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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3061–3063

Diels–Alder reactions of bis(spirodienone) derivatives of calix[4]arene with acetylenes: highly regio- and stereoselective synthesis of bisbicyclo[2.2.2]octenone derivatives

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Received 31 January 2005; revised 25 February 2005; accepted 1 March 2005

Abstract—Highly regio- and stereoselective Diels–Alder reactions of bis(spirodienone) derivatives of calix[4]arene with acetylenes that provide easy access to bisbicyclo[2.2.2]octenones are described.

Calix[*n*]arenes and their derivatives constitute an important class of compounds by virtue of their unique place in host–guest chemistry.[1] They have been reported to be good hosts for metal ions, anions and neutral molecules depending on the coordination properties of the functional groups attached to the calixarene framework. Biali and co-workers[2–7] have reported a mild oxidative cyclization of calix[4]arenes which resulted in yet another versatile class of compounds (**1A**, **1A′** and **1B**) with bis(spirodienone) moieties interconnected with methylene groups. The compounds have two spiro stereo centres and an alternant or non-alternant cyclic disposition of carbonyl and ether binding sites which make them attractive candidates as ionophores (see Fig. 1).

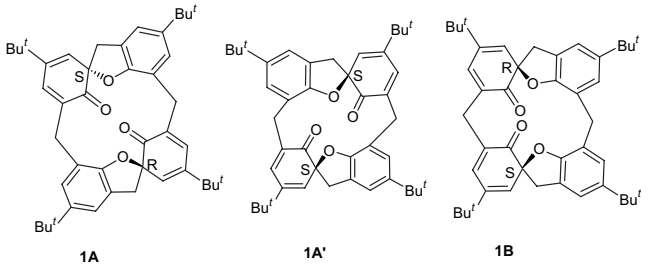

Figure 1.

The chemistry of the bis(spirodienones) of calixarenes has so far been centerd around the functionalization of calixarenes. Functionalization of the calixarene scaffold at the extraannular positions, modification at the methylene groups,[8] replacement of one or two –OH groups[9] etc., are some of the modifications that have been pursued. The bis(spirodienones) appeared attractive from the vantage point of their transformation to novel structural frameworks with potentially useful properties. Of special interest to us has been their Diels–Alder reactivity. The Diels–Alder reactions of simple spirodienones have been investigated earlier.[10] Except for an isolated report on the reaction of benzyne with the calix[4]arene derived bis(spirodienones), the Diels–Alder cycloadditions of these systems have not been investigated.[4] We have initiated work in this area and our preliminary results are presented in this letter.

We commenced our work by reacting dimethyl acetylenedicarboxylate (DMAD) with **1A** and **1B** under ambient conditions (Scheme 1).

The reaction of 2 equiv of DMAD with the most stable isomer **1A** yielded the cycloadduct **2a** in quantitative yield.[11] After purification by column chromatography, the product was characterized by spectroscopic methods. The symmetry of the bis(spirodienone) is retained in the adducts as shown by the identical splitting pattern of the two pairs of doublets arising from the two pairs of methylene groups. The additions occurred with stereoselectivity as evident from the well-defined ^{1}H NMR spectrum. The IR spectrum showed the ester carbonyl

Keywords: Calixarenes; Diels–Alder reaction; Acetylenes; Spirodienone.
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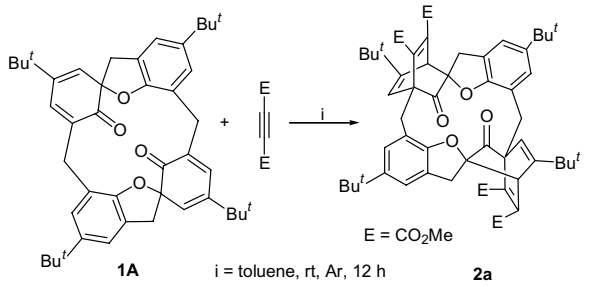
doi:10.1016/j.tetlet.2005.03.010



Scheme 1.

absorption at 1746 cm^{-1} and dienone carbonyl absorption at 1710 cm^{-1}. In the ^1H NMR spectrum, the aromatic protons appeared as two singlets at δ 7.06 and δ 6.89. The olefinic proton and the ring junction proton Ha appeared at δ 4.82 and δ 4.35, respectively, both showing allylic coupling ($J = 2.13$ Hz). The methoxy groups of the DMAD appeared as two singlets at δ 3.87 and δ 3.79. In the ^{13}C spectrum, the signals due to the ring carbonyl and ester carbonyl appeared at δ 192.7, 166.0 and 163.0 and the spiro carbon resonated at δ 77.2. Conclusive evidence for the structure and stereochemistry was obtained by single crystal X-ray analysis (Fig. 2).[12] A selective approach of the dienophile from the face opposite to the dihydrofuran oxygen results in the exclusive formation of the *exo-exo* isomer.[4]

The reaction was found to be general for activated acetylenes with electron withdrawing groups (Table 1). Diphenylacetylene and ethoxyacetylene failed to react with the substrate (entries 5 and 6), perhaps due to electronic reasons. The bisadducts were obtained in excellent yields.

The products **2c** and **2d** (entries 3 and 4) were obtained exclusively as single regioisomers. The regiochemistry of

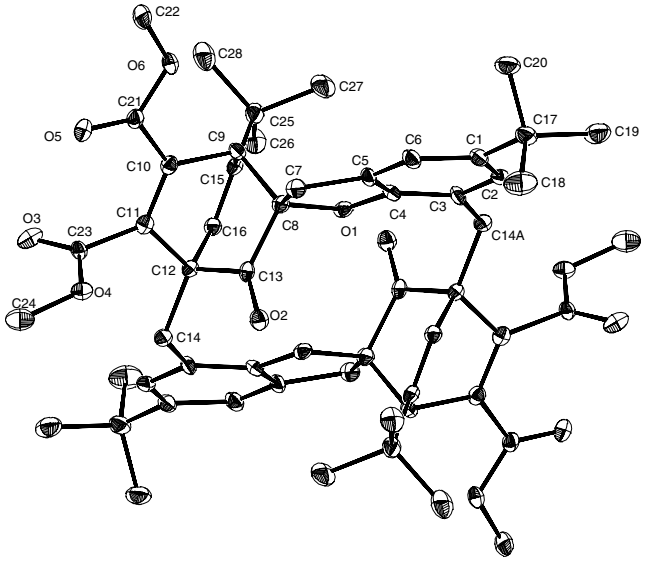
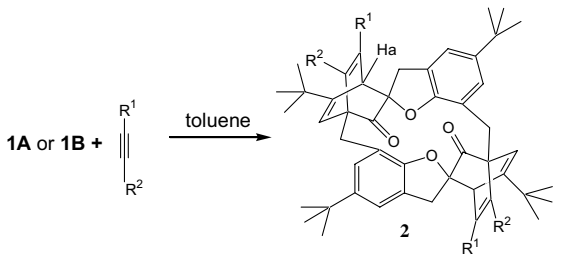


Figure 2. ORTEP diagram of the compound **2a** with 40% for the thermal ellipsoid (hydrogen atoms are omitted for clarity).

Table 1.



Entry	Substrate	R^1 and R^2	Temp (°C)	Time (h)	Yield (%)
1	**1A**	$R^1 = CO_2Me$ $R^2 = CO_2Me$	25	12	**2a**, 99
2	**1A**	$R^1 = CO_2{}^t$Bu $R^2 = CO_2{}^t$Bu	110	12	**2b**, 99
3	**1A**	R^1 = Ph $R^2 = CO_2Me$	110	12	**2c**, 88
4	**1A**	R^1 = H $R^2 = CO_2Me$	110	12	**2d**, 94
5	**1A**	R^1 = Ph R^2 = Ph	110	12	No reaction
6	**1A**	R^1 = H $R^2 = OC_2H_5$	110	16	No reaction
7	**1A**	$R^1 = CO^t$Bu $R^2 = CO_2Me$	110	18	**2e**[a], 98
8	**1A**	$R^1 = CH_3$ $R^2 = CO_2Et$	110	18	**2f**[b], 66
9	**1B**	$R^1 = CO_2Me$ $R^2 = CO_2Me$	25	36	**2a**, 98

[a] Mixture of two regioisomers in the ratio 1:3.
[b] Mixture of two regioisomers in the ratio 1:1.

2d was ascertained from its ^1H NMR spectrum as the proton (R^1 = H) appeared as a doublet ($J = 6.5$ Hz) at δ 7.23. This was further proved by proton decoupling experiments. By irradiating the doublet at δ 7.23, the multiplet at δ 3.85 due to proton Ha was reduced to a doublet.The lower regioselectivities in the cases of **2e** and **f** might be the result of marginal differences in steric demands of the acetylene substituents.

When DMAD was reacted with **1B**, the reaction took almost 36 h at room temperature for the complete disappearance of the starting materials. After work up, the product obtained was found to be exclusively **2a**. This is easily explainable as the stereoisomers **1A** and **1B** exist in equilibrium in solution.

In conclusion, we have unraveled a novel reactivity pattern for the bis(spirodienones) of the calix[4]arenes with activated acetylenes. The bisadducts were obtained in quantitative yields with very good diastereofacial selectivity. The bisadducts could undergo a plethora of synthetic transformations and it is conceivable that the present methodology may open up possibilities for the construction of highly functionalized macromolecules with favourable properties from the calix[4]arene skeleton. Further studies aimed at gaining a deeper understanding of the regioselectivity are currently underway.

Acknowledgements

V.B.G. thanks the Council of Scientific and Industrial Research, New Delhi for research fellowship. L.V. thanks the Department of Science and Technology, Government of India (Project No. SR/S1/1C-19/2003) for financial support. The authors thank Dr. Vijay Nair and Dr. K. V Radhakrishnan for useful discussions. We also thank Ms. Saumini Mathew for recording NMR spectra and Ms. S. Viji for elemental analysis.

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11. Typical experimental procedure: Calix[4]bis(spirodienone) **1A** (50 mg, 0.078 mmol) was dissolved in dry toluene (8 mL) under an inert atmosphere. Dimethyl acetylene dicarboxylate (23 mg, 0.163 mmol) was added to it and the mixture stirred at rt for 12 h. The solvent was removed under vacuum and the residue subjected to silica gel column chromatography using 85:15 hexane–ethyl acetate mixture to afford **2a** as a white solid (70 mg, 99%). Mp > 300 °C (decomp). IR (KBr) ν_{max}: 2957, 1746, 1613, 1480, 1261, 1056, 895 cm^{-1}. ^1H NMR: δ 7.05 (s, 2H), 6.89 (s, 2H), 4.82 (d, 2H, J = 2.1 Hz), 4.35 (d, 2H, J = 2.1 Hz), 4.09 (d, 2H, J = 14.4 Hz), 3.87 (s, 6H), 3.79 (s, 6H), 3.31 (d, 2H, J = 15.6 Hz), 3.00 (d, 2H, J = 15.6 Hz), 2.55 (d, 2H, J = 14.5 Hz), 1.30 (s, 18H), 0.98 (s, 18H). ^{13}C NMR: δ 192.7, 166.0, 163.0, 153.5, 150.8, 144.2, 135.5, 127.5, 125.5, 120.0, 118.3, 77.2, 59.5, 52.5, 38.8, 34.3, 31.7, 27.6. Mass spectrometric analysis (FAB) calculated for $C_{56}H_{64}O_{12}$+H: 929.4398. Found: 929.7322. Anal. Calcd for $C_{56}H_{64}O_{12}$: C, 72.39; H, 6.94. Found: C, 72.04; H, 7.20.
12. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 261693.