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CHEMOSELECTIVITY IN MOLYBDENUM CATALYZED ALCOHOL AND ALDEHYDE OXIDATIONS

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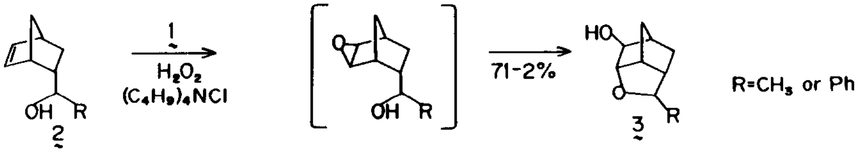
SUMMARY: Hydrogen peroxide in the presence of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and potassium carbonate is a chemoselective method to oxidize secondary alcohols to ketones and to oxidize aldehydes to acids, the latter also accelerated by cerium chloride.

In conjunction with our studies of the use of molybdenum complexes for organic synthesis,[1] we initiated our work in molybdenum oxidations. While at the time we began, molybdenum catalyzed epoxidations were well appreciated,[2] molybdenum based oxidations of alcohols were virtually unknown although several reports have appeared subsequently.[3] We wish to report that commercially available $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (**1**) catalyzes the oxidation of secondary alcohols to ketones by hydrogen peroxide. Furthermore, by controlling pH, such oxidations are chemoselective in that alcohol oxidation can dominate over olefin epoxidation[4] and a secondary alcohol can be oxidized over a primary one.[5] Furthermore, a hindered alcohol can be oxidized in preference to a less hindered one.

A typical procedure involves stirring a mixture of the ammonium molybdate (0.2-2 mmol), tetra-n-butylammonium chloride (0.2-0.3 g), potassium carbonate (2-4 mmol), and the alcohol (2 mmol) in THF at room temperature. Hydrogen peroxide (1 ml of 30% aqueous solution) was added and the reaction proceeded at room temperature. Additional portions of hydrogen peroxide would be added until alcohol was consumed. After ether extraction and washing the ether layer with water and brine, the product was purified by distillation or chromatography. The Table summarizes the results.

The alcohol oxidation in preference to olefin epoxidation (entries 3, 6, 12, 13, 14) stems from the presence of potassium carbonate. For example **2**



leads to **3** in the absence of base in contrast to the results of the Table (entries 6 and 13). The product presumably arises from cyclization of an intermediate epoxide.

TABLE. Oxidation of Alcohols

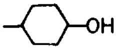
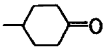
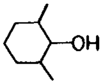
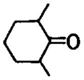
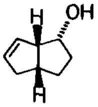
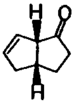
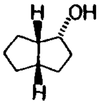
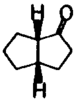
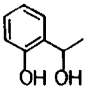
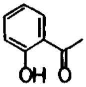
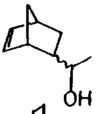
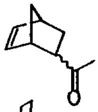
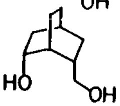
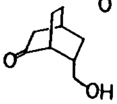
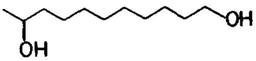
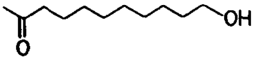
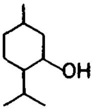
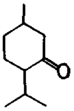
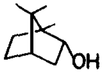
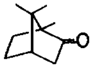
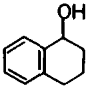
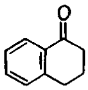
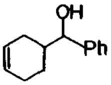
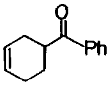
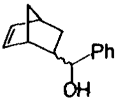
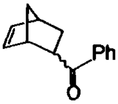
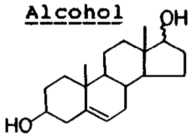
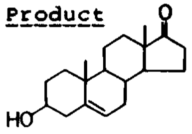
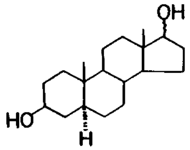
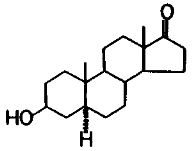
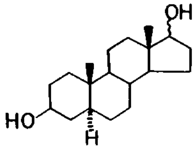
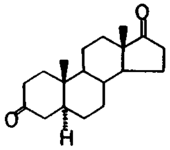
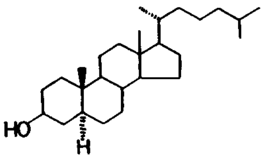
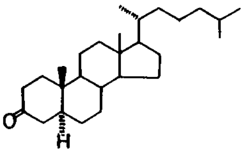
Entry	Alcohol	Time(d)	Product	Yield[a]
1		4		85
2		4		76
3		5		42(49)
4		4		73
5		5		52
6		6		59(69)[b]
7		1		88
8		7		79(89)
9		5		70(86)
10		1		87
11		2.67		82
12		4		88
13		7		73[c]

TABLE. Oxidation of Alcohols (contd.)

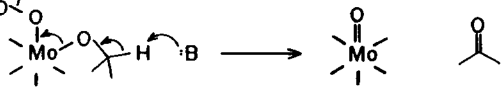
Entry	Alcohol	Time(d)	Product	Yield[a]
14		6		90
15		2		65[d]
16		5		56[e]
17		4		80(94)

(a) All yields are for isolated pure ketones. Yields in parentheses are based on recovered starting material. (b) Endo/exo ratio was 3:1 by NMR and GC. (c) Endo/exo ratio was 7:4 by NMR. (d) Diketone was obtained in 14% yield. (e) Epiandrosterone was obtained in 17% yield.

Since primary alcohols are not oxidized under these conditions, selective oxidation of a secondary alcohol in the presence of a primary one presents no problem (entries 7 and 8). Most noteworthy is the fact that a more hindered alcohol is oxidized more rapidly than a less hindered one. For example, in a competition between 2,6-dimethylcyclohexanol and cyclohexanol, the former is oxidized to the extent of 87% in 24 h and the latter to the extent of 48%. This observation combined with the greater ease to oxidize a cyclopentanol compared to a cyclohexanol[6] leads to good selectivity in the oxidation of a 17-hydroxyl group in the presence of a 3-hydroxyl group in a steroid (entries 14 and 15). The efficacy of this method is apparent by comparing this direct oxidation of 3,17-dihydroxy-5-androstene to 3-hydroxy-5-androsten-17-one (entry 14) to the three step method reported in the literature.[7] By addition of excess hydrogen peroxide and extended time, both alcohols can be oxidized (entry 16).

The dependence of the rate of oxidation on pH (i.e., the presence of potassium carbonate accelerates the reaction) and steric factors lead us to suggest that a molybdenum alkoxide such as **4** may be involved. The effects of

4



such steric factors is reminiscent of the chromium oxidations.[8]

In an ancillary series of experiments, the oxidation of aldehydes to acids was examined under the above conditions. 10-Undecenal is converted to the corresponding acid in 45% yield (70% based upon recovered starting material) and the steroid **5** to its acid[9] in 87% yield. Assuming the hydrate of the alcohol is the species being oxidized, $CeCl_3 \cdot 7H_2O$ was added to the undecenal example. Indeed, the yield jumped to 87% in the same period of time. Thus, these preliminary studies strongly suggest this molybdenum based oxidation is a good approach for the delicate oxidation of aldehydes to carboxylic acids as well.

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