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25-Alkoxy-26-benzoyloxycalix[4]arenes: the reaction mechanism of benzoyl migration

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ABSTRACT

In the presence of K_2CO_3 as reaction base, the 25-alkoxy-27-benzoyloxy-calix[4]arenes were converted into 25-alkoxy-26-benzoyloxy derivatives by benzoyl-migration. A benzoyl-migrated reaction mechanism with a cyclic orthobenzoate-like intermediate was proposed, and the mechanism was supported by the identical reaction results on the conversion of 25-ethoxy-27-benzoyloxycalix[4]arene to 25-ethoxy-26-benzoyloxycalix[4]arene, and vice versa.

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It is known that, with only two special exceptions,^{1,2} the introduction of the second substituent onto the calix[4]arene 'lower rim' yielded the 1,3-disubstituted calix[4]arene derivatives.^{3–6} It is generally believed that the formation of the second substituent-linkage at the distant 3-position rather than the more available proximal 2-positions was due to the steric hindrance effect. Hence, the inherent steric hindrance problem of the proximal positions has to be solved first in order to achieve the preparation of the 1,2-disubstituted calix[4]arenes.

To aim the goal of preparing the 1,2-disubstituted calix[4]arenes, several multi-step synthetic routes^{5–7} had been explored in the past few years. In one of the synthetic routes for the 25,26-dialkoxycalix[4]arenes, it was observed that the benzoyl moieties were migrated in several alkyl halide cases.⁶ In order to illustrate the formation of the unexpected 25,27-dialkoxy-26-benzoyloxy products, a benzoyl-migration reaction mechanism with cyclic orthobenzoate-like intermediate was then proposed. Additionally, with the purpose of further comprehending the migration behavior of the benzoyl moieties, a weaker base K₂CO₃, which was shown to enhance the migration behavior,⁵ was selected in this investigation.

In this Letter we will utilize the benzoyl migration behavior to convert the easily accessible 25-alkoxy-27-benzoyloxycalix[4]arenes into 25-alkoxy-26-benzoyloxycalix[4]arenes, a new set of calix[4]arene derivatives have not been reported in the literature.

* Corresponding author. E-mail address: lglin@faculty.pccu.edu.tw (L-G. Lin). We will also demonstrate that the benzoyl moiety is migrated via cyclic orthobenzoate-like intermediate as in our earlier proposed mechanism.⁶

Results and discussion

It was reported⁶ that the etherification of 25-alkoxy-27-benzoyloxycalix[4]arenes yielded two isomeric dialkoxy-products, 25,26-dialkoxy-27-benzoyloxycalix[4]arenes and 25,27-dialkoxy-26-benzoyloxycalix[4]arenes, in approximately equal amounts. To elucidate the formation of the unexpected 25,27-dialkoxy-26benzoyloxycalix[4]arenes, a benzoyl-migrated reaction mechanism with a cyclic orthobenzoate-like anionic intermediate was proposed as shown in Figure 1.

Preparation of 25-alkoxy-26-benzoyloxycalix[4]arenes via benzoyl-migration route

In our proposed mechanism, we speculated that the alkyl halides were probably more favorable to approach the cyclic orthobenzoate-like anionic intermediate from the less hindered 3-position side, as shown in Figure 1, and yielded the benzoyl-migrated 25,27-dialkoxy-26-benzoyloxy products. We also anticipated that, with or without the presence of alkyl halides, the breaking of cyclic orthobenzoate ring would occur eventually and afford either the starting materials or the corresponding benzoyl-migrated derivatives. Therefore, the refluxing reaction conditions of 25-alkoxy-27-benzoyloxy-calix[4]arenes **1–4** with K₂CO₃ in CH₃CN were





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Figure 1. A proposed benzoyl-migrated reaction mechanism.

undertaken to investigate the unusual benzoyl-migration behavior. (Scheme 1).

In the most accessible 25-ethoxy-27-benzoyloxy case, the TLC analysis of the reaction crude products indicated that the product mixtures contained, along with the starting material **1**, a small amount of known hydrolyzed compound and a new major



Scheme 1. Synthetic scheme for 25-alkoxy-26-benzoyloxycalix[4]arenes 5-8.

component 5. The isolation of the new product 5 was performed in a two-stage recrystallization procedure. The symmetrical starting material 1 was crystallized as the first crop, and a further evaporation of the mother solution yielded the second crop with product 5 as predominant component. Further recrystallization of the second crop yielded the product **5** in pure form.⁸ Although the spectral integral ratio of product 5 indicated that no protoncontaining moiety was introduced and/or removed during the refluxing periods, but the resulting proton NMR spectrum was substantially different from its starting material 1, as shown in Figure 2. A total of eight sets of doublets (δ 3.2–4.5) for the eight different calix[4]arene's methylene protons strongly suggested that the structure of the product **5** contained no symmetry elements. The upfield shift of 0.60 ppm for the ethoxy's methyl protons also indicated that the magnetic environment for the ethoxy moiety had been changed. An intramolecular migration of benzoyl moiety from distant 3-position to proximal 2-position seemed to be the only reasonable explanation for the chemical shift of the ethoxy's methyl protons and a complete vanishing of the symmetry element on product 5. Based on the benzoyl-migrated assumption and the spectral evidences, the molecular structure of product 5 was easy to assign as 25-ethoxy-26-benzoyloxycalix[4]arene.

All the other 25-alkoxy-27-benzoyloxycalix[4]arenes **2–4** yielded the similar crude product mixtures, and the corresponding benzoyl-migrated 25-alkoxy-26-benzoyloxy products **6–8** were characterized with the isolating yields of 20–28%.⁹ It was interesting to notice that such proximal structural isomers had never been reported in the literature.

Benzoyl-migration behavior of 25-ethoxy-27-benzoyloxycalix [4]arene and 25-ethoxy-26-benzoyloxycalix[4]arene

In our proposed reaction mechanism, the benzoyl-migrated products were afforded by ring-opening of the cyclic orthobenzoate-like intermediates. The proposed mechanism also suggested that both of the 25-alkoxy-27-benzoyloxycalix[4]arenes and 25-alkoxy-26-benzoyloxy-calix[4]arenes produced the same cyclic



Figure 2. The ¹H NMR spectrum of 25-ethoxy-26-benzoyloxycalix[4]arene 5.

intermediates. Therefore, it is reasonable to anticipate that the benzoyl-migrated reaction of 25-alkoxy-27-benzoyloxycalix[4] arenes and/or 25-alkoxy-26-benzoyloxy-calix[4]arenes will yield the same product mixtures. The isolation of 25-alkoxy-26-benzoyl-oxy-calix[4]arenes in the previous section provided an opportunity to verify the proposed reaction mechanism.

In a preliminary study of the ethoxy case, both of the 25-ethoxy-27-benzoyloxycalix[4]arene (1) and 25-ethoxy-26-benzoyloxycalix[4]arene (5) were refluxed with K₂CO₃ in acetonitrile for 16 h. When the proton NMR spectra of those reaction crude product mixtures were taken¹⁰, two almost identical proton NMR spectra were attained.¹¹ A semi-quantitative analysis by spectral integration of the ethoxy's methyl proton (displayed as a triplet at 1.79 ppm for compound **1**, at 1.17 ppm for compound **5**, and at 1.86 ppm for hydrolyzed compound) indicated that the ratio of the amount of compound **1** to compound **5** was identical in both crude product mixtures, and the discrepancy between two spectra were arisen only from a slight difference in the amount of the hydrolyzed compound. Since the formation of compound **1** and/ or compound 5 involved both chemical bond-breaking and bondforming, therefore, the benzoyl-migrated reactions starting either from 25-ethoxy-27-benzoyloxycalix[4]arene (1) or 25-ethoxy-26benzoyloxycalix[4]arene (5) should have possessed a common reaction intermediate in order to produce an identical product mixtures. This result strongly supported our proposed benzoyl-migrated reaction mechanism with a cyclic orthobenzoate-like intermediate.

With all the results from this study on the benzoyl-migration phenomena in calix[4]arene system, we concluded that the benzoyl moieties not only provide 'neighborhood group effect' to stabilize the cyclic reaction intermediate, but also set up a stage for the migration to occur. We believe that such acyl-migratory behavior also occurs in the nature, and the acyl migration may then create a vast varieties of alkylated and/or acylated polyhydroxy-derivatives in the plant kingdom. Furthermore, one can even imagine that the phosphated carbohydrate systems, for example ribose phosphate, may possess the cyclic phosphate diester analog, and the parallel phosphate-migratory behavior will have the chance to evolve into an enormous amount of species in the nature.

Acknowledgment

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Supplementary data

Supplementary data (copies of ¹H NMR spectra of 25-alkoxycalix[4]arenes and compounds **1–8**; and copies of ¹³C NMR spectra of compounds **5**, **7**, and **8** are available.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.tetlet.2012.04.138.

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- 25-Ethoxy-26-benzoyloxy-27,28-dihydroxycalix[4]arene (5): a colorless crystals, isolated yield 56%; mp 185–190 °C; ¹H NMR (CDCl₃) δ 9,70 (s, 1H, ArOH), 9.14 (s, 1H, ArOH), 8.62–8.64 (d, 2H, Ar'H), 7.59–7.70 (t, 3H, ArH and Ar'H), 6.59–7.28 (m, 12H, ArH), 4.29–4.39 (2d, 2H, ArCH₂Ar), 4.01–4.16 (m, 3H, ArCH₂Ar and OCH₂CH₃), 3.83–3.88 (m, 1H, OCH₂CH₃), 3.45–3.55 (dd, 3H, ArCH₂Ar), 3.29–3.33 (d, *J* = 12.8 Hz, 1H, ArCH₂Ar), 1.21–1.25 (t, 3H, OCH₂CH₃); ¹³C NMR (CDCl₃) δ 166.4, 152.2, 152.0, 149.5, 144.9, 135.6, 133.7, 133.4, 133.3, 133.3, 130.8, 130.2, 130.1, 129.7, 129.5, 129.3, 129.1, 129.0, 128.6, 128.5, 128.4, 128.0, 127.7, 127.4, 127.4, 126.2, 126.0, 121.7, 119.8, 72.9, 32.7, 31.9, 31.7, 30.4,

14.8; FAB-MS m/e: 557 (M*+1); HRMS (FAB) m/e: Calcd for $C_{37}H_{32}O_5\text{+}H^{+}\text{:}$ 557.2329; Found: 557.2333.

9. The three benzoyl-migrated products 6,7, and 8 were isolated in a same procedure as ethoxy case with a slight difference in solvent system (products 6: EtOAc-CH₃OH, isolated yield 20%; products 7 and 8: CHCl₃-CH₃OH, isolated yield 26% and 28%, respectively). The 25-allyloxy-27-benzoyloxycalix[4]arene also migrated to its benzoyl-migrated derivative, 25-allyloxy-26-benzoyloxycalix[4]arene required chromatographic separation. With a lack of molecular symmetry, 25-allyloxy-26-benzoyloxycalix[4]arene displayed a very complex proton NMR spectral

pattern and the exact molecular structure was unable to assign accurately without any doubt.

- 10. The NMR spectral samples of those benzoyl-migrated reactions were prepared by removing the solvent and adding CDCl₃ to retrieve the reaction crude product mixtures.
- 11. Copies of the benzoyl-migrated ¹H NMR spectra of 25-ethoxy-27benzoyloxycalix[4]arene (1) and 25-ethoxy-26-benzoyloxycalix[4]arene (5) and copies of the benzoyl-migrated time-interval ¹H NMR spectra of 25ethoxy-27-benzoyloxycalix[4]arene (1) are attached as part of the Supplementary data.