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Unexpected Formation of Novel Butenolides by Thermolysis of *o*-Carboranyl Substituted Cyclobutenones

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Abstract: On thermolysis, *o*-carboranyl substituted 4-aryl-4-hydroxycyclobutenones **5a-d** undergo electrocyclic ring opening followed by ring closure to yield substituted butenolides **6a-d**. This is in contrast to the thermolysis of cyclobutenones which generally produces substituted quinones. Published by Elsevier Science Ltd.

Synthesis of highly functionalized quinones or hydroxyquinones *via* the thermolysis of 4-hydroxycyclobutenones bearing an alkenyl, alkynyl, or aryl at the 4-position was independently discovered by Liebeskind[1] and Moore.[2] The thermal rearrangement of 4-hydroxycyclobutenones was shown to undergo conrotatory electrocyclic ring opening to the conjugated ketene followed by ring closure involving intramolecular attack of the electrophilic ketene with the inward unsaturated moiety to yield quinones. In contrast, photochemical ring expansion of 4-hydroxycyclobutenones furnished exclusively butenolides in moderate yields.[3] Formation of these butenolides under photochemical conditions was envisaged by the stereoselective disrotatory electrocyclic ring opening to the conjugated ketene in which the C_4 hydroxyl group rotates inward followed by ring closure of the hydroxyl group to the ketene moiety. In addition, very few examples were reported on the formation of butenolides by thermolysis of cyclobutenones in which the C_3 and C_4 have electron donating groups.[4] In this communication, we report that the thermolysis of *o*-carboranyl substituted 4-aryl-4-hydroxycyclobutenones furnish exclusively butenolides.

Addition of one equivalent of monolithiated *o*-carborane (prepared *in situ* by lithiation of *o*-carborane with *n*-BuLi)[5] to diisopropyl squarate (**1**) in THF at -40 °C furnished the monoadduct cyclobutenone **2**[6] as the only product in 83% yield. We envisaged that the intramolecular entrapment of vinylketene generated by the thermolysis of **2** with *o*-carborane may afford the carboranoquinone **3**. However, thermolysis of **2** under standard annulation reaction conditions[1] resulted in recovery of the starting material.

Next, we decided to synthesize carboranyl substituted quinones. However, the hydrolysis of compound **2** did not proceed under standard acidic conditions.[7] The desired

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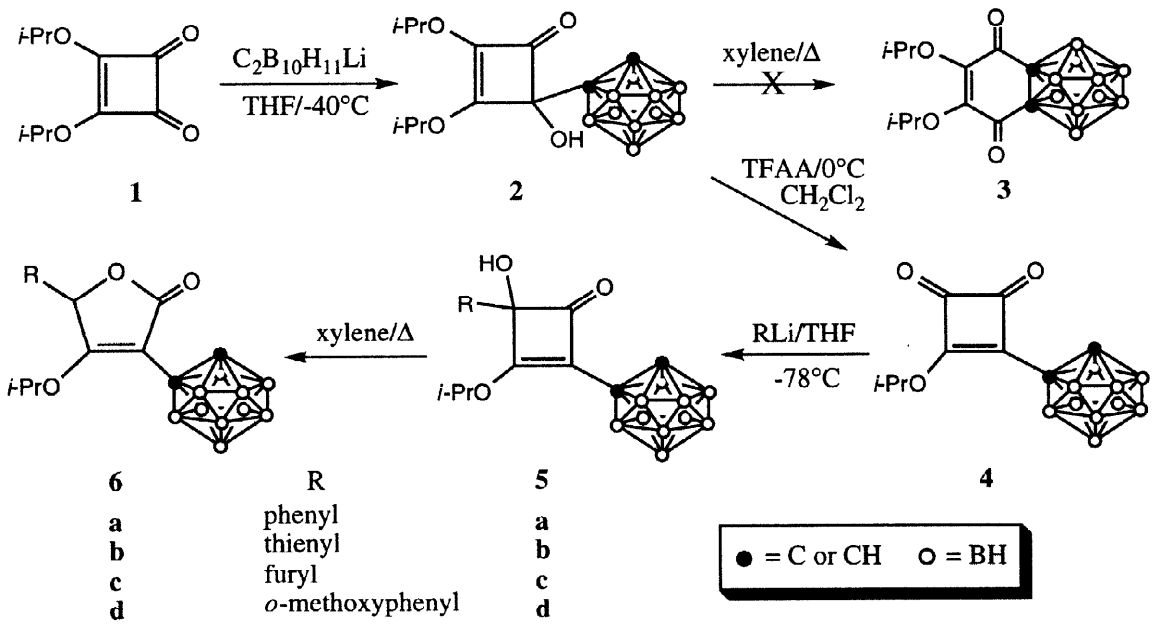
cyclobutenedione **4**[6] was achieved using trifluoroacetic anhydride (TFAA)[8] in the presence of pyridine at 0 °C in 79% yield, after flash chromatography (Scheme 1). Reaction of the cyclobutenedione **4** with different aryllithium reagents (phenyllithium, 2-thienyllithium, 2-furyllithium,[9] and 2-lithioanisole[9]) at -78 °C provided the regiospecific addition products 4-aryl-2-*o*-carboranyl-4-hydroxycyclobutenones **5a-d**.[6] Thermolysis of the hydroxycyclobutenones **5a-d** in refluxing *p*-xylene for 1 h gave crystalline products in fair to good yield. The structures of the products were determined primarily by their ^1H and ^{13}C NMR spectra. In their proton NMR, the same number of protons were observed between the products and their corresponding precursors **5**. This indicates that quinones were not formed since in the proton NMR quinones would show one less aromatic protons than their corresponding precursors. All the products showed a singlet resonance around δ 6 ppm in the ^1H NMR and a doublet at δ 70-77 ppm in the ^{13}C NMR, confirming the existence of a deshielded methine group bearing no adjacent proton. Singlet carbonyl peaks around δ 175 ppm were also observed in the ^{13}C NMR of the products. According to these spectroscopic features, the products were assigned as 5-aryl-3-*o*-carboranyl-4-isopropoxy-2(5*H*)furanones **6a-d**.[10] In addition, the IR spectrum of **6a** showed an absorption at 1750 cm^{-1}, confirming the presence of the sole conjugated carbonyl moiety.

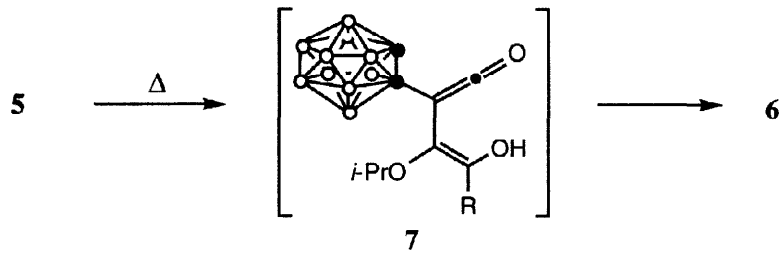


6	R	5
a	phenyl	a
b	thienyl	b
c	furyl	c
d	*o*-methoxyphenyl	d

Scheme 1

The formation of the butenolides **6** can be rationalized by the electrocyclic ring opening of the cyclobutenones **5** involving intermediate ketenes **7** in which the C_4 hydroxyl group rotates inward to the ketene functionality. The intermediate ketenes **7** then furnished the butenolides **6** by an intramolecular ring closure (Scheme 2). In an earlier report Rondan and

Houk[11] demonstrated that the outward rotation of the hydroxyl group (conrotatory) was more favorable by about 14.0 kcal/mol than the inward (disrotatory) process. In addition, it was postulated that steric effects were of secondary importance in controlling the direction of rotation. Our experiment showed a clear but important role of the carboranyl moiety in directing the reaction process, probably through an electronic effect.



Scheme 2

Our work indicates that the presence of the carboranyl substituent of the hydroxycyclobutenone influences the outcome of the annulation reaction under thermolytic conditions. Thus, we have shown that under these conditions, the carboranyl substituted 4-aryl-4-hydroxycyclobutenones **5** undergo an annulation reaction to yield novel carboranyl substituted butenolides **6**. Further investigations regarding the scope of the annulation reaction and the potential application of these compounds for boron neutron capture therapy are under investigation.[12]

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6. Compounds **2**, **4**, and **5a-d** were characterized by ^{1}H and ^{13}C NMR, MS, microanalyses and/or HRMS.
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10. All final compounds **6a-d** gave satisfactory spectroscopic data. Compound **6a**: m.p. 168-171°C; IR (Nujol cm^{-1}) 3079, 2979, 2590, 1750, 1646, 1396; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.54 (m, 5H, arom.), 5.92 (s, 1H, methine proton), 5.62 (bs, 1H, $B_{10}H_{10}CH$), 4.40 (sep, 1H, Me_2CH), 3.40-1.25 (br, 10H, $B_{10}H_{10}$), 1.38 (d, J = 7 Hz, 3H, CH_3), 0.95 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.69, 169.20, 132.49, 130.78, 129.80, 127.72, 97.93, 77.75, 77.63, 66.45, 57.31, 22.77, 21.86; MS/FAB m/z 361 $(M + H)^+$. Anal. Calcd for $C_{15}H_{24}O_3B_{10}$: C, 49.98; H, 6.71. Found: C, 50.26; H, 6.81. **6b**: m.p. >200°C (dec.); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 5.2 Hz, 1H, arom.), 7.17 (d, J = 3.2 Hz, 1H, arom.), 7.09 (dd, J = 3.2 and 5.2 Hz, 1H, arom.), 6.02 (s, 1H, methine proton), 5.60 (bs, 1H, $B_{10}H_{10}CH$), 4.53 (sep, J = 6.0 Hz, 1H, Me_2CH,), 3.20-1.40 (br, 10H, $B_{10}H_{10}$), 1.39 (d, J = 6 Hz, 3H, CH_3), 1.10 (d, J = 6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.88, 168.53, 134.68, 128,91, 127.68, 97.90, 77.65, 72.12, 66.17, 57.28, 22.91, 21.97; LSIMS/FAB m/z 367 $(M - H)^+$. Anal. Calcd for $C_{13}H_{22}O_3B_{10}S$: C, 42.61; H, 6.05. Found: C, 42.60; H, 6.08. **6c**: m.p. 199-200°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 1H, arom.), 6.54 (d, J = 3.6 Hz, 1H, arom.), 6.48-6.47 (m, 1H, arom.), 5.86 (s, 1H, methine proton), 5.59 (bs, 1H, $B_{10}H_{10}CH$), 4.47 (sep, J = 6.0 Hz, 1H, Me_2CH,), 3.20-1.40 (br, 10H, $B_{10}H_{10}$), 1.38 (d, J = 6 Hz, 3H, CH_3), 1.10 (d, J = 6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.18, 168.82, 145.04, 144.75, 111.96, 111.43, 98.07, 77.77, 70.29, 66.17, 57.28, 22.91, 22.03; LSIMS/FAB m/z 351 $(M - H)^+$. Anal. Calcd for $C_{13}H_{22}O_4B_{10}$: C, 44.56; H, 6.33. Found: C, 44.48; H, 6.33. **6d**: m.p. 196-197°C (dec.); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.42 (m, 1H, arom.), 7.04-6.97 (m, 3H, arom.), 6.20 (s, 1H, methine proton), 5.68 (bs, 1H, $B_{10}H_{10}CH$), 4.39 (sep, J = 6.0 Hz, 1H, Me_2CH,), 3.20-1.40 (br, 10H, $B_{10}H_{10}$), 1.36 (d, J = 6 Hz, 3H, CH_3), 0.95 (d, J = 6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.77, 169.82, 157.58, 132.09, 128,33, 121.62, 120.44, 111.67, 97.54, 77.29, 72.53, 66.70, 57.28, 55.87, 22.85, 21.97; LSIMS/FAB m/z 391 $(M - H)^+$. Anal. Calcd for $C_{16}H_{26}O_4B_{10}$: C, 49.22; H, 6.71. Found: C, 49.03; H, 6.68.
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