CHEM 231: Organic Form and Function

Laboratory 4

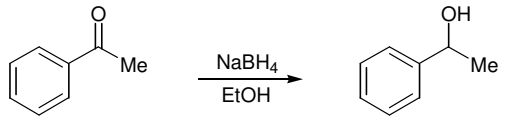
Nucleophilic Addition to Carbonyls (Ad_N)

Specific Practical Goals

- to carry out the reduction of a ketone to an alcohol
- to apply aqueous extraction to separate organic from inorganic products
- to determine percent yield of a reaction
- to characterize a product by infrared spectroscopy, refractive index, and HPLC

Mechanistic Background

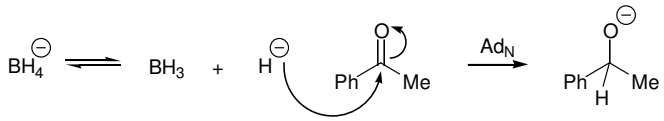
This laboratory continues to explore the concept of *functional group transformation*, this time through the conversion of a carbonyl group to a hydroxyl functionality. The reduction of ketones to alcohols represents a very important method for the synthesis of alcohols, and it can be carried out under a variety of conditions. The present laboratory examines the use of sodium borohydride ($NaBH_4$) in ethanol, as shown below.



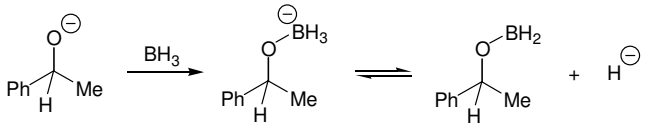
acetophenone
MW 120
d 1.033
mp 20.5° bp_{760} 202°

1-phenylethanol
MW 122
d 1.012
mp 19-20° bp_{745} 204°

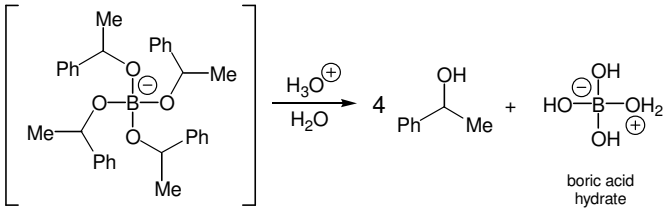
From a mechanistic standpoint, the borohydride can be viewed as a source of hydride anion, which engages in nucleophilic addition to the carbonyl carbon (Ad_N), as shown below.



In the reaction mixture, the alkoxide anion so formed can coordinate to the boron center that delivered the hydride to create a new source of hydride, as illustrated in the following equation:



Ultimately, this process can occur three more times, so that all four hydrides on the boron can be used for nucleophilic addition. The resulting species at the end of the reaction might be characterized as a boron atom surrounded by four alkoxide anions. Upon acidic aqueous workup, the alkoxides are protonated, and the boron is converted to boric acid.

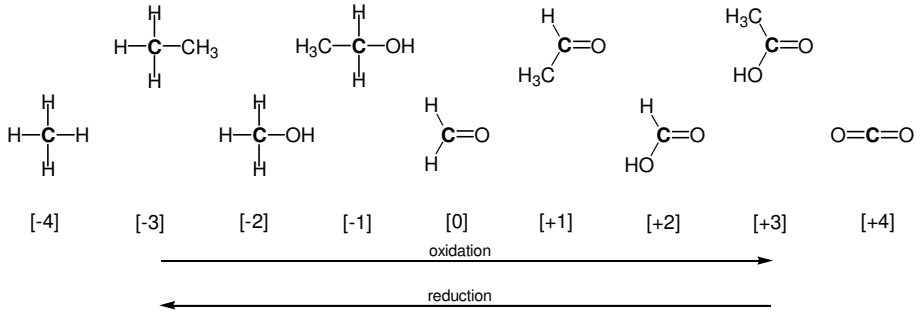


present after the completion of reaction but before workup

boric acid hydrate

Oxidation States of Carbon

The reaction of acetophenone with sodium borohydride is an example not only of functional group transformation, but also of *carbon-centered reduction*. In fact, one of the distinguishing features of carbon (and a significant feature of its versatility as a basis of life) is that it has nine common oxidation states, as exemplified in the redox spectrum below. Although it is often neglected, the consideration of carbon oxidation state can be a very useful tool in understanding organic reactions.



Redox spectrum of carbon [oxidation state of bold carbon in brackets]

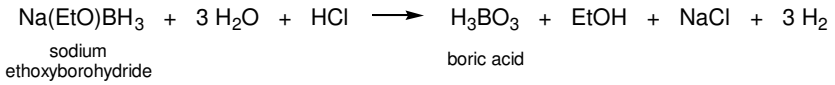
Week 1

Pre-lab Reading

Organic Laboratory Techniques, Fessenden, Fessenden, & Feist, 3rd ed., pp. 153-161

Procedural Considerations

The reaction between borohydride and acetophenone is highly exothermic; therefore, it is necessary to combine the reactants slowly (dropwise). In any reaction involving an exotherm, an ice bath should always be available in case the rapid removal of heat is required. After the reaction is completed, the mixture is treated with aqueous acid to protonate the alkoxides (*vide supra*) and to decompose excess hydride reagent, a process which evolves highly flammable hydrogen gas. Therefore, this step must be carried out in a fume hood.



Water and ethanol are *miscible*, that is, they are infinitely soluble in each other. Therefore, aqueous extraction from ethanol is impossible, since only one layer would be present. To circumvent this problem, the solvent ethanol is boiled off prior to aqueous extraction. When most of the ethanol has been removed, the product falls out of solution as an oil. Water and ether are then added to the residue for the extraction of the organic compounds from the inorganic salts. The ether layer is dried with magnesium sulfate, decanted, and concentrated to give the crude product.

Safety Considerations

You must abide by all laboratory safety rules

Acetophenone is a combustible liquid; harmful if swallowed; irritating to skin; risk of serious damage to eyes. Keep away from flame and other sources of ignition. Protect eyes and skin from exposure.

Sodium borohydride is a flammable, toxic solid; contact with water liberates extremely flammable gases; toxic in contact with skin and if swallowed; causes burns. Keep away from water. Protect eyes and skin from exposure.

Ethanol is a flammable liquid; irritating to eyes, respiratory system, and skin; target organs: nerves and liver. Keep away from flame and other sources of ignition; avoid contact.

1-Phenylethanol is a combustible, toxic liquid; harmful if swallowed; irritating to skin; risk of serious damage to eyes. Keep away from flame and other sources of ignition. Protect eyes and skin from exposure.

Diethyl ether is a toxic and extremely flammable liquid; may form explosive peroxides; harmful if swallowed; irritating to eyes, respiratory system, and skin; repeated exposure may cause skin dryness or cracking; vapors may cause drowsiness and dizziness; target organs: central nervous system and kidneys. Keep away from flame and other sources of ignition. Protect eyes and skin from exposure.

Procedural Overview

Place 0.040 mol of sodium borohydride in a 150 mL beaker equipped with a thermometer and stirbar. Add 30 mL 95% ethanol and stir until the solid is dissolved.[1]

Place 0.100 mol of acetophenone in a 50 mL Erlenmeyer flask and add dropwise to the stirred borohydride solution using a pipet, keeping the temperature of the reaction mixture between 30-50°C by controlling the rate of addition and by cooling in an ice bath as necessary. When the addition is complete (usually no more than 45 min), rinse the flask forward with a small amount (2-3 mL) of ethanol.

After allowing the reaction to stir at room temperature for 15 min, carefully add 10 mL 3M hydrochloric acid to the stirred reaction mixture in a fume hood. When the reaction subsides, heat the mixture to boiling on a hot plate in the fume hood until the mixture separates into two layers.

Cool the reaction mixture in an ice bath, then transfer to a separatory funnel and rinse the residual material forward with 20 mL of diethyl ether. If any inorganic salts precipitate, add 20-40 mL water, as necessary, to dissolve them.

Stopper and shake the separatory funnel, making sure to vent frequently; return the funnel to the ring stand, remove the stopper, and allow the phases to resolve. Collect the ether layer and set aside. Extract the aqueous layer with another 20 mL of fresh diethyl ether.

Wash the combined ether extracts with an equal amount of saturated sodium chloride solution (brine), dry over sodium sulfate, and transfer to a tared round-bottom flask. If time permits, remove the solvent by rotary evaporation. Otherwise, stopper the flask, label, and store properly until the next lab period.

Notes

[1] A small amount of solid may remain undissolved if the borohydride has been exposed to atmospheric moisture for extended periods. A light dusting should not adversely affect yield, since the borohydride is added in excess.

Week 2

Pre-lab Reading

Organic Laboratory Techniques, Fessenden, Fessenden, & Feist, 3rd ed., pp. 115-118

More Thoughts on Characterization

The mass of a reaction mixture can only be translated to yield once the purity has been established. For example, if the theoretical yield for a given product is 10.0 g and the reaction yields a total mass of 8.2 g, it is completely meaningless to claim an 82% yield, unless there is analytical evidence to claim 100% purity. In other words, the crude reaction mixture may contain residual starting material and other by-products. Thus, if the crude mass contained only 50% of the desired product (*i.e.*, 4.1 g of the 8.2 g mixture), then the yield would be 41%. Therefore, an accurate determination of yield requires careful measuring of the crude mass as well as an analysis of its composition. In this case, HPLC is used for determination of product purity.

As further supporting data for product identity, infrared (IR) analysis is used. Since IR absorptions can be correlated to functional groups, then the conversion of a carbonyl group (in the starting

material) to a hydroxyl group (in the product) should result in the disappearance of the C=O stretch (in the 1730 cm^{-1} range) and appearance of the characteristic –OH stretch (at around 3300 cm^{-1}).

Safety Considerations

You must abide by all laboratory safety rules

1-Phenylethanol is a combustible, toxic liquid; harmful if swallowed; irritating to skin; risk of serious damage to eyes. Keep away from flame and other sources of ignition. Protect eyes and skin from exposure.

Procedural Overview

If you have not done so already, remove the solvent from the product by rotary evaporation. After the yield has been determined, take an HPLC analysis of a diluted sample (one drop in 2.0 mL of methanol) using the procedure below.

HPLC Operating Procedure

a. Make sure you are operating in the proper software window (Instrument 1 is on the left)
b. Ensure that the system is available—a green "Ready" box will show in the upper left quadrant
c. On the top menu, go to RunControl → Sample Info; enter your name under Operator Name
d. Clean a 50 μL Hamilton syringe (handle with care!) by drawing methanol into it to full capacity; purge into a waste container; repeat
e. With injector in "Load" position (counterclockwise), flush out sample loop with methanol 4 or 5 times using a full syringe
f. Load sample into injector using at least 3 full injections, avoiding any air bubbles in the syringe; leave the syringe in the injector port after the last injection
g. Turn injector to "Inject" position (clockwise), leaving the syringe in the injector; software will set a zero point on the trace
h. Do not make any hardware adjustments while a run is in progress
i. When the sample has finished, your trace will automatically print out