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SUBSTITUENT-DIRECTED OXIDATION: TRANSANNULAR OXIDATIVE CYCLIZATION OF CYCLOALKENOLS TO β-KETO CYCLIC ETHERS.[1]

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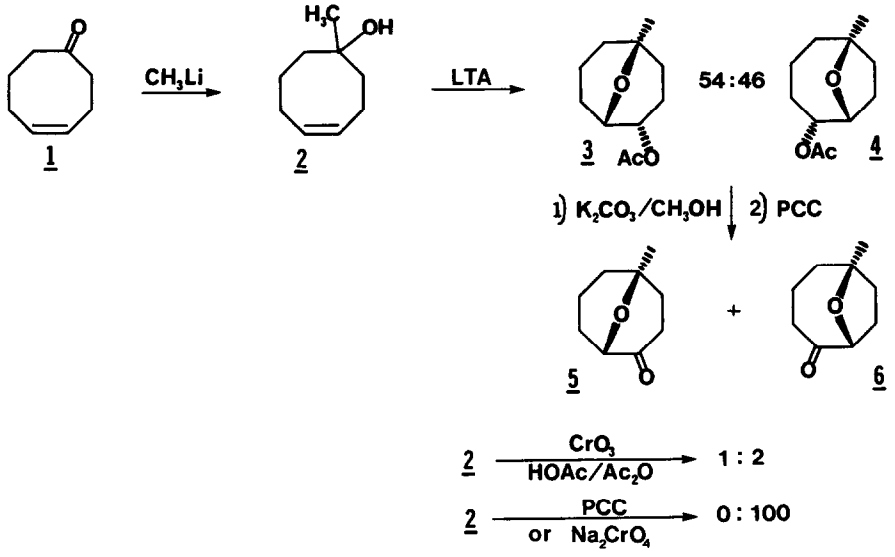
Summary: Treatment of the tertiary cyclooctenol 2 with lead tetraacetate or with chromium(VI) reagents results in transannular oxidative cyclization to β-functionalized bicyclic ethers, and the selectivity between the oxabicyclo[3.3.1]nonane and the oxabicyclo[4.2.1]nonane skeleton depends on the nature of the oxidizing agent.

In contrast to the spectacular success of the directed epoxidation reaction,[2] less progress is evident in substituent-directed oxidation reactions such as oxidative cyclization,[1,3] which could be used to prepare the oxygen-bridged bicyclic skeleta which appear in a number of biologically active natural products such as chapliatrin[4] and glycinoeclepin.[5]

These reactions are also of mechanistic interest, since a directing substituent in the substrate molecule such as a hydroxyl group can affect the oxidation reactivity generally in two ways: it can function as a ligand to bind the oxidant and guide its attack on the substrate site such as an alkene (Type I), or the substituent can exert its effect upon an activated complex or upon an intermediate oxidation product such as an epoxide (Type II).[6] The controlled relative geometry of a bound oxidant vs. the substrate site in the transition state is reflected in product selectivity, and our investigation seeks a more thorough understanding of these mechanisms, for a more predictable and general application of this class of reactions in synthesis.

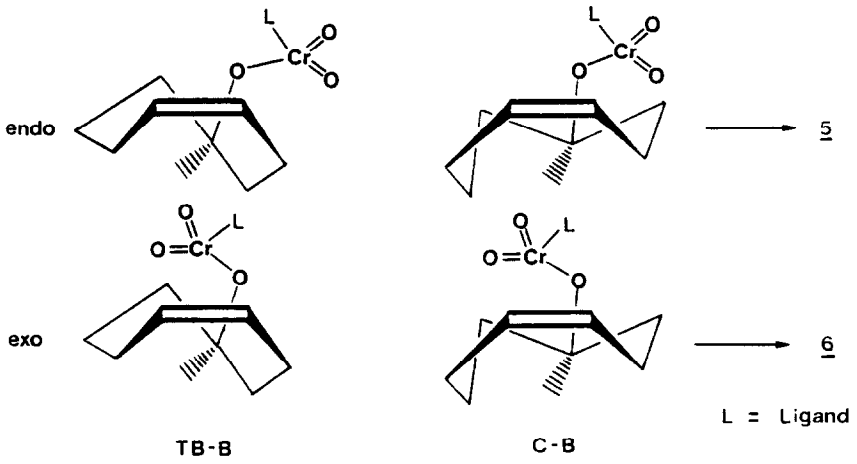
Moon and Cope found that the oxidative cyclization of cyclooct-4-en-1-ol with lead tetraacetate (LTA) gives a 3:2 ratio of products having the [3.3.1] vs. [4.2.1] oxabicyclononane skeleton, and Cope showed that similar treatment of 1-phenylcyclooct-4-en-1-ol resulted in a 1:1 ratio of the two corresponding products.[7] As a model substrate for our study, we have chosen 1-methylcyclooct-4-en-1-ol (2), prepared from the known[8] ketone 1 (CH_3Li/THF/87% yield). Treatment of 2 with LTA in either benzene or acetic acid gives a mixture of acetates 3 and 4 in a ratio of 54:46, which can be converted to ketoethers 5 and 6 by hydrolysis and oxidation.[9]

Exposure of 2 to the Fieser reagent (CrO_3/HOAc/Ac_2O, room temp., 12 h) gives rise directly to a mixture of 5 and 6 in a ratio of 1:2. Unexpectedly, reaction of 2 with pyridinium chlorochromate (PCC/CH_2Cl_2, reflux, 2 d) produces only ketoether 6 without a trace of 5.[9] It appears that this oxidative cyclization is acid-catalyzed, since sodium acetate inhibits the reaction (incomplete after three days) while acetic acid speeds it up (complete after one day).[10] Sodium chromate (HOAc, 90°C, 1 h) similarly yields 6 as the exclusive product. Pyridinium dichromate is likewise specific, although less effective in this reaction, but its efficacy is also increased in the presence of added acetic acid. With the chromium trioxide dipyridine complex (CH_2Cl_2, room temp. or reflux) no cyclization occurs, and 2 is recovered in good yield.



One possible mechanism for the Cr(VI) reactions involves an intermediate epoxide which undergoes internal opening by the hydroxyl to form hydroxyethers corresponding to the hydrolysis products of 3 and 4, which yield 5 and 6 on further oxidation. Treatment of 2 with mCPBA gives a 1:1 mixture of epoxides. One isomer (presumably trans) undergoes internal solvolysis under the epoxidation conditions to yield a 3:2 mixture of the β-hydroxyethers, which can be separated from the (presumably cis) remaining epoxide. The pair of hydroxyethers oxidize to 5 and 6 (resp) with either the Fieser reagent or PCC. The cis epoxyalcohol is attacked under both sets of conditions to give complicated mixtures of products, minor constituents of which are 5 and 6. Thus, barring an extraordinarily specific epoxidation and solvolysis of 2, it seems unlikely that an epoxide is involved in the regiospecific reaction with PCC or sodium chromate.

The change in selectivity can best be explained in terms of a Type II mechanism for the reactions involving LTA or epoxide opening, and a Type I mechanism for PCC, Na_2CrO_4 or PDC. In the former case, the lead(IV)-complexed alkene or the epoxide suffers a transannular anti attack by the hydroxyl group, which occurs with approximately equal facility at either carbon of the double bond. In the oxidation with chromium(VI) reagents,[11] it seems reasonable to postulate prior formation of a chromate ester of the hydroxyl group, which would be acid catalyzed. A syn addition of the tethered chromate ester moiety across the double bond would follow, with the possible intermediacy of a π-complex. The addition could take place either[12] via an electron transfer step and oxidative collapse, or by way of a [2+2] cycloaddition and rearrangement, to result in the chromium(IV) ester of the β-hydroxy cyclic ether, further oxidation of which yields 6. Although this mechanism is by no means proven, a conformational analysis offers some support. Comparing the two possible twist boat-boat (TB-B) or chair-boat (C-B) transition states for this type of addition, the exo arrangement (leading to 6) allows for a parallel



planes approach of the O=Cr-O and C=C functions that is not possible in the endo arrangement (leading to 5). The oxidation with Fieser reagent may proceed concurrently through both Type I and Type II mechanisms to give an average level of selectivity.

Our investigation is continuing with the study of substrates of other ring sizes and substitution patterns. A typical procedure follows: *A solution of 231 mg (1.65 mmol) of 2 in 20 mL of CH_2Cl_2 with 800 mg of Celite was charged with 802 mg (3.72 mmol) of PCC and was*

stirred at room temperature for 6 h, and then heated to reflux for 20 h. At this time, another 715 mg of PCC (3.3 mmol) was added and the mixture was heated to reflux for 20 h. The reaction mixture was filtered through Celite and concentrated and the residue purified by flash chromatography (14 g silica; ether:pentane, 1:1) to yield 151 mg (53%) of 6: IR (thin film) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.33 (s,3H), 1.55-3.1 (m, 10H), 4.21 (dd, 1H, J=2,9Hz); ^{13}C-NMR (C_6D_6) δ 20.56, 26.63, 29.63, 31.98, 33.16, 41.84, 88.33, 85.11, 216.43.

The reaction with LTA essentially followed the procedures of Moon and Cope (ref. 7). For the mixture of 5 and 6 obtained after hydrolysis and oxidation: IR (thin film) 1720, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (s, 0.54x3H), 1.33 (s, 0.46x3H), 1.51-2.99 (m, 10H), 3.97 (t, 0.54x1H, J= 3Hz), 4.21 (dd, 0.46x1H, J=2,9Hz).

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9) The mixture of acetates was hydrolyzed (potassium carbonate/methanol) and then oxidized (PCC). The ratios were determined by ^{1}H-NMR integration of both the ether O-C-H absorptions and the CH_3 absorptions, with a probable error of less than 1-2%.

10) This strong dependence on the presence of acid explains an earlier discrepancy between our results and those of the Chandarasekaran group (see ref. 3, and footnote 4 contained within ref. 1 above), and underscores the fact that some PCC samples may be significantly acidic.

11) For simplicity, the discussion of mechanism posits chromium(VI) species as the intermediates, although it is quite possible that chromium(V) and (IV) species could be important.

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