EXPERIMENT 7: Reduction of Carbonyl Compounds: Achiral and Chiral Reduction

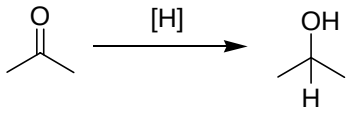
Relevant sections in the text: Fox & Whitesell, 3rd Ed. Chapter 12, pg.572-584.

A portion of this experiment is based on a paper in J. Chem. Ed. by N. Pohl, A. Clague and K. Schwarz Department of Chemistry, Iowa State University, Ames IA

Thanks to Barbora Bajtos, a former 283g'er, for working on aspects of this experiment.

General Concepts

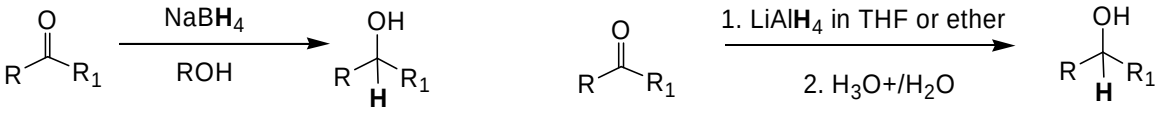
A reduction is often defined as the gain of two hydrogen atoms or the loss of an oxygen atom, or both. This leads to a very important conversion reaction, where aldehydes and ketones are reduced to primary and secondary alcohols.



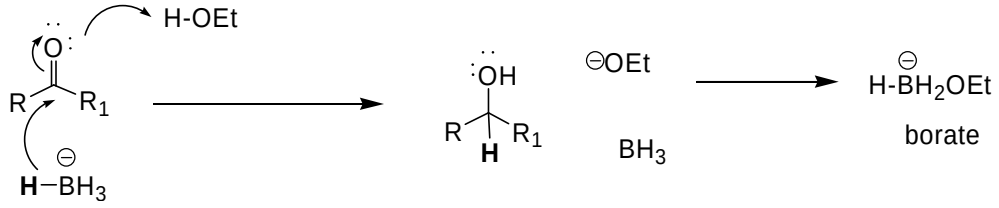
reduction of a carbonyl group

Although various methods for this conversion are possible, the most frequently employed is the use of complex metal hydride reagents such as lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). These particular reagents are also soluble in organic solvents and are not as reactive as a strong base, which is not true for other metal hydrides such as LiH, NaH and KH. Of the two most common reducing reagents, $LiAlH_4$ is the more powerful, reducing most carbonyl containing compounds including aldehydes, ketones, esters, and amides. A more selective reducing agent is $NaBH_4$, which only reacts with aldehydes and ketones due to its milder nature.

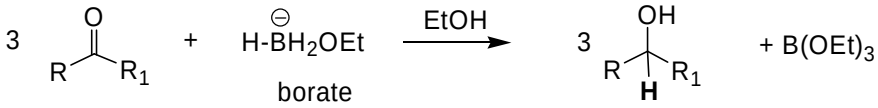
Both reducing agents are a source of H^-, which is transferred from the boron or aluminum to the carbonyl group. Since a reduction requires two hydrogen atoms, the second comes from the solvent (when using $NaBH_4$) or from added acid (when using $LiAlH_4$). Since $LiAlH_4$ is so reactive, it produces H_2 in polar solvents, so the reaction is performed in a polar aprotic solvent such as diethyl ether or THF. The two reactions equations are as follows:



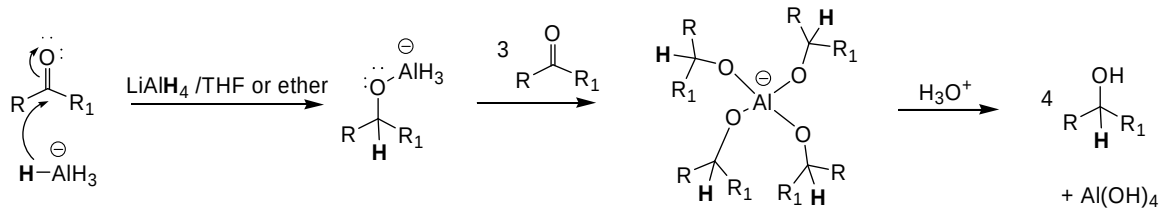
The mechanism for the reaction with $NaBH_4$ in ethanol (solvent) is shown below. The mechanism for $LiAlH_4$ is very similar. After the alcohol is produced, the remaining ethoxide (^-OEt) reacts like a Lewis base with BH_3, in the formation of a borate.



This borate compound can now continue to reduce another carbonyl compound since it has three remaining B-H bonds. In the laboratory, a small amount of reducing agent is commonly used to minimize side reactions, although one $NaBH_4$ molecule can potentially reduce up to four carbonyl functional groups.



Due to its reactivity, $LiAlH_4$ is carried out in aprotic solvents (in the absence of a proton source). The neutral AlH_3 binds to the negative oxygen atom forming an alkyl aluminate, which can be performed three additional times producing a tetra-alkyl aluminate. This complex is then hydrolyzed in a separate step to yield the final alcohol:



Treatment with aqueous acid decomposes the hydride reagent in both cases:

$$LiAlH_4 \xrightarrow{H_3O^+} Al(OH)_3 + LiOH + H_2(g)$$

$$NaBH_4 \xrightarrow{H_3O^+} B(OH)_3 + LiOH + H_2(g)$$

An important factor to be considered when converting ketones to alcohols is chirality. Reduction has the potential to transform achiral compounds into chiral ones.

Ketones that have different R groups on either side of the carbonyl (achiral) form chiral alcohols. Alternatively, if the R groups are identical the chiral ketone will produce an achiral alcohol. Since both $NaBH_4$ and $LiAlH_4$ are achiral, all reactions produce a racemic mixture. The activation energies leading to each enantiomer are of equal energy, so each will form in the same proportion.

However, if the reducing agent or solvent is chiral, the transition states leading to the two isomers are different and become diastereomeric. Thus, the amounts of each will not by equal. Chemists have been developing several chiral reducing agents, in combination with ligands, solvents and agents, to find the most efficient. One of the most common is L-tartaric acid, which selectively reduces one face of a ketone over the other.

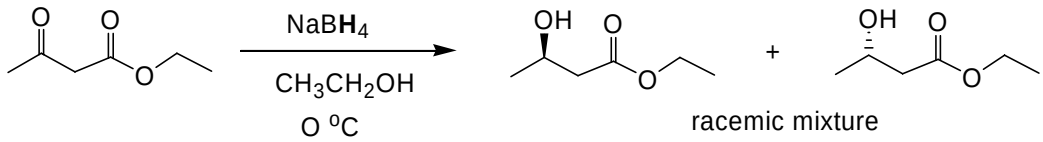
Although chemical reducing agents are effective, some of the most efficient enzymatic reducing agent can be found in nature. Baker's yeast is a chiral reagent that acts as an enzymatic reducing agent and can introduce chirality to a molecule. Transformation reactions involving these organisms are beneficial since they occur at ambient temperature and pressure.

In this experiment, a ketoester will be reduced with and without chiral reagents. The two different chiral reagents (Baker's yeast and tartaric acid) complexed to sodium borohydride will be examined to compare the procedures and the two opposite enantiomers produced by each. Both chiral and achiral versions of ethyl β-hydroxybutyrate from ethyl acetoactate will be synthesized.

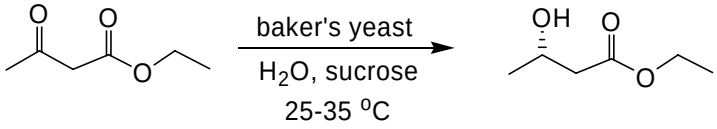
The milder reducing agent, $NaBH_4$, will be used to produce the racemic mixture since $LiAlH_4$ would cause reductions at both carbonyl groups (a ketone and an ester) of the starting material. This reaction involves the formation of the two enantiomers, ethyl S-3-hydroxybutanoate and ethyl R-3-hydroxybutanoate. In this experiment, you will also use an enzyme found in ordinary Baker's yeast to selectively prepare one of the enantiomers. Sucrose will be oxidized while the ethyl acetoacetate is reduced. Alternatively, L-tartaric acid will be used to selectively produce the opposite enantiomer.

The reaction yield will be determined along with the stereochemical preference (using chiral gas chromatography) which will allow you to determine the enantiomeric excess and absolute configuration of the alcohols that are formed. Your products will also be analysed by NMR and IR spectroscopy and Mass Spectrometry.

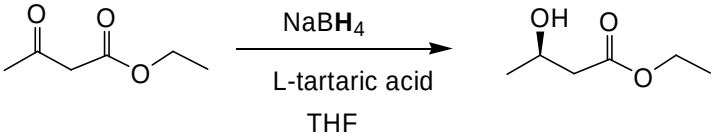
Procedure 1



Procedure 2



Procedure 3



Note: You will not do procedure 3 in 2006.

Procedure

***Hazards*:** As with any hydride reaction, hydrogen gas is evolved during the course of the reaction. Hydrogen must be kept away from ignition sources to avoid explosions. Tetrahydrofuran is an irritant. Deuterated chloroform used to make samples for NMR is highly toxic and a cancer suspect agent. Hydrochloric acid and sodium borohydride are corrosive and tartaric acid is an irritant. Standard chemical safety precautions should be practiced at all times.

Part A: Reduction of Ethyl Acetoacetate with Sodium Borohydride

- Add sodium borohydride (1.5 g, 40 mmol, MW 37.83) to 25 mL ethanol in a 100-mL round bottomed flask, and cool the resulting mixture to 0°C using an ice-bath.
- To this mixture add a solution of the ethyl acetoacetate (5.0 g, 38 mmol, MW 130.14, 1.028 g/mL) in 15 mL ethanol, and stir the resulting solution at 0 °C for 15 minutes, then allow to warm to room temperature and stir for an additional 15 minutes.
- Evaporate the solvents on a rotary evaporator, and suspend the resulting white solid in 30 mL dichloromethane.
- Cool the flask in an ice bath and then add 30 mL of 1 M hydrochloric acid drop wise, while stirring, to quench the reaction (destroy any unreacted hydride reagent). *Note*: The addition of HCl will cause frothing and will release H_2 gas.
- Separate the organic layer and extract the aqueous layer 2x 20 mL portions of dichloromethane.

- Combine the organic layers and dry using magnesium sulfate. Filter off the magnesium sulfate and evaporate the solvent using a rotary evaporator with a water bath temperature at *room temperature*.
- Record the actual yield.
- **Obtain the ^{1}H and ^{13}C NMR spectra and IR spectrum.**

Part B: Reduction of Ethyl Acetoacetate with Baker's Yeast

(i) Week 1 (complete this while performing Part A)

- Using a 250 mL Erlenmeyer flask, dissolve 40 g of sucrose and 0.25 g of disodium hydrogen phosphate (Na_2HPO_4) in 150 mL of warm (35°) tap water.
- To this, add ~ 8 g of dry baker's yeast and swirl to suspend the yeast throughout the solution. In about 15 minutes, add 1.5 g of ethyl acetoacetate.
- Put some cotton in the mouth of the flask to stopper it (but still allow gas to escape), label the flask and store the flask in the oven at (30-35°) until next week.

(ii) Week 2

- Add about 5 g of Celite filtration aid to the flask, and remove the yeast cells by filtration with a Büchner funnel. Wash the cells with 25 mL of water. *Gently* scrape the filter paper to remove excess yeast cells if the funnel becomes clogged.
- Saturate the filtrate with sodium chloride to reduce the solubility of the product.
- Extract the saline solution 5 x 25 mL portions of diethyl ether. Shaking too vigorously may lead to the formation of an emulsion at the interface, which can be broken up with a small amount of methanol.
- Dry the ether layer over anhydrous sodium sulfate. After 5-10 minutes of drying, gravity filter the ether solution into a *pre-weighed* 250 mL round bottom flask, and remove the ether using the rotary evaporator.
- Record the actual yield.
- **Obtain a ^{1}H and IR spectrum**
- **Note: A chiral GC will also be provided.**

Final Lab Report

- Discuss the mechanisms and yields (compare/contrast the relative yields of the two methods and the spectroscopic data). Are there differences? If so, why?
- Gas chromatography traces measured using a column that separates enantiomers will be provided. Discuss these traces with respect to asymmetric synthesis.
- Draw a mechanism for the reduction using $NaBH_4$.

- Analysis of Infrared Spectrum:

Attach and analyze the IR spectra of the starting material (provided) and the products, assigning appropriate peaks. Compare and comment on the IR of the product form the two reduction methods.

- Analysis of NMR Spectrum of Product:

Attach the NMR spectra and assign a structure of your starting material (provided) and product by completely analyzing the ^{1}H and ^{13}C NMR spectra. How do you expect the NMR spectrum of the product obtained by the yeast reduction process to differ (i.e., would the NMR spectrum of an enatiomerically pure product differ from the racemic mixture?)

- Comment on which method you preferred from a chemical point of view. When would you use the yeast synthesis?

- Could you have used $LiAlH_4$ followed by acid work up to carry out this same transformation?
- Show a mechanism for the reaction of ethyl acetoacetate with [1] $LiAlH_4$ followed by [2] H_3O^+.