**A Green Electrophilic Aromatic Iodination[[1]](#footnote-1)**

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**Chemical Concepts**

Electrophilic aromatic substitution, vacuum filtration, melting point determination

**Green Lessons**

Benign solvents, safer reactants, more selective reagents

**Estimated Lab Time**

1.5 hours

**Scenario**

*The following is your next assignment from Lecher Consulting Enterprises:*

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*The following is your next assignment from Lecher Consulting Enterprises:*

*New Age Pharmaceuticals* has enlisted the services of *Lecher Consulting Enterprises* in the development of a ‘top secret’ new class of antipsychotic medication for the federal government. The targeted therapeutic application of the product will be in the treatment of overactive imagination and the illusion of free will.[[2]](#footnote-2)

As you may recall, *New Age Pharmaceuticals* products are manufactured from natural starting materials. In this, the first step of the synthesis, you will synthesize 5-iodovanillin from vanillin.[[3]](#footnote-3)



**Background**

The substitution chemistry of alkyl compounds is dominated by nucleophilic substitution processes. In contrast, aromatic compounds most often undergo electrophilic substitution reactions. In general, these electrophilic aromatic substitution reactions occur via a two-step addition/elimination process. The electrophilic reagent is first added to the aromatic ring by attack of the π electrons, generating a cationic intermediate. This intermediate then undergoes an elimination (usually a proton) to form the substitution product.[[4]](#footnote-4)

Consideration of this mechanism allows one to predict the effects of pre-existing aromatic ring substituents on the reactivity and regiochemistry of the substitution reaction. It is observed that electron-releasing substituents accelerate the reaction and preferentially direct the incoming substituent into the *ortho* and *para* positions, where resonance stabilization of the resultant positive charge is optimized.

Aromatic halogenation is an important tool for the elaboration of aromatic compounds. This is typically carried out through the addition of Cl2 or Br2 to the aromatic compound, with a catalyst usually required to mediate the reaction. However, there are multiple concerns with the use of Cl2 or Br2. Bromine is a volatile liquid that can cause serious chemical burns to the skin and eyes as well as severe to fatal irritation of the respiratory passages. Similarly, chlorine is a toxic gas that irritates the respiratory system.[[5]](#footnote-5)

Elemental iodine is relatively easy to work with, but has relatively low reactivity toward many aromatic systems. A mixture of iodine and a powerful oxidizing agent (e.g., nitric acid) is often used to effect aromatic iodination reactions. If the aromatic substrate bears strongly electron-donating groups (e.g., phenols), the iodination reaction is more facile, but it can be difficult to control the regiochemistry of the reaction, and therefore polyiodination is common.

**Green Considerations: In the Lab**

In this experiment, you will explore the use of a convenient alternative iodination procedure, using sodium iodide (instead of iodine) and sodium hypochlorite (common bleach) as an oxidizing agent in aqueous alcohol.[[6]](#footnote-6) These reaction conditions offer several advantages over the more traditional methods. The reaction is efficient and selective, leading to good yields of monoiodinated product. The method allows the use of more environmentally-benign reagents (NaOCI instead of HNO3) and more environmentally-benign solvent (ethanol instead of halogenated solvents). Additionally, the waste products for the reaction are NaCl and water, which are environmentally-benign.

**Green Considerations: Mercury in Bleach**

Bleach is used commonly in households, industries, hospitals, and laboratory facilities as a cleaner and disinfectant. Sodium hypochlorite, the active ingredient in bleach, is also utilized by chemists as a benign oxidant and as a chlorine source.

As green chemists, we must assess the lifecycle for all of the chemicals used in synthetic transformation. Therefore, we need to evaluate the process for the manufacturing of bleach. The ingredients for making sodium hypochlorite (sodium hydroxide and chlorine gas) are typically produced via the electrolysis of salt water. There are three industrial methods for the production of chlorine by electrolysis: mercury-cell electrolysis, diaphragm-cell electrolysis, and membrane-cell electrolysis. The three processes involve the application of an electrical current through a salt water solution (aqueous NaCl). This causes the chlorine ions to migrate to the anode and the sodium ions to migrate to the cathode. These ions must then be kept separate so that they can be isolated.

Mercury-cell electrolysis uses mercury at the cathode, causing the sodium ions to be amalgamated in the mercury as sodium metal. Mixing the mercury/sodium amalgam with water then yields sodium hydroxide, which can be mixed with the chlorine gas to produce sodium hypochlorite. The problem with mercury-cell electrolysis is that small but significant amounts of mercury are present in the resulting sodium hydroxide solution, which is carried into the bleach solution. As previously mentioned, the mercury-cell method is not the only way to isolate the sodium ions during saltwater electrolysis. Selective membranes can also be used, and these membranes do not introduce mercury contamination to the bleach product. When purchasing bleach, the green chemist would select bleach made at a facility that does *not* use mercury-cell electrolysis.



**Reaction Table**

 **Formula**

**Name Weight eq mmol wt or vol**

vanillin 152.15 1.00 6.6 1.00 g

NaI 149.89 1.20 7.9 1.18 g

NaOCl solution (0.70 M) [[7]](#footnote-7) 74.44 1.25 8.4 12 mL

HCl solution (3.0 M) 36.46 1.36 9.0 3 mL

*\*note: use YOUR weight and YOUR volume for your reaction table*

**Safety Precautions**

Sodium hypochlorite: Aqueous sodium hypochlorite is household bleach – it may bleach and / or damage clothing and skin.

Hydrochloric acid: Hydrochloric acid is corrosive and a chemical burn hazard. Avoid contact. If contact is made with the skin, wash the affected area with cold water for 15 minutes.

Ethanol: Ethanol is volatile and flammable; avoid open flames. The ethanol that we are using is denaturated (*a.k.a*. poisoned). Do not drink!

**Experimental Procedure**

*Reaction*

1. Weigh between 0.95 and 1.05 grams of vanillin (on weigh paper) and add to a 100 mL round bottom flask. Record the weight *directly* into your notebook to the maximum accuracy of the balance.
2. Weigh between 1.15 and 1.20 grams of NaI (on weigh paper) and add to the 100 mL round bottom flask. Record the weight *directly* into your notebook to the maximum accuracy of the balance.
3. Fill out your reaction table by calculating the mmol and equivalents of reagents used based on YOUR mass of vanillin. Show your calculations under the reaction table.
4. Completely dissolve both solids in 20 mL of ethanol with stirring.[[8]](#footnote-8)
5. Cool the reaction flask an ice water bath with stirring for about five minutes.
6. Position a separatory funnel above the 100 mL round bottom flask as depicted in the apparatus figure. Make sure the stopcock is closed. Add 12 mL aqueous sodium hypochlorite solution (0.70 M) to the separatory funnel.
7. Add the aqueous sodium hypochlorite solution DROPWISE with stirring to the reaction mixture over a period of 10 to 15 minutes. Add the first 2 mL *especially* slow, as a large amount of heat is evolved. Note any observations. Add additional ice to the bath as necessary.
8. Once the addition is complete, add 2 drops of 3 M HCl. Remove the ice batch, and allow the reaction mixture to passively warm to room temperature with stirring. Once at room temperature, continue to stir for ten minutes.

*Workup and isolation*

1. Add 5 mL of aqueous sodium thiosulfate to the reaction mixture with stirring. Note any color change.
2. Acidify the reaction mixture with 2 mL 3 M HCl aqueous hydrochloric acid. Check the pH with pH paper. If reaction mixture is not acidic, add additional HCl until acidic.
3. Cool the flask in an ice bath for 5-10 minutes.
4. Collect the solid by vacuum filtration. Use small portions (~2 mL) of **ice**-cold DI water to aid the transfer of the solid into the filter funnel and to wash the product. With the vacuum applied, allow the solid to dry on the vacuum for about two minutes. Save your solid. Place your filtrate in the container labeled EXP # 16 - Aqueous Filtrate.
5. Air dry product to a constant mass in the fume hood for at least 24 hours.
6. Weigh your dried product.

*Characterization and Calculations*

1. Determine the theoretical yield and percent yield for the reaction.
2. Determine the melting point of your substance using a Mel-Temp apparatus.
3. Generate an IR spectrum for your product. Record important signals in the data section of your notebook. Submit your spectrum when you turn in your notebook pages.
4. Generate a 1H NMR Spectrum for your product. Assign the signals for each hydrogen in the data section of your notebook. Submit your spectrum with question 1 in your assignment.
5. Confirm the identity of your product by:
	1. comparing your melting point data to the literature value
	2. comparing your IR data to a reference spectrum
	3. comparing your 1H NMR data to a reference spectrum

*Disposal*

1. When you are satisfied with your data and calculations, place your product in a 20 mL scintillation vial, labeling the vial as EXP #16 5-iodovanillin. Save this compound for a future experiment.

**Assignment**

In addition to the lab notebook, answer the following questions:

1. Attach your 1H NMR spectrum and assign the signals for each hydrogen. Obtain a 1H NMR spectrum for iodovanillin from your favorite spectral database and attach this spectrum for reference. Are the spectra consistent? Explain.
2. Compare the melting point range of your product to the literature value. What information does this give you about the purity and identity of your product?
3. What is the most acidic proton in your starting compound?
4. What is the approximate pH of the sodium hypochlorite (bleach) solution?
5. Considering the two previous questions, what would you expect to happen when the sodium hypochlorite solution is added to the starting compound?
6. What happened when you acidified the reaction mixture? Explain chemically why this occurred.
7. Based on the reaction scheme, what is the molar ratio between vanillin and sodium iodide?
8. What did you observe when you started your dropwise addition of the sodium hypochlorite solution? What are you creating?
9. What is the role(s) of the sodium hypochlorite in this reaction?
10. What is the role of the sodium iodide in this reaction?
11. Propose either a mechanism or an equation for the generation of the electrophile [either I+ or I2].
12. Propose a valid mechanism for the synthesis of 5-iodovanilin from vanillin (how it exists in basic solution) the electrophile [either I+ or I2]. Make sure to draw the reaction intermediates (including any charges) and to show the flow of electrons with curved arrows.
13. Discuss the regiochemistry of the reaction.
14. Calculate the atom economy for the reaction. For the reagents, make sure to account for the stoichiometry of the balanced chemical equation.

 Atom economy = (MW desired product / combined MW of all reagents) x 100%

1. Would you consider this reaction to be atom efficient? Justify your answer.
2. Calculate the effective mass yield. For the NaOCl and HCl, be sure to use the mass of the NaOCl and HCl, not the mass of the NaOCl and HCl solutions.

 Effective mass yield = (mass of desired product obtained / combined mass of all reagents used) x 100%

1. Identify the possible components of the aqueous filtrate. Is it appropriate to disposed of the filtrate via the drain? Explain your rationale.
2. What is the solvent for this reaction? Is this a green solvent? How does the absence of traditional solvents improve the greenness of the reaction?
3. How is the product isolated from the reaction mixture? How does this technique minimize the need for additional solvents?
4. Does the reaction need to be performed with the protection of a fume hood? How does this benefit the procedure?
5. Essay: Green Chemistry looks to eliminate both the use of hazardous reagents and the generation of hazardous products. Green chemistry minimizes environmental impact while maximizing safety. Evaluate the procedure, in its totality, for greenness.
	1. Describe at least 4 aspects of the procedure that contribute to its greenness (you may use those previously mentioned).
	2. Suggest at least two ways to improve the procedure.

**Requirements**:

Typing the text portion of your assignment is required. Chemical structures and mechanisms can be drawn by hand. Work calculations by hand.

**Due:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Result Submission Form**

**Lab Title: Electrophilic Aromatic Iodination**

**Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Semester and Year: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Reaction Scheme:**



**Your Reaction Table**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name** | **Formula Weight** | **density** | **eq** | **mmol** | **wt / vol** |
| vanillin  | 152.15 | -- |  |  |  |
| NaI | 149.89 | -- |  |  |  |
| NaOCl solution (\_\_\_\_\_\_\_\_\_ M) | 74.44 | -- |  |  |  |

**Your Results**

|  |  |
| --- | --- |
| **Mass of Product** |  |
| **Theoretical Yield** |  |
| **% Yield** |  |
| **Melting point range** |  |
| *other values not needed in this table* |  |
|  |  |

**Explain any reasons why your yield would be lower than expected:**

**Make at least 1 suggestion for improving the lab:**

1. Primary text reference: Doxsee, K. M.; Hutchison, J. E. *Green Organic Chemistry: Strategies, Tools, and Laboratory Experiments*, Brooks/Cole 2004. [↑](#footnote-ref-1)
2. Remember these are fictional scenarios. [↑](#footnote-ref-2)
3. The remainder of natural product synthesis will be address in a subsequent experiment. [↑](#footnote-ref-3)
4. Please see your text for a full mechanism. [↑](#footnote-ref-4)
5. Chlorine gas was first used as a weapon by Germany in World War I [↑](#footnote-ref-5)
6. For the primary literature reference, see: Edgar, K. J.; Falling, S. N. *J. Org. Chem*, **1990**, *55*, 5287-5291. [↑](#footnote-ref-6)
7. It is recommended that the titer of the NaOCl solution is verified before starting the reaction. [↑](#footnote-ref-7)
8. Safety note – As a general safety rule, solutes should be added to solvents. The resulting solution should go from dilute to more concentrated. This is because the solvation process for some compounds can be violently exothermic. [↑](#footnote-ref-8)