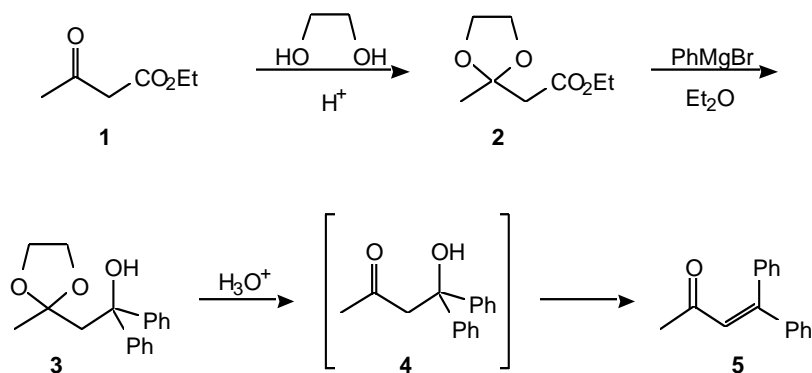


The Grignard Reaction: Synthesis of 4,4-Diphenyl-3-buten-2-one

Background

The Grignard reaction is a classic method of carbon-carbon bond formation. Compounds that contain carbonyl functions react readily with Grignard reagents to form the corresponding alcohol derivatives. As such, aldehydes and ketones react to give secondary and tertiary alcohols respectively, while esters, in the presence of excess reagent, react exhaustively to form the corresponding tertiary alcohols.

In this experiment, 4,4-diphenyl-3-buten-2-one (**5**) will be prepared from ethyl acetoacetate (**1**) using a Grignard reaction. As shown below, ethyl acetoacetate (**1**) contains two functional groups (ester and ketone), both of which are reactive toward Grignard reagents. In this case, the reactivity of these two groups can be modified simply by using a protecting group. The use of a protecting group allows a molecule with several active centers to undergo reaction selectively at one center while leaving the other intact. In the first part of this synthesis, we will utilize this important principle by converting the carbonyl group of methyl acetoacetate to a cyclic ketal (**2**) using ethylene glycol. This step involves the azeotropic removal of water using a Dean-Stark trap. In the second part of the experiment, the Grignard reaction is performed using the protected compound. Here, phenylmagnesium bromide is utilized as the Grignard reagent resulting in formation of the tertiary alcohol (**3**). The last step of the sequence involves removal of the protecting group under acidic conditions resulting in formation of 4,4-diphenyl-3-buten-2-one (**5**) via the intermediacy of the beta-hydroxyketone (**4**).



Procedure

A. Protection of a Ketone – Formation of Ethyl Acetoacetate Ethylene Ketal:

To a 100-mL round-bottomed flask containing 10 g ethyl acetoacetate (will need to convert to mL!), add 40 mL hexanes, 5.0 mL ethylene glycol, and about 50 mg p-toluenesulfonic acid. Swirl to mix, then add several boiling chips and a stir bar. Fit your flask with a Dean-

Stark trap and water condenser (Figure 1). Use a Keck clamp to secure the 25-mL round-bottomed water trap to the distillation head.

Carefully pour hexanes through the condenser so that the trap is completely filled. The excess will flow into the reaction vessel. While stirring vigorously, heat the mixture under hard reflux until no more water is collected and the reaction mixture is no longer cloudy; about 1 hour. Cool the mixture to room temperature and transfer it to a separatory funnel. Rinse your reaction flask with 30 mL ether and add this to the separatory funnel as well. Wash the organics with 15 mL of 10% NaOH, then with two 20-mL portions of water. Dry the organic layer over MgSO₄ and filter (gravity filtration through fluted filter paper) to remove the solids.

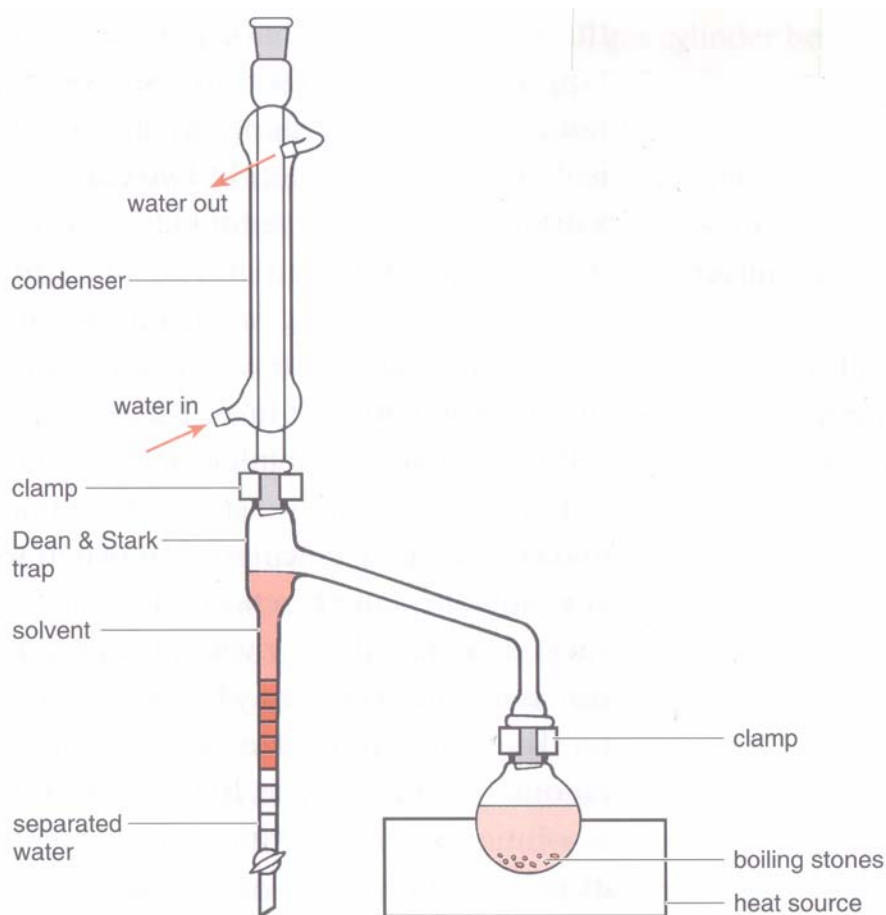


Figure 1: Dean-Stark Trap

Remove the solvent from the filtrate using the rotary evaporator. Take an IR of your product, and one of the starting ethyl acetoacetate. Note the differences between the two. Interpret the NMR spectrum of the ketal (this will be provided on ICON). Save a small sample of the product for TLC analysis which will be done at the end of the experimental sequence. This is generally the stopping point for the period because of the need for everyone to do the next step at the same time (see below).

B. Preparation of Phenyl Magnesium Bromide

NOTE! An open flame will be used in a procedure called “flame-drying” to remove residual traces of water from the glassware. Since many organic solvents are flammable, certain precautions must be taken to ensure that accidents do not occur. Thus:

1. It is essential that you get to lab on time! It will not be possible for you to run the reaction if the remainder of the students in your section have already added ether when you arrive.
2. Do not remove any flammable chemicals from the hood or your desk until your TA says that it is permissible to do so!

Prepare two drying tubes filled with calcium chloride (Drierite). Be sure the drying agent is fresh and not packed too tightly. Set these aside until after flame-drying is completed.

Equip a dry 250-mL three-necked flask with a stirbar, a condenser (do not attach the water hoses yet), a 125-mL addition funnel, and a glass stopper (see Figure 2). Grease all joints lightly. DO NOT PUT ANY KECK CLAMPS ON THE APPARATUS PRIOR TO FLAME DRYING. The flask should be clamped high enough that a heating mantle or ice bath can be easily set beneath it.

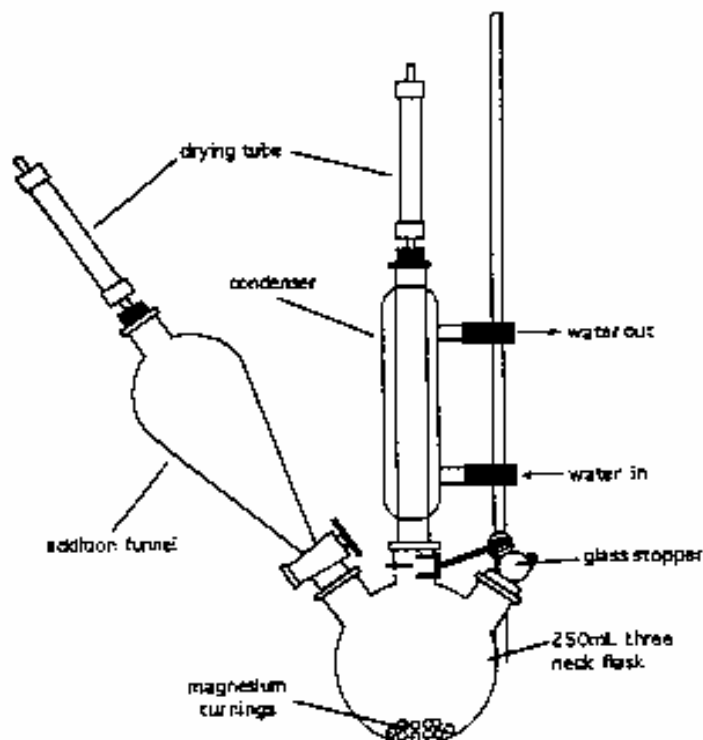


Figure 2: Apparatus for Grignard Reaction

Flame dry your apparatus, starting at the bottom and working up so that moisture is driven out through the top of the condenser and addition funnel. Turn off your flame. While the apparatus is still hot, attach the drying tubes. Allow your apparatus to cool to room temperature.

While you're waiting for the apparatus to cool, weigh out 4.0 g of magnesium turnings. Crush them with a mortar and pestle to expose a fresh surface on the metal. It is not necessary to grind them excessively before use. Add the magnesium to the flask (this may be done before the flask is fully cooled). Prepare an ice bath using your crystallizing dish; it may be needed for emergency cooling in the next few steps. When your reaction flask has cooled, attach the hoses to the condenser and turn on the water. Make sure that water is flowing through the condenser before proceeding.

DO NOT PROCEED BEYOND THIS POINT UNTIL YOUR TA ANNOUNCES THAT ALL FLAMES HAVE BEEN EXTINGUISHED!

When all flames have been extinguished, you may proceed. Obtain 7 mL of bromobenzene and 15 mL of dry diethyl ether (HIGHLY FLAMMABLE), and use the ether to wash the bromobenzene into the addition funnel. Be sure the layers mix! Add approximately 1/4 (*ca.* 6 mL) of the concentrated bromobenzene solution to your reaction flask, along with a crystal of iodine, to initiate formation of the Grignard reagent. Use the warmth of your hands to gently heat the mixture. The onset of reaction is indicated by the formation of bubbles on the surface of the Mg⁰ and by a slight cloudiness. As the reaction proceeds, the ether will begin to warm, then boil. As a last resort, ask your TA to add a few drops of methyl iodide.

After the reaction has started and is definitely refluxing, promptly add an additional 30 mL of dry diethyl ether to the addition funnel, and mix well. Add this solution dropwise at a rate such that reflux is maintained (*ca.* 1-3 drops per second). If the reaction begins to reflux too vigorously, cool it slightly in an ice bath. Do not overcool, as this will significantly retard the rate of reaction. When all the bromobenzene has been added, reflux the ether solution gently for 20 min using a warm water bath, then cool the reaction mixture in an ice bath. Some magnesium turnings will remain. Since the Grignard reagent deteriorates on standing, the next step should be started immediately.

C. The Grignard Reaction

Dissolve 5.00 g of the ethyl acetoacetate ethylene ketal (prepared in Part A) in 10 mL dry diethyl ether, then transfer it to the addition funnel. Use an additional 5 mL dry ether as a rinse to complete the transfer. Add this solution dropwise to your cold Grignard reagent via the addition funnel while stirring vigorously. It is important to add this solution carefully as the reaction is quite exothermic and the solvent volatile. Upon complete addition of the ketal, remove the ice bath and stir the mixture at room temperature for 30 minutes.

Carefully add 30 mL ice to the flask to quench any remaining Grignard reagent (you may need to use a spatula to help break up the solids), then add 10 mL of ether (it doesn't have to be dry) and stir the mixture until the gummy yellow solids (your product) dissolve and the mixture stirs freely. Carefully decant the yellow ether layer into an Erlenmeyer flask. Add 20 mL ether to the remaining white sludge, stir to extract any additional product, then decant again. Transfer the combined ether extracts to a separatory funnel and wash with 20 mL of water. Dry the organics over MgSO_4 , then filter to remove the solids. Remove the solvent by rotary evaporation. The residual yellow-orange oil is the crude tertiary alcohol, which may solidify on cooling. Calculate the crude % yield of this reaction.

Note: This is a good stopping place.

Note: It is possible, but not necessary, to recrystallize the product. If your instructor requires it, you should recrystallize from hexanes, adding the warm solvent slowly with swirling. Recall that the general procedure for recrystallization involves: 1) dissolving the solid in the minimum amount of boiling solvent; 2) performing hot filtration (if undissolved impurities are present); 3) allowing the solution to slowly cool; 4) initiating crystallization if necessary by scratching the flask's surface; 5) cooling the mixture of crystals and "mother liquor" on ice; 6) separating the crystals and mother liquor by vacuum filtration; 7) rinsing the crystals with a small amount of cold solvent. Calculate the yield of this reaction, and obtain the melting point and an IR spectrum. Interpret the NMR for the tertiary alcohol (provided on ICON). Save a small sample of the product for TLC.

D. Ketal Hydrolysis

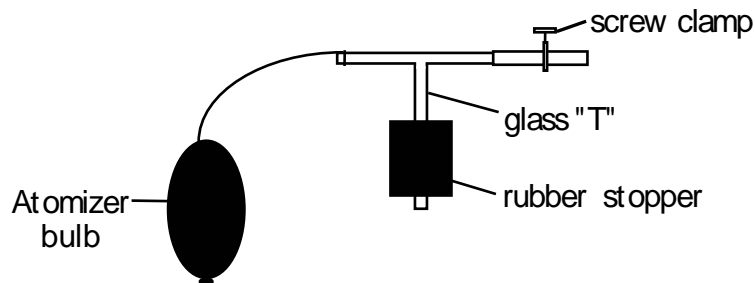
Note: During the 1-hour reflux time of part D, you should pack the column for Part E.

In a 100 mL round bottom flask, dissolve your tertiary alcohol in 25 mL acetone. Add 1.5 mL water and 1 mL concentrated HCl. Fit the flask with a condenser and warm to reflux. After 1 hour, cool the reaction mixture to room temperature and transfer it to a separatory funnel. Add 25 mL water, then extract the mixture with two 15 mL portions of ether. Combine the ether layers and wash with 15 mL saturated NaHCO_3 (aq), then 15 mL of water. Take care, as CO_2 is evolved upon addition of NaHCO_3 . Once you invert the separatory funnel, you must open the stopcock immediately to release the pressure. Dry the organics over MgSO_4 , filter, then remove the solvent on the rotary evaporator or by simple distillation. Calculate the yield of this reaction and obtain an IR. Save a small quantity of the crude product for TLC. Using the instructions provided below, purify a small sample (*ca.* 0.75 g) of 4,4-diphenyl-3-buten-2-one by column chromatography.

E. Column Chromatography

Compare your crude product with an authentic sample of 4,4-diphenyl-3-buten-2-one (if available) by TLC. Dissolve your crude sample in a little ether. The authentic sample should already be in solution. Develop the TLC plate using a 7:1 mixture of hexanes:ether. Visualize the plate by both UV light and in an iodine chamber. As always, be sure to record this information in your notebook. Using this information, comment on the purity (and identity) of your crude product.

Purify 0.75 g of the crude 4-diphenyl-3-buten-2-one by column chromatography. For best results, follow the directions below carefully. Be sure to consult your TA if you find the instructions unclear.



1. You should have a 24" column with a stopcock to be used to prepare your column.
2. Weigh out approximately 19 g of silica gel into a beaker. Set aside for later use.
3. Carefully plug the narrow end of the column with a small, rolled wisp of cotton either using a wood dowel. Your TA will demonstrate.
4. Clamp the column securely (use two clamps), tip down, and add just enough sand to cover the cotton (*ca.* 1cm).
5. Add *ca.* 100 mL of hexanes to the beaker of silica gel. Stir with a glass rod to make a slurry.
6. Carefully pour your slurry into the column. CAUTION! Rapid addition will result in trapped air bubbles which will lower the efficiency of the column. Add your silica gel slowly!
7. Once the silica gel has been added, open the stopcock and allow the solvent to drain. DO NOT LET THE COLUMN RUN DRY! Once the solvent level has dropped to about 2 cm above the silica gel, remove the "T" and allow the remaining solvent to drain slowly until the solvent level is just above that of the gel. Close the stopcock.
8. Using a little hexanes, rinse down any silica gel that sticks to the sides of the column. Again, slowly drain the column until the solvent level is just above that of the silica gel, then close the stopcock.
9. Add *ca.* 1cm of sand to the top of the column (use a funnel). The sand acts as a buffer so the surface of the silica gel is not disturbed during the steps that follow.
10. Get 100mL of 100:2 hexanes:ether in an Erlenmeyer flask. Set it aside for later use.
11. Carefully load 0.75 g of your crude 4,4-diphenyl-3-buten-2-one onto the column. Use a long Pasteur pipet to deliver your sample uniformly just above the surface of the sand. It is often best to touch the pipet tip to the wall of the column as near to the surface of the sand as possible, then gently add the sample. Be careful not to disturb the surface of the sand during this process.
12. Complete the transfer of your crude product to the column surface using two 0.5 mL increments of the 100:2 hexanes:ether solution. Thus, add 0.5 mL of this solution to your product flask, agitate the solution with your pipet (pull the mixture rapidly into and out of the pipet), then transfer the solution to the column as described above. Drain the liquid to just above the level of the sand, then repeat this process.

13. Carefully fill the column with the 100:2 hexanes:ether solution, being careful not to disturb the surface of the sand. It often works best to add about 10 mL of solvent with a (clean) pipet to create a buffer zone before adding the remaining solvent.

14. Elute the column into a 125-mL Erlenmeyer flask, refilling as needed with the remaining 100:2 hexanes:ether solution. Apply pressure to the top of the column to increase the rate of elution. A pale yellow band will begin to move down the column as the solvent elutes. Do not let the column run dry.

15. Once you have collected *ca.* 80 mL of eluent, drain the solvent to the level of the sand, then gently refill the column with a 7:1 solution of hexanes:ether.

16. Collect the eluent in ten 16 x 150 mm test tubes, refilling the column as needed (you will need approximately 350 mL of solvent all together). Again, apply pressure to increase the rate of elution. Be very careful not to let the column run dry. Once you have collected your fractions, close the stopcock.

17. Evaluate your fractions by TLC (you may need to use more than one plate). In one of the lanes on each plate, spot an authentic sample of 4,4-diphenyl-3-buten-2-one. Use a 7:1 hexanes:ether solution in your developing chamber. Visualize the plates first with UV light, and then in an iodine chamber. Use the information provided by your TLC analysis of the authentic sample to identify which fractions contain your pure product.

18. Transfer only the fractions that contain your pure product to a tared roundbottom flask, and concentrate using the rotary evaporator. Be sure to rinse out your test tubes with a little solvent (7:1 hexanes:ether is good) to complete the transfer. Record the weight of the pure product you obtain.

19. Prepare an NMR sample of the final purified product, and submit it to your TA. Interpret your NMR and compare it to the literature spectrum for 4,4-diphenyl-3-buten-2-one (provided on ICON).

20. When you are finished, clean out the column.. Sand and silica gel should be disposed of in the solid waste container. **Note:** Use compressed air to blow out the wet sand and silica gel.

F. Analysis of the Reaction Sequence by TLC

Show by TLC that the products at each stage of the sequence are different. Don't forget to include in your analysis the starting ethyl acetoacetate. Use a 9:1 toluene:methanol solution as the eluent, and visualize the compounds both with UV light and I_2 . Calculate the R_f value for each compound.

Results and Discussion

For this experiment, it is a good idea to separate your Results and Discussion section into parts, each clearly explaining why you believe your reactions were successful. As always, use your experimental data to support your conclusions and be sure to explain yourself clearly. Calculate the yield for each step in the sequence, and for the overall process (A-D). Be sure to take into account the fact that you may not have used all of the material produced for each subsequent step. Include your spectra (IR, NMR) in your report, as well as your TLC results. Note, when discussing the TLC, be sure to discuss the changes in R_f value relative to the polarity

of the starting material and product (e.g., is the ketone more or less polar than the ketal? What effect would you expect this to have on the R_f value of the product? Is this what you observe?).

Submit your data sheet, your isolated products (ketal, tertiary alcohol, and 4,4-diphenyl-3-buten-2-one) and your derivative to your TA along with your report.

References

G.M. Loudon "Organic Chemistry", 2nd ed.; Benjamin/Cummings: Menlo Park, CA, 1988, pp 787-791.

L.M. Harwood and C.J. Moody, "Experimental Organic Chemistry: Principles and Practice"; Blackwell Scientific Publications: Oxford, England, 1989, pg 447-449.

L.F. Fieser, "Organic Experiments", 2nd ed.; Raytheon Education Co.: Lexington, MA, 1968, pg 91-95.

Name: _____

Section: _____

Date: _____

Ethyl Acetoacetate Ethylene Ketal

Starting material (g): _____

Yield (g): _____

% Yield: _____

Grignard Product

Starting material (g): _____

Yield (g): _____

% Yield: _____

4,4-Diphenyl-3-buten-2-one

Starting material (g): _____

Crude Yield (g): _____

Amount used for purification (g): _____

Recovery from purification (g): _____

% Recovery from purification: _____

% Yield: _____

% Yield Overall: _____

R_f values:

Ethyl Acetoacetate: _____

Ethyl Acetoacetate Ethylene Ketal: _____

Grignard Product: _____

4,4-Diphenyl-3-buten-2-one: _____

Drawing of TLC plate: