EXPERIMENT FOUR
SYNTHESIS OF P-NITROACETANILIDE

Discussion:

The aromatic nitration of acetanilide is an exothermic reaction; the temperature must be carefully controlled by chilling, stirring, and the slow addition of reagents. Acetanilide is first dissolved in the solvent, glacial acetic acid, by warming. Glacial acetic acid is used because it is a polar solvent capable of dissolving acetanilide and the acetate ion is a poor nucleophile so no substitution is possible. After the solution is cooled, sulfuric acid is added; however, even with cooling, the temperature of the solution rises almost 40°C. Both the acetanilide solution and the nitrating solution (a mixture of HNO₃, and H₂SO₄) must be chilled to about 10°C before the reaction is begun.

To prevent dinitration of the acetanilide, the nitrating mixture is added in small portions to the acetanilide solution (and not vice versa) so that the concentration of HNO₃, is kept at a minimum. After all the HNO₃, H₂SO₄ solution has been added, the reaction mixture is allowed to warm slowly to room temperature. If the reaction mixture has been kept excessively cold during the addition, there will be a relatively large amount of unreacted HNO₃, present, which may cause the temperature to rise above room temperature. If this should happen, the mixture must be rechilled.

The work-up procedure consists of removal of the acids and crystallization of the product. Every trace of acid must be removed because hydrogen ions catalyze the hydrolysis of the amide to p-nitroaniline or its protonated cation. Most of the acid is removed by pouring the reaction mixture onto ice and water, then filtering the flocculent yellow precipitate of p-nitroacetanilide. The last traces of acetic acid are removed by neutralization. Because bases also catalyze the hydrolysis of amides, the neutralizing agent used is disodium hydrogen phosphate (Na₂HPO₄). This reagent reacts with acids to yield NaH₂PO₄. The result is a buffered solution with a pH near neutral.

The crude product is air-dried before crystallization. If all of the acid was removed, the product will be light yellow. A deep yellow to yellow-orange product is indicative of the presence of p-nitroaniline from hydrolysis. Unfortunately, p-nitroaniline is difficult to remove from p-nitroacetanilide by crystallization.
Equipment

- 250-mL beaker
- dropper or disposable pipet
- two 50-mL and one 125-mL Erlenmeyer flasks
- 10-mL graduated cylinder
- hot plate
- ice bath
- spatula
- stirring rod
- thermometer
- vacuum filtration assembly
- watch glass
- acetanilide, 6.5 g
- disodium hydrogen phosphate, 15 g
- 95% ethanol, 60 mL
- glacial acetic acid, 10 mL
- conc. nitric acid, 3.5 mL
- conc. sulfuric acid, 15 mL

Time Required: about two hours to crude product; 15-20 minutes for crystallization; two overnight dryings; 15 minutes for melting-point determination

STOPPING POINTS: during either of the two drying periods or while the product is crystallizing from ethanol

>>>>>>SAFETY NOTE 1: A mixture of concentrated nitric and sulfuric acids is used as the nitrating mixture. Use extreme caution when preparing and using this mixture.

>>>>>>SAFETY NOTE 2: Nitro compounds are toxic and can be absorbed through the skin. You may wish to wear disposable plastic gloves during portions of this experiment.

PROCEDURE

Place 6.5 g of acetanilide in a 125-mL Erlenmeyer flask, add 10 mL of glacial acetic acid (CAUTION: strong irritant), and warm the flask on a hot plate in a fume hood until the acetanilide dissolves. Cool the flask in an ice bath to about 20°C; then add 10 mL of cold, conc. sulfuric acid. The temperature of the mixture will rise to about 60°C. Chill the solution to about 10°C in an ice bath. (The solution will become very viscous.)

Mix 3.5 mL of conc. nitric acid and 5 mL of conc. sulfuric acid in a 50-mL flask, and chill the flask in an ice bath. When both solutions are cold, slowly add the HNO₃, H₂SO₄ solution, 1 mL at a time, to the acetanilide solution. Keep the reaction flask in an ice bath so that the temperature of the reaction mixture is maintained between 10-20°C. Stir the reaction mixture carefully after each addition. The entire addition requires about 15 minutes.
After the addition is completed, allow the reaction flask to stand at room temperature for 30 minutes. Monitor the temperature; if it rises above 25°C, chill the flask in an ice bath. Should the rechilling be necessary, allow the flask to stand for 30 minutes or more at room temperature after the rechilling.

Pour the reaction mixture into a 250-mL beaker containing 100 mL of water and 25 g of cracked ice. Using a large Buchner funnel, filter the heavy lemon-yellow precipitate with vacuum. Press out as much aqueous acid from the filter cake as possible with a spatula or clean cork while suction is being applied (CAUTION: see Safety Note 2). The precipitate is voluminous; use care in transferring it to the Buchner funnel or a substantial amount of product will be lost.

Transfer the filter cake to a clean 250-mL beaker, and add 100 mL of 15% aqueous disodium hydrogen phosphate. Stir the mixture to a paste-like consistency and refilter using vacuum. Wash the beaker with two 30-mL portions of cold water. Finally, wash the filter cake with an additional 50 mL of cold water. Press the filter cake with a spatula or clean cork to remove as much water as possible, then dry the solid overnight on a watch glass.

(Stopping point)

Determine the yield and melting point. The crude product can be purified by crystallization from 30-60 mL of 95% ethanol. (The crude product dissolves very slowly, even with heating; avoid using an excess of solvent.)
NAME ___________  DATE ________________

SYNTHESIS OF P-NITROACETANILIDE WORKSHEET

<table>
<thead>
<tr>
<th>Mass of Product</th>
<th>Melting Point</th>
<th>CRC Melting Point</th>
<th>Theoretical Yield (grams)</th>
<th>Actual Yield (Percent)</th>
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Problems

1. List at least two reasons for the choice of glacial acetic acid as the solvent for the nitration of acetanilide.

2. What would be the effects of each of the following changes of reaction conditions in this experiment, assuming that all other conditions are held constant? Some of these are simple dilutions while others are addition of extra reactants. Explain your answers.

   (a) increasing the amount of glacial acetic acid from 10 mL to 20 mL

   (b) increasing the amount of nitric acid from 3.5 mL to 7.0 mL

   (c) decreasing the amount of sulfuric acid from 15 mL to 5 mL

3. Write equations for the hydrolysis of p-nitroacetanilide in (a) aqueous acid; (b) aqueous hydroxide. The products of the reaction should be p-nitroaniline and acetic acid (or acetate ion in base).
4. Predict what would happen during the crystallization of p-nitroacetanilide from 95% ethanol if all
the acidic material had not been neutralized previously? Use an equation in your answer. You should
ask yourself, “What is the other 5% and what will it do to this reaction?”