Name: _________________________  TA Name: ___________________

Experiment # 14

Pre-lab exercises

Pre-lab write-up (Sections 1-VI)

Completed report (Sections VII-IX)

Answers to Assigned Problems (Section X)

Product (yield, purity, appearance)

Total

Score

This is your report cover.
Please fill this form out and attach it to your preLab.
Experiment 14: The Grignard Reaction: A Study of the
Stereochemistry of Carbonyl Addition

General Safety Considerations

1. Each of the three reaction steps in proposed sequence is highly exothermic. Follow the reagent addition instructions to the letter. Be very conservative. Have an ice bath ready at all times should any of the reactions get out of control. If your stirrer stops during addition of bromobutane or ketone (especially here!) stop stirring and get some help.

2. The Grignard reagent (R-Mg-X) is very sensitive to water. All glassware and reagents must be as anhydrous as possible before beginning. Do not wash any glassware before building your apparatus. Exposure to even small amounts of water will result in a highly exothermic reaction and possible, no yield of the desired alcohols.

3. All of the organic materials used in the proposed sequence should be considered to be toxic, irritating and flammable. Wear gloves and goggles at all times, work continuously in the hood and as always, no flames are allowed. At the risk of being overly-redundant, I will remind you again that ether is extremely flammable, and has a very high vapor pressure. Over-exposure to ether can cause sleepiness, headaches, and nausea. Do not allow containers of ether to sit open on the lab bench. Vessels holding ether should be at the very least, corked and in the hood. If necessary, a container of ether can be stored in an ice bath.

4. Magnesium is pyrophoric and moisture sensitive. Do not throw excess magnesium in the trash (chemicals should never be thrown in the trash) or sink. Do not leave it scattered around the balances. See your instructor or TA regarding the disposal of this chemical.

5. 6 M HCl is very corrosive. Use extra care when working with it. Wear gloves and goggles. Always work in the hood.

6. Generally speaking, please alert your instructor or TA of any large spills and chemical exposure. If you spill any of the listed chemicals on your person, the best remedy is flushing the exposed area for at least fifteen minutes with cold water.
Flow Chart For Experiment 14

Build Apparatus Delineated in Procedure and shown in diagram

1. Add 0.65 gram of Mg to 50 mL flask. Add crystal of iodine
2. From funnel, rapidly add about 3 mL of solution of 1-bromobutane in dry ether (2.8 mL of 1-bromobutane in 6.3 mL of ether).
3. Wait for reaction to start
4. Add 2 mL of dry ether through the condenser
5. Wait for reaction to slow down to a reflux rate of 1 drop per second.
6. Add remaining solution from dropping funnel slowly, maintaining reflux rate of 1 drop per second from condenser
7. Reflux additional 15 minutes using heating mantle - be cautious.
8. Cool Reaction to ice temperature in ice bath
9. Add ketone in ether from dropping funnel (continue cooling!) (3.9 g of ketone in 5 mL of dry ether - make it up outside the funnel) very slowly avoiding reflux.
10. Remove ice bath and allow reaction to stir for 20 additional minutes...
11. Slowly add 5 mL of 6 M HCl with stirring and occasional cooling. Mechanical stirring might be necessary
12. Filter reaction through glass wool into 125 mL separatory funnel
13. Rinse glass wool with ether if necessary. Combine rinsings with material in separatory funnel.

Note: stirring must be maintained through all reactions

filtrate

residue

Separate layers

aqueous layer

organic layer

discard as directed

re-extract with 4 mL of ordinary ether

combine with new ether layer

Combined organics

see next page
Experiment 14
The Grignard Reaction: A Study of the Stereochemistry of Carbonyl Addition

As you have studied in the lecture part of the course, the Grignard Reaction is a very important carbon-carbon bond forming reaction. In fact, it is a Nobel Prize winning reaction. To read about Francois Auguste Victor Grignard, the discoverer of the reaction and winner of the 1912 Nobel Prize in Chemistry, go to http://nobel.sdsc.eduichemistry/laureates/1912/grignard-bio.html on the web or to the history section of the Bryn Mawr College Organic Chemistry Web book.

From a synthetic organic perspective, the Grignard reaction is crucial because it allows chemists to make carbon-carbon bonds at an oxygen bearing carbon as seen in the generic reaction below. As illustrated, the key issue in making a carbon-carbon bond is having carbons of opposite polarity, one positive and one negative. Though carbon is typically relatively positive when in a functional group, the formation of the bond to a metal makes it relatively negative, resulting in strong nucleophilicity toward the electrophilic carbon of the carbonyl. The mechanism for this reaction will be gone over in some detail in lab lecture.

Grignard Reaction — general scheme:

$$\text{R-X} + \text{Mg} \rightarrow \text{RMgX} \rightarrow \text{RCH(OH)(R')_2}$$

1. $\text{R'COR'}$
2. $\text{H_2O}$

Note: alkyl group is attached to halogen rendering it delta +

Note: After reacting with magnesium, the carbon has undergone a reversal of polarity and is delta negative. It behaves like a carbanion - it is now nucleophilic.

The version of the Grignard reaction that you will carry out today in lab is particularly interesting because it will enable you to explore the stereochemistry of nucleophilic attack on carbonyls. In this reaction, 4- t-butylcyclohexanone will be treated with butyl magnesium bromide that you have prepared in the laboratory. The beauty of working with a t-butyl substituted cyclohexanone is that the starting material and products formed are well defined from a conformational standpoint (why?). Taking a kinetic approach to the outcome of the reaction, attack by the from the top or "axially" is different in terms of interactions that attack from the bottom or "equatorially". The top attack results in an equatorial OH group in the product where the bottom attack results in an axial OH in the product. Both attacks have energy raising issues. (Dung, B.W. Tetrahedron, 52:5263 (1996) ) The top attack suffers from the fact that there could be steric interaction between the approaching butyl group and the axial hydrogens at the 3 and 5 positions on the ring. The bottom or equatorial attack is problematic because as the carbon bearing the oxygen rehybridizes, the C-0 bond must pass through a fully eclipsed conformer,i.e., the C-0 is forced to be eclipsed with the flanking
equatorial hydrogens. Taking a thermodynamic approach, one would simply evaluate the stability of the resulting products. Which product should be more stable? Why?

**Grignard Reaction: Specific Reaction Sequence to be carried out:**

Two Approaches of the Grignard Reagent to the Ketone:
In preparation for this experiment, study the Grignard reaction, watch any provided youtubes, read about it in your textbook and answer the following prefab questions.

1. The following are several of the side reactions that can occur while carrying out a Grignard reaction. Propose reasonable mechanisms for all but the second reaction.
   
   \[
   \begin{align*}
   R\text{-}Mg\text{-}X + H_2O & \rightarrow RH + HOMgX \\
   2R\text{-}MgX + O_2 & \rightarrow 2ROMgX \\
   R\text{-}MgX + CO_2 & \rightarrow RCO_2MgX \\
   R\text{-}MgX + R\text{-}X & \rightarrow R\text{-}R + MgX_2
   \end{align*}
   \]

2. Why are reagents generally added drop wise with cooling in this Grignard reaction?

3. Why is vigorous stirring particularly important during the controlled addition of the ketone and later, 6M HCl?

4. Outline a mechanism to explain the initiation of Grignards with I\(_2\). You do not need to write an arrow formalism. (Hint: Mg + I\(_2\) + iodoalkanes react more readily with Mg than bromoalkanes, the process involves the formation of MgI\(_2\) and iodobutane).

**Some General Guidelines for the Experiment 14**

**Write-up Main Reaction and Mechanism**

These were covered in lecture and/or the lab manual. You do not need to write an arrow formalism for the reaction of the ketone with butyl magnesium iodide. Most of the 4-t-butylcyclohexanone molecules react with butyl magnesium **bromide molecules**.

**Side Reactions**

The main side reactions are covered in the pre-lab questions. Other side products are listed in part "10" of the procedure. Try to come up with reasonable reagents leading to these products. Another side reaction will be discovered upon studying the GCMS results.
Purification

The chemistry is over after step 13 on the flow chart. The filtration at step 14 is to remove any unreacted magnesium and insoluble magnesium salts. The ether extraction is an aqueous backwash step to isolate any organic product that is dissolved in the aqueous layer. The extraction of the combined organic layers with base is for the usual reasons. The extractions with saturated sodium chloride are to help dry the organic layer (to help draw water out of the layer). Potassium carbonate is a drying agent.

Table of Reagents

Since the Grignard reagent itself can't be quantified, all calculations have to be based on the materials used to make the Grignard reagent, the ketone attacked by the Grignard reagent and source of protons for the alkoxide initially formed.

Iodine should be treated as a catalyst, though it is not a catalyst.

Table of Products

Only the Grignard products should be included in this table. It is a solid and it is unlikely you will be able to find conventional data on the two stereoisomers.

Write down important observations and data during lab.

Results

See the last page of this lab for the specific breakdown. Most of this section is straightforward except possibly the NMR simulation. When attempting this simulation, keep in mind the peculiar aspects of alcohols and NMR. Realize also that although target molecule has a number of different types of hydrogens, the electronic environments around many of those hydrogens are very similar. You must consult a chemical shift table when you are predicting the spectrum and you should also be prepared for considerable overlap of peaks. Do not try to draw a spectrum, just prepare a table with approximate positions for the hydrogens.

Conclusion/Discussion

Try not to be repetitive in your discussion. If you have stated something once in one context, you do not have to restate it again in another context - just refer to it. Also, only discuss errors that occurred in your experiment. Write in the third person, passive voice.
Post-lab Problems

a 1. Watch out for acidic hydrogens!!!!!!

2. Straight forward, but don't add any reagents that are not written in the reaction.

3. Straight forward. Remember - bromine is quite selective for more reactive hydrogens.

b. A "hydrogen bonded hydrogen" in this case is a hydroxylic hydrogen that is involved in a hydrogen bond with an oxygen from another hydroxyl group. When answering this question keep in mind the spectroscopic peculiarities of hydroxyl groups in regard to hydrogen bonding. How does hydrogen bonding effect the NMR? IR? What issues would be likely to enhance or reduce hydrogen bonding?

Procedure

1. Assemble the apparatus shown on the next page, consisting of a 50 mL round bottom flask, an addition (dropping) funnel and a reflux condenser. No heating source is used at first. Make two drying tubes from curved adapters in the following way: cover the sidearm with a dropper bulb, and place a small amount of anhydrous calcium sulfate ("Drierite") in the curved part of the tube, using small plugs of glass wool both below and above the Drierite to hold it in place. Clamp a magnetic stirrer under the apparatus and place a stirring bar in the flask. No boiling chips are necessary, as the stir bar serves the same purpose. The apparatus should be clamped to the monkey bars at a height of 4-6 inches off the bench.

2. Bring a clean, dry Erlenmeyer flask, with cork, to the hood, and obtain about 20 mL of anhydrous ether. Please note that this anhydrous ether is the source of ether for the procedure below. Do not go back and obtain more ether as you read your procedure. Keep this flask corked when not in use.

3. Place 0.65 g (0.025 mole) of magnesium turnings and a small crystal of iodine in the 50 mL round-bottomed flask and re-attach the flask to the apparatus. Prepare a solution of 2.8 mL (ca. 0.025 mole) of pure, dry 1- bromobutane and 6.3 mL of anhydrous diethyl ether. Swirl this mixture thoroughly to insure complete solution; since the densities of these two liquids are very different they will not mix well without this swirling. Place this solution in the addition funnel (be sure the stopcock is closed!).
4. Have 4.0 mL of dry ether measured out and ready at hand. Also have an ice-water bath prepared for use in case the reaction generates too much heat. Turn on the stirrer, then open the stopcock and allow ca. 3 mL (cover the Mg turnings) of the bromobutane/ether solution to flow onto the magnesium in the flask. Ideally, the reaction will start spontaneously within 5-10 minutes: the iodine color will disappear, the ether solution will turn cloudy, and the ether will begin to boil from the heat of the exothermic reaction. If too much heat is being generated, the ether will boil so rapidly that your condenser will be unable to contain the vapor; you will see fumes emerging from the top of the condenser. In this case, use the ice-water bath to moderate the reaction. If, on the other hand, the reaction does not start within 5-10 minutes, add another small crystal of iodine to the flask (by momentarily removing the addition funnel) and warm the flask gently with a flask heater (support the heater on the magnetic stirrer - the stirring will work through the heater). Remove the flask heater when the ether starts boiling and observe whether the reaction continues on its own. If after heating the reaction still will not start or keep going, consult your instructor.

5. After the reaction has started and the ether is boiling satisfactorily on its own (i.e., not as a result of external heating), introduce about 4 mL of anhydrous diethyl ether through the top of the condenser (momentarily removing the drying tube). Why is this done?

6. Now begin adding the ether solution of 1-bromobutane dropwise from the addition funnel at such a rate that reflux is maintained (1 drop per second) without exceeding the cooling capacity of your condenser (look for vapor escaping from the top).
About 10-15 minutes may be required to complete the addition. When addition is complete, use a flask heater to maintain the reaction mixture under gentle reflux for a further period of about 15 minutes to complete the formation of the Grignard reagent. The heater should be at a very low setting – ether boils near room temperature.

7. Remove the flask heater and cool the reaction flask by placing an ice-water bath, in a plastic tray, between the stirrer and the flask, (A metal tray will interfere with stirrer operation.) Place a solution of 3.9 g, (ca. 0.025 mole) of 4-t-butylcyclohexanone and 5.0 mL of anhydrous diethyl ether in the addition funnel (be sure the stopcock is closed!). With the stirring on, add this solution drop wise and very slowly to the reaction mixture. Each drop will react vigorously and very exothermically, producing a hissing sound and forming a white solid which then dissolves. It is essential that stirring be continuous during this addition! If solid formation inhibits stirring, agitate the apparatus by hand! After all of the ketone has been added, remove the ice-water bath and allow the reaction mixture to stand for about 20 minutes with gentle stirring.

8. Cool the reaction mixture once again in an ice-water bath. Place 5.0 mL (0.06 mole, or a 20% excess) of 6 M hydrochloric acid in the addition funnel, and add it cautiously with swirling to the reaction mixture over a period of about 20 minutes. A solid nearly always forms here which inhibits stirring. If necessary, agitate the reaction mixture by hand between additions. If necessary, remove the ice bath periodically to allow the magnesium salts to dissolve upon warming (the magnesium salts impede stirring). After this addition is complete, filter the contents of the reaction flask through a small plug of glass wool in your largest stem-less funnel into your 125 mL separatory funnel. Separate the layers. Extract the water layer with 4.0 mL of ordinary, solvent grade, diethyl ether (i.e., not anhydrous) in the separatory funnel, and combine this ether extract with the original main ether layer. Return the resulting ether solution (which contains the desired product) to the separatory funnel, and wash it sequentially with two 4.0 mL portions of 5% aqueous sodium hydroxide solution (Why?) and then with two 4.0 mL portions of saturated aqueous sodium chloride solution (Why?). Transfer the washed ether layer to a small Erlenmeyer flask and dry it over anhydrous potassium carbonate. Depending on how you are doing you may have to stop here and finish this up next week. Consult with your instructor. If you are out of time, stopper your flask and place it in your locker. If you have a reasonable amount of time remaining, continue on.

9. Filter the dried ether solution by gravity into a dry, tared 50 mL round bottom. Rotavap the solution to dryness.

10. Measure the mass of the flask plus crude compound and then run a GCMS of .01g of your sample. See YouTube for instructions of how to make the sample.

11. Obtain an IR spectrum of your crude mixture. Make a solid film (see YouTube on making and running solid films). Your sample will be collected next week.

12. Using an NMR chemical shift table and your knowledge of splitting and integrals, simulate the proton NMR spectrum of your major product.

13. Your lab report should include answers to the following questions:
a. Write major products to the following reactions. Include stereochemistry where appropriate.

2. $\text{R} = \text{CH}_3$

1. $\text{R} = \text{CH}_2\text{CH}_2\text{OH}$

3. $\text{R} = \text{CH}_3$

b. What do you predict the effect of hydrogen bonding to be on the $^1\text{H}$ NMR chemical shift of a hydrogen bonded hydrogen. Given the fact that NMR spectra are usually run as dilute samples and that you have prepared a mixture of tertiary alcohols, roughly predict where the OH peak would appear in the NMR of this compound. How would you expect your IR spectrum to change if it was run at low concentration in a solvent like carbon tetrachloride? Explain.
-- A Carbon Eel
by Liza Donlon and Heather Campbell

The grape that can with Logic absolute
The Two-and-Seventy jarring Sects confute:
The sovereign Alchemist that in a trice
Life's leaden metal into Gold transmute.

*The Rubaiyat of Omar Khayyam*

Mere alcohol doesn't thrill me at all.

Cole Porter. *I Get a Kick Out of You*
Specific Point Breakdown

Experiment 14: The Grignard Reaction: A Study of the Stereochemistry of Carbonyl Addition

I. Pre-lab Exercises — 20 points total

1. 8 points
2. 3 points
3. 3 points
4. 6 points

II. Pre-lab write-up — 60 points total

Point breakdown:

- 8 points for introduction
- 4 points for writing mechanisms for the synthesis. The students should use the arrow formalism and show all intermediates.
- 8 points for the side reactions
- 10 points for purification
- 10 points for the completed table of reagents
- 8 points for the completed table of products

III. Completed Lab Report — 60 points total

- 4 points for observations and data
- 26 points for yield in moles
- 2 points for percent yield calculation
- 4 points for description of product appearance
- 4 points for GC with retention times for products and contaminants and peak identifications
- 6 points for IR with interpretation
- 8 points for NMR simulation
- 30 points for conclusion Breakdown
• 6 points for summary of evidence supporting identity of product (bp, GC, IR)
• ?? points for explanation of deviation of yield from 100%
• 8 points for discussion of purity of product and possible sources of contamination.
• 8 points for explanation of stereoselectivity

IV. Answers to Assigned Problems — 20 points total

   a1. 3 points
   a2. 3 points
   a4. 4 points
   b. 10 points

V. Products — (Quality) — 20 points total

• 8 points for quality of product yield
• 8 points for purity of product (use GC and IR here)
• 4 points for appearance of product