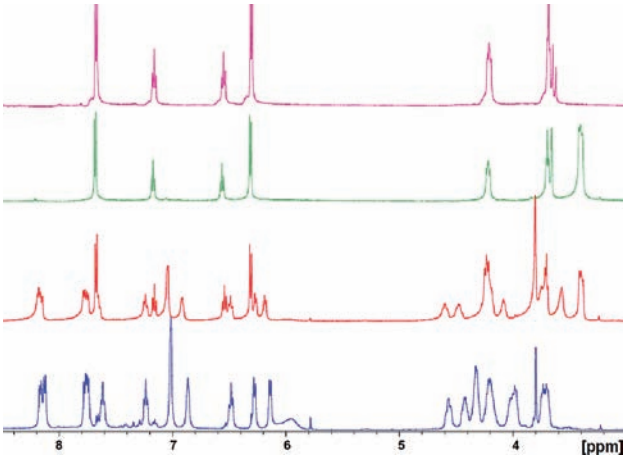
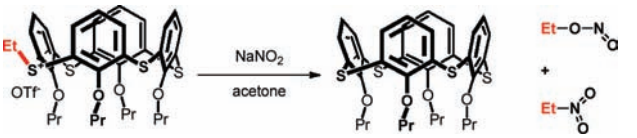


Figure 2. Reaction of **2a** with $Bu_4N^+I^-$ (CD_3COCD_3, 500 MHz): starting **2a** (blue); the reaction mixture after 2 h at rt (red); the reaction mixture after 24 h (green); sample of **1** for comparison (violet). Double set of signals corresponds to two *pinched cone* structures under slow exchange conditions. (All spectra measured at 193 K to avoid huge broadening of signals because of the coalescence phenomenon.)

The alkylation of nucleophiles[12] was further studied using 1 or 2 equiv of sodium iodide, potassium acetate, sodium nitrate, and pyridine to avoid overlapping of aliphatic signals with the TBA^+ cation in ^{1}H NMR spectra. The solutions of **2a**, **2b**, **3a**, and **3b** with the corresponding nucleophile were prepared directly in NMR tubes (acetone-d_6) and sonicated for several days at rt. In all cases, the formation of corresponding methyl and ethyl iodides, acetates, nitrates, and pyridinium triflates were observed. When $NaNO_2$ was used as a nucleophile, two sets of signals appeared in the ^{1}H NMR spectrum. This can be explained by the well-known ambivalent nature of nitrite nucleophile where *O*- and *N*-alkylation can occur simultaneously (Scheme 2).

Thus, in the case of the **3b**–$NaNO_2$ system, two quartets appeared at 4.55 and 3.56 ppm with the 1:2 ratio of intensities. The first signal corresponds to the methylene group in nitroethane (a product of *N*-alkylation). However, the second signal corresponds to the peak of methylene group in ethanol. As we did not observe any direct reaction of **3b** with water present in solvent, we suppose that the product of *O*-alkylation (ethyl nitrite) was instantly hydrolyzed to form ethanol.[13] The application of *S*-methyl derivative **2a** led to similar findings: the formation of nitromethane and methanol in the 1:2 molar ratio. Interestingly, the model alkylation reaction (ethyl iodide and $NaNO_2$) carried out under identical experimental conditions gave only a trace amount (< 1%) of nitroethane after 4 days. It indicates that the sulfonium salts of thiacalixarenes can be successfully applied as alkylating agents, which are able to distinguish between hard (oxygen) and soft (nitrogen) nucleophiles.

Scheme 2. Alkylation of $NaNO_2$ with **2b**



In conclusion, using strong alkylating reagents, we prepared the *S*-alkylated sulfonium derivatives of thiacalix[4]arenes for the first time. In addition to the well-known upper and lower rim substitutions, *S*-alkylation opens the way for a completely new type of substitution pattern in thiacalixarene chemistry. The thiacalixarene-based sulfonium salts possess very interesting conformational behavior and can play a role of unusual alkylating agents.

Acknowledgment. This research was supported by the Czech Science Foundation (Grant No. 203/09/0691) and by Grant Nos. 6046137301, 6046137302, and LC06070 from the Ministry of Education, Youth, and Sports of the Czech Republic.

Supporting Information Available. Experimental procedures, full characterizations, and the X-ray structure of **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Doyle, M. P.; Terpstra, J. W.; Pickering, R. A.; LePoire, D. M. *J. Org. Chem.* **1983**, *48*, 3379.