Nucleophilic Aromatic Substitution: The Reaction of 3,4-Dichloronitrobenzene with Sodium Methoxide

prepared by **Jerry Manion,** University of Central Arkansas

PURPOSE OF THE EXPERIMENT

Identify the product of a nucleophilic aromatic substitution reaction of 3,4-dichloronitrobenzene with sodium methoxide.

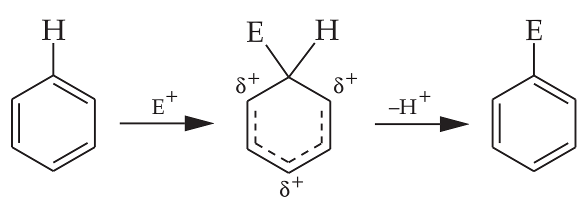
EXPERIMENTAL OPTIONS

BACKGROUND REQUIRED

You should be familiar with reflux, extraction, recrystallization, and melting point and mixture melting point measurements.

BACKGROUND INFORMATION

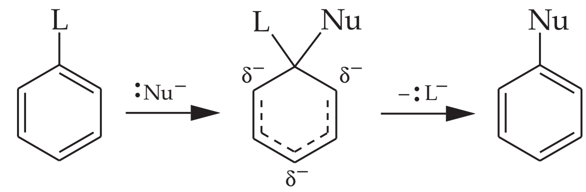
Aromatic rings characteristically undergo *electrophilic* substitution reactions in which one of the hydrogen atoms on the ring is replaced by an electrophile. The reaction is a two-step process involving a resonance-stabilized carbocation intermediate, as shown in Equation 1.



(Eq. 1)

The energy of this intermediate is lowered if electron-*donating* groups, such as –OH or $–NH_2$, are attached to the ring. Because the energy of activation required to reach this lower-energy intermediate is less, the ring is more reactive toward electrophilic substitution when these groups are present.

Under certain circumstances, aromatic rings can also undergo *nucleophilic* substitution reactions. Like S_N2 reactions, nucleophilic aromatic substitution reactions involve replacement of a good leaving group with a strong nucleophile. Unlike S_N2 reactions, nucleophilic aromatic substitution is a two-step process that proceeds through a resonance-stabilized carbanion intermediate, as shown in Equation 2.



(Eq. 2)

This carbanion intermediate is stabilized by the presence of strong electron-*withdrawing* groups, such as the nitro group ($–NO_2$). When these groups are present on the ring, the reaction occurs faster.

In both electrophilic substitution and nucleophilic substitution, the electrical charge is distributed to the positions that are *ortho* and *para* to the carbon at which the electrophile or nucleophile reacts. Because the effect of the stabilizing group is enhanced if it is directly attached to one of those positions, the reactivity of the compound depends greatly on the position of this group relative to the site of reaction on the ring.

When 3,4-dichloronitrobenzene is placed in a solution containing a strong nucleophile, it can potentially undergo substitution reactions involving either of the two chlorine atoms in the molecule. However, because the $–NO_2$ group is *meta* to one chlorine and *para* to the other, the effects that $–NO_2$ group exerts on the reactivity of the two chlorine atoms are not equal.

In this experiment, you will react 3,4-dichloronitrobenzene with methoxide ion, a strong nucleophile. You will identify the product formed.

The reaction system is illustrated in Figure 1.

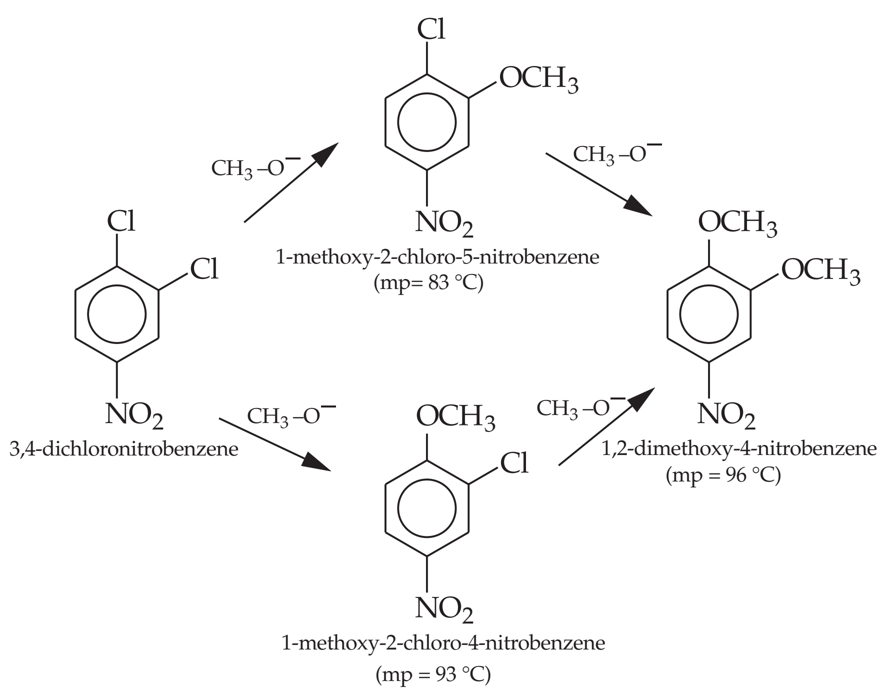


Figure 1 Reaction pathways for 3,4-dichloronitrobenzene

Three products might be formed in this experiment.

1. If only the chlorine atom meta to the $–NO_2$ group is replaced, the product is 1-methoxy-2-chloro-5-nitrobenzene (2-chloro-5-nitroanisole) (MM: 187 g/mol; mp: 83 °C).

2. If only the chlorine atom *para* to the $–NO_2$ group is replaced, the product is 1-methoxy-2-chloro-4-nitrobenzene (2-chloro-4-nitroanisole) (MM: 187 g/mol; mp: 93 °C).

3. If both of the chlorine atoms are replaced, the product is 1,2-dimethoxy-4-nitrobenzene (4-nitroveratrole)(MM: 183 g/mol; mp: 96 °C).

The product will be identified by its melting point. If the melting point is in the range of 83 °C, 1-methoxy-2-chloro-5-nitrobenzene is the product. If the melting point is in the range of 93–96 °C, you will use mixture melting points to identify your product because the melting points of 1-methoxy-2-chloro-4-nitrobenzene and 1,2-dimethoxy-4-nitrobenzene are too close to distinguish easily.

Semi-Microscale

Equipment

2 beakers, 250-mL *
boiling chips
condenser, reflux
5-mL conical vial
distilling head
50-mL Erlenmeyer flask
25-mL filter flask, with vacuum tubing
filter paper
flask heater with heat controller†
25-mL graduated cylinder
Hirsch funnel, with adapter
melting point capillary tube
microspatula
2 Pasteur pipets, with latex bulb
2 round-bottom flasks, 50-mL
separatory funnel
support ring
support stand
20 × 150-mm test tube
thermometer, –10 to 260 °C, with adapter
2 utility clamps
watch glass

*for ice-water bath and for hot-water bath
†or hot plate

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
dichloromethane	10 mL	85		40
3,4-dichloronitrobenzene	0.150 g	192	41–44	
1,2-dimethoxy-4-nitrobenzene*	0.005 g	183	96	
magnesium sulfate, anhydrous	0.100 g	120		
methanol	25 mL	32		65
1-methoxy-2-chloro-4-nitrobenzene*	0.005 g	187	93	
1-methoxy-2-chloro-5-nitrobenzene		187	83	
sodium methoxide, 25% in methanol	10 mL			

*for mixture melting point measurement. If necessary, use compound provided by your laboratory instructor.

Preview

- Assemble a reflux apparatus
- Mix 3,4-dichloronitrobenzene, methanol, and sodium methoxide solution
- Reflux the mixture for 1 hr
- Pour the reaction mixture into distilled or deionized water
- Extract the product into dichloromethane
- Remove excess dichloromethane by distillation
- Use air or nitrogen to evaporate the residual dichloromethane
- Recrystallize the product from a methanol/water mixture
- Measure the product melting point and mixture melting point

PROCEDURE

Caution: Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

1. Conducting the Reflux

Caution: 3,4-Dichloronitrobenzene is toxic and irritating. Methanol is flammable and toxic. Sodium methoxide is flammable and corrosive.

Place 0.150 g (150 mg) of 3,4-dichloronitrobenzene in a 50-mL round-bottom flask. Add a boiling chip. Add 15 mL of methanol and 10 mL of 25% sodium methoxide in methanol.

Assemble a reflux apparatus using the 50-mL round-bottom flask and a condenser, as shown in Figure 2. Support the flask heater with a support ring so that the heater can be removed easily. Place a clamp on the neck of the flask.

Gently reflux the solution for 1 hr.

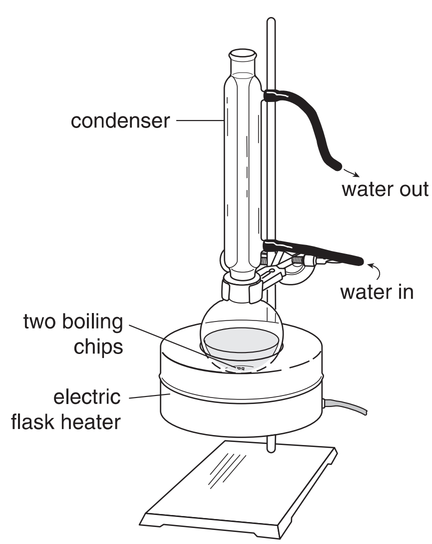


Figure 2 Reflux apparatus for semi-microscale glassware

2. Extracting the Product

Caution: Dichloromethane is toxic and irritating.

Pour 25 mL of distilled or deionized water into a separatory funnel. Pour the reaction mixture into the water to precipitate the product.

Add 10 mL of dichloromethane to the separatory funnel. Mix to dissolve the product in the dichloromethane. Drain the dichloromethane layer into a labeled 50-mL Erlenmeyer flask. Set aside the water layer to discard later.

Return the dichloromethane layer to the separatory funnel. Wash the dichloromethane layer with 10 mL of distilled water.

Drain the dichloromethane back into the 50-mL Erlenmeyer flask. Add up to 0.10 g of anhydrous magnesium sulfate ($MgSO_4$) to dry the dichloromethane layer. Allow the dichloromethane layer to dry for 10 min.

3. Removing the Solvent
[NOTE 1]

NOTE 1: Your laboratory instructor may indicate an alternative solvent removal procedure.

Assemble a simple distillation apparatus, using a second 50-mL round-bottom flask as a pot. Transfer the dried dichloromethane layer to the pot, leaving the $MgSO_4$ drying agent behind.

Add a boiling chip. Use distillation to remove most of the dichloromethane from the product.

Use a Pasteur filter pipet to transfer the residual dichloromethane solution to a 5-mL conical vial. In a ***fume hood,*** use air or nitrogen to speed evaporation of the remaining dichloromethane.

4. Recrystallizing the Product

Prepare a hot-water bath using a 250-mL beaker.

Add 10 mL of methanol to a large test tube. Heat the methanol in the hot-water bath.

Recrystallize the product by first dissolving it in a *minimum* amount of hot methanol. While keeping the solution hot, reduce the solubility of the product by adding distilled water to the methanol solution until it *just* becomes cloudy. Then add just enough hot methanol to clear the solution.

Set the solution aside to cool slowly to room temperature.

Prepare an ice-water bath using a 250-mL beaker. Once the crystallization solution has reached room temperature, cool the solution in the ice-water bath to complete the crystallization.

Collect the crystals by vacuum filtration. Transfer the product to a watch glass. Allow the product to air dry.

Measure the product mass. Measure its melting point.

Mix the product with an equal quantity of either 1-methoxy-2-chloro- 4-nitrobenzene or 1,2-dimethoxy-4-nitrobenzene. Measure the mixture melting point.

5. Cleaning Up

Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Microscale

Equipment

100-mL beaker*	hot plate
250-mL beaker†	melting point capillary tube
boiling chip	microspatula
condenser, reflux	2 Pasteur pipets, with latex bulb
2 conical centrifuge tubes	5-mL round-bottom flask
5-mL conical vial	sand bath§
5-mL conical vial or 5-mL round-bottom flask‡	separatory funnel
50-mL Erlenmeyer flask	support ring
25-mL filter flask, with vacuum tubing	support stand
filter paper	20 × 150-mm test tube
10-mL graduated cylinder	thermometer, –10 to 260 °C, with adapter
Hirsch funnel, with adapter	2 utility clamps
	watch glass

*for ice-water bath

†for hot-water bath

‡use glassware indicated by your laboratory instructor

§sand in crystallizing dish on electric hot plate or sand in electric heating well with heat controller

Reagents and Properties

substance	*quantity*	*molar mass (g/mol)*	*mp (°C)*	*bp (°C)*
dichloromethane	2 mL	85		40
3,4-dichloronitrobenzene	0.075 g	192	41–44	
1,2-dimethoxy-4-nitrobenzene*	0.005 g	183	96	
magnesium sulfate, anhydrous	0.050 g	120		
methanol	7.5 mL	32		65
1-methoxy-2-chloro-4-nitrobenzene*	0.005 g	187	93	
1-methoxy-2-chloro-5-nitrobenzene		187	83	
sodium methoxide, 25% in methanol	1.6 mL			

*for mixture melting point measurement. If necessary, use compound provided by your laboratory instructor.

Preview

- Assemble a reflux apparatus
- Mix 3,4-dichloronitrobenzene, methanol, and sodium methoxide solution
- Reflux the mixture for 1 hr
- Pour the reaction mixture into distilled or deionized water
- Extract the product into dichloromethane
- Remove the dichloromethane by evaporation
- Recrystallize the product from a methanol/water mixture
- Measure the product melting point and mixture melting point

PROCEDURE ***Caution:*** Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

Always use caution in the laboratory. Many chemicals are potentially harmful. Prevent contact with your eyes, skin, and clothing. Avoid ingesting any of the reagents.

1. Conducting the Reflux

Caution: 3,4-Dichloronitrobenzene is toxic and irritating. Methanol is flammable and toxic. Sodium methoxide is flammable and corrosive.

Place 0.075 g (75 mg) of 3,4-dichloronitrobenzene in a 5-mL round-bottom flask or conical vial. Add a small boiling chip. Add 2.4 mL of methanol and 1.6 mL of 25% sodium methoxide in methanol.

Assemble a reflux apparatus using the 5-mL round-bottom flask or conical vial and a condenser, as shown in Figure 3(a) or (b).

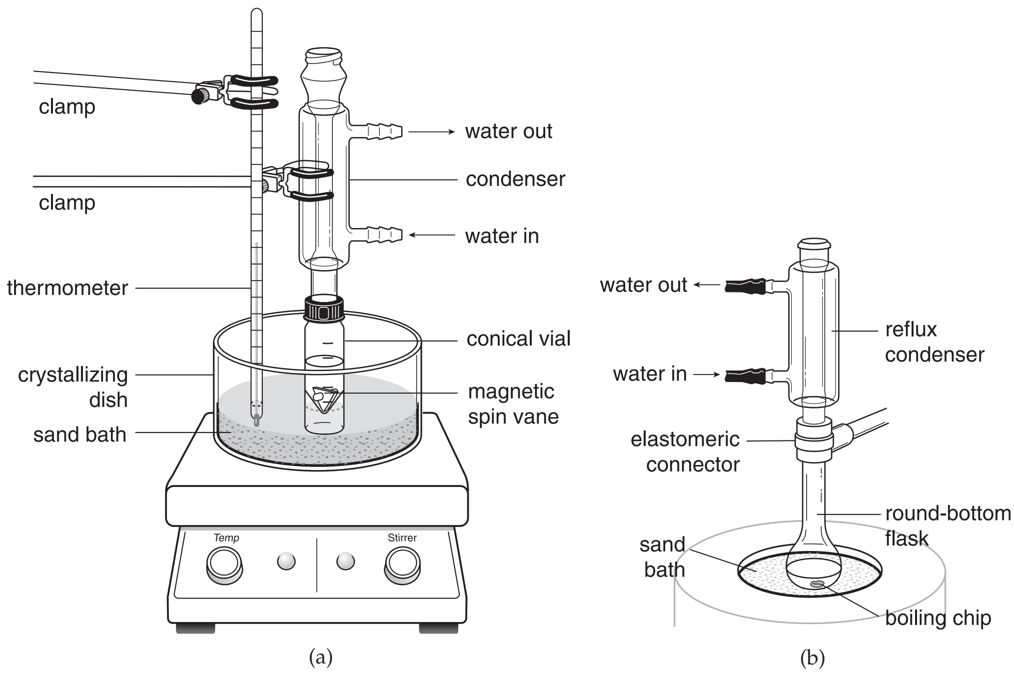


Figure 3 Reflux apparatus for (a) glassware using a conical vial or (b) glassware using elastomeric connectors

If you use a heating well, support the heating well with an iron ring so that the heat can be removed easily. Place a clamp on the neck of the flask.

Gently reflux the solution for 1 hr.

2. Extracting the Product

Caution: Dichloromethane is toxic and irritating.

Pour 4 mL of distilled or deionized water into a 15-mL conical centrifuge tube. Pour the reaction mixture into the water to precipitate the product.

Add 2 mL of dichloromethane to the centrifuge tube. Mix to dissolve the product in the dichloromethane. Transfer the dichloromethane layer to a clean, labeled 15-mL centrifuge tube. Set aside the water layer to discard later.

Wash the dichloromethane layer with 2 mL of distilled water. Transfer the dichloromethane layer to the original centrifuge tube. Add up to

0.05 g of anhydrous magnesium sulfate ($MgSO_4$) to dry the dichloromethane layer. Allow the dichloromethane layer to dry for 10 min.

Transfer the dried dichloromethane layer to a 5-mL conical vial, leaving the $MgSO_4$ drying agent behind. In a ***fume hood,*** use air or nitrogen to speed evaporation of the dichloromethane.

3. Recrystallizing the Product

Prepare a hot-water bath using a 250-mL beaker.

Add 5 mL of methanol to a test tube. Heat the methanol in the hot-water bath.

Recrystallize the product by first dissolving it in a *minimum* amount of hot methanol. While keeping the solution hot, reduce the solubility of the product by adding distilled water to the methanol solution until it *just* becomes cloudy. Then add just enough hot methanol to clear the solution.

Set the solution aside to cool slowly to room temperature.

Prepare an ice-water bath using a 100-mL beaker. Once the crystallization solution has reached room temperature, cool the solution in the ice-water bath to complete the crystallization.

Collect the crystals by vacuum filtration. Transfer the crystals to a watch glass. Allow the product to air dry.

Measure the product mass. Measure its melting point.

Mix the product with an equal quantity of either 1-methoxy-2-chloro-4-nitrobenzene or 1,2-dimethoxy-4-nitrobenzene. Measure the mixture melting point.

4. Cleaning Up

Use the labeled collection containers provided by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands thoroughly with soap or detergent before leaving the laboratory.

Post-Laboratory Questions

1. Use the melting point and mixture melting point data to identify the compound formed in your experiment.
2. Calculate the theoretical yield for your product.
3. Calculate the percent yield for your product.
4. Draw resonance structures for the anionic intermediate that would be produced by reaction of methoxide ion at the 3-position of 3,4-dichloronitrobenzene. If necessary, consult your textbook.
5. Draw resonance structures for the anionic intermediate that would be produced by reaction of methoxide ion at the 4-position of 3,4-dichloronitrobenzene.
6. Based on the resonance structures drawn for Post-Laboratory Questions 4 and 5, which intermediate is stabilized more effectively by the nitro group? Is this result consistent with the identity of the product formed in this experiment? Briefly explain.

NAME SECTION DATE

REAC 749/Nucleophilic Aromatic Substitution: The Reaction of 3,4-Dichloronitrobenzene with Sodium Methoxide

Pre-Laboratory Assignment

1. What are the hazards associated with
   (a) sodium methoxide?

   (b) methanol?

2. How does one obtain an appropriate mixture of methanol and water for recrystallizing a solid sample?

3. Explain how mixture melting points can be used to distinguish between two compounds with similar melting points. Use additional information sources, if necessary.

4. How does the intermediate produced in nucleophilic aromatic substitution differ from the intermediate produced in electrophilic aromatic substitution? How are the two intermediates similar? Briefly explain.

ISBN 0-53497-736-7