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Diels-Alder Reaction of Cyclopentadiene and Spiroepoxy-2,4-cyclohexadienones

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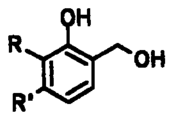
Abstract: Diels-Alder reaction of cyclopentadiene with spiroepoxycyclohexadienones obtained by Adler oxidation of salicyl alcohols affords mainly endo-endo adducts. Cope rearrangement of normal-electron-demand adducts and endo-endo inverse-electron-demand addition of 2a with ethylvinyl ether are also shown.

The oxidation of salicyl alcohols 1 by sodium periodate to give spiroepoxy-2,4-cyclohexadienones 2 has been first discovered by Adler in 1971.[1] The regio and stereoselective dimerization to 3 is usually observed, and may be prevented only in the case of the presence of bulky alkyl substituents at C-2 or C-4[2] or of a methoxy group at C-3.[3]



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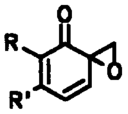

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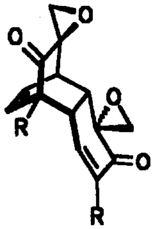

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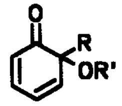

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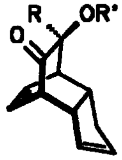

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a: R=R'= H; b: R= OCH_3, R'=H; c: R=H, R'= OCH_3

R= alkyl, R'= H or OAc

The structure of spiroepoxycyclohexadienones 2 suggests their possible use as either electron deficient dienes or dienophiles and thus a study of their regio and diastereofacial selectivity seems worthwhile to reveal their potentiality in the synthesis of natural products. Recently Singh[4] has used the stereoselective endo-endo[5] Diels-Alder cycloaddition of 6-hydroxy (or 6-acetoxy)-6-alkyl-2,4-cyclohexadienones 4, obtained by Wessely oxidation of the corresponding phenols, with dienes (or simple olefins) to generate annulated bicyclo[2,2,2]octenones such as 5 which underwent, after modification, a photochemical oxa-di-π-methane rearrangement to give the tricyclopentanoid skeleton of linear polyquinanes. Similarly Singh[6] has shown that spiroepoxycyclohexadienone 2b (obtained by phase-transfer catalyzed Adler oxidation of 2-hydroxy-3-methoxybenzyl alcohol) affords with cyclopentadiene a single endo-endo adduct 8b resulting from an apparent inverse-electron-demand Diels-Alder reaction.

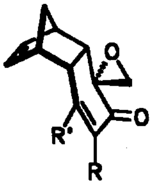
As part of a study on the chemical and biological properties of these dienones,[7] we now describe our preliminary results on the reaction of spirocyclohexadienones **2a-c** with cyclopentadiene under different conditions (Table). Since **2a** (obtained from 2-hydroxybenzyl alcohol) and **2b** do rapidly dimerize, Adler oxidation was carried out in presence of excess cyclopentadiene under usual (entries 1, 2, 4, 5) or phase-transfer conditions (entries 3, 6, 7) while the stable **2c** (obtained from 2-hydroxy-4-methoxybenzyl alcohol) was treated similarly for comparison (entry 8), or after isolation (entries 9, 10) with cyclopentadiene.

Table. Diels-Alder Reaction of **2a-c** with Cyclopentadiene.

Entry	Compound	[conc]	Conditions	Dimer	Products
1	**2a**	0.5 M	0°C, 23 h THF/H_2O 1/1	38%	**6a** (19%); **7a** (3%)
2	**2a**	0.13 M	0°C, 23 h THF/H_2O 3/1	-	**6a** (7%); **7a** (1%) **8a** (14%); **9a** (1%)
3	**2a**	0.13 M*	0°C, 2 h; 20°C, 4 h $CHCl_3$/H_2O 1/1	-	**6a** (32%) **8a** (51%)
4	**2b**	0.26 M	0°C, 23 h THF/H_2O 1/1	31%	**6b** (10%) **8b** (32%)
5	**2b**	0.13 M	0°C, 23 h THF/H_2O 3/1	21.5%	**6b** (16%) **8b** (37%)
6	**2b**	0.52 M*	20°C, 5 h $CHCl_3$/H_2O 1/1	31%	**6b** (2%) **8b** (33%)
7	**2b**	0.17 M*	0°C, 4 h; 20°C, 4 h $CHCl_3$/H_2O 1/1	11%	**6b** (12%) **8b** (40%)
8	**2c**	0.24 M	20°C, 24 h THF/H_2O 1/1	-	**6c** (38%); **7c** (5%)
9	**2c**	0.24 M	20°C, 96 h THF/H_2O 1/1	-	**6c** (25%); **7c** (12%)
10	**2c**	1.15 M	20°C, 16 h neat	-	**6c** (43%), **7c** (6%)

All reactions were done using 1.1 eq. of $NaIO_4$ (except entries 9 and 10) and 5 eq. of cyclopentadiene (except entry 10, solvent: cyclopentadiene). *: concentration of phenol with respect to the organic phase, 0.1 eq. of TEBA added.

2a affords, besides the corresponding dimer **3a**, mainly **6a** and **8a** whose structures are in agreement with their ^1H and ^{13}C NMR spectra.[8] The configuration of **6a** (endo) is confirmed by the observation of nOe's between H-2 and H-7 and one H-11 (NOEDIFF). In two sets of experiments (entries 1 and 2), two minor (1-3%) compounds, **7a** and **9a**, arising from endo-exo additions are also obtained. Unambiguous determination of the relative stereochemistry of the epoxide ring for these compounds is not possible based on NMR spectra. However it was found that adducts **6a** and **7a** are not stable in solution ($CDCl_3$) and that they rearrange cleanly to **8a** and **9a**. This process must imply a Cope rearrangement (which requires an endo adduct) and not a retro Diels-Alder reaction since no dimer **3a** is detected. Such a rearrangement has already been observed for the adduct of cyclopentadiene with *ortho*benzoquinone[9] but has never been reported for such spiroepoxy (or 6-hydroxy or 6-acetoxy-6-alkyl)-2,4-cyclohexadienone. Since **6a** rearrange to **8a** and by analogy with the results reported by Singh for such dienones, we assume that both compounds correspond to an endo-endo addition[5,10,11] although in the case of a bis(spirodienone) derivative of calix[4]arene Biali[12] has demonstrated by NMR that an exo-exo addition occurs with benzyne.



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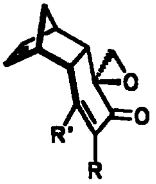

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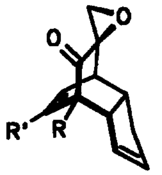

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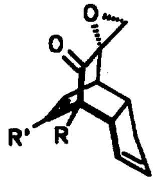

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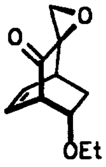
a: R=R'=H; **b:** R= OCH_3, R'=H, **c:** R=H, R'= OCH_3

In the case of **2b**, apart from the dimer **3b**, similar adducts **6b** and **8b** are isolated but not the anticipated minor adducts **7b** and **9b** (entries 4-7). Under all conditions the ratio **8b**/**6b** is higher than in the former case and especially using a high concentration of **2b** in $CHCl_3$ (entry 6). The stable dienone **2c** affords only the two adducts **6c** and **7c** without formation of the rearranged adducts **8c** and **9c**.

The results reported in the Table show that dimerization of **2a,b** is increased, as expected, at higher concentration of phenol (i.e. entry 1,2 and 3, or entries 4, 6 and 5, 7) and that the amount of adducts **8** and **9** is higher in $CHCl_3$ than in THF. More experiments are needed to show whether the Diels-Alder reaction of such spiroepoxy-2,4-cyclohexadienones (and thus the related 6-hydroxy (or 6-acetoxy)-6-alkylcyclohexadienones) with cyclopentadiene is purely a normal process followed by a Cope rearrangement or if competitive normal- and inverse-electron-demand additions are operating. In order to check the latter, Adler oxidation of **1a** in presence of 20 eq. of ethylvinyl ether has been done under usual (THF/H_2O 3/1, 20°C) or phase-transfer conditions ($CHCl_3/H_2O$ 1/1, 0.1 eq. TEBA) to give dimer **3a** (52 or 54%) and a single adduct **10** (17 or 22%).



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The structure of **10** is in agreement with the ^1H and ^{13}C NMR spectra,[8,13] the position and configuration of the ethoxy group being confirmed by the observation of the signals of endo (δ 1.57 ppm) and exo (δ 2.5 ppm) H-5 (together with NOEDIFF experiments) and by the relative shielding of C-8. The configuration of the epoxide ring is proposed by analogy with the previous Diels-Alder adducts.

Further experiments to extend the scope of such [4+2] cycloadditions of spiroepoxycyclohexadienones with other electron-rich dienophiles are underway.

References and Notes

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8. All new compounds have been characterized by spectral (^{1}H and ^{13}C NMR, MS and IR) and analytical (HRMS or microanalysis) data. Representative ^{1}H (200 MHz) and ^{13}C (50.13 MHz) NMR data are given below (δ in ppm (intensity, mult., J in Hz), TMS as internal standard, $CDCl_3$), using a BRUKER WP200SY spectrometer.

6a: δ 1.36 (1H, d, 9, H-11), 1.56 (1H, dt, 9 and 2, H-11), 2.52 (1H, dd, 8.5 and 4, H-2), 2.78 and 2.89 (2H, 2d, 7, H-12), 3.20 (3H, m, H-1 H-7 and H-8), 5.87 (1H, dd, 5.5 and 3, H-9), 6.02 (1H, d, 10, H-5), 6.22 (1H, dd, 5.5 and 3, H-10), 6.89 (1H, dd, 10 and 4.5, H-6) ppm. ^{13}C: δ 41.6, 41.9, 47.2, 48.2, 58.7, 59.0, 129.5, 135.3, 135.9, 150.7 and 193 ppm.

7a: δ 1.42 and 1.52 (2H, 2d, 9, H-11), 2.58 (1H, dd, 8 and 4, H-2), 2.91 (1H, d, 6, H-12), 3.0 (1H, m, H-1), 3.13 (1H, m, H-8), 3.23 (1H, dd, 8 and 4, H-7), 3.43 (1H, d, 6, H-12), 5.96 (1H, dd, 5 and 3, H-9), 6.13 (2H, m, H-5 and H-10), 6.94 (1H, dd, 9 and 4, H-6) ppm. ^{13}C: δ 41.6, 43.7, 47.9, 48.2, 51.6, 57.2, 130.1, 134.9, 136.7, 152 ppm (CO not observed).

8a: δ 2.03 (1H, dm, 17, H-3), 2.6 (2H, m, H-1 and H-3), 2.82 (1H, d, 6, H-12), 3.05 (1H, m, H-2), 3.10 (1H, d, 6, H-12), 3.37 (2H, broad d, H-6 and H-7), 5.47 and 5.71 (2H, 2m, H-4 and H-5), 6.12 (1H, broad t, 7.3, H-11), 6.40 (1H, broad t, 7.3, H-10) ppm. ^{13}C: δ 36.1, 38.4, 43.9, 50.3, 52.3, 52.7, 58.0, 129.2, 129.5, 132.1, 133.4 and 205 ppm.

9a: δ 2.07 (1H, dm, 17, H-3), 2.67 (2H, m, H-1 and H-3), 2.88 (1H, partly hidden, H-2), 2.88 (1-H, d, 5.9, H-12), 3.16 (1H, d, 5.9, H-12), 3.30 (1H, m, H-6), 3.40 (1H, d, 6.6, H-7), 5.49 and 5.73 (2H, 2m, H-4 and H-5), 6.18 (1H, dd, 7.4 and 6.6, H-11), 6.47 (1H, dd, 7.4 and 6.6, H-10) ppm. ^{13}C: δ 38.0, 38.7, 43.5, 48.9, 52.3, 52.7, 58.0, 128.2, 129.8, 133.2, 133.3 ppm (CO not observed).

10: δ 1.19 (3H, t, 7, CH_3), 1.57 (1H, dt, 13 and 2.5, endo H-5), 2.50 (2H, m, H-4 and exo H-5), 2.85 (1H, d, 6, H-9), 3.12 (1H, d, 6, H-9), 3.50 (2H, m, $O\text{-}CH_2$), 3.76 (1H, m, H-1), 4.06 (1H, m, H-6), 6.18 (1H, t, 7.5, H-8), 6.66 (1H, t, 7.5, H-7) ppm. ^{13}C: δ 15.10 (C-10), 31.4 (C-5), 37.5 (C-4), 53.1 (C-11), 53.8 (C-1), 57.3 (C-3), 63.9 (C-9), 74.8 (C-6), 126.2 (C-8), 134.4 (C-7), 204 (C-2) ppm.

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