Organic Chemistry I

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Alcohol synthesis by reduction can be reversed: chromium reagents

Alcohols make from aldehydes and ketones by reduction with hydride reagents. The reverse process is also possible: Alcohols may be oxidized to produce aldehydes and ketones.

A useful reagent for this purpose is a transition metal in a high oxidation state: chromium(VI).

In this form, chromium has a yellow-orange color. Upon exposure to an alcohol, the Cr(VI) species is reduced to the deep green Cr(III).

The reagent is usually supplied as a dichromate salt $(K_2Cr_2O_7 \text{ or } Na_2Cr_2O_7)$ or as CrO_3 .

Oxidation of secondary alcohols to ketones is often carried out in aqueous acid, in which all of the chromium reagents generate varying amounts of chromic acid, H_2CrO_4 , depending on pH.

$$pH > 6 \int \int CrO_4^{2-}$$
$$pH = 2-6 \int \int$$

 $CrO_3 + H_2O$

 $HCrO_{4}^{-} + Cr_{2}O_{7}^{2-}$

pH < 1

 H_2CrO_4

Oxidation of a Secondary Alcohol to a Ketone with Aqueous Cr(VI)



In water, primary alcohols tend to *overoxidize* to carboxylic acids. The reason is that aldehydes in water are in equilibrium with the corresponding diols, derived by addition of water.

One of the hydroxy functions of the diol then reacts further with the chromium reagent to the carboxylic acid.

$$CH_{3}CH_{2}CH_{2}OH \xrightarrow{K_{2}Cr_{2}O_{7}, H_{2}O} CH_{3}CH_{2}CH \xrightarrow{H^{+}, H_{2}O} CH_{3}CH_{2}CH \xrightarrow{OH} OH OH OVeroxidation CH_{3}CH_{2}COH$$

$$Propanal 1,1-Propanediol Propanoic acid$$

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In the absence of water, aldehydes are not susceptible to overoxidation.

A water-free form of Cr(VI) has been developed by reaction of CrO_3 with HCI, followed by the addition of the organic base pyridine.

The result is the oxidizing agent **pyridinium chlorochromate**, abbreviated as pyH^+ CrO₃Cl⁻ or just **PCC**, in which the hydrophobic cation portion of the salt imparts organic solvent solubility.

It gives excellent yields of aldehydes upon exposure to primary alcohols in dichloromethane solvent.





PCC oxidation conditions are often also used with secondary alcohols, because the relatively nonacidic reaction conditions minimize side reactions (e.g., carbocation formation) and often give better yields than does the aqueous chromate method.

Tertiary alcohols are unreactive toward oxidation by Cr(VI) because they do not carry hydrogens next to the OH function and therefore cannot readily form a carbon–oxygen double bond.

Chromic esters are intermediates in alcohol oxidation

Mechanism of the chromium(VI) oxidation of alcohols:

The first step is formation of an intermediate called a **chromic ester**; the oxidation state of chromium stays unchanged in this process.



The next step in alcohol oxidation is equivalent to an E2 reaction. Here water (or pyridine, in the case of PCC) acts as a mild base, removing the proton next to the alcohol oxygen.

This proton is made unusually acidic by the electron-withdrawing power of the Cr(VI). $HCrO_3$ is an exceptionally good leaving group, because the donation of an electron pair to chromium changes its oxidation state by two units, yielding Cr(IV).

This elimination furnishes a carbon–oxygen double bond.

The Cr(IV) species formed undergoes a redox reaction with itself to Cr(III) and Cr(V); the latter may function as an oxidizing agent independently. Eventually, all Cr(VI) is reduced to Cr(III).

Aldehyde Formation from a Chromic Ester: an E2 Reaction





8.7 ORGANOMETALLIC REAGENTS: SOURCES OF NUCLEOPHILIC CARBON FOR ALCOHOL SYNTHESIS

Attack by a carbon nucleophile on a carbonyl group would give an alcohol and simultaneously form a carbon–carbon bond.

To achieve such transformations, carbon-based nucleophiles, R:-, are formed. Metals, particularly lithium and magnesium, act on haloalkanes to generate new compounds, called **organometallic reagents**, in which a carbon atom of an organic group is bound to a metal.

These species are strong bases and good nucleophiles, which are extremely useful in organic syntheses.

Alkyllithium and alkylmagnesium reagents are prepared from haloalkanes

Organometallic compounds of lithium and magnesium are most conveniently prepared by direct reaction of a haloalkane with the metal suspended in ethoxyethane (diethyl ether) or oxacyclopentane (tetrahydrofuran, THF).

The reactivity of the haloalkanes increases in the order CI < Br < I; the relatively unreactive fluorides are not normally used as starting materials in these reactions.

Organomagnesium compounds, RMgX, are also called **Grignard reagents**, named after their discoverer, F. A. Victor Grignard.



Alkyllithium compounds and Grignard reagents are rarely isolated; they are formed in solution and used immediately in the desired reaction. Sensitive to air and moisture, they must be prepared and handled under rigorously air- and water-free conditions.

The formulas RLi and RMgX oversimplify the true structures of these reagents. The metal ions are highly electron deficient. To make up the desired electron octet, they function as Lewis acids and attach themselves to the Lewis basic solvent molecules.

For example, alkylmagnesium halides are stabilized by bonding to two ether molecules. The solvent is said to be **coordinated** to the metal. This coordination is rarely shown in equations, but it is crucial for the formation of the Grignard species.

Grignard Reagents Are Coordinated to Solvent



The alkylmetal bond is strongly polar

Alkyllithium and alkylmagnesium reagents have strongly polarized carbon-metal bonds; the strongly electropositive metal is the positive end of the dipole. The degree of polarization is sometimes referred to as "percentage of ionic bond character."

The carbon–lithium bond, for example, has about 40% ionic character and the carbon– magnesium bond 35%. Such systems react chemically as if they contained a negatively charged carbon.

To symbolize this behavior, we can show the carbon–metal bond with a resonance form that places the full negative charge on the carbon atom: a **carbanion**.

Carbanions, R⁻, are related to alkyl radicals, R⁺, and carbocations, R⁺, by successive removal of one electron.

Because of charge repulsion, the carbon in carbanions assumes sp^3 hybridization and a tetrahedral structure.

The preparation of alkylmetals from haloalkanes illustrates an important principle in synthetic organic chemistry: **reverse polarization.**

In a haloalkane, the presence of the electronegative halogen turns the carbon into an electrophilic center. Upon treatment with a metal, the $C^{\delta+}-X^{\delta-}$ unit is converted into $C^{\delta-}-M^{\delta+}$.

In other words, the direction of polarization is reversed. Reaction with a metal (metallation) has turned an electrophilic carbon into a nucleophilic center.

Carbon–Metal Bond in Alkyllithium and Alkylmagnesium Compounds



The alkyl group in alkylmetals is strongly basic

Carbanions are very strong bases. In fact, alkylmetals are much more basic than are amides or alkoxides, because carbon is considerably less electronegative than either nitrogen or oxygen and much less capable of supporting a negative charge.

Alkanes are *extremely* weak acids: The pK_a of methane is estimated to be 50. It is not surprising, therefore, that carbanions are such strong bases: They are the *conjugate bases* of alkanes.

Their basicity makes organometallic reagents moisture sensitive and incompatible with OH or similarly acidic functional groups. Therefore, it is impossible to make organolithium or Grignard species from haloalcohols or halocarboxylic acids.

On the other hand, such alkylmetals can be used as efficient bases to turn alcohols into their corresponding alkoxides. The by-product is an alkane.

Alkoxide Formation with Methyllithium



Similarly, organometals hydrolyze with water—often violently—to produce a metal hydroxide and alkane.

Hydrolysis of an Organometallic Reagent



The sequence Grignard (or alkyllithium) formation, also called metallation, followed by hydrolysis converts a haloalkane into an alkane.

A more direct way of achieving the same goal is the reaction of a haloalkane with the powerful hydride donor lithium aluminum hydride, an $S_N 2$ displacement of halide by H⁻.

The less reactive NaBH₄ is incapable of performing this substitution.



Another useful application of metallation-hydrolysis is the introduction of hydrogen isotopes, such as deuterium, into a molecule by exposure of the organometallic compound to labeled water.

Introduction of Deuterium by Reaction of an Organometallic Reagent with D₂O

 $(CH_3)_3CC1 \xrightarrow{1. Mg} (CH_3)_3CD$

8.8 ORGANOMETALLIC REAGENTS IN THE SYNTHESIS OF ALCOHOLS

Among the most useful applications of organometallic reagents of magnesium and lithium are those in which the negatively polarized alkyl group reacts as a nucleophile. They can attack the carbonyl group of an aldehyde or ketone to produce an alcohol (upon aqueous work-up).



In the first step, an electron pair from the alkyl group shifts to generate the new carboncarbon linkage, it "pushes" two electrons from the double bond onto the oxygen, thus producing a metal alkoxide.

The addition of a dilute aqueous acid furnishes the alcohol by hydrolyzing the metal-oxygen bond.

Formation of a Primary Alcohol from a Grignard Reagent and Formaldehyde



Aldehydes other than formaldehyde convert into secondary alcohols.



Ketones furnish tertiary alcohols.

