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EXPERIMENT

Martius Yellow: Preparation of Naphthol Derivatives

REFERENCES

- a. L. F. Fieser Experiments in Organic Chemistry
- b. K. L. Williamson; K. M. Masters Macroscale and Microscale Organic Experiments

SAFETY RECOMMENDATIONS

1-naphthol: Very hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion. Hazardous in case of inhalation. Slightly hazardous in case of skin contact (corrosive, permeator). Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Sulfuric Acid (H_2SO_4): Very hazardous in case of skin contact (corrosive, irritant, permeator), of eye contact (irritant, corrosive), of ingestion, of inhalation. Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Nitric Acid (HNO_3): Very hazardous in case of skin contact (corrosive, irritant, permeator), of eye contact (irritant, corrosive), of ingestion, . Slightly hazardous in case of inhalation (lung sensitizer). Liquid or spray mist may produce tissue

damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Prolonged exposure may result in skin burns and ulcerations. Over-exposure by inhalation may cause respiratory irritation. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Ammonium Hydroxide (NH_4OH): Very hazardous in case of skin contact (corrosive, irritant, permeator), of eye contact (irritant), of ingestion, . Non-corrosive to the eyes. Non-corrosive for lungs. Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Ammonium Chloride (NH_4Cl): Hazardous in case of eye contact (irritant). Slightly hazardous in case of skin contact (irritant, sensitizer), of ingestion, of inhalation.

Sodium Hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4$): Hazardous in case of eye contact (irritant), of ingestion. Slightly hazardous in case of skin contact (irritant), of inhalation.

Hydrochloric Acid (HCl): Very hazardous in case of skin contact (corrosive, irritant, permeator), of eye contact (irritant, corrosive), of ingestion, . Slightly hazardous in case of inhalation (lung sensitizer). Non-corrosive for lungs. Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Severe over-exposure can result in death. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Iron (III) Chloride (Ferric Chloride, FeCl_3): Very hazardous in case of ingestion. Hazardous in case of skin contact (irritant), of eye contact (irritant), of inhalation. Slightly hazardous in case of skin contact (permeator). Corrosive to eyes and skin. The amount of tissue damage depends on length of contact. Eye contact can result in corneal damage or blindness. Skin contact can produce inflammation and blistering. Inhalation of dust will produce irritation to gastro-intestinal or respiratory tract, characterized by burning, sneezing and coughing. Severe over-exposure can produce lung damage, choking, unconsciousness or death.

Acetic Anhydride (Ac_2O): Extremely hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Very hazardous in case of skin contact (corrosive). Hazardous in case of skin contact (permeator). Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Sodium Acetate (NaAc): Hazardous in case of ingestion, of inhalation. Slightly hazardous in case of skin contact (irritant), of eye contact (irritant).

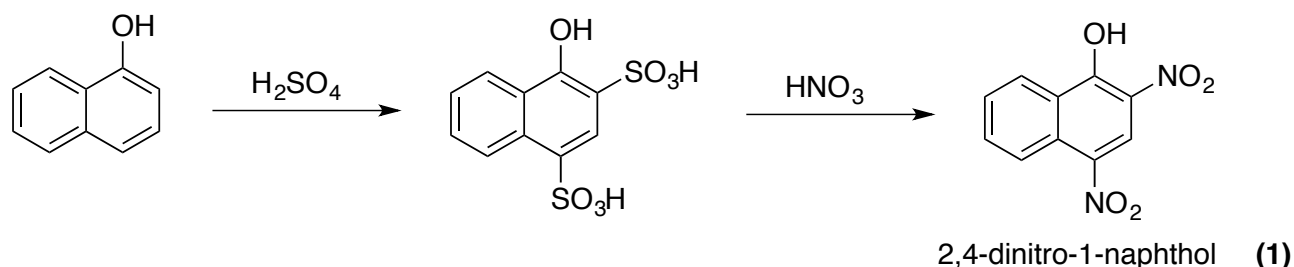
INTRODUCTION

One of the most famous undergraduate synthesis laboratory experiments is the Martius Yellow Competition designed by Louis Fieser at Harvard University (L. F. Fieser Experiments in Organic Chemistry). During this module you will synthesize and characterize a series of 1-naphthol derivatives, including 2,4-dinitro-1-naphthol (Martius Yellow), a commercially available dye used to stain cells for biological applications. The series of experiments described below illustrates certain operations of general importance and application in laboratory synthesis. According to Fieser, a skilled organic student can prepare all seven compounds in 3-4 h. You will have 3 lab periods to do the experiments. You may have a friendly competition with other people in the course performing the experiments.

PROCEDURE

General Note: Many of the compounds may be synthesized from moist precursors, but all compounds must be dry when characterizing them.

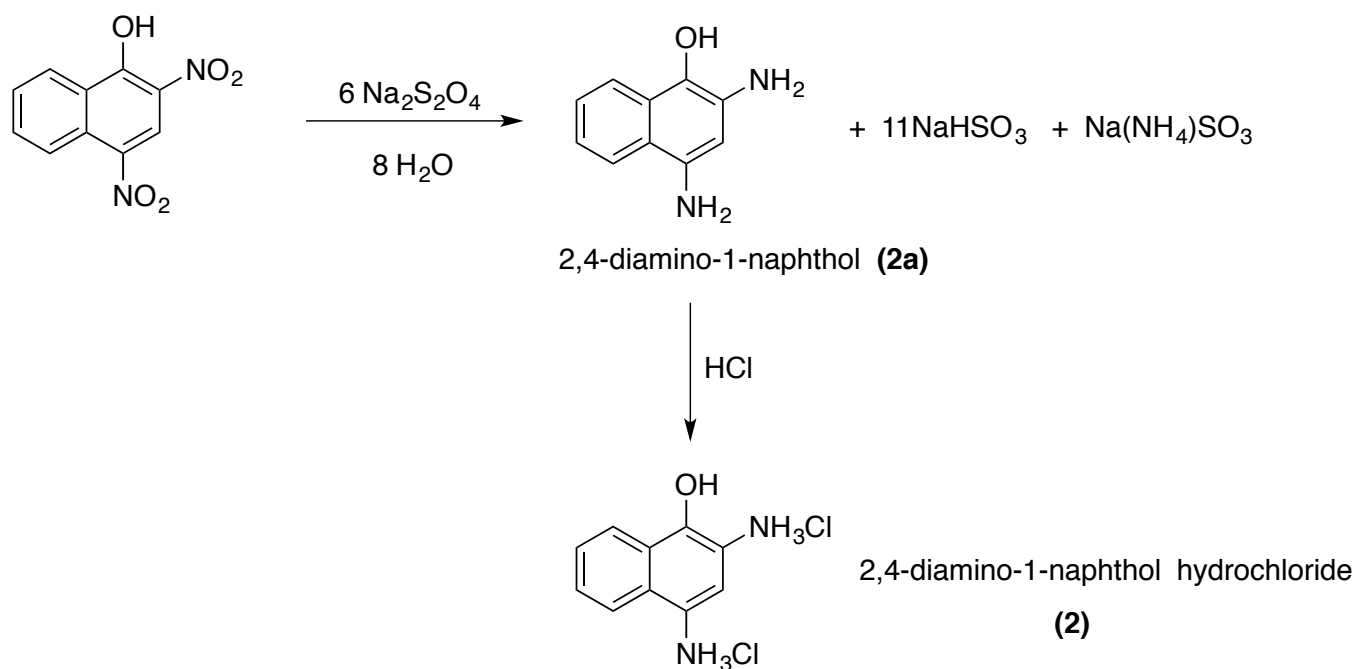
1st Lab Period



Preparation of 2,4-Dinitro-1-naphthol (1)

Place 2.5 g of 1-naphthol (also named α -naphthol) in a 50-mL Erlenmeyer flask, add 5 mL of concentrated H_2SO_4 , and heat the mixture on a hot plate for ~5 min. The solid should dissolve and the red color should be discharged. Cool in an ice bath, add 13 mL of water, and cool the solution rapidly to ~ -15°C (Ethylene glycol / dry ice bath). Add 3 mL of concentrated HNO_3 slowly to the chilled solution with swirling. After the addition is complete, let the solution sit for about 5 minutes and then warm the mixture to ~50°C. The product should separate as a yellow paste. Fill the Erlenmeyer flask with water and break up the paste with a stirring rod. Collect the product by vacuum filtration and wash it with water. Wash the product into a 250-mL beaker with ~50 mL of water. Add 75 mL of hot water and 2.5 mL of concentrated ammonium hydroxide, heat to the boiling point, and stir to dissolve the solid. Add 5 g of ammonium chloride to the filtrate to salt out the ammonium salt (Martius Yellow), cool in an ice bath, filter out the orange salt, and wash it with water containing 1-2% ammonium chloride. Save about 150 mg and characterize it when dry (**Take both ^1H NMR and IR of compound (1) and also IR of starting material (naphthol)**). The rest of the moist product can be used in the next step.

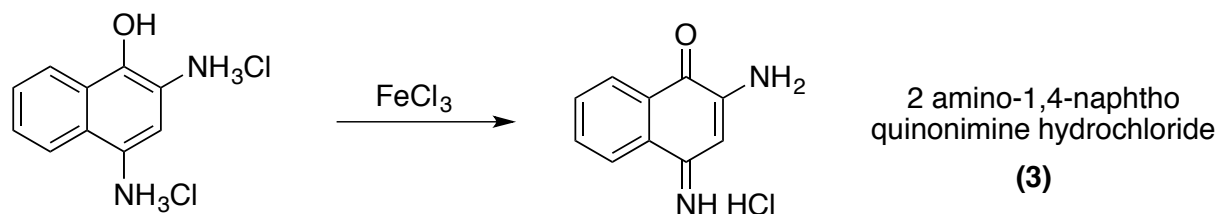
Preparation of 2,4-Diamino-1-naphthol (2a) and its hydrochloride (2)



Add the rest of the moist 2,4-dinitro-1-naphthol to a beaker with a total of ~100 mL of water. Add 2.0 g of sodium hydrosulfite and stir until the orange color disappears and a tan precipitate forms. Cool the mixture in ice. Prepare a solution of 1 g of sodium hydrosulfite in 50 mL water for washing. Also add 3 mL of concentrated HCl to a 250-mL beaker containing 12 mL of water. The tan product is not stable to oxidation by air. Filter the tan product and **avoid sucking air through the solid**. Wash the solid with the hydrosulfite solution and then immediately rinse the solid into the beaker containing the dilute HCl. Stir the mixture to convert to the dihydrochloride salt (2). Once the dihydrochloride salt is made the compound will be stable. The solution may be discolored by sulfur and filter paper. To fix this problem, suction filter the solution through decolorized charcoal in a Buchner funnel (don't use a Hirsch funnel since it will be too small). Divide the filtrate into two equal parts. Convert one part to 2-amino-1,4-naphthoquinonimine (3) and convert the other part to 2,4-diacetylamino-1-naphthol (5).

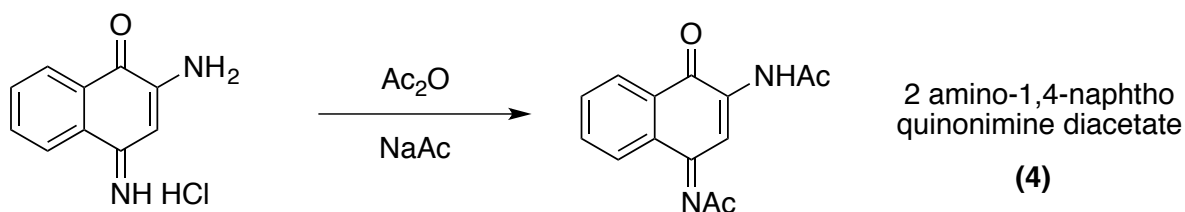
2nd Lab Period

Synthesis of 2-Amino-1,4-naphthoquinonimine (3)



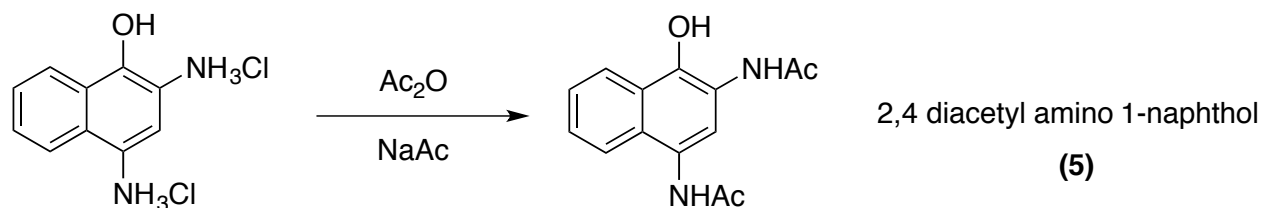
12.5 mL of 1.3M iron(III) chloride solution to $\frac{1}{2}$ of the diamine dihydrochloride solution, cool in ice, and wait for crystals to form. If no crystals form, try scratching the inside with a glass rod and/or add more hydrochloric acid. Collect the red crystals and wash with dilute HCl. Divide the moist product into three equal parts. Spread one part out to dry for conversion to (4). The other two parts can be moist for conversion to 7 and recrystallization. To recrystallize, dissolve in a minimum amount of hot water containing 2-3 drops of hydrochloric acid. Add a little decolorizing charcoal and filter. Add a little concentrated HCl and crystals should form on cooling. Collect the product by vacuum filtration, let it dry, and characterize it ($^1\text{H NMR}$).

Synthesis of 2-Amino-1,4-naphthoquinonimine Diacetate (4)



Mix 2.5 g of dry 3 with 0.25 g anhydrous sodium acetate and 1.5 mL acetic anhydride in a 5-mL conical vial. Add a spin vane and warm the mixture in a hot water bath. The red salt should soon turn into yellow crystals (the solution may still be red). Pour the mixture into 5 mL of water and stir for a few minutes. Collect the product and wash it with water. Recrystallize it from ethanol, dry and characterize it ($^1\text{H NMR}$).

Synthesis of 2,4-Diacetylamino-1-naphthol (5)

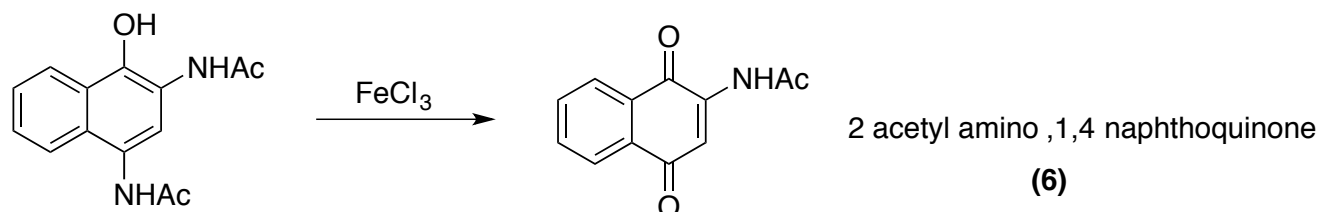


Add 1.5 mL of acetic anhydride to 1/2 of **2** from the experiment above and stir vigorously. Add a solution of 1.5 g sodium acetate and ~50 mg of sodium hydrosulfite in 10-15 mL of water. The diacetate (**5**) may precipitate as a white solid or it may separate as an oil that solidifies when the flask is chilled in ice and rubbed with a glass rod. Collect the product by filtration and then dissolve it in 2.5 mL of 3M sodium hydroxide and 25 mL of water at room temperature. This step will hydrolyze any triacetate which may be present. If the solution is colored, add a few mg of sodium hydrosulfite to bleach it. Acidify the solution by gradual addition of well-diluted hydrochloric acid (1 mL of HCl in 20 mL water). The product may be difficult to crystallize—cooling and scratching will probably be necessary. Collect the product and wash it with water. Recrystallize one third of the product and convert the other two-thirds into **6** (can be done while moist). To recrystallize, dissolve the moist product in a minimum amount of hot acetic acid, add a solution of a small crystal of tin(II) chloride in a few drops of dilute HCl (this inhibits oxidation), and dilute gradually with 5-6 volumes of water at the boiling point. Crystallization may be slow. Dry and characterize the product ($^1\text{H NMR}$).

3rd Lab Period

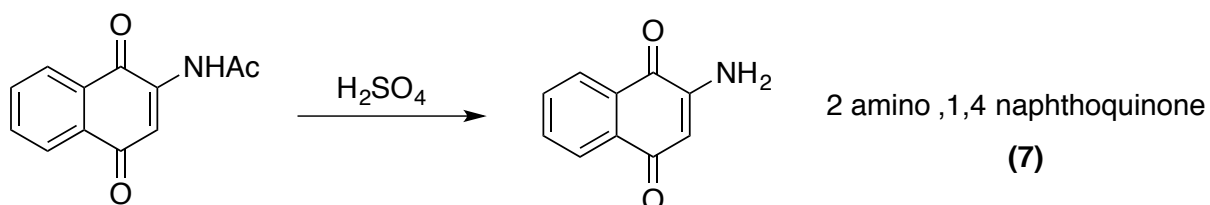
Synthesis of 2-Acetylamino-1,4-naphthoquinone (6)

Dissolve 0.75 g of moist **5** in 5 mL of hot acetic acid, dilute with 10 mL of hot



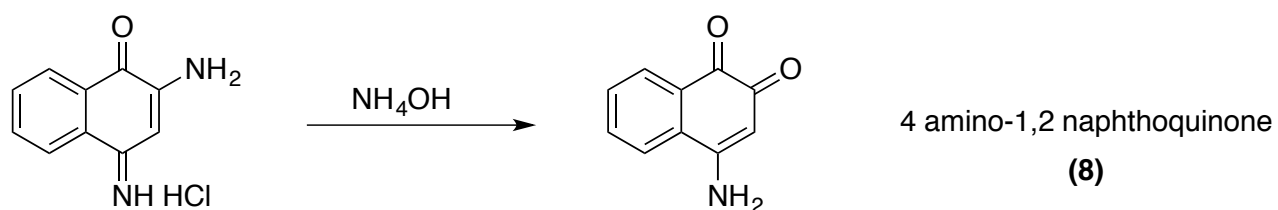
water, and add 5 mL of 0.13 M iron(III) chloride solution. Cool the solution, filter it, and wash the yellow solid with cold ethanol. Dry half the solid for conversion to **7**, and recrystallize the rest from ethanol/water. Dry and characterize the product ($^1\text{H NMR}$).

Synthesis of 2-amino-1,4-naphthoquinone (**7**)



Place 0.25 g of **6** to a 5-mL conical vial and add 1 mL of concentrated sulfuric acid to it. Heat the mixture with swirling to promote rapid solution. After 5 min, cool the deep red solution, dilute extensively with water, and collect the product. Wash it with water and then recrystallize it from ethanol/water. Collect, dry and characterize the product ($^1\text{H NMR}$).

Synthesis of 4-amino-1,2-naphthoquinone (**8**)



Dissolve 0.5 g of **2** in 12 mL of water, add 1 mL of concentrated ammonium hydroxide, and boil the mixture for 5 min. Cool, collect the solid, and then suspend it in about 25 mL of water containing 12.5 mL of 3 M sodium hydroxide. Stir the solution and remove any solid that remains (it will be **7** the isomer of **8**) by filtration. Acidify the filtrate with acetic acid and the orange **8** should precipitate. Filter it and recrystallize **8** from 250-300 mL of hot water (it will take awhile). Filter, dry and characterize the product ($^1\text{H NMR}$).

In your report, address the following points:

1. Overall, you need to record ^1H NMR spectra for compounds **(1)**, **(3)**, **(4)**, **(5)**, **(6)**, **(7)** and **(8)**. You also need to record IR spectra for naphthol and compound **(1)**. Analyze and compare the spectra of the different compounds.
2. Show a mechanism for the formation of 4-hydroxynaphthalene-1,3-disulfonic acid from 1-naphthol.
3. Why is 4-hydroxynaphthalene-1,3-disulfonic acid soluble in the reaction mixture and 2,4-dinitro-1-naphthol not?
4. Draw a Lewis structure for $\text{Na}_2\text{S}_2\text{O}_4$.
5. In the conversion of 2,4-dinitro-1-naphthol to 2,4-diamino-1-naphthol to the diamine compound **2a**, what is the role of sodium hydrosulfite?
6. How could you prove that compound **2** is the dihydrochloride salt?
7. Give a mechanism for the synthesis of 2-amino-1,4-naphthoquinonimine hydrochloride **(3)**.
8. What is the relationship between compounds **7** and **8**?
9. Explain why the reaction of **3** with NH_4OH gives **8** and not **7**.