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CHEMISTRY 113B

Organic Chemistry Laboratory

FALL 2014

Laboratory Experiments and Supplemental Information

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Checking-In Procedure

Upon checking in, make sure that you have all the items on the blue card in your locker or drawer, and that none of the glassware is broken or has cracks. These will be replaced at no charge only on the first day of class. *If you later discover that an item is missing or broken, you will likely be charged to replace the item.*

Write your lock combination in a safe place!

After the instructor signs your blue card, return it to the Service Center. You will be given a pad of "check out" slips. Keep this pad in a safe place, since they are coded, and someone else may use it to check out items under your name. Use your pad to check out:

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- Hall locker
- Bottle of acetone for cleaning
- "Chem 113B Starter Kit" which includes:
 - 12 9" Pasteur disposable pipettes
 - 3 rubber bulbs for pipettes
 - 1 pack capillary tubes for melting points
 - 3 size #1 corks (to fit 10 x 75mm test tubes)
 - 1 size # 9 cork (to fit 6 x 50mm test tube)
 - pack of TLC plates

Miscellaneous Information and Tips:

- Bring a PENCIL to each lab, since you will need it for certain operations. It is also a good idea to bring a permanent marker (e.g., SharpieTM brand) with black ink that will write on glass surfaces.

- Since we will use it so much in the lab, note that the following terms are equivalent: diethyl ether = ether = ethyl ether = EE These all refer to the same solvent (you should know the structure).

Note: "Petroleum ether" is NOT the same as "ethyl ether" (It is not even an ether, it is a hydrocarbon mixture!) Unless otherwise noted, use the ether from the 1-liter plastic bottle on the shelf. For dilutions of samples for gas chromatography, use only the ether from the 100ml brown bottle kept in the hood (this solvent is of higher purity).

- Some weights and measures need to be precise, whereas others may be approximated, and don't need to be measured as accurately. In general, a reagent or starting material for a reaction needs to be measured carefully. The amount of solution or substance used for extraction or drying steps is normally approximated.

- When using the disposable Pasteur pipettes, always transfer liquid with the tips facing *down*. If the liquid gets into the rubber bulb it may get contaminated, or worse, dissolve the bulb and get into your solution! Also, one "full" squeeze of the bulb is roughly 1 mL. You can practice this measurement with your graduated cylinder.

- Because floods and spills are fairly frequent occurrences in this lab, you should only have your lab notebook and writing tools on the benchtop. You should put your clothes, backpacks and books on the shelves by the windows. For the same reason, you should refrain from wearing expensive clothing and shoes to lab.

- We will NEVER use Bunsen burners or any open flame to heat reactions. The two heating methods we have are steam cones and thermowells. Steam is a most efficient way to heat a reaction quickly, but note it is *very hot*. Use care when turning on the steam, and keep your arm away from the top of the steam cone. NEVER turn the steam fully open, usually if you can hear the steam "sound" it is sufficient. Thermowells are plugged into the "powermites" which control the amount of heating. Unless otherwise told, never turn the powermite beyond a setting of 3 or 4. Be careful not to let your heated glassware go completely dry, since it will crack if all the liquid evaporates.

- When using glassware with ground glass joints, it is a good idea to put a tiny spot of stopcock grease on one part of the joint, then attach the other section and rotate to distribute the grease. Don't use a large amount of grease since it may dissolve into (and contaminate) your product.

...applied grease on one part of the joint, then turn the other section and repeat to distribute the grease. Don't use a large amount of grease since it may dissolve into (and contaminate) your product.

- Evaporation of solvents will be performed in a variety of ways. For amounts > 5ml, we will most likely use the *rotary evaporator*. For amounts < 5ml, we may allow the solvent to evaporate in the fume hood, or use a gentle stream of nitrogen to evaporate the solvent. In general, you should not evaporate solvents outside of the hood.
- Do not store solutions containing flammable solvents (e.g. ether, hexane, ethyl acetate, etc.) in your lab drawer or hall locker. Give them to the instructor to store in the hood until the next lab period.

Experiment Zero (0)

Identification of an Unknown Solid

The goal of Experiment Zero is to give all Chem 113B students a chance to familiarize themselves with several common experimental techniques we will be using throughout the semester. Each student will be given a sample of an unknown solid, which is from a list of 20 possible compounds (see below). Three methods will be employed to identify the unknown compound: melting points, solubility and thin-layer chromatography. Standard samples of all 20 compounds will be available for comparison. One goal of this experiment is not only to perform the measurements of the unknown, but also to logically determine the steps to prove the identity of the compound, given the available information. As will be seen, there may be more than one way to approach this question.

Some references to background reading are provided below, and should be reviewed before starting this experiment. It is expected that everyone in Chem 113B already has a good foundation from Chem 113A. In this and other experiments in Chem 113B, it may also be helpful to review the relevant material from a standard organic chemistry text (such as McMurry).

References:

Dr. Straus' Chemistry 113A website sections on:

Extraction
Melting Point
Thin Layer Chromatography

www.chemistry.sjsu.edu/straus/visioche.htm

Note: In order to receive your unknown sample, you must first prepare a "prelab writeup" in your lab notebook (see format below) and have it approved by the instructor. You should also provide a yellow "Report Summary Sheet" for the approval.

BE SURE TO WRITE YOUR UNKNOWN NUMBER IN YOUR NOTEBOOK

Use the three techniques indicated below to identify your unknown. Technical aspects of each method will be provided in lab. You may have to repeat ambiguous results. A standard sample of all 20 possible unknowns will be available for comparison. At a *minimum*, you **MUST** perform all three methods at least once on your unknown. (TLC should be performed with at least three developing solvents of varying polarities.)

It is strongly recommended that you test and discuss the results for multiple compounds, even if you think you know the ID early on. No report will receive higher than a C grade unless at least five knowns are subjected to full solubility and TLC testing. Select a variety based on acidity and polarity – this will provide context that will make the data easier to discuss.

You should obtain as much data as possible to prove your identification. It may be wise to repeat some measurements to make sure your results are reproducible.

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List of Possible Unknown Compounds:

Your unknown sample will be from one of the following 21 compounds. Reference samples of each will be available in the hood.

2-Naphthol
Acetanilide
Acetylsalicylic acid
Benzhydrol
Benzoic Acid
Benzophenone
Biphenyl
Ethyl p-hydroxybenzoate
m-Toluic acid
Maleic acid
Menthol
p-Dichlorobenzene
p-Dimethylaminobenzaldehyde
p-Hydroxybenzaldehyde
p-methoxyacetophenone
p-Toluic acid
Phenacetin
Phenylacetic acid
Resorcinol
Succinic acid
Thymol

Prelab writeup:

In your lab notebook, prepare a *table* containing the following information for each compound on the list above:

- name of compound
- structure
- molecular weight
- melting point (and boiling point, if available)
- solubility (if available)

This information is available from many sources. In Science 139 we have the following reference books:

- CRC Handbook of Chemistry & Physics
- Merck Index
- Dictionary of Organic Compounds
- Aldrich Catalog

- CRC Handbook of Chemistry & Physics
- Merck Index
- Dictionary of Organic Compounds
- Aldrich Catalog

You can also find the information from many online reference sources.

- For example see www.sigmaaldrich.com

In some cases, the name given is a "trivial" or non-IUPAC name so you may have to determine the formal name first.

Techniques Available:

For Experiment Zero, the following three methods only will be used to identify your unknown:

1. Solubility in water, aqueous acid or base, or organic solvents
2. Melting point*
3. Thin-layer chromatography (TLC) *with at least three different developing solvents.*

Details of each method will be provided in class. Also, the next page gives some general information on solubility testing. You should familiarize yourself with the background information in Dr. Straus' Chem 113A website before beginning each experimental method.

Report for Experiment Zero:

Submit a 3-page (maximum) typewritten report in which you justify the identification of your unknown. In the report, discuss the steps you took to rationalize how you eliminated the other possible compounds. Give as much detail and analysis as possible, and provide data (as much as possible) that justifies your answer.

Along with your report, turn in the duplicate pages of your notebook. Be sure to end your notebook section with a summary of the same results you describe in your report! On the due date of this Experiment (see the schedule) a brief quiz on Experiment Zero will be given at the start of the lab period.

(The format for the formal report for Experiment Zero is different than the reports for Experiments 1 through 4. Details of the formats of the other reports will be given later.)

*Suggestion: recall the use of *mixed melting points* from Chem 113A.

See for example:

<http://www.chemistry.sjsu.edu/straus/EXPTB%20https/FlowDiagramsB/FlowDiagramB2/B2FlowDiag06.htm>

Testing for Solubility of Organic Compounds

Experiment Zero

Organic compounds can be broadly classified as acidic, basic or neutral. The classification is determined by the functional group (s) present. Some examples:

Acidic:	Carboxylic acids, phenols
Basic:	Amines (in the "neutral" or "free base" form)
Neutral:	Hydrocarbons, alcohols, aldehydes, ketones, esters, amides, anhydrides ethers, nitriles, alkyl halides

(Note that this generality applies best when there is a single functional group present. Consider the results you may expect with combinations of functional groups from the above sets.)

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When dealing with unknown organic compounds, one useful aid in identification is determination of its solubility in water, dilute acid and dilute base.

Procedure:

- Place appx. 20 mg of the compound into four test tubes and label A-D.
- Add appx. 1 mL of liquid to each tube to each tube:

Tube A Water
 Tube B Dilute HCl (3M)
 Tube C Dilute NaOH (3M)
 Tube D 5% Sodium bicarbonate

- Shake each tube and note if the sample has dissolved. (Some compounds may be slow to dissolve.)

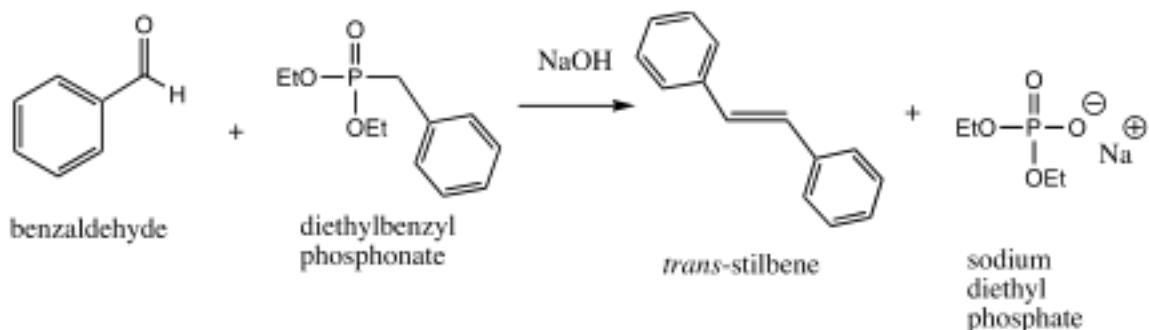
•Interpret your results. Knowledge of pKa's and polarity along with testing of a series of known compounds will be your guide.

Experiment One

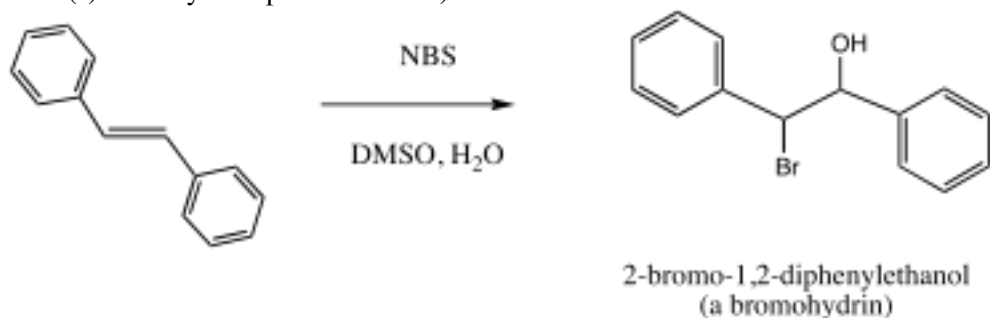
Synthesis of Stilbene and Derivatives

A Multistep Synthesis

Step A involves formation of a carbon-carbon double bond by a common variation on the Wittig reaction. You may want to review the Wittig reaction, and if you are taking Chem 112B concurrently you should definitely read ahead if you have not yet covered this topic.



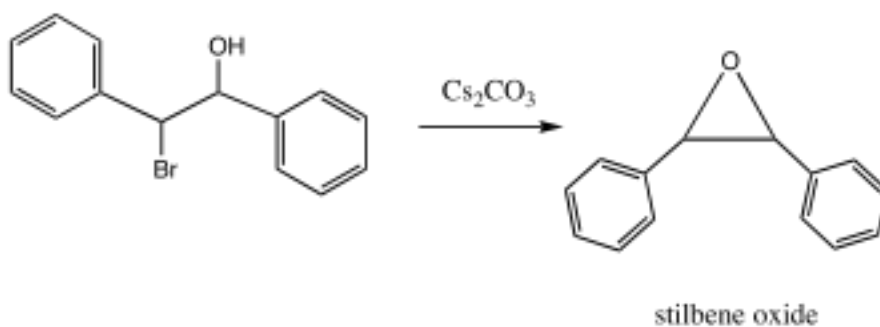
Step B is a fairly common oxidation – hydrobromination of an alkene. (Steps B and C of this procedure are adapted from Ciaccio, *J. Chem. Ed.* **1995**, 72, 1037). (Note that the product has two chiral centers and in principle can exist as four possible stereoisomers. Which stereoisomer(s) would you expect to obtain?)



Step C is an intramolecular elimination reaction of the bromohydrin from above to afford

(a bromohydrin)

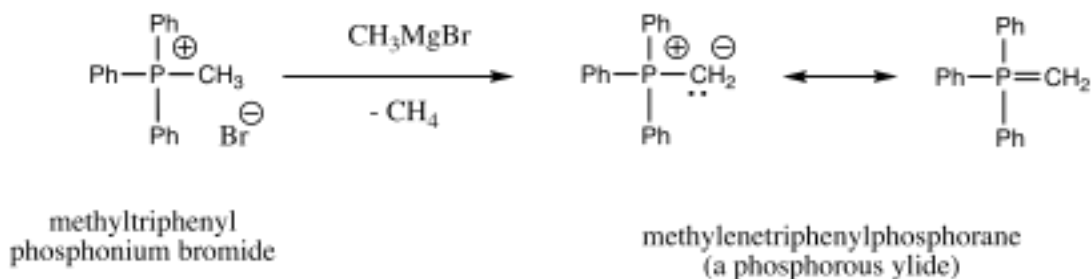
Step C is an intramolecular elimination reaction of the bromohydrin from above to afford stilbene oxide (an epoxide). How many stereoisomers are possible? Can you predict the stereochemistry of this product? (Of course you must know the stereochemistry of Step B.)



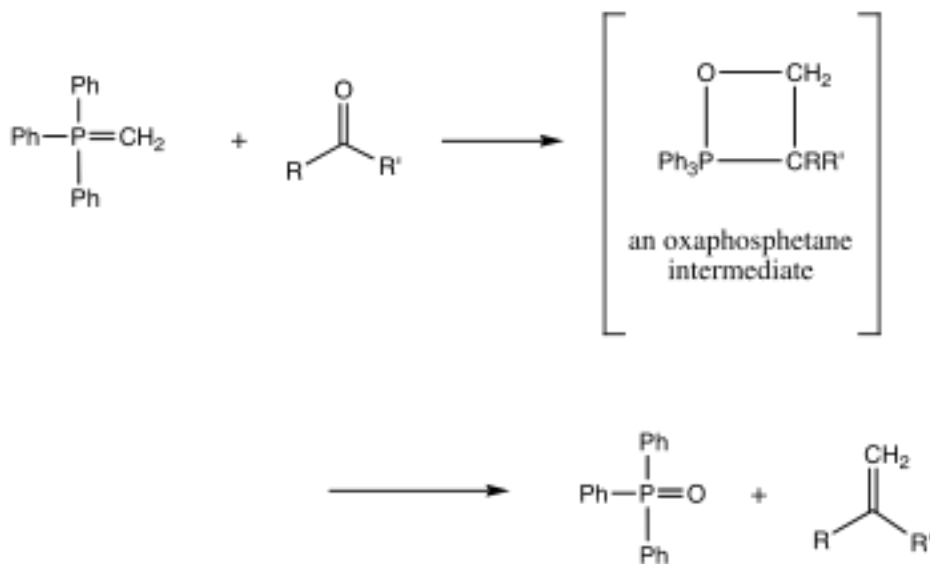
Step A - Preparation of *trans*-Stilbene

The classic Wittig reaction utilizes a triarylphosphorane in combination with an aldehyde or ketone to afford an alkene. It is a very versatile and specific reagent and for the discovery of this and related chemistry Georg Wittig was awarded the Nobel Prize in Chemistry in 1979.

Formation of a commonly used phosphorane is shown below:



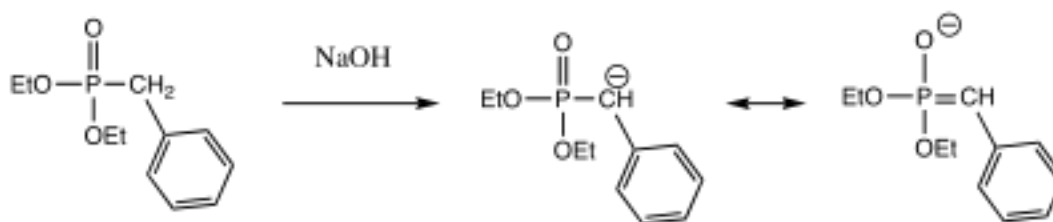
An ylide is a compound in which a carbon bearing an unshared pair of electrons is stabilized by an adjacent heteroatom, most often phosphorous or sulfur. A strong base such as a Grignard reagent, alkyl lithium, or NaNH_2 is required to form a phosphorane. Nonetheless, the ylide is somewhat stabilized by $p\text{-}d$ overlap. Although quite reactive, these compounds can be isolated salt-free and manipulated under air-free conditions, though they are usually generated and used *in situ* to form alkenes as shown below:



Some disadvantages of this reaction are the need for strictly anhydrous conditions (because of the strong bases used) and the difficulty in removing the triphenylphosphine oxide byproduct (due to its sparing solubility in most solvents).

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We will employ a modification of the classic Wittig reaction, sometimes known as the Horner-Emmons reaction. In this variation the ylide bears a formal negative charge that is delocalized to oxygen:



The phosphonate starting materials are less expensive and may be easily made from trialkyl phosphites via the Arbuzov reaction:



[You will not need to perform the Arbuzov reaction, as the diethylbenzylphosphonate will be provided for you, but as an exercise can you draw a mechanism for this reaction?]

Another advantage of the Horner-Emmons reaction is that a weaker base, sodium hydroxide, may be used, and therefore anhydrous conditions are not needed. A further advantage is that the phosphate byproduct is a salt that is readily extracted into water. (Yet another benefit of the H-E reaction is that the ylide is more reactive and will perform the reaction on some ketones not reactive to phosphoranes).

We will use a two-phase reaction system with Aliquat 336 as a phase-transfer catalyst.

Diethylbenzylphosphonate and benzaldehyde are both freely soluble in hexane but sodium hydroxide is not. Sodium hydroxide is dissolved in the water layer, and the organic reagents in the hexane (organic) layer. Aliquat 336 is a quaternary ammonium salt: trioctylmethylammonium chloride. The triocylmethlyammonium ion, with its long hydrophobic alkyl chains) helps transport the hydroxide ion to the organic phase. So Aliquat, in combination with vigorous stirring, greatly facilitates the reaction. It is only needed in catalytic amounts (why?)

Step A Procedure: Preparation of *trans*-Stilbene:

Notes: Aliquat 336 is very viscous and best measured by weighing it directly into the flask with a medicine dropper (the 50 mL round-bottom flask can be stood on a neoprene vacuum adaptor on the balance pan). To save time, you can weigh it out the period before and store it in your locker. You will be using a strong base, so it is essential to lightly grease the joint (alkaline conditions will cause ungreased glass joints to “freeze,” an often irreversible condition). Before you begin this lab you should wash your benzaldehyde 3x with sodium bicarbonate solution – why? [Note: benzaldehyde and water have similar densities so adding one volume of saturated sodium chloride to the 5% sodium bicarbonate will help in separation; wash several mL benzaldehyde rather than just the minimum amount specified.]

(The following procedure is an improvement that was developed by Chem 113B undergraduate Jessica Killian).

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Weigh 352 mg aliquat 336 (MW 404.17) into a 50 mL round-bottom flask. Add 400 mg of benzaldehyde, 750 mg of diethylbenzylphosphonate, 8 mL 40% NaOH, 8 mL hexane and a magnetic stirring bar. (No boiling chips are needed, why?) Fit the flask with a water cooled condenser and heat the mixture at reflux with vigorous stirring (why?) for 1 hour.

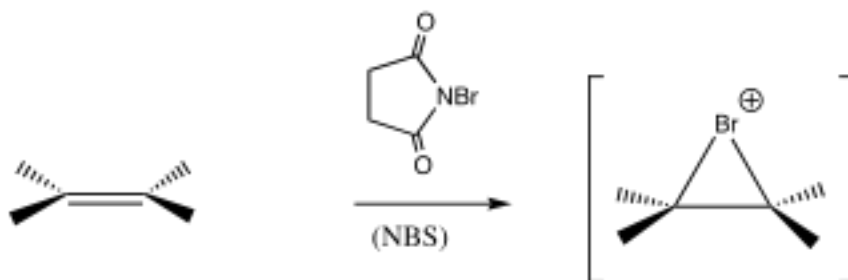
Remove from heat and remove the condenser. This is a good stopping point. Use a greased stopper to seal the flask and stand in a beaker in the locker until the next period.

Remove the grease with a paper towel moistened with hexane or high boiling petroleum ether and cool the mixture in an ice/water bath for at least 30 minutes. Check out a magnet from the service center. Set up for vacuum filtration, moistening the filter paper with water. Swirl the mixture, and using the magnet to hold the stirbar back, decant onto Buchner funnel. Wash the filter cake with two minimal portions of chilled methanol. Air dry on filter for 10 min. Check purity by TLC (hexane) and mp, and weigh the product.

Authentic *cis*-stilbene will be available. If TLC indicates any of the undesired *cis* isomer is present, the product should be recrystallized from denatured ethanol.

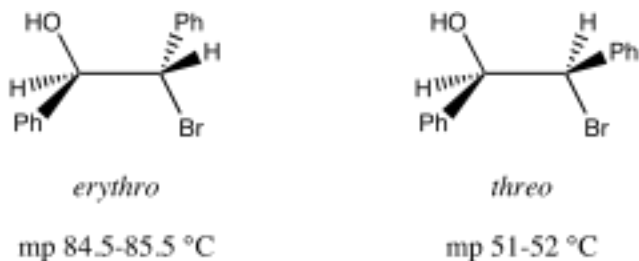
Step B - Preparation of 2-Bromo-1,2-diphenylethanol

N-Bromosuccinimide (NBS) serves as a source of "Br⁺." The resultant intermediate is a cyclic bromonium ion, and it is subject to nucleophilic ring-opening. You should review McMurry to appreciate the mechanistic and stereochemical aspects of the reaction.



DMSO is a convenient solvent as it dissolves the alkene, the bromonium ion, and also water.

Upon reaction with water a bromohydrin is formed (the reaction may be more complex than you would expect, see Dalton, et. al., *J. Am. Chem. Soc.* **1968**, 90, 5498.) In any case there are two diastereomers possible, *erythro* and *threo*:



Because diastereomers have different physical properties, you will be able to use melting point to distinguish these; values given above are from the literature (House, *J. Am. Chem. Soc.* **1955**, 77, 3070).

Step B Procedure: Preparation of 2-Bromo-1,2-diphenylethanol:

Note: Wear gloves when handling NBS and/or DMSO: the former is an irritant and the

Step B Procedure: Preparation of 2-Bromo-1,2-diphenylethanol:

Note: Wear gloves when handling NBS and/or DMSO; the former is an irritant and the latter makes the skin more permeable

Charge a 25 mL Erlenmeyer flask with 500 mg *trans*-stilbene (or if you obtained less than this in Step A, use that amount and modify your Table of Reagents as necessary. Do set aside a very small sample of your stilbene for TLC in the next step). [Note: consult with your instructor if you obtained less than 250 mg.] Add 0.25 mL water and 7.5 mL DMSO and swirl the mixture, which should be nearly* clear; if not warm the solution gently and add up to 2 mL DMSO. At room temperature with periodic swirling, add two equivalents of NBS in small increments over a five minute period.

*It is OK if some solid remains undissolved – this is normal.

Monitor the reaction progress by TLC (1:1 hexane:ether) every 10 minutes:

Special TLC conditions: If spotted as a DMSO solution, you will obtain a long streak since DMSO does not evaporate readily. Therefore, place 0.5 mL water in a test tube and add 2-3 drops of the reaction solution. Add approximately 0.5 mL (or less – just enough to form an organic layer) ether and shake vigorously. Spot the upper (organic) layer on your plate (the DMSO remains in the aqueous layer). Spot this ether solution and the starting *trans*-stilbene on each plate.

When little or no stilbene remains, decant the solution into a beaker containing 25 mL ice-cold water. The white slurry is then transferred to a separatory funnel, and the beaker is washed with 10 mL water then 15 mL of ether – both of which are added to the separatory funnel. Shake the funnel gently or you will obtain an emulsion.* Separate the layers and extract the aqueous layer with a fresh portion of 15 mL ether. Combine the ether layers and wash 1 x 25 mL water and 1 x 25 mL brine. Dry the ether layer over MgSO_4 and gravity filter and evaporate to obtain the crude bromohydrin. Weigh, and perform a mp analysis. Perform TLC spotting an ether solution and developing with 1:1 hexane:ether. Obtain the proton NMR in CDCl_3 .

*In the event of a persistent emulsion, perform a vacuum filtration through celite and return the contents to the separatory funnel.

Option: If your bromohydrin appears impure, you may recrystallize your product from high-boiling petroleum ether; this takes about 30 mL solvent per gram. Review recrystallization on Dr. Straus' web site.

Step C - Preparation of Stilbene Oxide

This is a nucleophilic substitution reaction. It is the most common method for preparing ethers and is one of the first “name” reactions one encounters in organic lecture (hint: begins with a “W”). In this intramolecular example, the product is an epoxide. If you know which diastereomer of the bromohydrin you have you should be able to use your knowledge of the $\text{S}_{\text{N}}2$ reaction to predict the stereochemistry of the epoxide (called stilbene oxide) that you will obtain. (By the way, there are really three stereoisomers of stilbene oxide, not two. What are they?) We once used K_2CO_3 but the reaction was very slow. Dr. Brook substituted the cesium salt – why do you suppose it works better? (Hint: the base is the same in either reagent)

Step C Procedure: Preparation of Stilbene Oxide

Transfer 150mg (0.54mmol) of your purified, dried bromohydrin to a 20 x 150mm test tube. Add anhydrous Cs_2CO_3 (300 mg, 0.92 mmol) and 2mL of methanol. Shake the test tube by hand. Check the progress of the reaction every 10-15min by TLC (20:1 petroleum ether:ethyl

Transfer 150mg (0.54mmol) of your purified, dried bromohydrin to a 20 x 150mm test tube. Add anhydrous Cs_2CO_3 (300 mg, 0.92 mmol) and 2mL of methanol. Shake the test tube by hand. Check the progress of the reaction every 10-15min by TLC (20:1 petroleum ether:ethyl acetate as developing solvent), spotting both the reaction mixture AND bromohydrin on the same TLC plate. Continue to shake and TLC until little or no bromohydrin remains. In some cases, it may help to put the test tube in a beaker of warm water. (Note it is not unusual for much of the solid to remain undissolved.) If the reaction appears to be going very slowly, cover with DuraSeal™ (plastic wrap) and leave until the next lab period.

When the reaction is complete, add 3mL of water and 7mL of low-boiling* petroleum ether. Use a pipette to draw up and expel the liquids in the test tube so that they mix well. Remove the organic layer (make sure you know which layer is which) to a clean test tube. Add a "pinch" of MgSO_4 to absorb any water from the solution. Filter and evaporate the solvent to obtain the solid trans-stilbene oxide product. When dry, weigh to obtain the yield. Measure melting point and check against literature value. Obtain a proton NMR in deuterated chloroform.

*The low-boiling petroleum ether is labeled 30-60 (the bp range in degrees C). (High-boiling, by contrast, is 60-90.)

Summary for Experiment One

Analysis:

- mp: obtain for all 3 products - trans-stilbene, bromohydrin and epoxide
- TLC: record the R_f values for trans-stilbene, bromohydrin and trans-stilbene oxide (and, of course the developing solvent used!)
- IR: no IR spectra will be measured for this experiment (not particularly informative)
- ^1H NMR: obtain for your bromohydrin and epoxide; spectra for stilbene will be provided

Remember that all your data (including a table of NMR data), must be recorded in your notebook. For instructions dealing with reporting IR and NMR data for all experiments see "Handouts" on Chem 113B Web Site:

<http://www.chemistry.sjsu.edu/straus/113BWEBSITE/HOME.html>

Key Discussion Points:

NOTE: Such points are mentioned at the end of every experiment, and are the minimal (but not only) items you should include in your discussion. The information for your report is not limited to the course texts or references provided, and you are encouraged to seek additional information to prepare an in-depth formal report.

Specific for the stilbene experiment: What is the role of Aliquat 336 in phase transfer catalysis? Compare the advantages/disadvantage of the Wittig vs. H-E reactions. Discuss the stereochemistry of the bromohydrin and epoxide reactions, and explain your results.

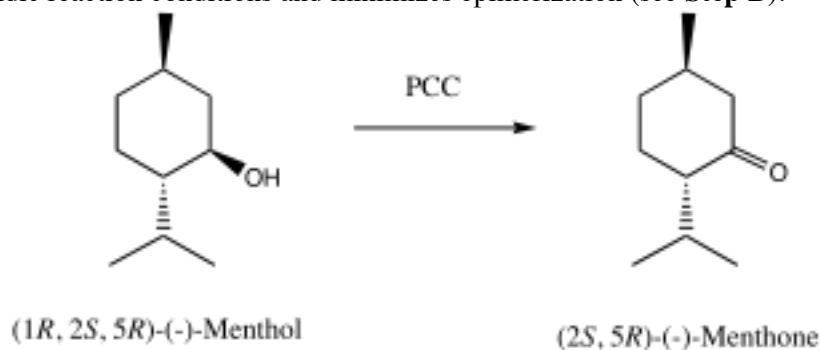
The following are common to this and ALL subsequent formal reports: Show the mechanism of all steps and discuss the major points of each step (not just show the scheme). Explain the key steps of your spectral data that support each structure (include stereochemistry where appropriate). Discuss any special problems or circumstances that may have affected your yield.

Experiment Two

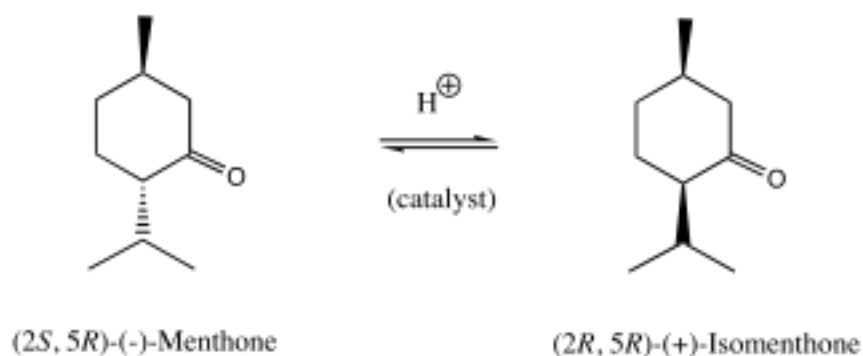
Reactions and Stereochemistry of (-)-Menthol and Derivatives

Step A is oxidation of the secondary alcohol (-)-menthol to the corresponding ketone, (-)-menthone. The procedure is a modification of the Jones reaction (chromic and sulfuric acid mixture) using pyridinium chlorochromate (PCC; the Corey reagent). This variation allows for less acidic reaction conditions and minimizes epimerization (see **Step B**).

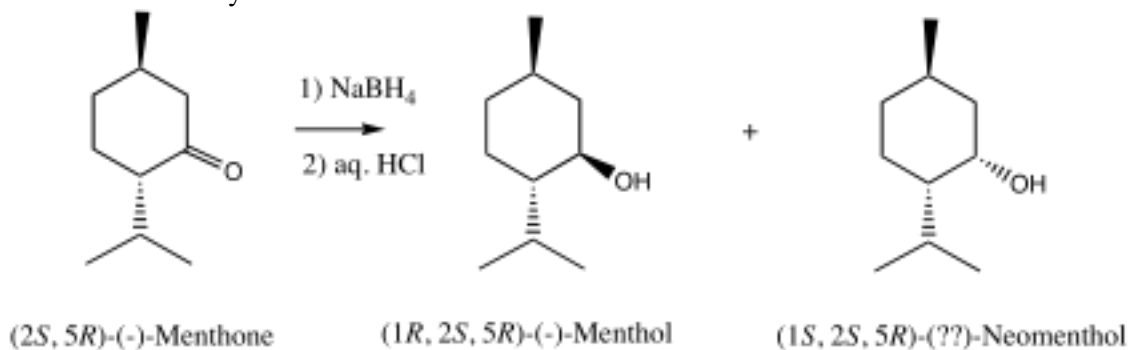
menthone. The procedure is a modification of the Jones reaction (chromic and sulfuric acid mixture) using pyridinium chlorochromate (PCC; the Corey reagent). This variation allows for less acidic reaction conditions and minimizes epimerization (see **Step B**).



Step B involves taking *a portion* of the menthone product from **Step A** and subjecting it to acid-catalyzed epimerization to afford an equilibrium mixture of (2S, 5R)-(-) menthone and (2R, 5R)-(+)-isomenthone. You should be able to account for this with a mechanism – see the chapter in McMurry dealing with α -substitutions. Draw (or make a model) of the chair conformations of these molecules to reach a prediction as to which is more stable.



Step C involves taking *another portion* of the menthone you made in **Step A** and reducing it with sodium borohydride to afford a mixture of diastereomeric alcohols:



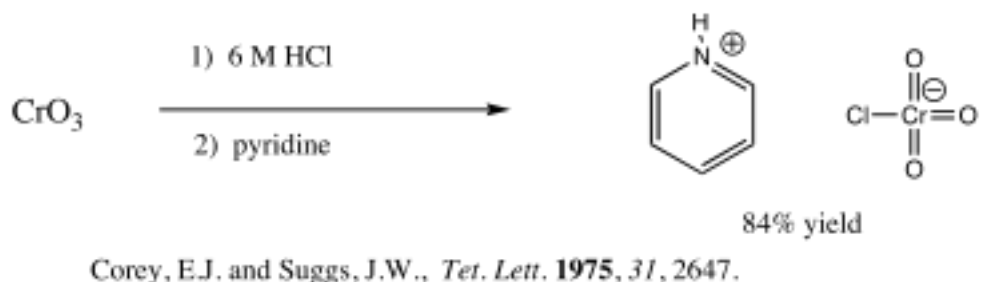
Step A - Preparation of (-)-Menthone

Prior to Fall 2007 we had been using a mixture of sodium dichromate in sulfuric acid (Jones reagent) for this oxidation. In order to minimize epimerization (**Step B**) a two-phase modification of the procedure was used (Brown, et. al., *J. Org. Chem.* **1971**, 36, 387.) This allowed the product to remain mostly in the organic layer, minimizing its contact with the strong acid. However, some epimerization did occur, reaction was sometimes incomplete, and workup was quite messy since two very darkly colored layers had to be separated.

We explored the use of household bleach (aq. NaOCl) to effect the oxidation in place of chromic acid. There were reports of this, many from the early 1980's (for example: Mohrig, et.al., *J. Chem. Ed.* **1985**, 62, 519 and Stevens, et. al., *J. Org. Chem.* **1980**, 45, 2030). In our hands, we found the trouble with these is that the conditions called for (bleach and glacial acetic acid) lead to further reaction of the ketone formed, as revealed most tellingly by GCMS. (Bleach, like Cl_2 , is a source of "Cl" – what byproducts do you expect?). More recent texts have dropped this experiment.

round the trouble with these is that the conditions called for (bleach and glacial acetic acid) lead to further reaction of the ketone formed, as revealed most tellingly by GCMS. (Bleach, like Cl_2 , is a source of “ Cl^+ ” – what byproducts do you expect?). More recent texts have dropped this experiment.

So we went back to chromium but used the milder, less acidic pyridinium chlorochromate:



This complex was first prepared in 1899, but was adapted for use in organic synthesis much more recently. Elias J. Corey was awarded the 1990 Nobel Prize in Chemistry for this and many other contributions to the theory and methodology of synthetic organic chemistry. Here, as with the Jones reagent, Cr(VI) is reduced to Cr(III) in the process of oxidizing the organic substrate. Though the reagent can be used in dichloromethane solution, we chose a procedure that involves admixture with silica gel to afford a solid byproduct that is readily removed by filtration.

Step A Procedure: Preparation of (2S, 5R)-(-)-Menthone

[This improved procedure was adapted by SJSU undergraduate Tory Johnson from the following source: Luzzio, F.A., et. al., *J. Chem. Ed.*, **1999**, 76, 974-975.]

Weigh out approximately 4.85 g *each* of pyridinium chlorochromate (PCC; 22.5mmol) and silica gel (70-230 mesh) and grind together using a mortar and pestle. (**Note:** since the grinding procedure produces a fine, airborne dust it should be done in the hood). Place the powder in a 250 mL Erlenmeyer flask fitted with magnetic stir bar. Add 50 mL methylene chloride and briskly stir at room temperature. Dissolve approximately 2.34 g (15.0 mmol) of (-)-menthol crystals in 10 mL methylene chloride and add to the PCC solution. The solution will turn dark brown in color. Place a watch glass over the flask to contain any solution that might splash up, and maintain brisk stirring. Allow 90 minutes of reaction time.

While the reaction is proceeding begin setting up for vacuum filtration using a #2A (LARGE) Buchner funnel with 9 cm filter paper. Place approximately 6 g of celite in a 50 mL beaker, and approximately 22 g of silica gel (70-230 mesh) into a 100 mL beaker. When the reaction is about 5 minutes short of completion (much earlier and the filter pad will dry out and may develop cracks as it does) add approximately 40 mL of methylene chloride to the celite, and approximately 50 mL of methylene chloride to the silica gel, producing a slurry in each beaker.

With the vacuum on, wet the filter paper with a small amount of methylene chloride. Turn the vacuum off and carefully pour in the freshly stirred celite slurry atop the filter paper, creating as even a layer as possible. Turn the vacuum on briefly to remove some of the methylene chloride and to slightly compact the celite. Turn the vacuum off and repeat the above steps with the silica slurry in order to layer it atop the celite. (Remove the methylene chloride from the collection flask before filtering the reaction mixture).

When the reaction has proceeded for 90 minutes, remove the Erlenmeyer flask from the magnetic stirrer and add 50 mL of diethyl ether. Stir well with a metal spatula and carefully pour the solution through the filtration set-up with the vacuum turned on. Using an **additional** 70 mL of ether, divided into four or five portions, wash the remaining solids in the Erlenmeyer flask. After each addition, stir well with the metal spatula and filter before adding an additional portion of ether.

Transfer the resulting brown solution into a 500 mL round-bottom flask and evaporate off the solvents using the rotary evaporator---this should only take about 3 minutes. Typically there will be some brownish chromium residue. Add approximately 20 mL of hexane. Swirl well and

Transfer the resulting brown solution into a 500 mL round-bottom flask and evaporate off the solvents using the rotary evaporator---this should only take about 3 minutes. Typically there will be some brownish chromium residue. Add approximately 20 mL of hexane. Swirl well, and then filter the solution via gravity filtration into a *tared* 100 mL round-bottom flask washing 2 x 5 mL hexane. Evaporate off the hexane using the rotary evaporator (about 5 minutes). The product may be stored in this flask (fitted with a lightly greased glass stopper) for use in Steps B and C.

Weigh the flask with the menthone to determine the yield and obtain a GC (use same column for *all GC's in this experiment*) and optical rotation

Clean up: Be sure to remove the magnetic stir bar from the Erlenmeyer flask before dumping the brown residue into the solid waste jar. To dissolve solids stuck on glassware, wash with an equal mixture of sodium hydroxide and ethanol (about 20 mL *each*) and place on the basic waste container, then rinse with water and acetone.

Step B - Epimerization of (-)-Menthone

This is a fairly straightforward acid-catalyzed process that affords an equilibrium mixture and thus allows comparison of the stability of two diastereomers. If you understand the mechanism you will know why the stereochemistry at C-2 but not C-5 is affected. What ratio of products would you expect if you used a base catalyst instead of acid?

Step B Procedure: Epimerization of Menthone

In a 25mL round bottom flask, measure 0.5mL of your menthone product from Step A. IN THE HOOD, add 2.5mL of *glacial* acetic acid (what is this?) and 2.5mL of 1M HCl (you'll have to prepare this from the 3M HCl provided). Set up magnetic stirring and attach a water-cooled reflux condenser, then set the flask in a sand bath in a thermowell. Reflux gently for 30 minutes. Remove the flask from the heat and allow to cool to room temperature. Add sufficient 3M NaOH to bring the pH of the solution to approximately pH 10 (use pH paper) - you may have to add 30mL or more. Extract the aqueous mixture with 2 x 15mL ether. Combine the ether layers and dry with magnesium sulfate. Filter the ether layer into a round bottom flask and evaporate the solvent using the rotary evaporator. If you see water droplets in the oily residue, or if it appears cloudy, you may have to add ether and repeat the drying and evaporation steps.

Determine your yield of the product (a mixture of 2 compounds). Measure the GC *using the same column you used in Step A*; note that one product should have the same retention time as your product of Step A. Measure the optical rotation, along with the other products and reference (-)-menthol. Record a neat IR spectrum.

Step C - Reduction of (-)-Menthone

Step C involves reduction of a portion of the menthone from **Step A** with sodium borohydride.

Sodium borohydride was developed by Herbert C. Brown as a battlefield source of hydrogen for launching reconnaissance balloons during WWII. After the war, Brown developed the use of sodium borohydride and related compounds (particularly boranes) for the selective reduction of several classes of organic compounds. This borohydride reagent is especially useful for reduction of aldehydes or ketones – it may be handled in air, and is reasonably stable in protic solvents such as methanol or ethanol. For his cumulative contributions to the organic chemistry of boron, Brown shared the Nobel Prize in Chemistry with Georg Wittig in 1979. The following is excerpted from his obituary (2005, age 92) in Chemical and Engineering News:

Brown is survived by his son, Charles A. Brown of San Jose, and by his wife, Sarah Baylen, whom he credits with drawing his attention to boron chemistry. Brown related in his Nobel Prize lecture that, when he completed his bachelor's degree in 1936, his soon-to-be wife presented him with a book on the hydrides of boron and silicon as a graduation gift. This was the time of the Depression, and none of us had much money," he recalled. "It appears that she selected as her gift the most economical chemistry book (\$2.06) available in the University of Chicago bookstore. Such are the developments that can

gift. This was the time of the Depression, and none of us had much money," he recalled. "It appears that she selected as her gift the most economical chemistry book (\$2.06) available in the University of Chicago bookstore. Such are the developments that can shape a career." (<http://pubs.acs.org/cen/news/83/i01/8301notw4.html>)

Step C Procedure: Reduction of Menthone

(NOTE: Use your product from **STEP A** - NOT from STEP B!)

Prepare a solution of (-) menthone (0.500 g; 3.24 mmol) in methanol (1 mL) in a 10 mL round bottom flask. Insert a magnetic stir bar. From your instructor, obtain sodium borohydride solid* (123 mg; 3.24 mmol; 4.0 equivalents). Add the borohydride in portions to the reaction flask over five minutes with stirring. Note any changes as you add the borohydride reagent. Stir the solution for an additional 10 min. Transfer the mixture to a separatory funnel.

Carefully add 15 mL of 1M HCl (prepare from the 3M HCl stock solution) with periodic swirling of the separatory funnel. Extract with dichloromethane (3 x 4 mL). (Be sure you know which layer is which!) Place the combined organic layers in the separatory funnel. Wash with water (1 x 10 mL). Dry the organic layer with magnesium sulfate, gravity filter into a *tared* round bottom flask.

Evaporate the solvent on the rotary evaporator. The product oil should be clear and show no droplets of water. (If water is present, redissolve in dichloromethane and repeat the drying and evaporation steps.)

Measure the GC and optical rotation of the reaction mixture. Obtain a neat IR spectrum and proton NMR in deuterated chloroform.

Summary of Analysis:

Perform the following analytical measurements on your products and (-) menthol where noted. ***In some cases, the data is provided for you in the Appendix.*** You must include this data in your final report as if you had measured it yourself.

•**GC:** Use capillary GC to analyze the products of Steps A, B and C. The GC will be set for 120°C isothermal measurements. Besides the expected products, be sure to note if any unreacted starting material or byproducts are observed. For Steps A and C especially, compare your GC traces to the GC of reference menthol. Remember to use the *same column* on the GC for all of your measurements for this experiment.

•**IR:** The IR spectra for reference (-)-menthol and (-)-menthone are provided in the Appendix. Measure the IR spectra for Step B and C products as "neat" solutions. Be sure there is ***no water*** in your sample before you apply sample to the salt plates!

•**¹H NMR:** A reference ¹H NMR for (-)-menthol is provided. You will record only the ¹H NMR of your Step C product (in CDCl₃).

•**Mass Spectra:** Mass spectra for reference (-)-menthol and (-)-menthone are provided.

•Optical Rotation:

Your instructor will explain the procedure. Record the optical rotation for reference (-)-menthol and all three product(s) that you prepared. Calculate the amounts of each product you need for the range of 1 to 2% w/v solutions in ethanol with a final volume of 5mL. Obtain four 5 mL volumetric flasks from the stockroom. For each sample, get an *accurate* weight within the 1-2% range. Add ethanol to the fill line in the volumetric. Prepare all four solutions before beginning your measurements. You will be shown how to measure the observed rotation $[\alpha]_{\text{obs}}$ using the polarimeter. Use these values to calculate either the specific rotation $[\alpha]_{\text{D}}$ or the composition of

range. Add ethanol to the fill line in the volumetric. Prepare all four solutions before beginning your measurements. You will be shown how to measure the observed rotation $[\alpha]_{\text{obs}}$ using the polarimeter. Use these values to calculate either the specific rotation $[\alpha]_{\text{D}}$ or the composition of a mixture of products.

Stereochemical Analysis:

One of the main objectives of this experiment is to investigate the stereochemical outcomes of the products obtained in the three Steps. The optical rotation will give an indication of the optical purity of the products. Compare the results you obtain by optical rotation to those from GC and NMR (for the Step C product). For Step C, use the observed product ratio (obtained by GC and NMR) and the observed rotation to determine both the sign and rotation (+ or -) of the specific rotation for (??) neomenthol. Fill out the Menthol Experiment Worksheet and submit it with your formal report.

Key Discussion Points:

- chromic acid oxidations in organic synthesis.
- hydride reductions in organic synthesis; use of sodium borohydride vs other alternatives; stereochemical outcomes.
- explain the terms "kinetic control" and "thermodynamic control"; which term applies to which Step and how does it explain the outcome?
- explain the epimerization in Step B, why does it occur at all since one product has an axial substituent?
- explain the ratios of your Step C product; is this expected or not?
- what does optical rotation tell you about stereochemistry?
- compare and contrast the outcomes of the analytical procedures (GC, optical rotation, NMR) to determine the product ratios, which is more accurate and why?
- for the NMR of the Step C product, explain the difference in appearance of the two methine patterns between δ 3 and 4 ppm (use chair structures and coupling "trees").
- interpret the spectra provided in the Appendix* (write assignments on the spectra and turn in with your report); in your Experimental Section, include the spectral data for *all* of the compounds.

Experiment Three

Preparation of an Unknown Ester and 2-D NMR

In Chemistry 113A, you synthesized an ester starting with an unknown alcohol and acetic acid, and you used NMR to identify the structure. Experiment Three is an extension of this process and with the added dimension of a commonly used structure identification method: 2D "COSY" NMR spectroscopy.

In Experiment Three, the esterification will be performed on a microscale using an unknown **10-carbon aromatic acid** ($\text{C}_{10}\text{H}_{12}\text{O}_2$) and an unknown **4-carbon aliphatic alcohol** ($\text{C}_4\text{H}_{10}\text{O}$). Each student will have a different combination of alcohol and acid, but note that all of the esters will have the same molecular formula ($\text{C}_{14}\text{H}_{20}\text{O}_2$) and molecular weight. Instead of a liquid form of

carbon aromatic acid ($C_{10}H_{12}O_2$) and an unknown **4-carbon aliphatic alcohol** ($C_4H_{10}O$). Each student will have a different combination of alcohol and acid, but note that all of the esters will have the same molecular formula ($C_{14}H_{20}O_2$) and molecular weight. Instead of a liquid form of an acid (e.g., HCl), we will use a solid "ion exchange resin" known as DOWEX 50X2-100 as the acid catalyst. DOWEX is a polymer consisting of repeating subunits with the formula - $(CH(C_6H_4)-4-SO_3H)CH_2)_n$. The free sulfonic acid groups act as the source of protons for the reaction. After the reaction is complete, the resin is conveniently removed from the reaction solution by filtration.

Note that because each combination of alcohols and acids is unique, the rate of the ester formation may differ. Some esters may form more rapidly (kinetic) and others more favorably (thermodynamic). While it is not necessary to reach a point near "100%" formation of ester, a conversion of at least 50% is desirable so that sufficient product is obtained for 2D NMR analysis. The workup should remove any unreacted acid, but it is important to monitor the progress by TLC. While not impossible, it is more challenging to interpret an NMR consisting of a mixture of compounds!

References:

McMurry, J. or any textbook on organic chemistry, review ester formation (especially Fisher esterification)

Pavia and Silverstein texts, sections on 2D COSY NMR

Prelab:

Write a detailed Mechanism and Table of Starting Materials and Products assuming 328 mg 4-phenylbutyric acid and 0.300 mL 1-butanol as the "unknown" mixture. **Procedure: Preparation of Unknown Aromatic Ester**

Reaction:

Upon approval of your prelab writeup in your lab notebook, you will be given a coded 3mL reaction vial containing a mixture of your unknown alcohol and unknown acid.

IMMEDIATELY remove the paper label from the bottom of the vial and place it on your yellow "Lab Report Summary" sheet; you should also write the code in your notebook (this code **MUST** be included in your formal report or it will not be possible to verify you have the correct structure!)

Your vial contains 2.0mmol (328mg) of the unknown acid, and 0.3mL of the unknown alcohol (use the density of n-butanol to calculate the mmol of alcohol used). Weigh 50 to 75mg of DOWEX 50X2-100 (it is rather "sticky"). Put most of the DOWEX into the reaction vial - don't worry about getting every resin bead into the vial. Add *one* silicon carbide boiling chip. Using the Ace microkit, attach the **water-cooled** condensor to the vial, using the proper O-rings and seals, and attach a cap with a blue septum to the top. **IMPORTANT:** *puncture the septum with a syringe needle (from the Stockroom) to allow the pressure inside to vent when you heat this otherwise sealed system and leave the vent needle in during the operation.* Clamp the apparatus to a ring stand and insert in a sand bath. Turn on the thermowell to a setting **NO HIGHER** than 3, and monitor for the start of reflux. When bubbling begins, start timing for 1 hour. If necessary, reduce the thermowell setting to reach a gentle reflux. (a common problem in this experiment is to have the temperature too high, causing the alcohol to evaporate before reaction occurs).

After 60min, turn off the thermowell and remove the apparatus from the sand bath.

When it is cool to the touch, disassemble the glassware. Before you begin the full workup, take one drop of the reaction mixture and dissolve it in 0.5mL of ether. Perform TLC on the solution to check the progress of the reaction. You will need to determine an appropriate developing solvent. Check the TLC by UV light. There may be up to 2 UV active spots (what are they?) of different R_f values (which should be the lower or higher

TLC on the solution to check the progress of the reaction. You will need to determine an appropriate developing solvent. Check the TLC by UV light. There may be up to 2 UV active spots (what are they?) of different R_f values (which should be the lower or higher R_f ?). If it appears that there is still >50% of acid remaining, reassemble the apparatus and continue to reflux for another 30min, then re-check by TLC. When <50% of acid remains, continue to the workup steps.

Workup Steps:

Add 1-2mL ether to your cooled reaction vial. Using a pipette, carefully draw up the solution, but leave the DOWEX beads behind. Transfer the ether to a 16 x 150mm test tube. Rinse the beads with 2 x 2mL portions of ether, and combine with the first extract. Extract the ether solution with 3 x 5mL solutions of *saturated* sodium bicarbonate; use your pipette to mix and remove the aqueous solutions. **CHECK THE ETHER LAYER AT THIS POINT BY TLC.** If you still see a noticeable amount of acid remaining, continue to extract with bicarbonate until most of the acid is removed.

Dry the ether layer with magnesium sulfate, filter into a *tared* 50mL round bottom flask and evaporate using the rotary evaporator. Place the flask in the vacuum desiccator until the next lab period (label the round-bottom with your sample and place a loosely fitting Kimwipe tissue in the neck to keep any sand particles from the desiccator from entering). Note your yield of ester product. Using all* of your product, prepare an NMR sample using CDCl_3 . Then recover an IR sample from the NMR solution.**

*The 2D NMR requires a fairly concentrated sample, and takes a very long time for more dilute samples. Even with long acquisition times, dilute samples may give noisy spectra. Here is how to get as concentrated a sample as possible: have the Service Center add 0.5 mL CDCl_3 with TMS directly into your round-bottom flask, dissolve your sample (which may be a solid or an oil depending on your unknown) and pipet all of it into a clean NMR tube. [If the liquid level does not come up to 4.0 cm in the tube, ask to have a small amount more CDCl_3 added to the tube just to bring it to the 4.0 cm level.)

**Refer to the Chem 113A web site, Oil of Cloves Experiment Flow Chart Part I for IR of crude clove oil (<http://www.chemistry.sjsu.edu/straus/EXPTG%20htms/Flow%20Diagram%20G1/flowdiag1J.htm>). You do not need to dry your sample (you already did!) just apply a small portion of it to a single salt plate and evaporate the solvent using a heat lamp as described in the reference procedure.

Analysis:

- TLC: Check progress of the reaction and workup; sketch TLCs in your notebook and record the R_f s measured.
- IR: Record and interpret for the ester product (be sure there is no water!)
- NMR: Prepare a sample of at least 25-35mg (50mg is better) in 1mL CDCl_3 . A "regular" 1D and 2D COSY spectra will be measured for you with expansions. Depending on the complexity of the products, one or more expansions may be provided so be careful to look at them. Impure products that contain residual acid, alcohol or ether will be difficult to interpret. In addition to the sections on 2D NMR, pay particular attention to "diastereotopic protons" (see Silverstein, 4.12 and 4.16; Pavia 5.14 and 5.15)

Product to Submit with Report: Your remaining ester (yield not graded)

Key Discussion Points:

Key Discussion Points:

Discuss the Fisher esterification reaction and compare with other esterification methods. Describe the particular aspects of your experiment, including the importance of the stoichiometry, apparatus, and key experimental steps. What are the reasons for using a resin over another type of catalyst? Discuss your yield and any factors that may have affected it.

Give a clear and detailed rationale of how you arrived at the structure of your unknown ester (and hence your alcohol and acid) using 1D and 2D COSY NMR. Give a proper chemical name for all three compounds. Explain how you eliminated other possible structures.

Experiment Four

Synthesis of Dimedone and Derivatives

A Multistep Synthesis

In Experiment Four, you will apply several classical reactions, which involve carbonyl compounds (review carbonyl chemistry in McMurry or other organic text) to synthesize 5,5-dimethyl-1,3-cyclohexanedione, or "dimedone." Dimedone is a β -diketone that is quite interesting due to its chemical and spectral properties. In solution, dimedone exists in equilibrium as keto/enol tautomers, depending on the conditions under which it is measured, such as concentration and solvent (this will be discussed in more detail in class). We can get a *quantitative* measure of the keto/enol ratio by ^1H NMR spectroscopy.

After synthesizing dimedone, each student will prepare a ^1H NMR sample of dimedone using a *unique* combination of concentration and deuterated solvent. After measuring your ^1H NMR spectrum, you will determine the keto/enol ratio for your sample, and the results from all students in the class will be compiled on the "Worksheet for Keto/Enol Ratios" (see Appendix B). In your report, you should discuss and explain any trends seen (or not seen) considering the results obtained from the entire class.

Step A – Synthesis of Dimedone

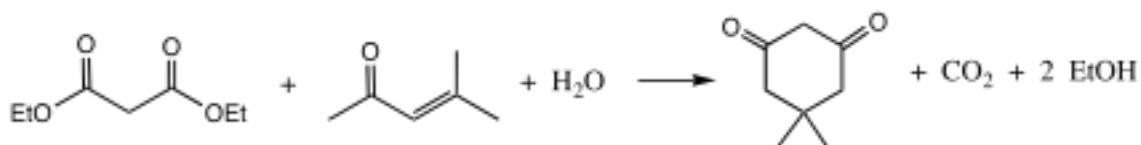
NOTE: The synthesis of dimedone involves two 1-hour refluxes plus several other manipulations, and must be completed in one lab period or you will have to start over. *It is essential that the lab day before you plan to do this synthesis, you **MUST***

-have your prelab notebook approved

-wash and dry all your glassware

You will not be able to complete the synthesis unless you plan ahead!

The *overall reaction* for **Step A** is as shown:

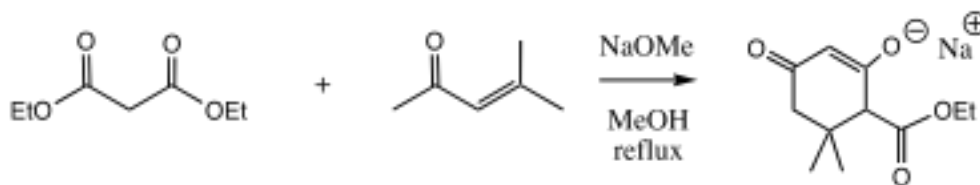


Procedurally, the reaction is performed in three steps (**A1**, **A2** and **A3**) that involve classical carbonyl reactions, such as the Michael addition and Claisen condensation. Consult an organic textbook such as McMurry to help you deduce the mechanisms of these three steps (shown on next page).

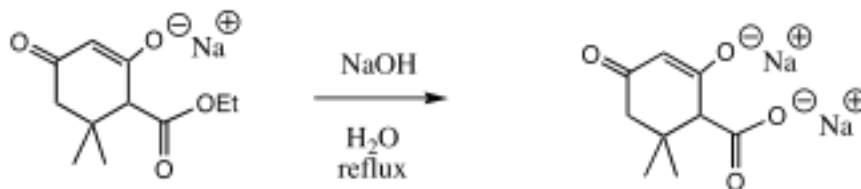
Step A1.

carbonyl reactions, such as the Michael addition and Claisen condensation. Consult an organic textbook such as McMurry to help you deduce the mechanisms of these three steps (shown on next page).

Step A1:



Step A2:



Step A3:



Step A Procedure: Synthesis of Dimedone

To a 100ml round bottom flask, add 25.0 mmol diethyl malonate. Add 5.0 mL of 30% sodium methoxide* in methanol [or 6.0 mL if 25% strength] (~28 mmol, prepared for you in hood). Add a stir bar and clamp to a ring stand; the flask should be in a thermowell and on top of a stir plate.

Attach a West condensor (**important!! lightly grease the joint before attaching**); clamp the condensor to the ring stand. Turn on the thermowell (no more than a setting of "3" or "30%") and *gently* heat until just the first drops of reflux are observed.

Raise the flask and condensor above the thermowell and put your long neck funnel in the condensor; slowly add 3.0 mL (~26 mmol) of freshly distilled mesityl oxide** [**NOTE!! avoid breathing vapors**] in small portions over 2 to 3 minutes while swirling or stirring with the magnetic stirrer. [**DO NOT let mesityl oxide drip into the hot thermowell**] Replace the flask and condensor into the thermowell, and reflux for 40 minutes (timing begins with bubbles appear). A solid should form during reflux.

*A the 30% indicates w/v ratio (ie., grams/mL) thus 5.0 mL would contain 1.5 g solute.

**[Use a *fresh* vessel for the mesityl oxide, not the same one as for the methoxide solution]. Raise the flask above the thermowell. When boiling subsides, remove the condensor and affix a vacuum adaptor that is plugged with a glass stopper. Attach a vacuum tube to the adaptor and connect to the vacuum line. Using the clamp as a handle, hold the flask over a steam cone and swirl to facilitate the evaporation of the methanol. The mixture will be a solid-liquid mass at this point. When about half the volume is evaporated (5 minutes maximum), remove the vacuum adaptor

Add 20mL of 3.0M aq. NaOH and attach the West condensor. Put the flask back in the thermowell (setting 6 or 7) and reflux for 40 minutes. While refluxing, in a 250 mL beaker prepare 18 mL of 6.0M aq. HCl. When the reflux is completed, **IN THE HOOD**, slowly pour the reflux mixture into the beaker containing the HCl, use a glass stir rod to mix while adding [**NOTE: you're adding base to acid, so the reaction will be exothermic. HCl vapors may be**

prepare 18 mL of 6.0M aq. HCl. When the reflux is completed, IN THE HOOD, slowly pour the reflux mixture into the beaker containing the HCl, use a glass stir rod to mix while adding [NOTE: you're adding base to acid, so the reaction will be exothermic. HCl vapors may be released)]

Prepare a "funnel hood" over a steam cone using an inverted funnel attached to the vacuum line with rubber tubing. Put your solution atop a wire gauze (you can check out a 4x4 gauze – if you use the one from your desiccator it will be wet when you need it) on the steam cone and heat for 10 min. A vigorous bubbling will be observed (what is this?) at first, which should subside after a while. A solid should appear. Place in an ice bath for 10 minutes and vacuum filter, washing with cold water.** Dry in a desiccator, or if time permits recrystallize from acetone directly. Record the weight and set aside a small sample for melting point measurement.

**Keep the filtrate until next period – it may yield more crystals!

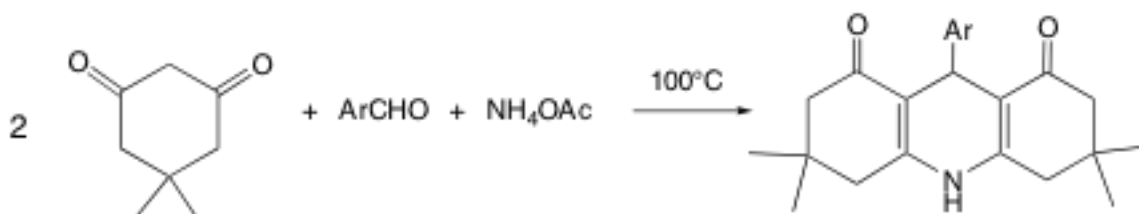
Recrystallization:

Recrystallize from acetone (appx. 8 mL/g dimedone). Wash with two small portions of cold water and dry in a jar desiccator. (As always, keep the filtrate until you are satisfied with your recovery.) Record the weight and mp range.

Record an IR by dissolving some dimedone in dichloromethane and applying a drop or two to a salt plate; once the dichloromethane fully evaporates record a spectrum using this single salt plate.

Sign up for one of the combinations of concentration and NMR solvent to dissolve your dimedone sample. Analyze your ^1H NMR spectrum for the keto/enol ratio, and enter your values on the posted "Worksheet for Keto/Enol Ratios." Also, be sure to copy down the keto/enol ratios from the rest of the class; you will need these for your formal report.

Step B - Preparation of Hexahydroacridinedione Derivatives:



This procedure was adapted from the literature¹ by Sarah E. Lee, an SJSU undergraduate and Chem 113B alumnus.

Start heating a 250 mL beaker of water on a stirrer hot plate at the beginning of the period. Water should be at 100°C when test tube is placed in water bath. Maintain gentle boiling.

Place dimedone and assigned aldehyde in a 15 X 120 mm test tube in a 2:1 molar ratio. Use approximately 2 mmol of dimedone and calculate the needed amount of aldehyde. Also add 92 mg of ammonium acetate and an octagonal stirring bar, $\frac{1}{2}$ " L x $\frac{1}{8}$ " D.

When water is boiling, immerse the test tube so that the mixture is well below the water level. For the stir bar to begin moving, some readjustments of your set up may be required. Placing the bottom of the test tube as close as possible to the bottom of your beaker and the center of the hotplate may help. Depending on your aldehyde, reactants may need to liquefy before the stir bar can begin moving.

Leave the test tube in boiling water bath for at least 45 minutes.

can begin moving.

Leave the test tube in boiling water bath for at least 45 minutes.

When the reaction is complete remove test tube from water bath and allow to cool to room temperature. Add 5 mL of water and stir the solution vigorously. It may help to scrape the test tube walls. Solids may be stuck to the stir bar, and can be knocked loose using a spatula. Crude product is collected using vacuum filtration, washed with a small portion of water, and air-dried.

If time permits, product can be recrystallized. Add a minimal portion (< 5 mL) of EtOH:H₂O 9:1 solution to the wet crude product and heat while swirling over a steam cone. When product no longer appears to go into solution and particles remain, and another portion of EtOH:H₂O 9:1 solution. Continue until the product has gone into solution. When no solids remain, add H₂O drop-wise until product begins to precipitate out. Again, add EtOH:H₂O (drop-wise) until solution clears. Allow to cool to room temperature, then place the mixture in an ice bath for at least 20 minutes. Solid product is collected using vacuum filtration and washed with water and air-dried. Dry in a desiccator overnight.

Obtain ¹H NMR to characterize the product. Also, measure the melting point.

1. Y.-B. Shen and G.W. Wang, *ARKIVOC* **2008** (xvi) 1-8.

Analysis Summary:

- mp: record for dimedone and hexahydroacridine derivative
- IR: interpret spectra for mesityl oxide and diethyl malonate (provided in the Appendix)
obtain IR for dimedone by dissolving in dichloromethane and applying a thin film on one salt plate
- ¹H NMR interpret spectra for mesityl oxide and diethyl malonate (provided in the Appendix)
Prepare and interpret ¹H NMR for your combination of concentration and solvent
Prepare and interpret NMR of your hexahydroacridine derivative (CDCl₃)
- ¹³C NMR and MS: interpret spectra for mesityl oxide, diethyl malonate and dimedone (provided in the Appendix)

Product to be submitted with Report: Dimedone

Key Discussion Points:

Discuss the mechanisms of all steps, especially the various carbonyl reactions involved. Discuss the role of pK_a and keto/enol tautomers in reactions (where appropriate). What is the relation of the Michael, Claisen, and Dieckmann reactions in this experiment? What factors influence keto/enol equilibria? Discuss in detail the outcomes of the keto/enol ratios observed by the entire class. Do ALL of the values make sense - what is consistent and is anything inconsistent with your data? Explain the difference in NMR chemical shifts of the hydrogens specific to the keto and to the enol forms. Interpret the proton NMR spectrum for the hexahydroacridine derivative. (*How many* sets of hydrogens are there in the derivative?) Also, in the report interpret the spectral data provided (MS, IR, NMR) of the starting materials, and include this data in the Experimental Section.

