

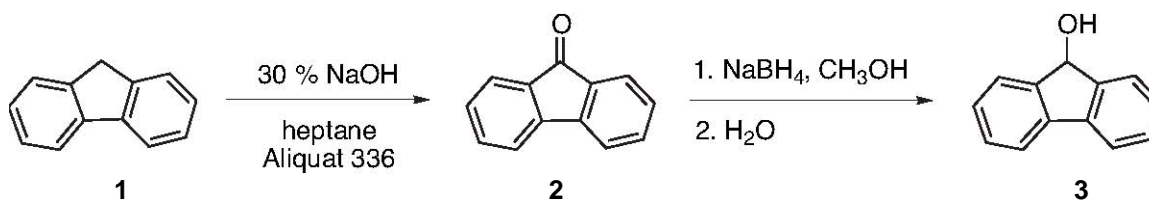
Section F: Synthesis of 9-Fluorenone from Fluorene

Background / Purpose

The next several lab meetings will be spent in a multi-step synthetic route to an aromatic alcohol (9-fluorenone) starting with an unfunctionalized hydrocarbon (fluorene). Please note that it takes two reactions to achieve the desired substance; the transformation cannot be done directly in a single step. This is often the case in trying to obtain complex organic molecules. For example, Woodward synthesized reserpine, a psychoactive drug with five stereocenters, in 47 steps.

Care must be exercised in each step to obtain reasonable percent yields and to isolate pure product. For example, if you performed a ten step synthesis with 100 g of starting material in which each step gives 75% yield (a respectable yield for any single step), you would end up with 5.6 g of product (assuming the molecular weights of the starting material and product were the same). As a matter of fact, Woodward's reserpine synthesis started with 2 tons of starting material, and he was able to get about 50 mg (0.050 g) of reserpine (an overall yield of < 1%)!

The two steps you will be carrying out in this multi-step series are an oxidation of fluorene (**1**) to fluorenone (**2**) followed by reduction of **2** to 9-fluorenone (**3**). You will employ several organic synthesis methods for monitoring progress, isolating product, and characterizing product.



Procedure Outline (Week 1): Oxidation of Fluorene to Fluorenone

Adapted and modified from: Lehman, John W., Operational Organic Chemistry, 3rd Ed., 1999.

The 9-position of fluorene is more reactive than most typical hydrocarbons by virtue of this position being doubly benzylic. This experiment will utilize atmospheric oxygen in a basic solution as the oxidizing agent. A two phase reaction mixture and a phase-transfer catalyst will also be employed that will assist and accelerate this reaction. Once the ketone is isolated in pure form, further reactions typical of ketones can then be performed such as a reduction to the corresponding alcohol.

PROCEDURE: In a 125 mL Erlenmeyer equipped with a medium sized stir bar, mix 400 mg (record the amount you use) of fluorene with 8 mL of heptane (or hexanes). Carefully add 4 mL of 30% aqueous sodium hydroxide and ~10 drops of Aliquat 336 (tricaprylmethylammonium chloride). Set the stirring rate such that you get a frothing of bubbles on the mixture surface. The stirring should continue for at least one hour. You should monitor the reaction by TLC approximately every 15 minutes. Look for the appearance of product and the disappearance of the starting material (20%

dichloromethane in hexanes should be a good choice for TLC elution) Next, transfer the reaction mixture to a test tube and cool it in an ice bath. Carefully remove the aqueous layer and then collect the crude fluorenone product by vacuum filtration with a Hirsch funnel. Wash the solid with a small amount of 1 M HCl followed by a small amount of water. Allow the solid to dry. The crude product will be purified in the next lab session by column chromatography. At that time weigh the dried crude solid and take a small amount to evaluate by TLC.

Column Chromatography Separation of Fluorenone

This portion of the multi-step reaction sequence will involve the isolation and purification of fluorenone (**2**) from the previous oxidation reaction. The purification method will utilize column chromatography to separate out byproducts and unreacted starting material. This is arguably one of the most common and universally practical methods of purification used by organic synthetic chemists. Once separated and characterized the pure fluorenone will be used in the final reduction step during week 3.

Procedure Outline (Week 2):

Weigh your dried crude product from week 1 of this sequence. You should be able to calculate a “crude percent yield”. It is sometimes interesting to note crude yields to overall yields of the pure isolated material. Also, you should check your crude product mixture by TLC and use this record to determine which fractions from the column you will combine as product, starting material, and mixed fractions.

TLC Check:

Take a small sample (only a mg or two is necessary) and dissolve it in a sample vial with a minimum amount of appropriate solvent (probably dichloromethane or acetone). Spot a TLC plate with this solution to check for product formation. You should include a spot with starting material as well as a spot with an authentic fluorenone sample to compare with your reaction spot. Make note of the location, shape, intensity under the UV lamp, and of course, the R_f value for each component. Determining the eluting solvent often requires some experimentation, but for this experiment you should begin with 20% dichloromethane in hexanes.

Column Chromatography:

Prepare a column of alumina for separation as described in the supplemental material and demonstrated by your instructor. Be sure you have all glassware (clean and dry) and solvents ready prior to beginning the actual separation.

Once the column is prepared, add as much of the solid product mixture directly to the top of the column as possible. Place a small layer of sand (approx. 2-5 mm) directly on top of the solids previously added. Begin eluting the column with 20% dichloromethane in hexanes (be sure to never let the column go dry). Collect fractions in small, clean dry Erlenmeyer flasks (have several ready). Typically you should collect equal volume fractions unless you see a clear indication (like a color change and/or turbidity change) that the eluent solution has changed in content. At those points you should switch to another flask. For this particular separation you will be able to visually see the yellow band of fluorenone move down the column, and you

should obviously switch to a new Erlenmeyer flask when that band reaches the bottom of the column and begins to come off. **At this point you should also begin adding 100% dichloromethane** to the column to speed the elution of the product band. When the yellow band is fully eluted you can stop collecting fractions.

Each fraction collected from the column should be checked by TLC for content (i.e. is it one component or a mixture, and which compound is in each). If any two fractions have the same components (as judged by TLC), then you may combine these into one round bottom flask. Finally, remove the solvent from the fractions using the rotary evaporator. Weigh each round bottom you use in advance to aid your yield calculations. If you had fractions that contained significant amounts of unreacted starting material, you can also combine those in a separate round bottom flask, evaporate and calculate the mass of recovered starting material. It is not uncommon in the literature to report reaction yields based upon recovered starting material.

You can verify your isolated and purified product via several methods. You should take an IR and NMR of the product. Additionally, a pure compound should have a very specific (“tight”) melting point range that corresponds to accepted literature values. Therefore, you should also take a melting point and compare this to authentic fluorenone. Finally, carbon-NMR should be quite interesting in observing the change in the 9-position carbon as the compound is transformed from fluorene to fluorenone and finally to fluorenol. If time permits, as a class you can collect C-13 spectra of each of these compounds to evaluate, otherwise sample spectra will be provided for you.

Retain your fluorenone product for the final reduction reaction (next lab period).

Synthesis of 9-Fluorenol from Fluorene

This is the final reaction of the multi-step sequence for preparing 9-fluorenol (**3**) from fluorene (**1**). It is a standard ketone reduction utilizing sodium borohydride as the hydride source followed by an aqueous work-up to supply the proton. You should recall the mechanism of this type of reaction and be prepared to discuss it. At the completion of this experiment, you should show complete evidence that you have indeed prepared the desired compound and individual yield calculations for each step as well as an overall percent yield for the complete transformation. Additionally, you should calculate a percent yield based upon recovered starting material if you were able to recover a significant amount of starting material.

Procedure Outline (Week 3): Reduction of Fluorenone to 9-Fluorenol

In a round bottom flask, dissolve a known mass of your fluorenone in the minimum volume of methanol required. Warming may be necessary to effect solvation. Weigh out 1/3 molar equivalent of sodium borohydride and place it in a clean dry test tube.

Add the sodium borohydride (solid) in small portions, with stirring (magnetic bar), to the fluorenone solution. As the reduction nears completion (~20 minutes), the yellow color of the fluorenone begins to fade to a near colorless solution. Discharge any last trace of yellow color with a **small** amount of additional sodium borohydride. Next, add 20 mL of distilled water. A

thick white solid will likely form almost immediately. Stir and warm this suspension on a hot plate or sand bath until warm to the touch and then let it stand for 10 minutes at room temperature. Then add 20 mL of ice-water and extract the resulting mixture with diethyl ether (2 x 25 mL) in a separatory funnel. Dry the combined ether extracts over anhydrous sodium sulfate or magnesium sulfate. Filter the solution into a pre-weighed, clean, dry 100 mL round bottom flask and remove the solvent on the rotary evaporator. Recrystallize the crude fluorenol from a mixture of hexane and ethyl acetate. Collect the crystals by suction filtration, dry them in the lab drawer until the next lab period, or in a vacuum oven according to your instructor's recommendations. Weigh the purified product and make all necessary calculations. Be sure to get NMR and IR spectra, melting points, and any other physical data you feel necessary.

Notebook:

Each of the two reactions are to be recorded in your notebook, using the proper style discussed and developed in Organic Chemistry 1. Every new reaction begins at the top of a new right-hand side page. Each reaction has the following sections:

Title – at top of page.

Reaction – this is our hypothesis.

Table of Physical Constants – compound name, weight used, moles, molecular weight, mp, bp density if available are included. Include all reactants, reagents and solvents. Do not included wash solutions and drying agents.

References – reference journal articles, handbooks or lab manual as appropriate.

Procedure – a past tense, third person, passive voice account of your work, observations, and data.

Summary Box – including % yield, and any physical constants collected.

Write on right-hand side pages only. Left-hand side pages can be used for calculations, notes, plans or other organizational material. More information about notebook keeping can be found in your Organic 1 laboratory notebook and in the Zubrick manual.

Formal Report:

The formal report must include the following:

Heading – Title, Your full name, Where the work was performed

Abstract

Introduction or Background

Results and Discussion

Experimental Procedure

References

See the Organic 1 laboratory manual for details. Also, chemical structures and reactions are typically depicted to easily convey the chemistry performed. Your chemical structures and reactions must be included using one of the chemical structure drawing programs, such as ChemDraw or ChemIntosh. The ChemDraw student edition can be obtained free from Cambridge Software's website: www.camsoft.com.

Name: _____

Summary Sheet

Fluorene to Fluorenol multi-step synthesis

- A. What mass of fluorene did you start with? _____
- B. What was the mass of the crude oxidation product? _____
- C. What was the mass of **pure** fluorenone you isolated? _____
- C1. What was the mp. of the pure fluorenone? _____
- C2. What was the percent yield of step 1? _____
- C3. If you isolated starting material; how much? _____
- C4. What was the percent yield based on recovered SM? _____
- D. What was the mass of pure fluorenone you used in step 2? _____
- E. What was the mass of pure fluorenol you isolated in step 2? _____
- E1. What was the mp of the pure fluorenol? _____
- E2. What was the percent yield of step 2? _____
- F. What was the overall percent yield for the two reactions? _____
1. Discuss how IR would allow you to verify product isolation both in step 1 and step 2.

