9 May 2025

Experiment 7 & Tutorial 7: Aromatic Substitution - Iodination of Vanillin

Objectives of this experiment: to investigate the selectivity of an electrophilic aromatic substitution; to practice recrystallization as a method of purification; to interpret ^1H NMR data in order to identify a reaction product.

General Information

This is a two-period experiment. Full personal protective equipment is required for the 4-hour (E) period. An in-lab assignment analyzing the ^1H NMR spectrum of the starting material will be completed during the E period. The 2-hour (T) period will focus on data processing and analysis and does not require PPE. The SLI specialist for this experiment is Michelle Mills.

Read the introduction below and the relevant sections of the Appendix in the manual for more info on specific techniques. Videos of techniques are available on the website and Brightspace. You may also want to review the tutorial content on IR and NMR that you have covered previously in this course.

Submit the pre-laboratory assignment (see instructions on Brightspace) at least one hour before the start of the "E" period of this experiment, it will not be accepted late.

Prepare your notebook: A reagents and products table will be required, along with a flowchart or procedural plan.

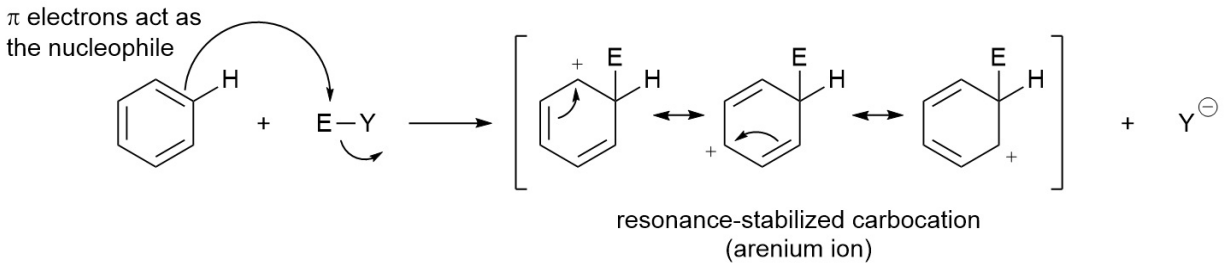
Introduction

Electrophilic Aromatic Substitution

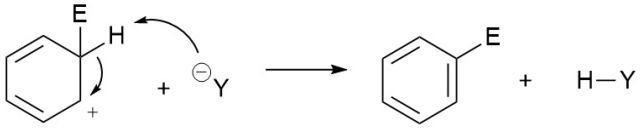
Electrophilic aromatic substitution (EAS) is a fundamental reaction in organic chemistry where an electrophile replaces a hydrogen atom on an aromatic ring, such as benzene. An electrophile is an electron-deficient atom or molecule that can accept a pair of electrons from a nucleophile to form a new covalent bond. An electrophile is considered a Lewis acid because it accepts an electron pair during a reaction. The general pattern for an EAS reaction is shown below, where E is the electrophile and Y is a leaving group.

Most electrophiles are either positively charged, have a partially positive atom, or contain an atom lacking a full octet of electrons, making them reactive toward electron-rich species. Common electrophiles in EAS reactions include halogens (e.g., Cl^+), nitronium ions (NO_2^+), and acylium ions (RCO^+), introduced through reagents like $Cl_2/FeCl_3$, HNO_3/H_2SO_4, and acyl chlorides/$AlCl_3$, respectively. The reaction of benzene with an electrophile proceeds through a two-step mechanism.

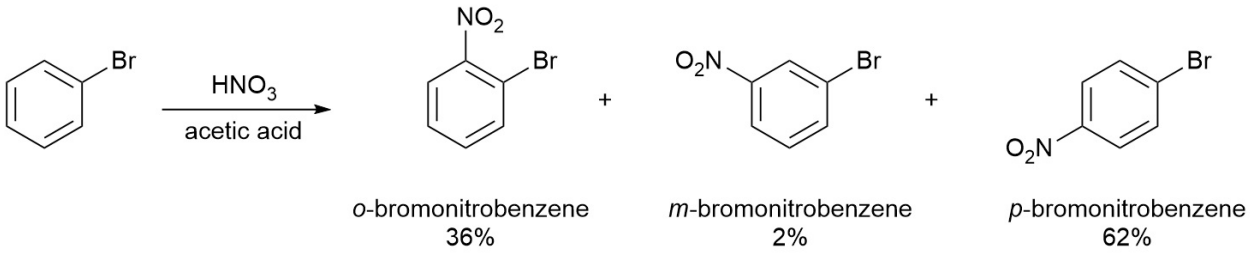
First, the aromatic π system attacks the electrophile, forming a *resonance-stabilized* carbocation intermediate called an arenium ion. Resonance stabilization refers to the delocalization of the positive charge over multiple atoms in the aromatic ring, which spreads out the charge and lowers the energy of the intermediate.This delocalization makes the arenium ion more stable than it would be if the charge were localized on a single carbon atom.



In the second step, a proton is removed from the carbon bearing the electrophile, restoring the aromaticity of the ring. Removing this proton can be achieved using weak base. The base is generally supplied by the reaction solvent (e.g., alcohols, water) or anions that were introduced with reagents as the leaving group (e.g., Cl^-, acetate, HSO_4^-).

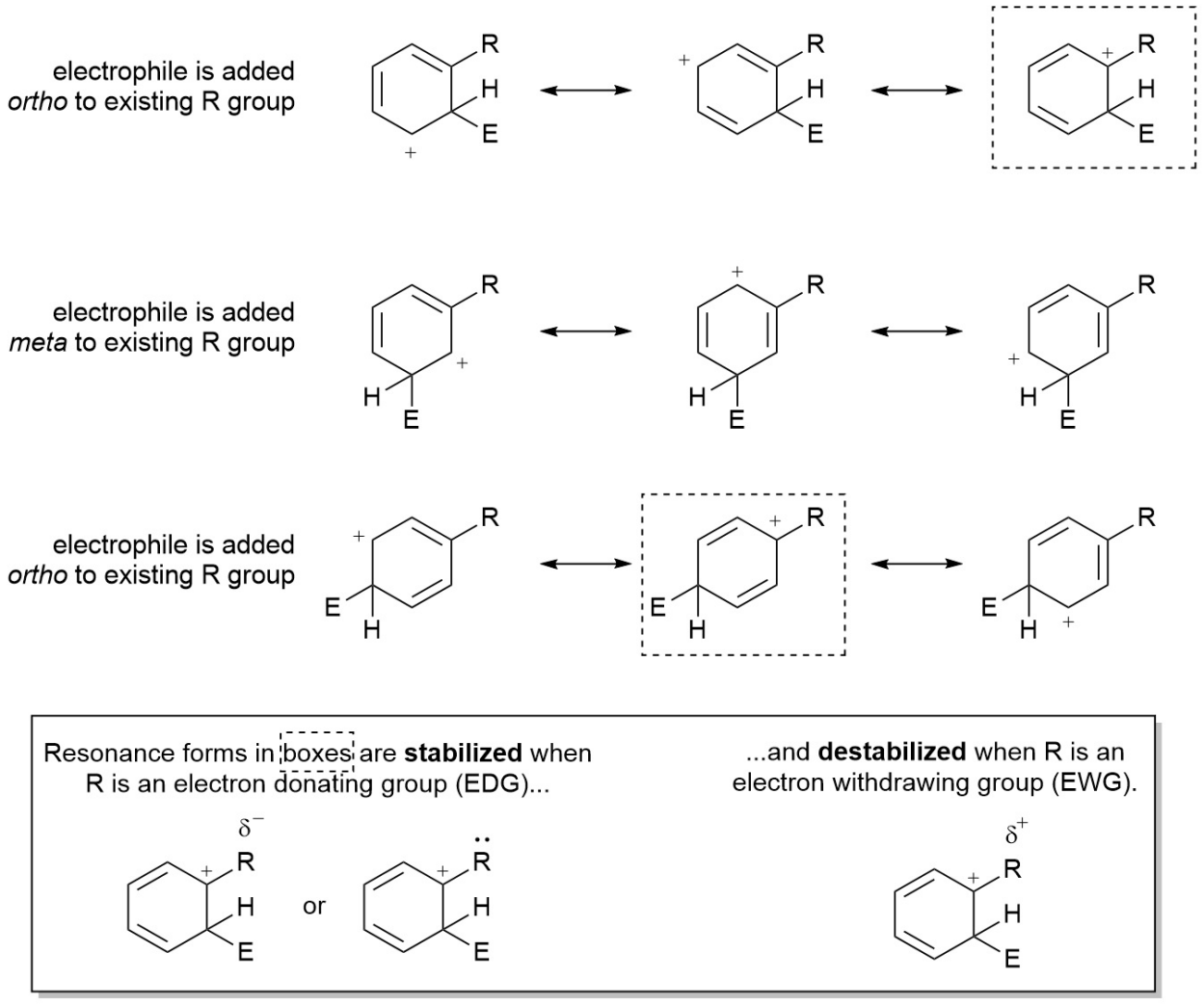


If a monosubstituted benzene molecule were to undergo an EAS reaction, such as the nitration of bromobenzene in the example below, there would be three possible reaction products. The three products are isomers that differ only in the placement of the nitro group with respect to the bromo substitutent: *ortho*, *meta*, or *para*. If the substitution reaction were random (i.e., unselective), a product ratio of 40% ortho, 40% meta, and 20% para would be expected (since there are two ortho, two meta, and 1 para position available). However, the actual ratio of isolated products is quite different, indicating that the EAS reaction is *regioselective*. The % yield of the three products is given in the reaction scheme below. Notice that there is very little *meta* product!



Substituent groups already attached to the aromatic ring significantly influence both the rate of EAS and the position (regioselectivity) where the new electrophile is introduced. These effects arise from the electronic nature of the substituent, which can either donate or withdraw electron density through resonance and/or inductive effects. The resonance forms of the arenium ion formed by *ortho*, *meta*,

and *para*-substitution are shown on the next page. Electron-donating groups (EDGs) stabilize the arenium ion intermediate through resonance, especially at the ortho and para positions, where one of the resonance forms places the positive charge on the carbon bearing the substituent—creating a stabilized tertiary carbocation if the group donates electrons by resonance. In contrast, electron-withdrawing groups (EWGs) destabilize the intermediate at the ortho and para positions because the positive charge ends up adjacent to an electron-deficient atom, resulting in unfavorable charge–charge interactions. As a result, EDGs direct substitution to the ortho and para positions, while EWGs favor the meta position where this destabilization is avoided.



As a result, electron-donating groups (EDGs), such as –OH, $–OCH_3$, and $–NH_2$, activate the ring by stabilizing the arenium ion and generally direct new substituents to the *ortho* and *para* positions. Conversely, electron-withdrawing groups (EWGs), such as $–NO_2$, –CN, and –COOH, deactivate the ring by removing electron density, and typically direct substitution to the *meta* position, where the intermediate is least destabilized.

An important consideration is that not all directing effects follow a simple EDG/EWG classification. For example, halogens have high electronegativity (inductive effect), but they also have lone pairs, leading to ortho/para direction. This example highlights the interplay between resonance and

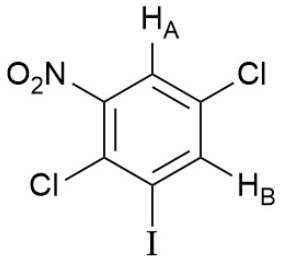
inductive effects in determining substituent behavior. Understanding these effects allows chemists to predict and control the outcome of EAS reactions.

NMR Analysis

During the four-hour Experiment lab period, you will interpret the ^{1}H NMR spectrum of the starting material as an in-lab assignment. You have already covered much of the background you need to do this in the odd-numbered tutorial periods, including tabulation of chemical shift (δ, in ppm), coupling (in Hz), and integration of peaks. All of these things will be revisited to assign the starting material spectrum, and later your product spectrum, but we will also be employing the use of a simple formula for predicting the chemical shift of protons in benzene rings. There is a table in the yellow pages in this manual that tabulates the predicted effect that non-proton substituent neighbours have on the chemical shift of a given phenyl proton depending on whether that substituent is *ortho*, *meta*, or *para* to the proton in question. The general formula is:

$$\delta_H = 7.27 \text{ ppm} + \Delta_{ortho} + \Delta_{meta} + \Delta_{para}$$

For example, if you had synthesized the molecule on the right and wanted to predict the chemical shifts of protons H_A and H_B, you could plug the values from the table in the yellow pages into this formula. H_A has: two non-proton *ortho*-substituents, Cl and NO_2; one non-proton *meta*-substituent, Cl; and one non-proton *para*-substituent, I. Using the corresponding values from the table, the predicted chemical shift for H_A is:



$\delta_{HA} = 7.27 \text{ ppm} + \Delta_{ortho} + \Delta_{meta} + \Delta_{para}$
$\delta_{HA} = 7.27 \text{ ppm} + 0.01 \text{ ppm}$ (*o*-Cl) + 0.94 (*o*-NO_2) - 0.06 (*m*-Cl) - 0.02 (*p*-I)
$\delta_{HA} =$ **8.14 ppm**

Try to calculate the predicted chemical shift for H_B using the same method. You should get a value of **8.00 ppm**. The actual chemical shifts for H_A and H_B are 8.16 ppm and 7.98 ppm, respectively. So, although our calculations didn't produce the exact experimental values, they were very close! These calculations can be used as a supplementary tool when trying to decide which signal is which proton in aromatic systems, or when deciding between two potential aromatic products with the same substitution pattern (but different substituents).

Recrystallization

The technique of recrystallization involves dissolving a solid in a solvent and then allowing the crystals to reform. It is a phenomenon which depends on solubility differences of a compound in hot and cold solvent, or in solubility differences in two different solvents. Most organic compounds dissolve in a number of solvents with absorption of heat, and therefore an increase in temperature increases the solubility of the compound in the solvent. If a compound is dissolved in a minimum amount of hot solvent and the solution is allowed to cool, crystals will reform due to decreasing solubility with decreasing temperature. Purification by recrystallization is a technique which depends on solubility differences between a compound and its impurities. Ideally, the solubilities should be such that either the impurities remain in solution while the desired compound crystallizes in pure form, or the impurities never dissolve and can be filtered out when the mixture is hot (leaving only the desired product dissolved, which will then crystalize on cooling).

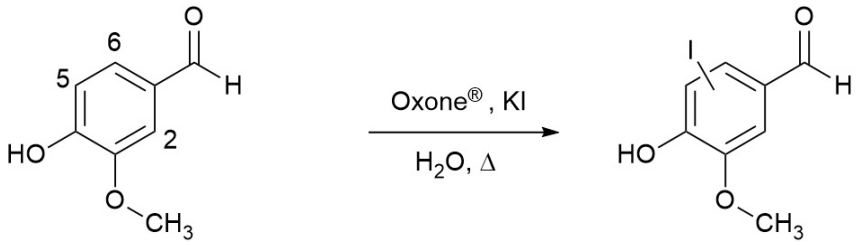
In some instances, no single solvent may be found which is acceptable. A compound may be far too soluble in one solvent and too insoluble in another solvent. In such cases mixed solvent pairs work well, with the solubility of the compound in one solvent being reduced by the addition of a second solvent in which the compound is much less soluble. The solvents must be completely miscible. Examples of such mixed solvent systems include ethanol-water, ethyl acetate-hexanes and ether-methanol. The art of purification by recrystallization is only briefly introduced here, but many more details are available in the Appendix. A variety of techniques exist and are selected based on the solubility of the target compound as well as the presence and solubility of impurities and side products.

Melting Range Analysis

The definition of melting point (or freezing point) of a pure compound is: The temperature at which the solid and liquid phases of the compound are in equilibrium. This definition requires that the pressure is constant, and the normal melting point of a compound is taken at one atmosphere pressure. Adding heat to a mixture of solid A and liquid A at the melting point will cause solid to be converted to liquid, without increasing the temperature, until all solid has been converted to liquid. If heat is removed, the temperature will remain constant until all the liquid has been solidified. In practice, this conversion is usually observed over a temperature range, and thus the term "melting range" is more suitable.

The melting range is narrow for most pure substances, less than 2 °C, and as small as 0.5 °C. Impurities in the compound will both widen and lower the melting range (see the appendix if you would like to learn why). It is this phenomenon that allows the observed melting range to be used as a gauge of purity. The observed melting range narrows and melting temperature increases as the purity of the compound approaches 100%.The most common procedure of determining a melting range follows. Place a small amount of sample in a thin-walled capillary tube sealed at one end. The capillary tube is placed in a metal block, which is in contact with a thermometer. The metal block is electrically heated, and the tube is monitored for changes. The start of the melting range is recorded when the first drop of liquid is visible and the end is recorded as the final speck of solid disappears.

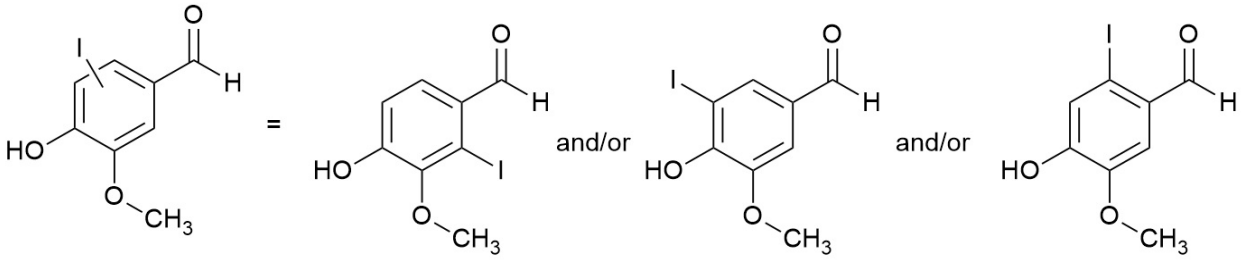
The Experiment



4-hydroxy-3-methoxybenzaldehyde
"vanillin"

You will perform an electrophilic aromatic substitution reaction and determine the substitution pattern of the product. The starting material for this reaction is vanillin. Vanillin is an aromatic compound with a methoxy, hydroxyl, and formyl (aldehyde) group on a benzene ring, responsible for the characteristic flavor and scent of vanilla. The source of our electrophile (E) in the reaction

of vanillin will be a combination of Oxone® and potassium iodide. You will use spectroscopic data to determine the regioselectivity of the reaction (i.e., whether the substitution occurs at position 2, 5, 6, or some combination of those options).



Oxone® serves as a "green" oxidant by generating electrophilic iodine species *in situ* from iodide under aqueous conditions, avoiding the need for hazardous reagents like molecular halogens or strong acids, and aligning with sustainable chemistry principles through its low toxicity, minimal waste, and water-based reaction medium. The "active ingredient" is $KHSO_5$, which reacts with the potassium iodide to generate the electrophile. A more thorough description of the generation of an electrophile using Oxone® and potassium iodide is provided at the end of this section (page E7-8), but you can consider the electrophile in this case to be equivalent to I^+.

Experimental

Note that only the mass amount for Oxone® is provided in these instructions - you will need to calculate how much of each other material to use yourself this time!

A) Iodination

In a 100 mL round bottom flask, add vanillin (**6 mmol**), potassium iodide (**6 mmol**), water (**10 mL**), and a stir bar. Securely clamp the round bottom flask in your fumehood and then assemble a reaction apparatus containing a Claisen head adapter, a reflux condenser, and a dropping funnel. Make sure the stopcock on the dropping funnel is closed! A heating mantle and variac will be used to heat the reaction, and a stir plate is needed.

In a separate small, clean beaker or Erlenmeyer flask, prepare a solution of Oxone® (**1.95 grams**, 6.3 mmol of $KHSO_5$) in **10 mL** of water. Stir with a stir rod to fully dissolve - you might need to break up larger chunks of solid. Once it is fully dissolved, add the Oxone® solution to the dropping funnel.

Stir and heat the vanillin solution (set the variac to 50 to start and increase if needed) until reflux is achieved. Once the solution has reached reflux, open the stopcock *carefully* and add the Oxone® solution from the dropping funnel at a rate of approximately 1 drop every 2 seconds, maintaining reflux and stirring. The addition should take 5-10 minutes. Once the addition is complete, close the stopcock of the addition funnel and continue to reflux the reaction mixture for 1 hour. During this time you can work on the NMR analysis of the starting material.

After the hour of reflux is complete, remove the heating mantle and allow the reaction to cool enough that you can touch the flask. You may notice purple crystals of iodine that have formed as a side product - use a long-stemmed pipette to wash any solids stuck in the Claisen head into the reaction flask using **20 mL** of water. Add a spatula-tip portion of sodium bisulfite to remove any excess oxidizing reagent and swirl the flask. Then, collect the insoluble product using vacuum

filtration. Wash the solid thoroughly with water and allow at least 5 minutes after the last wash for the product to dry. Collect the crude product and obtain a crude yield. You can weigh the crude material into a 125 mL Erlenmeyer flask, as you will need to transfer it to one for the recrystallization anyway.

B) Recrystallization

Add a stir bar to the 125 mL Erlenmeyer flask containing your product, then add an 80:20 mixture of isopropanol and ethyl acetate. How much you need will depend on your crude yield. For every gram of crude product, use 30 mL of the recrystallization solvent. Heat the mixture to boiling on a hot plate (set to at least 90 °C). Once the crude product has dissolved, add warm water by pipette, about 2 mL at a time, until precipitate starts to form. Then, place the flask in an ice bath and allow crystallization to continue for at least 5 minutes. Collect the product by vacuum filtration, this time washing only with cold isopropanol (not water!). Transfer your purified product to a vial to submit.

C) Product Analyses

NMR: Prepare a sample for NMR spectroscopy, and submit this sample for analysis. The preparation and submission will be demonstrated in class. In the **T** period you will process the 300 MHz ^{1}H-NMR spectrum of your product, along with an expansion of the aromatic proton signals.

Melting range: Record the melting range of your recrystallized product. Compare to the value provided in the SDS page from the commercial supplier (Millipore Sigma, 183 - 185 °C).

Waste Disposal

All containers for waste disposal are labelled, and are kept in the fume hoods. If you weigh out excess Oxone®, please do not throw it in the garbage! Instead, put excess in the labelled special waste container.

Samples

Hand in your remaining sample of your reaction product in a vial with a label detailing (at minimum) your name, the date and section number, the name or a drawing of the compound, and the mass of compound.

Report

Use the report template and grading guidelines posted on the course website to prepare your report.

References

If you have taken a course that covers electrophilic aromatic substitution, you may wish to consult that text or lecturebook. It would be wise to review the NMR spectroscopy material covered in previous tutorials.

Notes on the Reaction and the Formation of the Electrophile

Reactions (or reaction schemes) in synthetic organic chemistry are presented such that the starting materials are on the left of the arrow, reagents and conditions are listed above and below the arrow, and the organic product is shown to the right of the arrow. Inorganic byproducts are not shown, nor are details of the "workup" that removes these byproducts. Intermediates are not explicitly described. A reaction scheme is good in that it communicates the information quickly, using organic structures to show the changes to the functional groups. The reaction scheme is less good in that the technical information is not as clearly presented.

Oxone® is a strong oxidizing agent. When it reacts with iodide ions (I^-) from KI, it can oxidize them to molecular iodine (I_2) or even further to electrophilic iodine species. Below is a simplified mechanism showing how oxone oxidizes iodide (I^-) to form electrophilic iodine species. The exact pathway can vary with pH and conditions, but this general overview captures the key steps.
The first step is the oxidation of I^- by the active oxidizing species in Oxone®, HSO_5^-:

$$HSO_5^- + 2I^- + H^+ \rightarrow I_2 + HSO_4^- + H_2O$$

At reflux conditions, I_2 can react with water to form hypoiodous acid (HOI) and iodide:

$$I_2 + H_2O \rightleftharpoons HOI + I^- + H^+$$

In refluxing water, the above equilibrium favours HOI, which acts as the electrophile in the reaction. HOI has the structure H-O-I, and in this molecule the iodine is in the +1 oxidation state, making it electron-deficient and capable of accepting electrons (i.e., making it an electrophile). The -OH acts as a leaving group.

So, while I^+ is a more classical textbook example of an electrophile, HOI acts as a "soft" source of I^+, delivering the iodine atom without fully dissociating into free I^+. Using HOI is what allows us to achieve the iodination of vanillin using mild and aqueous conditions. Reagents that provide free I^+ require much harsher conditions, chlorinated solvents, and often strongly acidic media.