Fries Rearrangement in Calixarene Esters: A New Entry for the Synthesis of *p*-Substituted Calixarenes

Takashi ARIMURA, Seiji SHINKAI,* Tsutomu MATSUDA, Yoshimi HIRATA,†
Hiroshi SATOH,† and Osamu MANABE†
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812
†Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852
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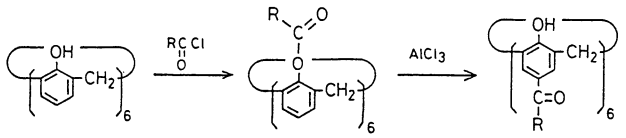
Synopsis. The Fries rearrangement was found to be a convenient method to synthesize *p*-acylcalixarenes from *O*-acylcalixarenes, the yields being relatively good (29—34%) as a synthetic method for *p*-substituted calixarenes.

Calixarenes are cyclic oligomers made up of benzene units as cyclodextrins are made up of glucose units. Since calixarenes possess a novel cylindrical architecture, they are expected to be useful for designing cavity-shaped host molecules.[1,2] In order to obtain functionalized calixarenes for host molecules, it is indispensable to find new synthetic methods to introduce various substituents into calixarenes. The first method is the direct substitution of the *p*-position (sulfonation, nitration, etc.).[1-5] However, this method is hampered by a fact that it is fairly difficult to isolate a fully-substituted product from lower-substituted by-products. Thus, the application of this method is limited to the very clean reactions. The second method is the rearrangement of the substituents on the OH groups to the *p*-position. Gutsche and Levine[6] introduced the Claisen rearrangement of the allyl ether of calixarenes to *p*-allylcalixarenes, but the allyl group is rather useless as an intermediate for functionalized calixarenes. We here address a new method to synthesize *p*-acylcalixarenes by the Fries rearrangement from esters of calix[6]arenes. The acyl group is a more versatile functional group to derive alcohols, imines, oximes, etc.



1 2 3

a: R = $CH_3(CH_2)_4$- b: R = $CH_3CH_2CH(CH_3)$-

Experimental

Acylation of calix[6]arene (**1**) was carried out according to the method of Gutsche and Lin for 25,26,27,28-tetraacetoxycalix[4]arene.[7] 37,38,39,40,41,42-Hexakis(hexanoyloxy)calix[6]arene (**2a**); recrystallized from hexane, mp 198—200 °C, yield 50%. IR (KBr): $\nu_{C=O}$ 1755 cm^{-1}, no ν_{OH} ^1H MNR (Me_2SO-d_6, 100 °C): CH_3, δ=0.84, 3H; $(CH_2)_3$, 1.24—1.49, 6H; $COCH_2$, 2.98, 2H; $ArCH_2Ar$, 3.66, 2H; aromatic protons, 6.80, 3H. Found: C, 76.42; H, 7.84%. Calcd for $(C_{13}H_{16}O_2)_6$: C, 76.44; H, 7.89%.

37,38,39,40,41,42-Hexakis[(2-methylbutanoyl)oxy]calix[6]-arene (**2b**); recrystallized from *N*,*N*-dimethylformamide (DMF), mp 332—335 °C, yield 51%. IR(KBr): $\nu_{C=O}$ 1750 cm^{-1}, no ν_{OH}. ^1H NMR (Me_2SO-d_6, 160 °C): CH_3, δ=0.83 and 1.02, 3H each; CH_2, 1.42 and 1.63, 1H each; CH, 2.68, 1H; $ArCH_2Ar$, 3.62, 2H; aromatic protons, 6.84, 3H. Found: C, 75.17; H, 7.44; N, 0.41%. Calcd for $(C_{12}H_{14}O_2)_6 \cdot 0.35$DMF: C, 75.18; H,7.47; N, 0.42%. It was difficult to remove a trace amount of DMF which is possibly included in **2b** as a clathrate complex.

A typical experimental run for the Fries rearrangement of **2** to **3** is as follows: a mixture of **2** (0.88 mmol) and $AlCl_3$ (2.3 g, 15.8 mmol) was stirred in 40 ml of chlorobenzene at 45—50 °C for 17 h under a nitrogen atmosphere. After cooling water was added to the reaction mixture and the organic phase was diluted with 100 ml of chloroform, washed with 1 mol dm^{-3} HCl and water, and then dried over $MgSO_4$. The solution was concentrated in vacuo, and the oily residue was recrystallized from acetone. The crystals **3** were collected by centrifugation and then recrystallized from tetrahydrofuran for **3a** and chloroform-methanol for **3b**. The products gave satisfactory elemental analyses and spectral properties (IR, NMR) consistent with **3**.

5,11,17,23,29,35-Hexahexanoylcalix[6]arene (**3a**); mp 227—230 °C, yield 29%. IR (KBr): ν_{OH} 3375 cm^{-1}, $\nu_{C=O}$ 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): CH_3, δ= 0.91, 3H; $(CH_2)_3$, 1.38—1.72, 6H; $COCH_2$, 2.91, 2H; $ArCH_2Ar$, 4.00, 2H; aromatic protons, 7.87, 2H; OH, 10.42, 1H. Found:C, 76.41; H, 7.84%. Calcd for $(C_{13}H_{16}O_2)_6$:C, 76.44; H,7.89%.

5,11,17,23,35-Hexakis(2-methylbutanoyl)calix[6]arene (**3b**); >mp 360 °C, yield 34%. IR (KBr): ν_{OH} 3370 cm^{-1}, $\nu_{C=O}$1665 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): CH_3, 0.89 and 1.13, 3H each; CH_2, 1.50 and 1.79, 1H each; CH, 3.36, 1H; $ArCH_2Ar$, 4.01, 2H; aromatic protons, 7.88, 2H; OH, 10.47, 1H. Found: C, 75.15; H, 7,14%. Calcd for $(C_{12}H_{14}O_2)_6 \cdot 0.09CHCl_3$: C, 75.15; H, 7.36%. A weak peak of included $CHCl_3$ was observed in the NMR spectrum when ^1H NMR was taken in Me_2SO-d_6.

All the ^1H NMR spectra were measured with JEOL GX-400.

Results and Discussion

We first tried the Fries rearrangement of 37,38,39,40,41,42-hexaacetoxycalix[6]arene. However, the rearrangement did not take place under the reaction conditions described in Experimental. When the more drastic reaction conditions (high temperature, increase in $AlCl_3$, etc.) were employed, the product was black resin insoluble in any solvents.** We thus used **2a** and **2b** as starting esters and found that the Fries rearangement really takes place.

It is not easy to enhance the yield for the synthesis of *p*-substituted calixarene derivatives. If the rearrange-

** It is not clear why the Fries rearrangement of the acetyl derivative does not take place. It is known that Friedel-Crafts acylation of benzocrown ethers catalyzed by aluminium chloride is impractical: W. W. Parish, P. E. Scott, and C. W. McCausland, *J. Org. Chem.*, **43**, 4597 (1978) and F. Wada and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **53**, 421 (1980). The peculiar behavior may be attributable to an interaction between the smaller $AlCl_3$-CH_3COCl complex with the ionophoric calixarene ester.

Table 1. Melting Points, Yields, and Coalescence Temperatures of **2** and **3**

Calix[6]arene	Appearance	Mp θ_m/°C	Yield/%	T_c/°C[a]
2a	Colorless prisms	198—200	50	5
2b	Colorless prisms	332—335	51	50
3a	Colorless powder	227—230	29	−3
3b	Colorless powder	>360	34	0
p-Hexylcalix[6]arene[b]	Colorless powder	305—307	22[b]	−70

a) Pyridine-d_5. The methylene protons in these compounds (except **2a**) gave a singlet above T_c, whereas those in **2a** gave the two peaks in 2 : 1 ratio. b) This compound was synthesized from *p*-hexylphenol and formaldehyd[9].

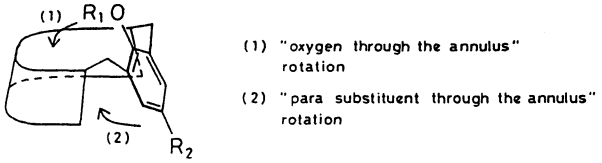


Fig. 1. Two possible rotation mechanisms in calixarenes.

ment is assumed to occur successively, the total yield for fully-substituted calix[6]arene becomes only 26.2% (=0.80^6) even though the yield for each benzene unit is 80%. This is a special situation in the modification of cyclic compounds. The yields obtained in the Fries rearrangement (29—34%) are apparently low. But, they are classified as good yields for the synthesis of *p*-substituted calix[6]arenes since these values imply that the rearrangement in each benzene unit occurs in 81—85% yields (i.e., 0.81^6=29%, 0.85^6=34%). The yields are higher than that for the Claisen rearrangement in calix[6]arene (21%).[7] This suggests that the Fries rearrangement well competes with or is superior to the Claisen rearrangement as a synthetic method for *p*-substituted calixarenes. Since the yield for **3b** is comparable with that for **3a**, this reaction is not so subject to the steric effect.

It is known that the temperature-dependent ^{1}H NMR spectrum of calix[6]arenes displays a few sets of overlapping pairs of doublets for the $ArCH_2Ar$ methylene hydrogens at low temperature and a singlet resonance at high temperature.[8] This behavior is interpreted in terms of conformational change form "cone" (or "hinged cone") to "alternate",[1,2] resulting in a coalescence temperature (T_c) at the intermediate. Determination of the T_c of **2** and **3** in pyridine-d_6 (−70—90 °C) (Table 1) showed that compounds **2** have the T_c higher than **3**, indicating that increased freezing of the partial conformations can be observed for the ester derivatives. In particular, **2b** has the very high T_c (50 °C) probably due to the bulky *s*-butyl group. Two possible mechanisms have been proposed for the rotation of the benzene unit, (1) oxygen through the annulus rotation and (2) para substituent through the annulus rotation (Fig. 1).[8] The fact that the T_c becomes higher only when the substituent is introduced into the OH group supports that the conformational change occurs according to the "oxygen through the annulus" rotation mechanism: that is, the T_c is sensitive to steric bulkiness of the substituent (R_1) on the oxygen but not so much to that of the para substituent (R_2).

Interestingly, the T_c values for **3a** and **3b** are surprisingly higher than those for calix[6]arene (−70 °C),[8] *p-t*-butylcalix[6]arene (−54 °C),[8] and *p*-hexylcalix[6]arene (−70 °C)[9] in pyridine-d_5. The origin of the remarkable T_c difference between *p*-acylcalix[6]arenes and *p*-alkylcalix[6]arenes is still a matter of controversy. We believe that the most probable rationale is the lower shift of the pK_a of the OH groups due to the electron-withdrawing *p*-acyl groups, which would strengthen the hydrogen-bonding interaction among the OH groups and stabilize accordingly the "cone" conformation in solution.

In conclusion, the present paper indicated that the Fries rearrangement is very useful for the synthesis of *p*-acylcalixarene derivatives. Further functionalization of *p*-acylcalixarenes is now under investigation in these laboratories.

References

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