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# SUBSTITUENT-DIRECTED OXIDATION: A SIMPLE PREPARATION OF γ- AND δ-LACTONES BY OXIDATIVE CYCLIZATION OF HYDROXYALKENES.[1]

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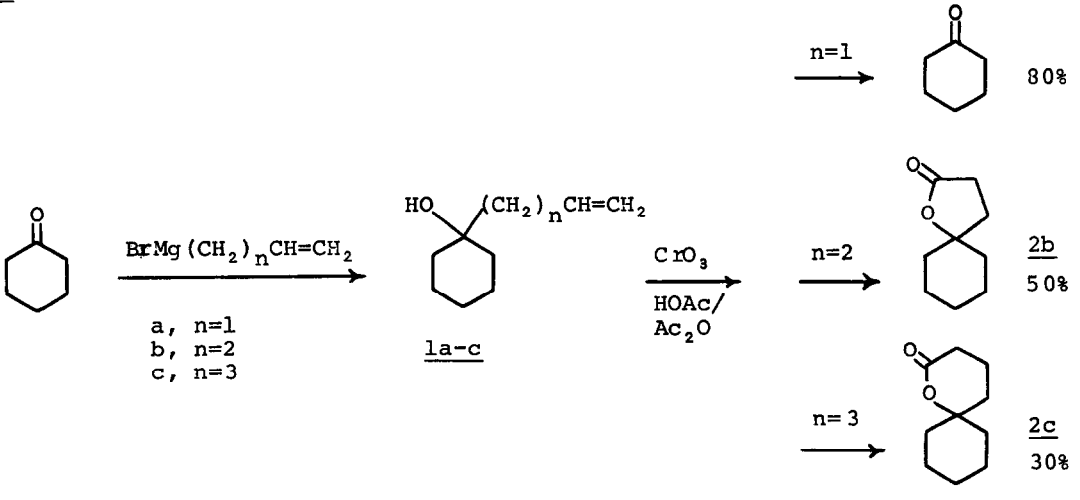
Summary: Treatment of tertiary γ- and δ-hydroxyalkenes with chromium trioxide in acetic acid/acetic anhydride gives reasonable yields of γ- and δ-lactones by oxidative cyclization, with loss of one carbon. A mechanism is proposed involving formation of a chromate monoester, followed by intramolecular oxidative attack on the alkene.

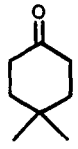
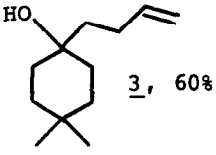
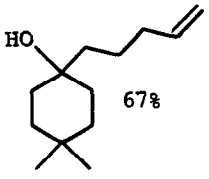
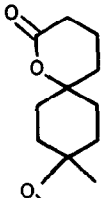
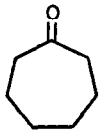
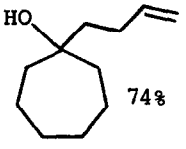
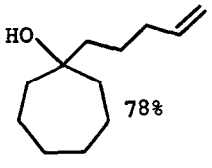
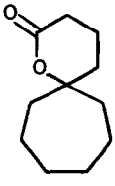
Substituent-directed oxidation reactions have great potential, which so far has been underutilized. The ability of a hydroxyl substituent to direct epoxidation of an alkene has been studied by Sharpless and others.[2] We are investigating the mechanistic and synthetic aspects of alternate oxidative pathways in this system, and recent reports in this area[3] prompt us to communicate our results at this stage.

The adducts of ω-alkenyl Grignard reagents with cyclic ketones provide simple models (e.g. 1a-c) to test substituent-directed oxidation, as shown below.



With two molar equivalents of the modified Fieser reagent ($CrO_3$/acetic acid/acetic anhydride) we find that 1b and 1c undergo a net oxidative cleavage to give, resp., γ-lactone 2b and δ-lactone 2c. The homoallylic alcohol 1a suffers oxidative cleavage of the allyl group and yields the starting cyclohexanone. A few other examples are shown in Table I.

Table I

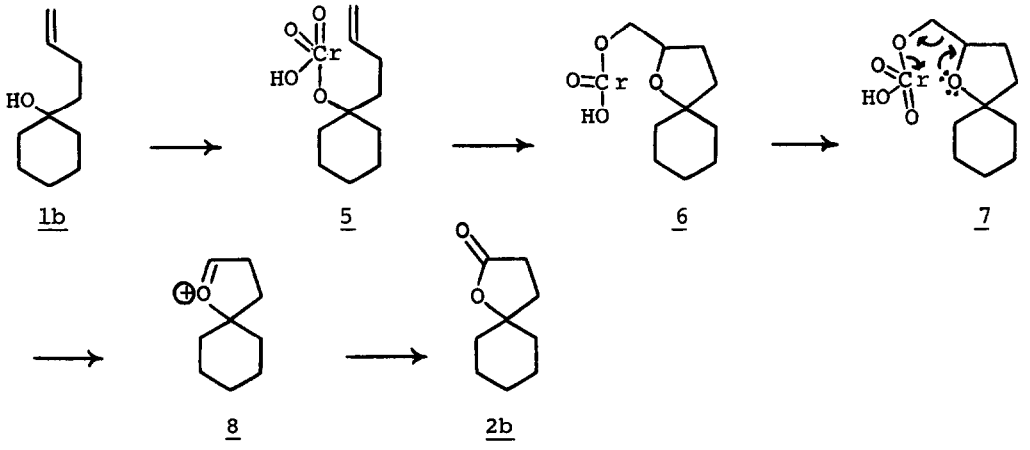
| Ketone | Adduct | Lactone |
|---|---|---|
|  |  3, 60% |  4, 57% |
| " |  67% |  42% |
|  |  74% |  80% |
| " |  78% |  68% |

Simple alkenes such as 1-dodecene react only partially with this chromate reagent, to give mixtures of starting material, epoxides, acids, etc. In an attempt to define the role of the hydroxyl, both the acetate and the methyl ether of alcohol 3 were prepared. Under the standard conditions (2 mol eq of $CrO_3$, 4 hr at room temp) these derivatives remained essentially unchanged, although the chromium (VI) underwent reduction, probably by attack on the solvent.

Interestingly, $CrO_3 \cdot (pyridine)_2$ and pyridinium chlorochromate have no effect on alcohol 3.[4] Treatment with Jones reagent under standard conditions ($H_2CrO_4/H_2SO_4$/acetone/$0^0C$) slowly gives the isolable chromate diester, which decomposes under ambient conditions to unchanged 3 and

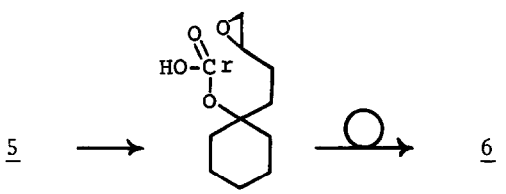
chromia. Since it is known that alcohols are rapidly acylated by chromate,[5] we favor a mechanism involving prior formation of the chromate monoester 5, as shown in Scheme I. A syn electrophilic addition would lead to the chromium (IV) ester 6. Reoxidation of the metal by excess reagent

Scheme I




leads to chromium (VI)ester 7, suitably disposed for oxidative fragmentation to oxonium 8, which could capture additional reagent and further oxidize to the lactone 2b. Oxidative fragmentations of the type 6 → 2b are precedented,[6] and we believe that the $CH_2$=O fragment is trapped by the solvent and not further oxidized. This scheme is consistent with the need for only two molar equivalents of chromium (VI) to achieve complete consumption of starting material.

An alternative pathway for the transformation 5 → 6 proceeds through epoxidation and solvolytic opening, as shown below. The epoxidation could involve a metalloxetane of the type sug-




gested by Sharpless,[7] or prior single electron transfer, followed by oxygen transfer, as suggested by Kochi.[8] Recent reports[3] offer evidence of an important role for chromium (V), which could be produced in our case by disproportionation. Studies involving more highly substituted

alkenes, other types of substrates, and optimization of the method are underway, and will be reported at greater length elsewhere. A typical procedure follows:

To a mixture of 5 mL of acetic acid and 2 mL of acetic anhydride at 10°C (cool water bath) was added 170 mg (1.7 mmol) of anhydrous $CrO_3$, and this was stirred for 10 min under a drying tube. A solution of 154 mg (0.85 mmol) of alcohol 3 in a total of 1.5 mL of acetic acid was added dropwise to the cool solution of chromate. The orange solution darkened over the next few minutes, and by 4 hr the reaction was complete by tlc. The solvents were removed in vacuo (∿1 torr and 35°C), and the viscous green residue was partitioned between 15 mL each of methylene chloride and water. The aqueous layer was extracted twice with 15 mL of methylene chloride, and the combined organic portions were extracted with 20 mL of brine, dried ($MgSO_4$) and concentrated to give 100 mg of an oil, which was purified by flash chromatography (5%ether/hexane) to yield 87 mg (57%) of 4 as an oil: IR (thin film) 2940, 2870, 1765 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 1.02 (s,6H), 1.27-1.99 (m,8H), 2.16 (t,2H,J=8 Hz), 2.81 (t,2H,J=8 Hz); Anal., Calcd. for $C_{11}H_{18}O_2$: C, 72.32%; H, 9.92%. Found: C, 72.49%; H, 9.95%.

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