10 July 2024

NEW Experiment 13: Green Chemistry Considerations for an Amide Coupling Reaction

Objectives of this experiment: to work in a small group to investigate the conditions of an amide coupling reaction; to consider the Principles of Green Chemistry to select the ideal reaction conditions; to participate in a class discussion comparing multiple methods; to consider the industrial implications of small-scale lab chemistry.

General Information

This is a two-period experiment where the experimental work is completed in the E period, and a class discussion will take place during the T period. Full personal protective equipment is only required for the 4-hour (E) period. The SLI specialist for this experiment is Michelle Mills.

You will be working as a member of a group, but carrying out your own synthesis using one of the provided procedures. Your group members will complete the other experiments and you will share results.

Read the introduction and experimental sections. A number of resources are included in the reference section that you can also look at before the lab. Printed copies of these resources will be available in the lab.

There is no prelaboratory assignment for this experiment. Instead, the report for this experiment will be completed and submitted before the end of the 2-hour (T) period.

Prepare your notebook for a synthetic experiment. Complete a table of reagents and products in your notebook.

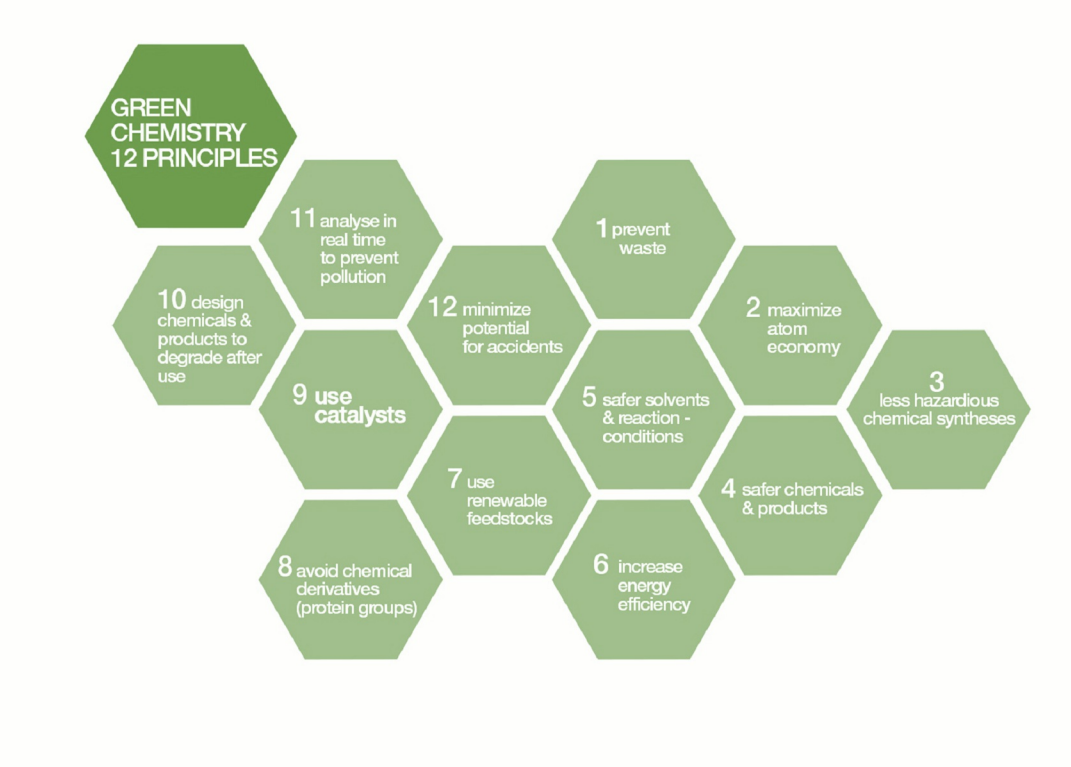
Introduction

Green Chemistry

At its core, the focus of green chemistry is to shift towards chemistry that is safer for both people and the planet. Established by Anastas and Warner in 1998, the Twelve Principles of Green Chemistry are guidelines to consider when designing more environmentally friendly chemical processes. Below are the 12 Principles, while not all may be applicable in this experiment, you may wish to begin to think about how they could be applied in this experiment and previous experiments.

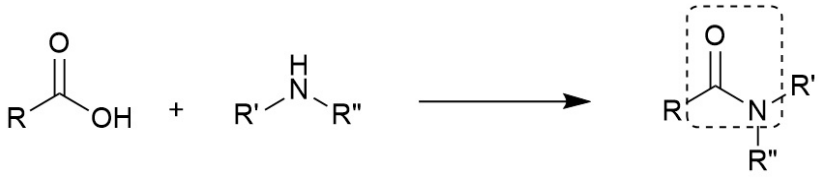
1. **Prevention**: It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy**: Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Syntheses**: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**: Chemical products should be designed to affect their desired function while minimizing their toxicity.

5. **Safer Solvents and Auxiliaries**: The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**: Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**: Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided, if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis**: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation**: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-time analysis for Pollution Prevention**: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.



Amide Coupling

Amide coupling reactions form **amide bonds** (a key functional group in organic chemistry) by linking a carboxylic acid and an amine. Amide coupling reactions are vital in the pharmaceutical industry for the synthesis of drugs and bioactive peptides. They enable the construction of complex molecules with high precision, crucial for developing therapeutic agents. In materials science, these reactions are essential for creating polymers and resins with desired mechanical and chemical properties. Their ability to form strong, stable bonds underpins the synthesis of various industrial products, making them indispensable in manufacturing and research.



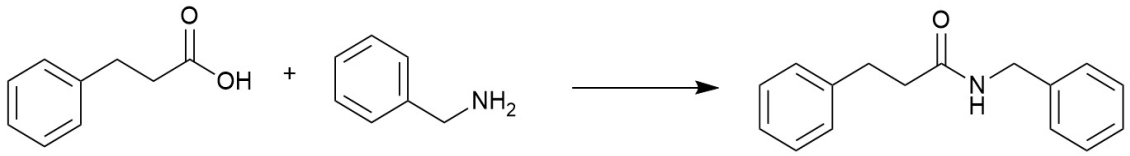
A variety of reaction conditions to form amide bonds are used by chemists, and the development of amide coupling reactions has taken place over decades, with early methods focusing on direct condensation techniques. Commonly used techniques use reagents like oxalyl chloride or thionyl chloride, which while widely applicable are lachrymatory and toxic, and produce dangerous byproducts like carbon monoxide. Uronium salts (e.g., hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU)) are also popular but produce byproducts with very high molecular weight (i.e., they have quite poor atom economy).

The advent of carbodiimide reagents in the mid-20th century revolutionized the field by providing more efficient and less harsh coupling conditions, though early iterations of this class of reagents (e.g., dicyclohexyl carbodiimide (DCC)) are strong sensitizers and therefore not attractive for large-scale industrial chemistry. Solid-phase peptide synthesis further refined these methods, allowing for the rapid and automated assembly of peptides. Modern advancements continue to enhance the efficiency, selectivity, and sustainability of amide coupling reactions, integrating principles of green chemistry. Common methods for modern amide couplings include using safer carbodiimide coupling agents (e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)) or catalytic systems that facilitate the formation of the amide bond under mild conditions.

In this experiment, you will work in your group to compare varying conditions of an amide-forming synthesis method. You will determine which of the conditions for that pathway is the "best" by assessing both the yield and how well it adheres to the Principles of Green Chemistry. In the tutorial period, your group will present your assessment to the class, and listen to the findings of the groups who tried other synthetic methods. Then, the two methods will be compared as a class. This is not meant to test or assess your presentation skills – it is just a way to facilitate a group discussion ☺

The Experiment

All groups will be performing the same reaction – an amide coupling of hydrocinnamic acid (a solid) and benzylamine (a liquid).



Two methods will be investigated, with two groups working on each (to check for reproducibility of the results). Everyone will use the same amount of hydrocinnamic acid, and add a slight excess (1.1 equivalents) of benzylamine.

Method 1: Catalysis with Boric Acid

The groups working in fumehoods 1-10 will do a boric acid-catalyzed reaction to form the amide. Boric acid works through a catalytic mechanism and is therefore required only in small amounts, but the reaction requires high temperatures to work so a solvent with a high boiling point must be used. The group will vary the solvent and amount of catalyst to find the best reaction conditions for this method. The conditions that each student will test are in the table below.

Seat Number	Solvent	Equivalents of Boric Acid	Procedure to follow
14 & 19	toluene	0.1	A
13 & 18	toluene	0.2	A
12 & 17	*p*-xylene	0.1	A
11 & 16	*p*-xylene	0.2	A

Toluene boils at 110 °C, and *p*-xylene at 139 °C. You will need to calculate how much boric acid to weigh out ahead of time.

Method 2: Reactions with CDI

The groups working in fumehoods 11-20 will investigate amide-forming reactions using 1,1'-carbonyldiimidazole (CDI). CDI reacts with water to form carbon dioxide, so make sure it is handled with caution, wearing gloves and inside a fumehood. Unlike boric acid in method 1, CDI is used stoichiometrically. So, rather than varying the amount of reagent added, your group will be looking at the effect of varying the solvent, and at the difference between a traditional solvent-based synthesis and liquid-assisted grinding. Liquid-assisted grinding (LAG) is a technique used in *mechanochemical* (chemistry via mechanical force) synthesis. Although many mechanochemical reactions will occur without solvent, using a small amount of solvent can be useful to enhance reactivity or shorten reaction time.

Seat Number	Solvent	Procedure to follow
2 & 7	tetrahydrofuran	B
3 & 8	2-methyltetrahydrofuran	B
4 & 9	tetrahydrofuran	C
5 & 10	2-methyltetrahydrofuran	C

Experimental

A)

Place hydrocinnamic acid (**0.3 g**, **2 mmol**) and benzylamine (**1.1 equivalents**) in a 50 mL round bottom flask with a stir bar, then add your assigned solvent (**6 mL**). Add your assigned amount of boric acid (**0.1 or 0.2 equivalents**), then stir the reaction at reflux in air for 90 minutes (for toluene, set the variac around 50 to start, and around 60 for *p*-xylene). After the reflux is complete, remove the reaction from heat and allow the glassware to cool to the touch before dismantling the set-up. Once cool, pour the reaction mixture into 10 mL of hexanes and stir to form a precipitate. Collect the solid by vacuum filtration and wash the solid three times, first with hexanes (**10 mL**), then distilled water (**10 mL**) and finally hexanes again (**10 mL**). Allow the product to dry by pulling air through the filter for at least 5 minutes. Record the yield of the amide product and collect an IR.

B)

Place hydrocinnamic acid (**0.3 g**, **2 mmol**) in a 50 mL round bottom flask and then add your assigned solvent (**15 mL**). In a few small portions, add CDI (**2 mmol**) to the flask, then stir at room temperature for 1 hour. Add benzylamine (**1.1 equivalents**) and reflux the reaction in air for 30 minutes (Variac setting around 35 to start). After the reflux is complete, remove the reaction from heat and allow the glassware to cool to the touch before dismantling the set-up. Remove the solvent using the rotatory evaporator to yield a oily residue. Dissolve the residue in ethyl acetate (**20 mL**). Wash the organic layer via liquid-liquid extraction with aqueous citric acid (**20 mL** of solution contains about 1.3 grams of citric acid in water). Wash the organic layer a second time with **10 mL** of saturated aqueous sodium bicarbonate and put the organic layer into a clean Erlenmeyer flask. Dry the organic layer with a scoop of sodium sulfate. Gravity filter the solution into a clean pre-weighed round bottom flask to remove the drying agent. Concentrate using the rotatory evaporator to isolate the solid product. Record the yield of the amide product and collect an IR.

C)

Place hydrocinnamic acid (**0.3 g** / **2 mmol**) and CDI (**2 mmol**) into a mortar and pestle, then add a few drops of your assigned solvent. Grind the reactants together for 20 minutes using the pestle. Do not worry if the solvent evaporates during this time. Add benzylamine (**1.1 equivalents**) to the mortar and grind the mixture for another 20 minutes. To the mortar, add a small amount (**~ 5 mL**) of ethyl acetate to suspend and collect the solids – you may need to use a spatula to loosen it off the sides of the mortar. Transfer the product into a beaker and add more ethyl acetate (**15 mL**). Wash the organic layer via liquid-liquid extraction with aqueous citric acid (**1.31** g in approx. **20 mL** water). Wash the organic layer a second time with **10 mL** of saturated aqueous sodium bicarbonate and put the organic layer into a clean Erlenmeyer flask. Dry the organic layer with a scoop of sodium sulfate. Gravity filter the solution into a clean pre-weighed round bottom flask to remove the drying agent. Concentrate using the rotatory evaporator to isolate the solid product. Record the yield of the amide product and collect an IR.

D) Product Analyses

Yield: Calculate the yield assuming that all solid collected is product.

IR spectroscopy: We will use IR to determine whether all of the products made by your group are the same, by comparing the spectra. We will also compare the IR spectra to IR spectra of the starting materials.

Waste Disposal

All containers for waste disposal are labelled, and are kept in the fume hoods.

Samples

Please show your TA your sample and then add it to the collection jar.

Report

Due by the end of the tutorial period! You will be able to finish most of the report in the E period, and we will provide a paper copy of the template for you to work on. Make sure you bring this copy back to the tutorial period, as you will need to finish it and hand it in.

Take a look at the template before you come to class, and come prepared to complete the report by the time you leave the T period!

References

If you have taken a course that covers amide coupling reactions, you may wish to consult that text or lecturebook. Some valuable references for Green Chemistry background info are below, and the resources at these links will be printed out and available in the lab for your group to consult while you assess your reaction.

1. The CHEM21 Solvent Selection Guide
Summarized nicely here: https://learning.acsgcipr.org/guides-and-metrics/solvent-selection-guides/the-chem21-solvent-selection-guide/, and originally published as: D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296. DOI:10.1039/c5gc01008j

2. The Glaxo-Smith-Kline Reagent Selection Guide (we will specifically look at the one for amide coupling)
Described here: https://learning.acsgcipr.org/guides-and-metrics/reagent-guides/gsk-reagent-selection-guides/, and originally published as: J. P. Adams, C. M. Alder, I. Andrews, A. M. Bullion, M. Campbell-Crawford, M. G. Darcy, J. D. Hayler, R. K. Henderson, C. A. Oare, I. Pendrak, A. M. Redman, L. E. Shuster, H. F. Sneddon and M. D. Walker, Development of GSK's reagent guides – embedding sustainability into reagent selection, *Green Chem*., 2013, **15**, 1542-1549. DOI: 10.1039/c3gc40225h

3. **The Pfizer Reagent and Solvent Guides**
K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chem*., 2008, **10**, 31–36. DOI: 10.1039/b711717e