

Experiment 4

Converting Aniline to Brominated acetylide: A Multistep Synthesis

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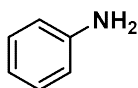
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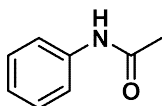
PURPOSE OF THE EXPERIMENT

Conduct a multistep synthesis: protection of aniline and bromination.

BACKGROUND INFORMATION¹



(a) aniline



(b) acetanilide

Figure 1. Aniline and acetanilide

The objective of the experiment 8 is to gain experience in aromatic halogenation reactions without being exposed to the hazards presented by traditional bromination procedures. In contrast to the old method of bromination using bromine in acetic acid, the bromine used to perform the reaction is generated *in situ* from acidic solution of sodium hypochlorite and sodium bromide. Both reagents used to generate the bromine (sodium bromide and sodium hypochlorite, which are found in bleach) are more benign to handle than liquid bromine.

The amine group of aniline should be protected prior to the bromination. In using this greener method, the amine group is protected for two reasons. First, the protection helps to minimize the production of multi-substituted products. Second, the amine group on aniline can be converted to dangerous chloramines when mixed with sodium hypochlorite. Therefore, acetylation of the amine group will reduce safety concerns.

Reference 1

J. Chem. Educ. **2012**, *89*, 1061–1063.

Acetylation of aniline

There exist various protecting groups for amine functionality. Acetyl group is one of the readily available amine-protecting group. In this experiment, an amine group in aniline (Figure 1a) will be protected with the acetyl group.

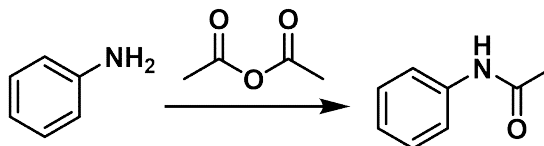


Figure 2. Acetylation of the amine group in aniline.

Bromination of acetanilide

Via electrophilic aromatic substitution, halogen atom like bromine can be substituted into an aromatic ring. The reaction site is determined by the directive effects of substituted functional groups on the aromatic ring; here we have an *N*-acetyl group.

Traditional electrophilic aromatic substitution reactions have required the use of (or created as byproducts) harmful halocarbons: one example being the synthesis of bromobenzene. Typical procedures to generate bromobenzene include electrophilic substitution of bromine (from Br₂) onto benzene via some metal Lewis acid catalyst such as AlCl₃ and SbCl₄. With the use of sodium bromide and sodium hypochlorite, however, aromatic bromination can be achieved without being exposed to the hazards presented by traditional procedures.

The reaction mechanism can be considered as acid-assisted reaction to form bromine as shown in Figure 3 followed by electrophilic aromatic substitution step.²

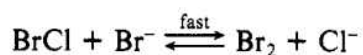
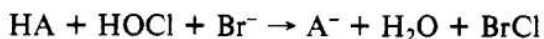


Figure 3. Mechanism of *in situ* generation of bromine.³

Reference 2 *J. Org. Chem.* **1990**, *55*, 5287-5291.

Reference 3 *Inorg. Chem.* **1987**, *26*, 2706-2711.

EXPERIMENT A Acetylation of aniline

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (<i>g/mol</i>)	<i>mmol*</i>	<i>mp</i> (°C)	<i>bp</i> (°C)	<i>density</i> (<i>g/mL</i>)
aniline	2.0 mL	93.13				
acetic anhydride	4.0 mL	102.09				1.08

*Calculate these values and find equivalency of the reaction

PROCEDURE

Caution: Wear lab coats and safety goggles at all times while in the lab. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Wearing contact lens is strictly prohibited.

Caution: Dichloromethane, ethyl acetate and hexane are toxic and irritating. Ultraviolet radiation can cause severe damage to the eyes. Do not look directly into the UV lamp.

1. Preparing TLC reference

Obtain standard samples of aniline (starting material) and acetanilide (product) from your TA. Prepare a developing chamber by adding proper amount of ethyl acetate and hexane. By performing TLC analysis, find appropriate separation condition. View the plate under UV light to visualize the spots.

Caution: Acetic anhydride is corrosive. Use a fume hood.

2. Setting Up the Apparatus

In the fume hood, dissolve 1 mL of aniline in 2 mL acetic anhydride in a 125 mL Erlenmeyer flask.

Cool the solution in an ice bath to at least 5 °C. Then, let the reaction occur over 5 minutes with occasional stirring.

Caution: Dichloromethane is toxic and irritating.

3. Monitoring the Reaction

After 5 minutes, take small amount of the reaction mixture to the 5mL-vial followed by pouring about 1 mL of dichloromethane to make TLC sample.

When no starting material remained, stop the reaction by adding 30 mL of a 0.5 M NaOH (prepared by dissolving 0.6 g of solid NaOH in about 30 mL water, concentration need not be exact) to the organic solution.

4. Isolating Product

Warm to room temperature the mixture to dissolve the solids (add more water if necessary).

Allow the solution to slowly cool down to enhance crystallization.

Isolate the crystals by vacuum filtration. Wash the crystals with least amount of distilled water.

Under the vacuum, allow your product for 10 min in the filter funnel by passing the air.

After drying the product, weigh the product and record the mass.

5. Characterizing the Product

Measure the melting point of your dry product. Obtain the NMR spectrum as directed by your TA.

EXPERIMENT B Reagents and Properties

Bromination

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (g/mol)	<i>mmol*</i>	<i>mp</i> (°C)	<i>bp</i> (°C)	<i>density</i> (g/mL)
acetanilide	1.0 g *	135.16				
sodium hypochlorite	5.0 mL					
sodium bromide	1.8 g	102.89				
95% ethanol solution	6.0 mL					
acetic acid	5.0 mL	60.05				
sodium thiosulfate	1.0 g	158.11				
sodium hydroxide	1.0 g	40.00				

* Adjust the reagents to match the amount of acetanilide you made. If it exceeds 1.0 g, use 1.0 g of acetanilide for further reaction. This is a reference scale for 1.0 g of acetanilide.

PROCEDURE

6. Conducting the Reaction

Caution: Ethanol is flammable and toxic. Keep away from flames or other heat sources.

Note. Ask your TA for useful tips.

In a 125 mL Erlenmeyer flask, dissolve acetanilide and sodium bromide using 95% ethanol solution and acetic acid based on reference scale. Cool the resulting solution in an ice bath to at least 5 °C. In the fume hood, add sodium hypochlorite by 5 mol%.

Let the reaction occur for about one minute in an ice bath.

Allow the reaction to warm up to room temperature over 15 minutes – use stopper cork or invert a beaker over the selected glassware's mouth to suppress the vapors.

Caution: Sodium hydroxide and sodium thiosulfate are toxic and corrosive. *Open only in a fume hood.*

7. Recovering the brominated product

At the end of the 15 minutes, the reaction mixture is placed in an ice bath, and 1 g of sodium thiosulfate and 1 g of sodium hydroxide are added to quench the remaining bromine without reacting in the bromination reaction. Allow the quenching agent to dissolve completely in a sand bath at about 70 °C for 10 minutes. before recovering the precipitated product. The reaction mixture is cooled to room temperature and The precipitate was collected by vacuum filtration and washed with distilled water and 95% ethanol.

After drying the product, weigh the product and record the mass.

8. Characterizing the Product

Obtain the NMR spectrum as directed by your TA.

Pre-Laboratory Questions

1. Summarize all MSDS's of chemicals used in this experiment.
2. Draw the mechanism for the entire reaction the pertains to the aromatic ring.
 - a) Reaction of acetic anhydride with aniline
 - b) Reaction of bromine(Br₂) with acetanilide
3. In this experiment, the amine group was protected as an amide to prevent side reactions from occurring. Describe one other protecting group by addressing what functional group is protected and why it is necessary to use the protecting group.

Post-Laboratory Questions

Acetylation of aniline

1. Calculate the percent yield of the reaction.
2. Use your TLC data to explain whether or not the acetylation reaction went to completion.
3. Assign peaks in ¹H NMR spectrum to confirm the formation of the desired product.

Bromination of acetanilide

3. Calculate the percent yield of the reaction.
4. Calculate the overall percent yield of aniline to the final product.
5. Assign peaks in ¹H NMR spectrum to confirm the formation of the desired product.
6. Explain how we could obtain *para*- brominated acetanilide selectively.
7. Address the role of sodium thiosulfate and sodium hydroxide respectively.

8. List at least 2 ways to improve the reaction yield.

Additional questions

9. When TLC spots are too high to distinguish each other, which portion of solvent should be increased? (TLC eluent is a mixture of ethyl acetate and hexane.)