THE COLLEGE OF WOOSTER

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Spring 2007 — Peter Blass

PROJECT I: SYNTHESIS OF A PROPYL BENZHYDRYL ETHER FROM BENZOPHENONE[1]

This experiment is a multi-week project with several steps. Correspondingly, there are numerous intermediate goals leading to the final goal. You may proceed at your own pace during the allotted laboratory time, but you must:

1) Follow proper safety guidelines and procedure. (Safety is always more important than speed.)

2) Complete all laboratory work by the end of lab on Week 6 (Feb 20, 21, or 22). If you complete all laboratory work before this deadline, you may leave early, but you should still attend the beginning of each class.

   No additional laboratory time will be provided. It is your responsibility to ensure that the project is complete on time.

   Detailed experimental plans, complete pre-lab data in the notebook, and a bit of mental preparation will help to ensure that the laboratory work proceeds smoothly and efficiently.

3) Submit assignments *promptly* at the beginning of your laboratory period. See the Chemistry 212 Schedule for a list of assignments and due dates.

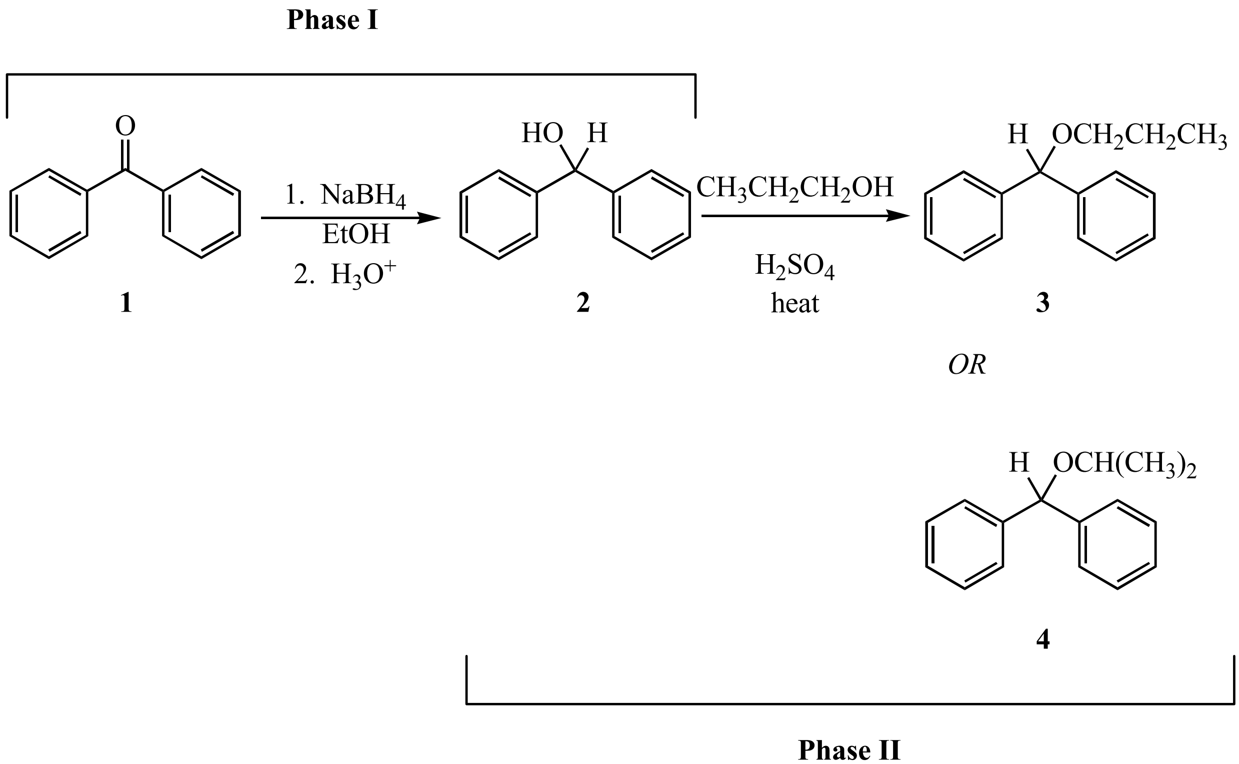
4) Attend the purification discussion (Week 5), the NMR discussion (Week 6), Library Session (Week 7), and Lab Quiz (Week 8).

Overview

Sometimes a desired compound cannot be prepared with a single reaction. In a multi-step synthesis, several reactions are carried out in sequence, with the product of one reaction becoming the starting material for the next one, ultimately leading to the final target. There are often intermediate purification and characterization steps that take place along the way. In this project, you will prepare an ether from a ketone by way of an alcohol intermediate.

Alcohols are common synthetic intermediates that can be converted into alkyl halides, alkenes, ethers, and other functional groups. They are frequently prepared by reducing a carbonyl compound with an organometallic reagent (such as a Grignard reagent) or a hydride reagent (such as $NaBH_4$ or $LiAlH_4$). This project will demonstrate the utility of benzhydrol **2** as a synthetic intermediate in the multi-step synthesis of a propyl benzhydryl ether **3** or **4** from benzophenone **1** (Scheme 1).

Scheme 1.



The project will be conducted over several weeks with each student proceeding at their own pace. **Remember that Experimental Plans and other assignments are due at the *beginning* of the laboratory period. Deadlines will be *strictly enforced.* Please prepare to work efficiently and productively so that you complete all laboratory work by the end of the allotted time.** Recall that the Experimental Plan describes the procedures for a single given day rather than for the entire project.

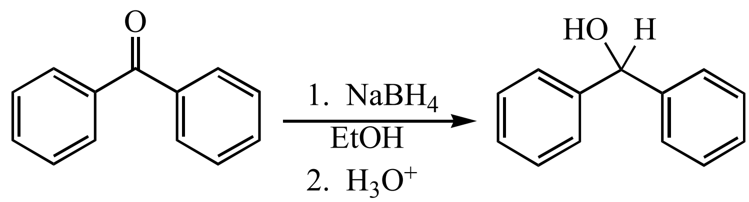
The principal scientific goal of this project is to synthesize a propyl benzhydryl ether and to determine its identity (1- or 2-propyl as shown in Scheme 1). The project consists of multiple reactions, analyses, and procedures, so there are several intermediate steps and goals that must be successfully completed to reach the ultimate goal of preparing and identifying the ether. To simplify the project and to highlight the intermediate steps, the project is divided into two major segments (Phase I and Phase II in Scheme 1).

Phase I. Isolation of Purified Benzhydrol

Phase I, Part A. Reduction of Benzophenone to Benzhydrol

The first reaction is the synthesis of the alcohol synthetic intermediate (benzhydrol) from benzophenone (Scheme 2).

Scheme 2.



1 **2** (2)

The main goals of this phase are to:

a) reduce benzophenone to benzhydrol
b) determine the crude yield of the reaction
c) determine the identity and composition of the product by TLC (standard solutions of the ketone and alcohol will be provided)
d) purify the crude benzhydrol by recrystallization
e) determine the purified yield
f) assess the purity of the recrystallized material by TLC and melting point analysis

<u>Prelab Guidelines</u>

The prelab notebook entries and Experimental Plan should contain all information necessary to complete the reaction safely and efficiently for that day.

It may be helpful to complete the Reaction Stoichiometry Worksheet before writing in the notebook. Calculate the mass of sodium borohydride necessary to reduce 10 mmol of benzophenone, keeping in mind that (i) 1 mole of $NaBH_4$ delivers about 2 moles of hydride ion, and (ii) you should use twice the amount of $NaBH_4$ than is stoichiometrically necessary. The reduction will be carried out with ethanol as the solvent, with the initial benzophenone concentration as close as possible to 1.2 M. For simplicity, you may assume that the volume of the benzophenone solid contributes negligibly to the total volume of the solution.

CAUTION: Sodium borohydride is a flammable, corrosive, hygroscopic solid. Weigh it out quickly and recap the bottle. Wear gloves when using $NaBH_4$, and if you spill it on the counter, wash it immediately with water. Weigh out the $NaBH_4$ immediately before you are ready to add it to your reaction.

The following solvents will be available in the laboratory: ethanol, methanol, acetone, ethyl acetate, diethyl ether, methylene chloride, hexanes, and ligroin. The Experimental Plan should mention which of these will be tried first for TLC analysis.

Experimental Procedure[2]

Select a reasonably sized Erlenmeyer flask and add a stir bar. Dissolve 10 mmol of benzophenone in enough 95% ethanol to prepare a 1.2 M solution. Place the flask in a cool water bath. Place a thermometer in the bath. (Be sure the thermometer is secure and cannot fall and break.) While stirring the solution, add the $NaBH_4$ in small portions. The portions should be small enough to cause moderate hydrogen gas evolution and to keep the temperature of the water bath below 40 °C (add ice if necessary). If the solution becomes too thick to stir, add a few more drops of 95% ethanol.

Once the $NaBH_4$ addition is complete, stir the reaction for 10 minutes at room temperature, then with moderate heat (warm, but not boiling) for 5 minutes. Heat the mixture to its boiling point for 30 seconds to complete the reduction. Remove the flask from the hot plate and cool to room temperature. Quench the reaction with H_2O (twice the volume of the ethanol solution).[3] Add 3 M aqueous HCl dropwise until hydrogen gas evolution stops. Verify with pH paper that the aqueous solution is acidic (but "Do not ever dip the test paper into any solution. Ever.")[4]

CAUTION: The quench can be vigorous. Add the water and acid slowly and have an ice bath on hand to slow the quench if necessary.

Extract the reaction mixture three times with ether.[5] For each individual extraction, the volume of the organic solvent should be about the same as the volume of the reaction mixture. (Your Experimental Plan should include the specific target volumes that you plan to use.) Wash the combined organic layers with cold water (again using a volume of washing solvent equal in volume to the mixture being washed) followed by saturated sodium chloride solution. Dry the organic layer with Na_2SO_4. Decant or filter the solution into a weighed round bottom flask and remove the ether using a rotary evaporator.

- Once all the solvent is gone, determine the crude weight of the resulting solid to obtain the crude yield.
- Analyze the crude product by TLC. Standard solutions of the ketone and alcohol will be provided.
- Determine whether you can proceed to recrystallization or if you need to repeat the reduction.

To proceed to recrystallization, you must have at least 1.0 g of crude benzhydrol. If you have too little, you may either repeat the reduction once at no penalty or "buy" crude benzhydrol from your instructor for a 10-point deduction from your technique grade for the project. If you repeat the reduction and still do not have enough benzhydrol, you may "buy" crude benzhydrol for 5 technique points.

Phase I, Part B. Recrystallization of Benzhydrol

Recrystallization is one of the most effective methods for purifying a solid. A successful recrystallization relies on the use of a suitable solvent and an appropriate amount of solvent. You must make these determinations independently in this project.

Solvent Choice

a) The product should be as soluble as possible in hot solvent and as insoluble as possible in cold solvent.

b) The impurities should be either completely soluble or completely insoluble in the solvent (regardless of whether hot or cold) so that they can be removed by filtration.

c) If a single solvent does not meet these requirements, a mixed solvent system can be used.

Prelab Guidelines

To recrystallize the crude benzhydrol, you will need to know the solubility of benzhydrol in various solvents (hot and cold). If you know the identity of any impurities, you will also need to consider their solubility in the solvent.[6]

You may be able to find solubility information in a handbook. More likely, you may have to determine for yourself which recrystallization solvent is most suitable (see Zubrick, p. 104). The identity and amount of the solvent will depend on the amount and purity of the crude benzhydrol sample. The recrystallization step will require careful and thoughtful planning; the Experimental Plan should include a specific and detailed description of the steps you will carry out. The most common error is using too much solvent and having the crystals fail to appear.[7]

Experimental Procedure

Follow the procedure given in Zubrick for choosing a recrystallization solvent (p 104). You may need to adapt the procedure for your material. Carry out the recrystallization once you have determined a suitable solvent.

The following solvents will be available in the laboratory for use in recrystallization and TLC analysis: ethanol, methanol, acetone, ethyl acetate, diethyl ether, methylene chloride, hexanes, and ligroin. (Remember that a mixture of solvents is also a possibility.) Once you have recrystallized the product, let any residual solvent evaporate before determining the purified yield and melting point. TLC analysis, however, can be carried out at any point after the recrystallization.

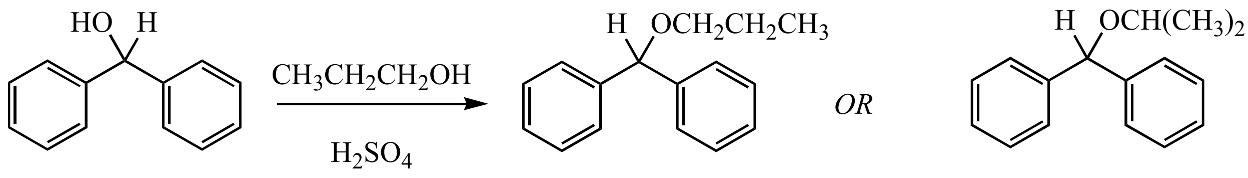
To proceed to the benzhydryl ether synthesis (Phase II), you must have at least 0.5 g of reasonably pure benzhydrol based on the TLC and melting point data. If you have too little material, you may "buy" pure benzhydrol from your instructor for 10 technique points and then proceed to the benzhydryl ether synthesis. Alternatively, you may "buy" 1.0 g of impure benzhydrol for 5 technique points and then repeat the recrystallization.

Phase II: **Isolation and Identification of a Propyl Benzhydryl Ether**

A. Synthesis of a Propyl Benzhydryl Ether from Benzhydrol.[8]

The second phase of the project involves the synthesis of a propyl benzhydryl ether from benzhydrol with propanol under acidic conditions (Scheme 3). In theory, two products may be possible: either 1-propyl benzhydryl ether **3** and/or 2-propyl benzhydryl ether **4**.

Scheme 3.



2 **3** **4**

The goals of this phase are to:

a) synthesize a benzhydryl ether
b) determine the crude yield of the reaction
c) assess the purity of the product by TLC, IR spectroscopy, and NMR spectroscopy. Standard data for the ethers will not be provided.
d) Determine whether 1- or 2-propyl benzhydryl ether was formed
d) explain, using mechanisms and fundamental chemical principles, *how* the major product formed and *why* it is the predominant product

Prelab Guidelines

The prelab notebook entries and Experimental Plan should contain all information necessary to complete the reaction safely and efficiently for that day.

Using the amount of recrystallized benzhydrol obtained in Phase I, calculate the volume of solvent necessary to prepare a 1.6 M solution of benzhydrol in 1-propanol. (Note that 1-propanol serves as both a reagent and as the solvent in this reaction. You may want to mathematically verify that benzhydrol will be the limiting reagent.) Determine what volume of concentrated sulfuric acid catalyst is required to make up 10% of the total volume of the reaction mixture.

CAUTION: H_2SO_4 is corrosive and can cause severe burns. Use gloves and tremendous care when handling it.

Experimental Procedure

Place the benzhydrol, 1-propanol, concentrated H_2SO_4, and a stir bar in a reasonably sized round bottom flask. (Select a flask that will be no more than half full). Attach a reflux condenser (with water lines) and reflux the mixture (with stirring) for 25 minutes. Remove the flask from the hot plate and cool the mixture to room temperature.

Quench the reaction with an equal volume of water. Extract the mixture with three portions of heptane. (Use the extraction guidelines outlined in Phase I.) Wash the combined organic layers once with water and once with aqueous 0.5 M sodium carbonate solution. **CAUTION: Vent the separatory funnel often**. Check the pH of the carbonate aqueous wash; it must be basic. If it is not, wash the organic layer with additional carbonate solution. Dry the organic layer with Na_2SO_4. Filter or decant the solution into a weighed round bottom flask and remove the heptane by rotary evaporation.

- Once all the solvent is gone, determine the crude weight of the resulting material to obtain the crude yield.
- Prepare and submit a sample for NMR analysis.
- Collect IR and TLC data. Standard data for the ethers will not be provided.
- Determine the identity and purity of the product.

Evaluation

Notebook
Your duplicate notebook pages and Data Archive Folder will be collected. Selected portions will be graded for completeness and adherence to the guidelines outlined in the *Organic Chemistry Laboratory Information Guide*.

Report
The laboratory report for this project makes up a substantial portion (20%) of your final grade in the course. You will write and submit a *full* laboratory report that includes:

Cover page (with informative title)
Abstract
Introduction
Experimental
Results and Discussion*
Conclusion
References
Appendix with calculations and copies of relevant data

* In the "future work" portion of the Results and Discussion, propose a *detailed* method for purifying the crude ether.

You should refer to the *Organic Chemistry Laboratory Information Guide* and the Writing Tutors for general guidelines and specific advice. We will also have several writing activities that will help you to write a high-quality report.

References and Notes

1. Adapted from an earlier work by Judith Amburgey-Peters.

2. Adapted from Amburgey, J. C.; Haynes, L. W. *211 Laboratory Syllabus;* 1998.

3. If you selected a reasonably sized Erlenmeyer flask at the beginning, you should be able to just add the water to the flask. If there is insufficient space in flask, transfer the ethanol solution to a separate Erlenmeyer flask that contains the necessary volume of H_2O.

4. Zubrick, J. W. *The Organic Chem Lab Survival Manual*, 6th ed.; John Wiley: Hoboken, NJ, 2004; p 130.

5. Remember that multiple small extractions are more effective than one large extraction (reference 4, pp 136-139).

6. Impurities usually cannot be readily identified and are present in small amounts, so the choice of recrystallization solvent depends primarily on properties of the product.

7. Reference 4, p 103.

8. Adapted from *Experimental Organic Chemistry*; Mohrig, J. R., Hammond, C. N., Morrill, T. C., Neckers, D. C., Eds.; W. H. Freeman, 1998; p. 129.

Questions for Consideration

You do not need to write a response to the questions below, but the answers will help with your experimental plan, efficiency of lab work, conversations with the instructor, and upcoming quixams:

- In the reduction reaction, what is a "reasonably sized" Erlenmeyer flask? Consider the steps ahead to predict what volume of liquid the flask will ultimately need to hold.
- Why is it advantageous to wash the crude benzhydrol solution with cold (rather than room temperature) water? Why perform the final wash with saturated aqueous NaCl rather than ordinary water?
- After recrystallizing benhzhydrol, why is it alright to perform TLC analysis immediately but necessary to wait before taking a melting point or determining yield?
- What role does the aqueous sodium carbonate solution play in the workup of the crude ether?
- What other set of reagents and conditions could have been used to synthesize a benzhydryl ether?